Tampere University

TIIA ISTOLAHTI

Electrocardiographic Interatrial Block, P-Terminal Force, ST level, and T-wave Inversion in General Population

Prevalence, Characteristics, and Prognostic Value

Tampere University Dissertations 760

Tampere University Dissertations 760

TIIA ISTOLAHTI

Electrocardiographic Interatrial Block, P-Terminal Force, ST level, and T-wave Inversion in General Population

Prevalence, Characteristics, and Prognostic Value

ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine and Health Technology
of Tampere University,
for public discussion in the auditorium F114
of the Arvo building, Arvo Ylpön katu 34, Tampere,
on 14 April 2023, at 12 o'clock.

ACADEMIC DISSERTATION
Tampere University, Faculty of Medicine and Health Technology
Finland

Responsible supervisor	Professor (emeritus) Kjell Nikus Tampere University Finland	
Supervisor and Custos	Professor Jussi Hernesniemi Tampere University Finland	
Supervisor	Professor Mika Kähönen Tampere University Finland	
Pre-examiners	Docent Marit Granér University of Helsinki Finland	Docent Tuomas Rissanen University of Eastern Finland Finland
Opponent	Professor Juha Hartikainen University of Eastern Finland Finland	

Cover design: Roihu Inc.

ISBN 978-952-03-2803-0 (print)
ISBN 978-952-03-2804-7 (pdf)
ISSN 2489-9860 (print)
ISSN 2490-0028 (pdf)
http://urn.fi/URN:ISBN:978-952-03-2804-7

Carbon dioxide emissions from printing Tampere University dissertations have been compensated.

PunaMusta Oy – Yliopistopaino
Joensuu 2023

To my family.

ACKNOWLEDGEMENTS

This dissertation was carried out at the Faculty of Medicine and Health Technology Tampere University, Finland. The project was financially supported by the Doctoral Programme in Medicine and Life Sciences, Faculty of Medicine and Health Technology, Tampere University; the Heart Hospital, Tampere University Hospital; the Finnish Medical Foundation; the Ida Montin Foundation; the Maire Taponen Foundation; the Finnish Foundation for Cardiovascular Research, and the Vaasa Medical Association.

Firstly, I want to acknowledge the personnel and participants of the Health 2000 and Health 2011 surveys, and the enormous work they have done in preparing the materials. Secondly, I want to thank all the people who helped and supported me throughout this project, directly or indirectly. I especially want to express my gratitude to the following people:

I owe my deepest gratitude to my main supervisor, Professor Kjell Nikus, MD, most of all for being available and present whenever needed. He took me onto this project and introduced me to the world of ECG. His expertise in the field is tremendous and I am happy for all he has shared with me. It is easy to say that without his help and guidance this thesis would not exist.

Thank you to my other supervisors Professor Jussi Hernesniemi, MD, and Professor Mika Kähönen, MD. Jussi's expertise and critical view took my projects to another level. He guided me especially in the methodological part of this study in ways I would not have figured out for myself.

A special thank you goes to co-author Heini Huhtala, MSc, for teaching me, and pushing me to learn about the statistical part of the publications. Her patient assistance and availability played a major role while conducting this study. I also owe special thanks to Antti Eranti, MD, PhD, for sharing with me his knowledge about the P waves and making a major contribution to planning the P-wave Studies I and IV.

Thank you to my thesis committee, Ismo Anttila, MD, PhD, Docent Markku Eskola, MD, and Professor Terho Lehtimäki, MD, and great thanks also to other co-writers Leo-Pekka Lyytikäinen, MD, Professor Antti Jula, MD, Harri Rissanen, MSc, Professor Antoni Bayés de Luna, MD, and Professor Tuomo Nieminen, MD,

for your contribution to the manuscripts. Especially to Leo-Pekka for preparing the computerized ECGs, to Tuomo for contributing to the methodology of Study II and to Antoni for sharing his special knowledge about the interatrial block.

Thank you, Docent Marit Granér, MD, and Docent Tuomas Rissanen, MD, the pre-examiners of the thesis, for your valuable comments.

I would like to thank the chiefs of cardiology and internal medicine in Vaasa Central Hospital, Mari-Anne Vaittinen, MD, and Otto Knutar, MD, for letting me take time off from clinical work to conduct this study. Thank you also to all fellows-in-training and senior colleagues at Vaasa Central Hospital for providing a clinical point of view for this study, and for pleasant company. Special thanks to Tomi Toukola, MD, PhD, for his continuous questions and comments on my research projects.

I would like to thank Docent Laura Kivelä, MD, for being a role model and a dear friend helping me in the stupidest little things with which I have been too ashamed to bother anyone else. Thank you also to my other best (and nicest) friends from medical school for peer support.

My sincerest thanks to my mum, Päivi Miettinen, who has been the first and the most enthusiastic supporter of my career as a researcher, to my dad, Asko Miettinen, for all his support in every aspect of life and to my sister, Minna Miettinen, who has just started her own ECG research. Thank you also to Asko and Leena Istolahti for your respect for my studies.

My most loving gratitude is due to my husband, Tuomo Istolahti. Without his support in our daily life this project would have never succeeded. Thank you also for your sincerest respect and belief in me in this project and in every other part of our life.

And finally, to Elsa, the joy of my life.

Vaasa, February 2023

Tiia Istolahti

ABSTRACT

The resting electrocardiogram (ECG) is the most commonly performed cardiovascular diagnostic procedure in clinical practice. The ECG gives information about the electrical activity and the structure of the heart, as well as its pathological changes. Interatrial block (IAB), P-terminal force (PTF), ST depression, and T-wave inversion are abnormalities seen in ECG.

Cardiovascular diseases in general are the leading cause of mortality worldwide, and are related to major healthcare costs. Atrial fibrillation (AF) is the most common sustained arrhythmia in general population, increasing the risk of stroke, mortality, and dementia. Stroke and coronary heart disease (CHD) are both among the major causes of serious disability worldwide.

IAB and PTF are changes in the P wave reflecting underlying electromechanical and structural changes in the atria of the heart. They have been associated with increased risk of AF and ischemic stroke in general population. ST depression and T-wave inversion are markers of repolarization abnormalities of the ventricles in the heart. They are considered to reflect myocardial ischemia, although many other diseases can result in ST depression and T-wave inversion. In general population, ST depression and T-wave inversion in resting ECG have been associated with increased risk of CHD, as well as cardiovascular and total mortality. The location of ST depression and T-wave inversion in 12-lead ECG differs in different pathological conditions, and some studies have proposed that the prognostic significance of these repolarization abnormalities may depend on the location, also in general population.

The aims of this study were to examine the prevalence and characteristics of these four ECG abnormalities, IAB, PTF, ST level, and T-wave inversion in general population and their prognostic significance for the above-mentioned cardiovascular diseases. Regarding repolarization abnormalities, the focus was on the prognostic value of the location of the changes.

This study was based on the prospective Health 2000 and Health 2011 Surveys carried out 2000–2001 and 2011–2012 in Finland. The Health 2000 population was designed to cover a nationally representative population sample of the Finnish population and consisted of 8,028 individuals aged 30+, of whom 79% (6,354 individuals) participated in the health examination, which included ECG recordings.

All available participants of the Health 2000 Survey year 2011 were invited to take part in the Health 2011 Survey, and corresponding measurements were made. The follow-up data was collected from the national registries and the follow-up period lasted for over 15 years. The ECG parameters were obtained from computer analysis.

Prevalence of advanced IAB was 1% and of partial IAB around 10%. According to the study results, IAB and PTF are highly labile ECG abnormalities in general population as the reversion rate to normal varied 40.0% – 79.3% in serial ECG measurements taken 11 years apart. Traditional cardiovascular risk factors, including arterial hypertension, higher body mass index, and hypercholesterolemia were associated with incident IAB or progression/persistence of IAB. Partial and advanced IAB were associated with increased risk of AF in general population, and advanced IAB was associated with increased risk of stroke or transient ischemic attack, also independently of incident AF. PTF was not associated with increased risk of AF in our study population.

Lower lateral (leads I, aVL, V5 and V6) ST level as a continuous parameter was associated with increased mortality in both men and women. The adverse prognosis of lower lateral ST level in women seemed to be largely caused by left ventricular hypertrophy in the ECG. Nearly one-fifth (19.6%) of the participants had negative T waves in at least one lead group. Lateral T-wave inversion was associated with increased risk of mortality and CHD, and anterior T-wave inversion was associated with increased risk of CHD. Inferior repolarization abnormality (lower ST level or T-wave inversion) was a benign phenomenon in this study.

In conclusion, in this nationally representative population-based study partial and advanced IAB, lower lateral ST levels, and lateral and anterior T-wave inversions were associated with adverse prognosis. The P-wave abnormalities studied were labile findings in general population, hence the prognostic significance of diminution of P-wave abnormalities should be investigated in further studies. The location of repolarization abnormalities in resting 12-lead ECG had a major effect on prognostic significance, which should be taken into consideration in everyday clinical practice.

TIIVISTELMÄ

Sydänfilmi (elektrokardiogrammi [EKG]) on yleisin sydän- ja verisuonitautien diagnosoimiseen käytetty tutkimusmenetelmä. EKG:sta saadaan tietoa sydämen sähköisestä toiminnasta, rakenteesta ja sydämen patologisista muutoksista. Interatriaalinen katkos (IAB), P-terminaalinen voima (PTF), ST-lasku ja negatiivinen T-aalto ovat EKG:ssa havaittavia poikkeavuuksia.

Sydän- ja verisuonitaudit ovat yleisin kuolinsyy maailmanlaajuisesti, ja niihin liittyy korkeita terveydenhuoltokustannuksia. Eteisvärinä on yleisin vallitseva rytmihäiriö, ja se lisää aivohalvauksen, kuolleisuuden ja dementian riskiä. Aivoinfarktiin ja sepelvaltimotautiin liittyy merkittävä toimintakyvyn heikkeneminen maailmanlaajuisesti.

IAB ja PTF ovat P-aaltopoikkeavuuksia, jotka heijastavat sydämen eteisten sähköisiä ja rakenteellisia muutoksia. Aiemmissa tutkimuksissa ne ovat olleet yhteydessä lisääntyneeseen eteisvärinä- ja aivoinfarktiriskiin yleisessä väestössä. ST-lasku ja negatiivinen T-aalto heijastavat sydämen repolarisaatiohäiriöitä. ST-laskua ja negatiivista T-aaltoa on pidetty sydämen hapenpuutteesta (iskemiasta) johtuvina EKG-muutoksina, vaikka niitä nähdään myös monissa muissa tilanteissa. ST-lasku ja negatiivinen T-aalto lepo-EKG:ssa ovat aiemmissa yleiseen väestöön perustuvissa tutkimuksissa lisänneet riskiä sairastua sepelvaltimotautiin, sekä riskiä sydän- ja verisuonitauteihin liittyvään kuolleisuuteen ja kokonaiskuolleisuuteen. ST-laskun ja negatiivisen T-aallon sijainti 12-kytkentäisessä EKG:ssa vaihtelee eri sairauksissa. Myös joissain yleiseen väestöön perustuvissa tutkimuksissa näiden repolarisaatiopoikkeavuuksien ennusteellinen merkitys on vaihdellut sijainnin mukaan.

Tutkimuksen tavoitteena oli tutkia näiden neljän EKG-poikkeavuuden, IAB:n, PTF:n, ST-laskun ja negatiivisen T-aallon, esiintyvyyttä ja ominaisuuksia yleisessä väestössä, sekä niihin liittyvää ennustetta suhteessa edellä mainittuihin sydän- ja verisuonitauteihin. Lisäksi repolarisaatiopoikkeavuuksissa erityinen mielenkiinto kohdistui näiden muutosten sijainnin ennusteelliseen merkitykseen 12-kytkentäisessä EKG:ssa.

Tämä tutkimus perustui Suomessa vuosina 2000–2001 ja 2011–2012 tehtyihin prospektiivisiin Terveys 2000- ja Terveys 2011 -tutkimuksiin. Terveys 2000 -

tutkimus suunniteltiin kattamaan valtakunnallisesti edustava otos Suomen väestöstä ja koostui 8028:sta yli 30-vuotiaasta henkilöstä, joista 79 % (6354 henkilöä) osallistui terveystarkastukseen, johon sisältyi myös EKG. Terveys 2011 -tutkimukseen kutsuttiin Terveys 2000 -tutkimuksen osallistujat vuonna 2011, jolloin osallistujista kerättiin vastaavat tiedot. Seurantatiedot kerättiin kansallisista rekistereistä ja seurantajakso kesti yli 15 vuotta. EKG:t analysoitiin tietokoneella.

Vaikea-asteisen IAB:n esiintyvyys oli 1 % ja osittaisen IAB:n noin 10 %. IAB:n ja PTF:n esiintyvyys vaihteli runsaasti 11 vuoden seurannassa, ja muutoksista 40,0 % – 79,3 % palautui normaaliksi 11 vuoden seurannassa. Perinteiset sydän- ja verisuonitautien riskitekijät, kuten verenpainetauti, lihavuus ja rasva-aineenvaihdunnan häiriöt, olivat yhteydessä lisääntyneeseen riskiin IAB:n ilmaantumiselle tai etenemiselle/säilymiselle EKG:ssa. Osittainen ja vaikea-asteinen IAB olivat yhteydessä lisääntyneeseen eteisvärinäriskiin, ja vaikea-asteinen IAB oli yhteydessä lisääntyneeseen riskiin sairastua aivoinfarktiin tai ohimenevään aivoverenkiertohäiriöön, myös eteisvärinän ilmaantumisesta riippumatta. PTF ei yhdistynyt lisääntyneeseen eteisvärinäriskiin tässä tutkimusväestössä.

Madaltuva ST-taso EKG:n sivuseinäkytkennöissä (I, aVL, V5 ja V6) jatkuvana muuttujana oli yhteydessä lisääntyneeseen kuolemanriskiin sekä miehillä että naisilla. Naisilla madaltuvaan ST-tasoon liittynyt huonompi ennuste johtui pääosin vasemman kammion hypertrofiasta EKG:ssa. Lähes viidenneksellä (19,6 %) osallistujista oli negatiivinen T-aalto vähintään yhdessä kytkentäryhmässä. Negatiivinen T-aalto sivuseinäkytkennöissä oli yhteydessä lisääntyneeseen kuolleisuuteen ja riskiin sairastua sepelvaltimotautiin, ja negatiiviseen T-aaltoon etuseinäkytkennöissä yhdistyi lisääntynyt riski sairastua sepelvaltimotautiin. EKG:n repolarisaatiopoikkeavuus (madaltuva ST-taso tai negatiivinen T-aalto) alaseinäkytkennöissä ei lisännyt riskiä kummallekaan päätetapahtumalle.

Yhteenvetona, tässä kansallisesti edustavassa väestöpohjaisessa tutkimuksessa osittainen ja vaikea-asteinen IAB, madaltuva ST-taso EKG:n sivuseinäkytkennöissä, sekä negatiivinen T-aalto EKG:n sivu- ja etuseinäkytkennöissä olivat yhteydessä huonompaan ennusteeseen. Tutkitut P-aaltopoikkeavuudet eivät olleet pysyviä muutoksia väestössä ja tämän takia tulevaisuudessa tulisi selvittää näiden väistyneiden P-aaltomuutosten ennusteellinen merkitys. EKG:n repolarisaatiopoikkeavuuksien sijainti 12-kytkentäisessä lepo-EKG:ssa vaikutti suuresti muutosten ennusteelliseen merkitykseen, mikä tulisi huomioida kliinisessä työssä.

CONTENTS

List of Figures

List of Tables

ABBREVIATIONS

ACS	acute coronary syndrome
ACEI	angiotensin converting enzyme inhibitor
AF	atrial fibrillation
ARB	angiotensin II receptor antagonist
BMI	body mass index
CCB	calcium channel blocker
CHA_2DS_2-VASc	congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 – 74 years, sex
CHD	coronary heart disease
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRHC	Care Register for Health Care
DM	diabetes mellitus
ECG	electrocardiogram
ECG-LVH	left ventricular hypertrophy defined by electrocardiogram
ESUS	embolic stroke of undetermined source
HAS-BLED	arterial hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (> 65 years), drugs/alcohol concomitantly
HDL	high-density lipoprotein
HR	hazard ratio
HTA	arterial hypertension
IAB	interatrial block
ICD	international classification of diseases
IQ	interquartile range
IVCD	intraventricular conduction disorder
LDL	low-density lipoprotein
LVH	left ventricular hypertrophy
n	number

OR	odds ratio
PCI	percutaneous coronary intervention
PRWP	poor R-wave progression
PTF	P-terminal force
SD	standard deviation
TIA	transient ischemic attack

ORIGINAL PUBLICATIONS

This thesis is based on the following four original publications, which are referred in the text by the Roman numerals I-IV.

Publication I Istolahti, T., Eranti, A., Huhtala, H., Lyytikäinen, L.-P., Kähönen, M., Lehtimäki, T., Eskola, M., Anttila, I., Jula, A., Bayés de Luna, A., Nikus, K., Hernesniemi, J. (2020). The prevalence and prognostic significance of interatrial block in the general population. Annals of Medicine, 52:3–4, 63–73. doi: 10.1080/07853890.2020.1731759

Publication II Istolahti, T., Nieminen, T., Huhtala, H., Lyytikäinen, L.-P., Kähönen, M., Lehtimäki, T., Eskola, M., Anttila, I., Jula, A., Rissanen, H., Nikus, K., Hernesniemi, J. (2020). Long-term prognostic significance of the ST level and ST slope in the 12-lead ECG in the general population. Journal of Electrocardiology, 58, 176–183. doi: 10.1016/j.jelectrocard.2019.12.010

Publication III Istolahti, T., Lyytikäinen, L.-P., Huhtala, H., Nieminen, T., Kähönen, M., Lehtimäki, T., Eskola, M., Anttila, I., Jula, A., Rissanen, H., Nikus, K., Hernesniemi, J. (2020). The prognostic significance of T-wave inversion according to ECG lead group during long-term follow-up in the general population. Annals of Noninvasive Electrocardiology, 26:e12799. doi: 10.1111/anec.12799

Publication IV Istolahti, T., Eranti, A., Huhtala, H., Tynkkynen, J., Lyytikäinen, L.-P., Kähönen, M., Lehtimäki, T., Eskola, M., Anttila, I., Jula, A., Nikus, K., Hernesniemi, J. (2022). Interatrial block and P terminal force in the general population – Longitudinal changes, risk factors and prognosis. Journal of Electrocardiology, 73, 12–20. doi: 10.1016/j.jelectrocard.2022.04.006

AUTHOR CONTRIBUTIONS

Publication I Tiia Istolahti participated in conceiving the study, in developing the software, contributed to methodology, performed the formal analysis, and wrote the original draft of the manuscript.

Publication II Tiia Istolahti participated in conceiving the study, contributed to methodology, performed the formal analysis, and wrote the original draft of the manuscript.

Publication III Tiia Istolahti conceived the study, contributed to methodology, performed the formal analysis, and wrote the original draft of the manuscript.

Publication IV Tiia Istolahti participated in conceiving the study, in developing the software, contributed to methodology, performed the formal analysis, and wrote the original draft of the manuscript.

1 INTRODUCTION

The resting electrocardiogram (ECG), which has been in clinical use for over a century, is nowadays the most commonly performed cardiovascular diagnostic test in clinical practice. Changes in the ECG yield information about the electrical activity and the structure of the heart, as well as its pathological changes such as arrhythmias, hypertrophy, scarring, and fibrosis. The ECG is used as a diagnostic tool to detect cardiac diseases, as well as a risk marker for cardiovascular morbidity and mortality. Technical development in recent years has resulted in new ECG modalities, including more or less continuous ECG recording with smart watches and other wearables.

Interatrial block (IAB) in the ECG represents a conduction disorder between the right and the left atrium in the heart. In partial IAB, there is a prolonged P-wave duration, while in the advanced type there is additionally a biphasic morphology of the P waves in the inferior leads. The first publication of a patient case with IAB appeared already in 1941. However, only in recent decades has the interest in this ECG abnormality increased. (Baranchuk, 2017)

P-terminal force (PTF) is a P-wave abnormality expressed as a prominent negative deflection of the terminal part of the P wave in lead V1. PTF is considered abnormal when the area of the negative terminal part exceeds –4 mVms. PTF was first described in 1964 in patients with left-sided valvular disease (Morris, Estes, Whalen, Thompson, & Mcintosh, 1964). In later studies, PTF has been associated with elevated left atrial pressure, left atrial enlargement, and slowed interatrial conduction (Heikkilä, Hugenholtz, & Tabakin, 1973; Platonov, 2012).

Both IAB and PTF have been associated with atrial fibrillation (AF) and stroke in general population (Huang et al., 2020; Kamel et al., 2014; Skov et al., 2018). They are regarded as markers of atrial cardiomyopathy, a condition affecting atrial structure and function, making the atria more susceptible to arrhythmias and thromboembolism. Atrial alterations related to atrial cardiomyopathy have been associated with increased risk for AF and ischemic stroke (Hirsh, Copeland-Halperin, & Halperin, 2015). The prevalence and clinical characteristics of IAB and PTF in general population have not been extensively studied, and research on the

association between these P-wave abnormalities and stroke or other clinical endpoints are rare.

The ST level and T wave in ECG are expressions of the repolarization phase of the heart. Repolarization abnormalities result in changes of the ST level and the T waves (Rautaharju, Surawicz, & Gettes, 2009). ST-segment depression and T-wave inversion in the resting 12-lead ECG have been associated with cardiovascular disease and worse outcome in general population (Larsen et al., 2002). Some studies have proposed that the location of the repolarization abnormality in the ECG carries significant clinical information (Anttila et al., 2010), although the prognostic significance has not been established in earlier studies.

Cardiovascular diseases are the leading cause of death globally ("Global, Regional, and National Age–Sex Specific All-Cause and Cause-Specific Mortality for 240 Causes of Death, 1990–2013," 2015). Furthermore, they are associated with major health care costs (Meretoja et al., 2011). AF is the most common sustained arrhythmia in general population. AF is an independent risk factor for stroke, dementia, and mortality (Benjamin et al., 1998; Santangeli et al., 2012; Wolf, Abbott, & Kannel, 1991). Stroke and coronary heart disease (CHD) are both among the major causes of serious disability worldwide (C. J. Murray & Lopez, 1997). Thus, it is justified to seek methods to diagnose and prevent these diseases at the population level.

The aim of this study was to examine the prevalence, characteristics, and prognostic significance of four ECG abnormalities, IAB, PTF, ST level, and T-wave inversion with respect to the previously mentioned cardiovascular diseases in general population. Regarding the ST level and T-wave inversion, the focus was on prognostic differences depending on the localization of these changes in resting 12-lead ECG.

2 REVIEW OF THE LITERATURE

2.1 Resting electrocardiogram

The ECG is a drawing of the electrical conduction of the heart. It registers the heart's electrical activity on the body surface and gives information about the electrophysical function and disorders of the heart. The ECG records potential differences between electrodes placed at standard positions on the body surface. The change in the voltage over the cell membrane creates an action potential, which is the reflection seen in the surface ECG. The depolarization and repolarization phases are drawn into the ECG as different sized, shaped, and directed waves (Figure 1).

The first wave in the ECG is the P wave, which reflects the depolarization of atria; the initial part of the P wave reflects right atrial depolarization, while the terminal part expresses left atrial depolarization. The QRS complex reflects the depolarization of the ventricles. The repolarization of the ventricles is expressed by the T wave (Franz, Bargheer, Rafflenbeul, Haverich, & Lichtlen, 1987). In some cases, especially during slower heart rates, a U wave may be recognizable. The origin of the U wave is somewhat uncertain, but mechanoelectrical forces have been suggested as potential background factors (Eyer, 2015). The point between the QRS complex and ST segment is called the J point.

ECG changes give information about the electrical activity of the heart, and many arrhythmias can be diagnosed this way. The ECG also provides information about structural changes of the heart, including ventricular hypertrophy, congenital diseases, heart failure, scarring, and fibrosis of the heart. ECG can be used as a risk marker for cardiovascular morbidity and mortality, and as a diagnostic tool, e.g., in case of acute coronary syndrome (ACS). Even though the surface ECG has been in clinical use for more than one hundred years, it still is the most commonly performed cardiovascular diagnostic procedure in clinical practice (Kligfield et al., 2007). Technical developments in recent years have made ECG even more popular and the option to record ECGs in people's daily living, e.g., with smart watches and other wearables, expands the utilization of the diagnostic information provided by the ECG.

Compared to resting ECG, ECG recorded during physical exertion gives additional prognostic and diagnostic information. In this thesis, ECG refers to the resting 12-lead ECG unless otherwise specified.

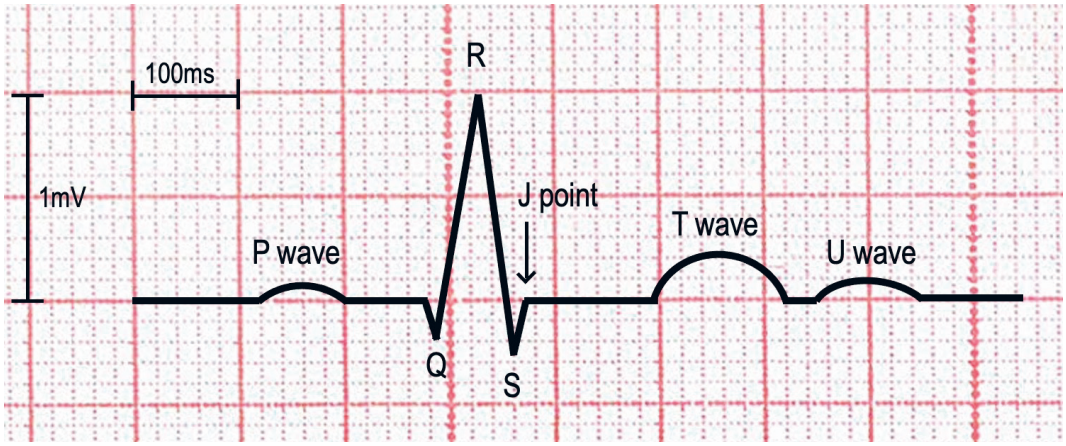

Figure 1. Waves in a normal ECG.

2.1.1 History of 12-lead ECG

In 1887, Augustus D. Waller was already able to detect the cardiac action currents from his dog and from the human body with a mercury capillary electrometer (Sykes, 1987). The first practical electrocardiograph was a galvanometer constructed by Willem Einthoven in 1902 (Einthoven, 1903). At the beginning of the 20th century, Einthoven introduced the three standard ECG leads I, II and III, which constitute the equilateral Einthoven's triangle (Barold, 2003). Einthoven himself believed in the great potential of electrocardiography, and also received the Nobel prize in 1924 for his discoveries (Bayés de Luna, 2019).

In the 1930s Frank Wilson introduced the central terminal, which enabled the construction of the unipolar leads VR, VL, and VF (Wilson, Johnston, Macleod, & Barker, 1934). Charles Wolferth and Francis Wood described the use of precordial (chest) leads (Burch, 1978). In 1938 the American Heart Association and the Heart Society of Britain and Ireland published recommendations for standardization of the chest leads ("Standardisation of Precordial Leads," 1938). Finally, in 1942 Emanuel Goldberger increased the voltages of Wilson's unipolar leads, resulting in the augmented limb leads aVR, aVL, and aVF (Goldberger, 1942); this completed the standard 12-lead ECG.

Sir Thomas Lewis and F. Wilson were pioneers in the diagnostic use of the ECG. Lewis, at the beginning of the 20th century, focused on the electrocardiographic study of arrhythmias. He described the ECG of AF in 1909. Wilson made major contributions to the diagnostic usefulness of the ECG in bundle branch blocks, ventricular hypertrophy, and myocardial infarction. (Barold, 2003)

2.1.2 Localization of the changes in 12-lead ECG

The electrical activity of the heart conducts from cell to cell and spreads through the myocardium in a certain direction, starting from the sinoatrial node in the right atrium, ending in the base of the ventricles, from endocardium to epicardium. The direction and intensity of these electrical currents create vectors, which can be recorded with the ECG electrodes placed in the standard positions on the body surface. Electrical activity directed towards an electrode is seen as a positive deflection, while activity directed away from the electrode results in a negative deflection. The summation of the multitude of electrical vectors recorded by ECG electrodes constitutes the different waveforms of a 12-lead ECG. The greatest summation corresponds to the main electrical axis of the heart (normally between –30° and +90°), which is roughly oriented along the anatomical longitudinal axis of the heart. The repolarization of the heart causes opposite currents, but as the repolarization normally spreads in the reverse direction compared to depolarization, the repolarization T waves mainly point in the same direction as the largest wave seen in the depolarization phase (QRS complex).

The limb leads (I, II, III, aVR, aVL and aVF) view the heart in the frontal plane and the precordial leads (V1–V6) in the horizontal plane (Figure 2). The different ECG leads "explore" different anatomical sites of the heart. In general, leads I, aVL, V5, and V6 are considered lateral i.e., they view the heart from the left lateral side, while the leads II, III, and aVF are defined as inferior, and leads V1–V4 as anterior. Especially in the setting of an ACS, additional (supplementary) leads V7–V9 and V3R–V6R can be used. Leads V7–V9 are placed on the back at the corresponding level to leads V4–V6, and view the heart from the posterior side. Leads V3R–V6R are placed on the right side of the chest as a mirror image to the standard leads V3-V6. Especially the lead V4R is used to detect right ventricular ischemia.

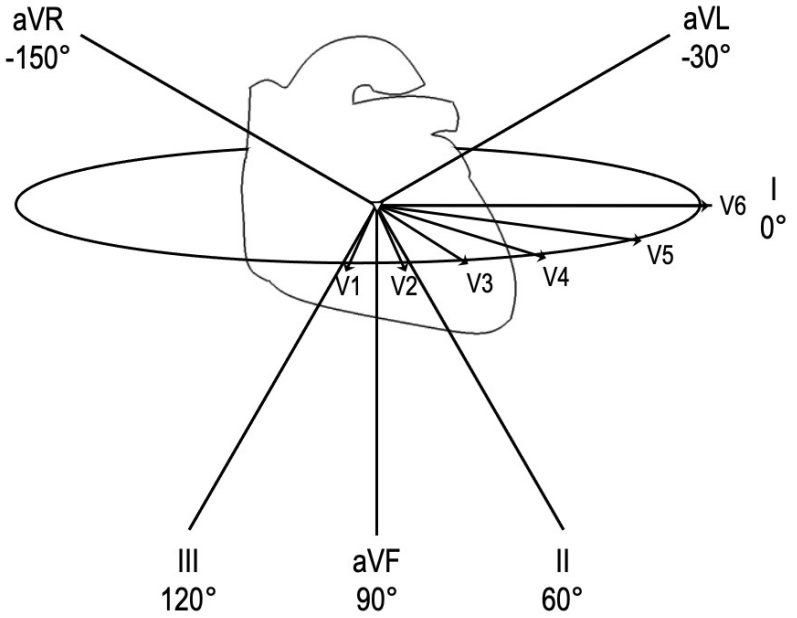

Figure 2. Limb leads (I, II, III, aVR, aVL and aVF) and precordial leads (V1-V6) of the 12-lead ECG. The limb leads view the heart in the frontal plane and the precordial leads in the horizontal plane.

The classical clinical example of the localization of ECG changes is in an acute ST-elevation myocardial infarction, where the disease-causing culprit coronary artery lesion can be predicted by the location of the ST elevations in the 12-lead ECG (Maseri, Parodi, Severi, & Pesola, 1976). The coronary anatomy varies widely between individuals, but in general, occlusion of the proximal left anterior descending coronary artery leads to anterior or anterolateral ST elevation in the ECG, while occlusion of the left circumflex coronary artery may result in inferior or lateral (including "posterior") ST elevation. Finally, occlusion of the right coronary artery results in inferior, lateral (formerly named "posterior") or right-sided (V4R) ST elevation (Birnbaum, 2003). From the temporal point of view, ST elevations are often followed by T-wave inversions in the same leads corresponding to the affected myocardial regions (Bayés de Luna et al., 2014).

Arrhythmogenic cardiomyopathy and pulmonary embolism are other examples of diseases where the ECG changes are determined by the location of the disease process. These diseases are often associated with T-wave inversions in the right

precordial leads, reflecting the pathological changes in the right ventricle (Bayés de Luna et al., 2014; Hayden, Brady, Perron, Somers, & Mattu, 2002). In ventricular tachycardia the site of the origin of the arrhythmia can be estimated from 12-lead ECG (Josephson et al., 1981; K.-M. Park, Kim, & Marchlinski, 2012), and in ventricular pre-excitation, the distribution of the delta wave in the different leads aids in determining the location of the accessory pathway (Crinion & Baranchuk, 2020).

The localization of the ECG abnormalities also has prognostic significance, e.g., lower ST and T-wave level as a continuous variable was associated with cardiovascular mortality in women in a population study, but this was seen only in the lateral lead group (Anttila et al., 2010). The classical left ventricular hypertrophy and "strain" pattern, ST depression, and T-wave inversion in the lateral leads, identify patients at increased risk of cardiovascular-related as well as all-cause morbidity and mortality, especially in hypertensive heart disease (Okin et al., 2004). As the prognostic value of ECG abnormalities may depend on the location of the changes, it is important to consider the distribution of ECG changes in the 12-lead ECG.

2.1.3 P wave

The P wave reflects the depolarization of the atria. Its morphology depends on the origin of the rhythm, localization of the left atrial breakthrough site, and the geometry of the atria. Abnormalities of the electrical activity or in the structure of the atria also affect the P-wave morphology (Platonov, 2012). Normally, the electrical activity in the heart begins in the sinoatrial node at the upper part of the right atrium. The electrical potentials of this principal pacemaker of the heart are too small to be recorded from the body surface. The electrical activity spreads along the right atrial walls and breaks through the interatrial wall via the Bachmann's bundle region to the left atrium (Bachmann, 1916). The main vector of atrial depolarization is normally approximately +60 degrees and is normally seen in the surface ECG as a positive P wave in leads I, II, and aVF, and, with some variability, also in leads III and aVL (Platonov, 2012). The normal duration of the P wave is defined as < 120ms (Bayés de Luna, Baranchuk, Alberto Escobar Robledo, Massó van Roessel, & Martínez-Sellés, 2017).

Abnormalities in the P-wave morphology have been associated with left atrial enlargement, conduction delay, and elevated atrial pressure (Ariyarajah, Mercado,

Apiyasawat, Puri, & Spodick, 2005; Bayés de Luna et al., 2012; Heikkilä et al., 1973). P-wave abnormalities have also been linked with fibrosis (Tiffany Win et al., 2015), which is an important component of atrial cardiomyopathy. Atrial fibrosis results from an accumulation of fibrillar collagen deposits, most commonly as a process to replace degenerated myocardial parenchyma and is a marker of arrhythmogenic structural remodeling. Fibrosis causes localized conduction slowing and increasing conduction heterogeneity, which further provides a basis for conduction blocks (Burstein & Nattel, 2008). These conduction abnormalities, as well as structural remodeling, are reflected in the ECG as abnormalities in the P-wave morphology.

Atrial fibrosis is a common feature of clinical AF (Burstein & Nattel, 2008), hence it is not surprising that many P-wave abnormalities have been associated with AF (Chen et al., 2022). P-wave abnormalities were recently shown to be associated with an increased risk of stroke, even when adjusting for incident AF (Kamel et al., 2015; O'Neal, Kamel, et al., 2016). It has been suggested that atrial fibrosis is a marker of chronic atrial injury leading to increased thrombogenicity of the atria, and generation of atrial emboli and subsequent stroke (Hirsh et al., 2015). P-wave abnormalities in the surface ECG are easy to detect and could therefore be suitable for identifying patients at increased risk of stroke.

P-wave abnormalities include IAB (Bayés de Luna et al., 2012), PTF (Morris et al., 1964) and abnormal P-wave area (Chen et al., 2022), axis (Maheshwari et al., 2017), voltage (J.-K. Park et al., 2016), and dispersion (Dilaveris et al., 1998). The first two are discussed below in greater detail.

2.1.3.1 Interatrial block

IAB in the ECG describes a block, or delayed conduction, between the right and left atrium of the heart. As early as in 1916, Bachmann reported that an injury in a dog's heart at the interatrial branch led to a prolongation of left atrial contraction. Bachmann reported the first case of partial IAB in 1941, and Paul Puech reported the first case of advanced IAB in 1956. However, only since the 1980s has IAB become a topic of growing interest among researchers. One of the leading researchers in the field is Prof. Antoni Bayés de Luna. Accordingly, the eponym for the association between IAB and supraventricular tachyarrhythmias is Bayés' syndrome. (Bacharova & Wagner, 2015; Baranchuk, 2017)

The delay in interatrial conduction through the Bachmann's bundle region, mainly caused by fibrosis, leads to prolongation of the P-wave duration. Prolongation of the P-wave duration to ≥ 120ms is defined as first degree IAB or

partial IAB. If the interatrial stimulus is completely blocked, electrical conduction from the right to the left atrium takes an alternative route through the lower parts of the interatrial septum, via the fossa ovalis and coronary sinus. This leads to a caudo-cranial activation of the left atrium, represented in the surface ECG as a biphasic (+/-) morphology in the leads II, III, and aVF in addition to prolongation of the P-wave duration ≥ 120ms. This ECG manifestation is defined as third degree IAB or advanced IAB. (Baranchuk, 2017) An ECG example of advanced IAB is presented in Figure 3.

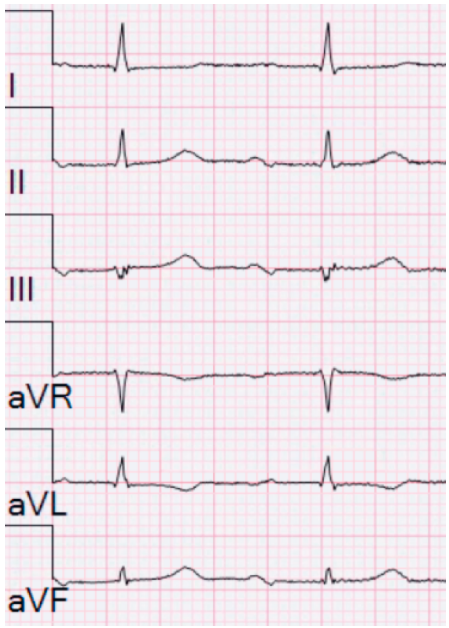

Figure 3. Limb leads of an ECG with advanced interatrial block. P-wave duration is 140ms and the P wave is biphasic in the inferior leads (II, III, and aVF). The paper speed is 25mm/s and calibration of 10mm/mV is used. Originally published in Study I, Figure 1.

Atypical patterns of advanced IAB have also been described by Bayés de Luna et al, (Bayés de Luna et al., 2018). The criteria include P-wave duration ≥ 120ms with three different morphologies in the inferior P waves. The diagnostic criteria for the different types of advanced IAB are presented in Table 1.

Finally, in second degree IAB, the interatrial conduction varies between normal and third degree IAB in the same ECG recording (Baranchuk, 2017).

Table 1. Diagnostic criteria of advanced (third degree) interatrial block (Baranchuk, 2017; Bayés de Luna et al., 2018).

A. Classical pattern

- Biphasic P wave in II, III and aVF
- P-wave duration ≥ 120ms
- Open angle between the two parts of the P wave

B. Atypical patterns

- P-wave duration ≥ 120ms
  - Type 1: Biphasic P wave in leads III and aVF and the end of the P wave is isodiphasic in lead II
  - Type 2: Biphasic P wave in leads III and aVF and the end of the P wave is biphasic in lead II
  - Type 3: Biphasic P wave in lead II, and leads III and aVF are isodiphasic with final negativity

The prevalence of IAB increases with age and depends on the population studied. In studies on general population, the prevalence of partial IAB has varied from 9.9% among middle-aged participants to 59% among elderly Greek study participants (Table 2). In general hospital population, the prevalence of IAB has been 41 – 47% (Asad & Spodick, 2003; Jairath & Spodick, 2001). The prevalence of partial IAB (defined as ≥ 110ms) was much higher (40%) in 55 patients with cryptogenic stroke than in controls (13%) (Cotter et al., 2011). The prevalence was also higher in hypertensive patients (11.9%) compared to non-hypertensive (7.2%), using the cut-off ≥ 120ms (Lehtonen et al., 2018).

Two large population-based studies reported a 0.5% prevalence of advanced IAB, while in a study of centenarians, the prevalence was 26% (Table 2).

Both partial and advanced IAB have been associated with increased risk of AF in studies on general population (O'Neal, Zhang, et al., 2016; Skov et al., 2018). In the very large Copenhagen ECG study, the risk of AF seemed to increase with the number of affected biphasic inferior leads (Skov et al., 2018). In the same study, IAB also improved the risk prediction of AF when added to a conventional risk model. In addition, IAB has been associated with incident AF after isthmus ablation for atrial flutter and after implantation of cardiac resynchronization therapy pacemakers in patients with heart failure, as well as with AF recurrence after pharmacological cardioversion, and after successful pulmonary vein isolation (Baranchuk et al., 2018).

In earlier studies, IAB, especially the advanced form, has been associated with increased risk of stroke in general population (O'Neal, Kamel, et al., 2016; Skov et al., 2018). The association between IAB and stroke may be partly explained by the increased risk of AF in patients with IAB, but research has shown that the risk of stroke persists after adjusting for coexisting AF (O'Neal, Kamel, et al., 2016). Cotter et al. reported an increased prevalence of P-wave duration ≥ 110ms in younger adults with cryptogenic stroke and patent foramen ovale (Cotter et al., 2011). One potential explanation for the increased stroke risk associated with IAB is the thrombogenicity of the fibrotic atria, which will be discussed more in detail in Chapter 2.2 "Atrial cardiomyopathy".

Authors have reported an association between diffuse coronary atherosclerosis and IAB, and they stated that their findings support the concept that IAB may result from persistent atrial ischemia (Alexander et al., 2017). Álvarez-García et al. demonstrated that patients with an occlusion of the atrial coronary artery branches during percutaneous coronary intervention had a three times greater incidence of new-onset IAB and also a greater post-procedure increase in P-wave duration than patients without occlusion (Álvarez-García Jesús et al., 2016). In addition, the rate of incident intra-atrial conduction delay was much higher in patients with atrial branch occlusion. In another study, Alexander et al. found that among patients undergoing coronary angiography and carotid ultrasonography, presence of either partial or advanced IAB was associated with more severe CHD and greater carotid intima-media thickness (Alexander et al., 2018). IAB also occurred more often in patients with evidence of ischemia during an exercise test, and combining presence of IAB with the results of the exercise test improved the sensitivity to detect ischemia (Apiyasawat, Thomas, & Spodick, 2005).

Studies have also shown an association of advanced and partial IAB with increased risk of total and cardiovascular mortality (Magnani, Gorodeski, et al., 2011; Skov et al., 2018). Martínes-Sellés et al. found that dementia was more frequent among centenarians with IAB than among individuals with normal P waves, and the association was stronger in participants with advanced IAB than in those with partial IAB (Martínez-Sellés et al., 2016).

Despite the reported prognostic significance of IAB in different clinical scenarios, there are currently no evidence-based guidelines which include IAB.

Table 2. Examples of the prevalence of partial and advanced interatrial block (IAB) in general population, in populations of different ages, and with different diagnostic criteria.

Reference	Prevalence (%)	Age of the study population (years)	Number of participants	Diagnostic criteria
Partial IAB				
(Skov et al., 2018)	16	50-90	152,759	Computerized, P wave ≥ 120ms
(Martínez-Sellés et al., 2016)	20[a]	100+ (mean 101.4 ± 1.5)	80	Manual, P wave ≥ 120ms
(Lehtonen et al., 2017)	9.9	30+ (mean 51.5 ± 14.1)	5,667	Computerized, P wave ≥120ms
(Ninios, Pliakos, Ninios, Karvounis, & Louridas, 2007)	59	65+[b]	678	Manual, P wave ≥ 120ms[c]
Advanced IAB				
(O'Neal, Zhang, et al., 2016)	0.5	45-64 (mean 54 ± 5.8)	14,625	P wave ≥ 120ms, II, III and aVF
(Skov et al., 2018)	0.5	50-90	152,759	Computerized, P wave ≥ 120ms, II, III and aVF
(Martínez-Sellés et al., 2016)	26[a]	100+ (mean 101.4 ± 1.5)	80	Manual, P wave ≥ 120ms, II, III and aVF[d]

[a]Prevalent atrial fibrillation was not excluded.

[b]Mean age 72.4 ± 5.8 years with IAB and 72.3 ± 5.4 without IAB.

[c]P-wave duration was measured separately from all leads.

[d]In lead II, the final part of P wave could be isodiphasic.

2.1.3.2 P-terminal force

PTF in the ECG is defined as the product of the length and the amplitude of the negative terminal portion of the P wave in the lead V1, mostly considered abnormal with an area of ≤ –4mVms (or ≤ –0.04mVs) (Figure 4) (Morris et al., 1964). PTF was first described in 1964 in patients with left-sided valvular disease (Morris et al., 1964). The authors compared 87 patients with left-sided valvular disease to 113 patients without apparent cardiovascular disease and PTF ≤ –4mVms was present in 92% of the patients with aortic or mitral valve impairment. In earlier studies, PTF has also been associated with higher left atrial pressure, left atrial enlargement, and slowed interatrial conduction (Heikkilä et al., 1973; Platonov, 2012).

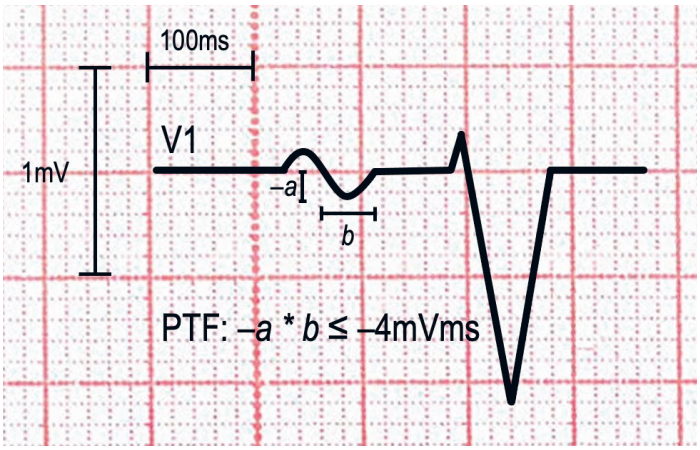

Figure 4. An illustration of the definition of PTF in ECG. PTF is defined as the product of the length (*b*) and amplitude (*-a*) of the negative terminal portion of the P wave in lead V1.

The prevalence of PTF was 7.5% in a Finnish population study of middle-aged subjects (Eranti et al., 2014). In the ARIC study of 14,542 community-dwelling middle-aged subjects, the prevalence was 10.1% (Kamel et al., 2015). An earlier study reported reference values for PTF in a population free of clinically apparent cardiovascular disease (Soliman et al., 2013). The 95% reference range for PTF among middle-aged white subjects without cardiovascular disease was from 0 to –4.4mVms, but it extended down to –5.9mVms among females over 65 years of age. The prevalence of PTF has been pronounced among participants with arterial hypertension (HTA) (9.8% in normotensive and 20.4% in hypertensive) (Lehtonen et al., 2016) and obese individuals (body mass index [BMI] > 30kg/m^2) had 0.24μVs (95% confidence interval [CI] 0.16 – 0.32) higher PTF than those with normal or low BMI (< 25kg/m^2) (Magnani et al., 2012).

PTF also has prognostic value. In a recent meta-analysis of 12 studies, the conclusion was that PTF, as a continuous (odds ratio [OR] 1.27 [95% CI 1.02 – 1.59] per 1 standard deviation [SD] change) and categorical (OR 1.39 [95% CI 1.08 – 1.79]) variable, is associated with AF in populations with and without cardiovascular disease (Huang et al., 2020). Regardless of this, there has been some controversy regarding the association between PTF and AF in earlier studies, especially those on general population. Magnani et al. reported an associated risk of PTF for AF in two different large population-based studies; the Framingham Heart Study and the ARIC study (Magnani et al., 2015). They found an increased risk of AF in the ARIC study, but not in the Framingham Heart Study. In a Finnish general population study PTF ≤ –4mVms was not associated with incident AF (Eranti et al., 2014). However, in

the same study PTF was associated with increased risk for total mortality and AF when using a higher cut-off of ≤ –6mVms.

PTF has also been associated with increased risk of ischemic stroke in general population (hazard ratio [HR] 1.31 [95% CI 1.10 – 1.57]), even after adjustment for incident AF (Kamel et al., 2015, 2014). Furthermore, PTF was associated with increased risk of cardiac death (HR 2.46 [95% CI 1.25 – 4.82]) (Perkiomaki, Zareba, Greenberg, & Moss, 2002) and death or hospitalization due to heart failure (HR 2.72 [95% CI 1.24 – 5.99]) (Liu et al., 2013) in patients with prior myocardial infarction.

2.1.4 ST segment

The ST segment in ECG is an isoelectric phase, during which all regions of the ventricles are depolarized. Abnormalities in the ST segment are expressed as elevation or depression compared with the baseline (TP or PR level), and reflect repolarization abnormalities of the ventricles. Changes in the ST level may be primary or secondary, i.e., reflect abnormalities in ventricular depolarization. Figure 5 presents an ECG example of an ST-segment abnormality, ST depression, in leads I and aVL.

The electrical systole (ST level) and electrical diastole (TP level) are normally isoelectric in surface ECG. Some conditions, e.g., hypoxemia, may cause local alterations in the ion currents in the myocardium. This causes electronic flows between the healthy and the affected myocardium. These injury currents are mostly diastolic, because they are most prominent when the rest of the myocardium is repolarized. However, the ECG device corrects the TP level to isoelectric and the injury currents are therefore seen in the surface ECG as ST depression or elevation, depending on the direction of the ST vectors. (Klabunde, 2017; Mäkijärvi, Nikus, Raatikainen, Parikka, & Aro, 2019a)

ST-segment changes are normally measured at the junction of the QRS complex with the ST segment, which is defined as the J point. The most important exception is exercise testing, where the ST-segment changes are measured at 40ms to 80ms after the J point (Rautaharju et al., 2009). In addition to the ST level, the direction of the ST segment likewise has prognostic value. Especially in exercise testing, a downward sloping ST segment is considered typical for CHD (Froelicher & Myers, 2000). A downward sloping ST segment together with T-wave inversion in the lateral leads in resting ECG, the "strain pattern", is a marker of left ventricular remodeling, often associated with anatomical left ventricular hypertrophy (LVH). This ECG

pattern was associated with increased all-cause mortality, systolic dysfunction, and myocardial scar in a population study (Inoue et al., 2017). The strain pattern has also been associated with larger left ventricular mass and worse outcome in HTA (Okin et al., 2001, 2009).

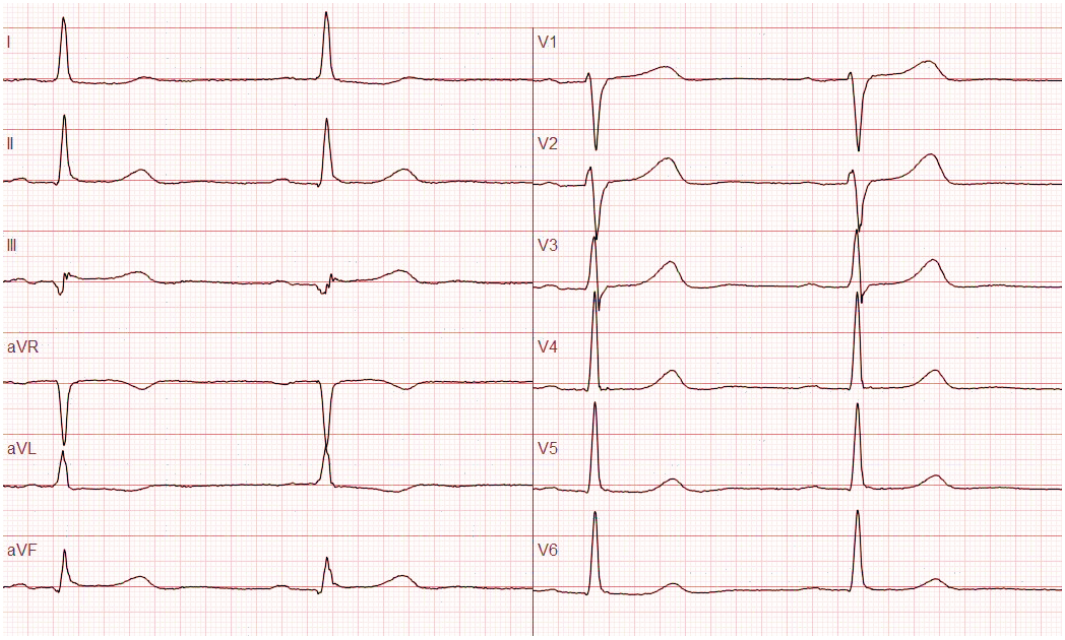

Figure 5. Resting ECG example from a patient with minor ST depression in the lateral leads I and aVL. The paper speed is 50mm/s and calibration of 10mm/mV is used.

The primary changes in the ST level are caused by various etiologies, e.g., ischemia, sympathetic activity, electrolyte disturbances, and various drugs. Secondary changes in the ST level are caused by alterations in depolarization with broad QRS complex, typically ventricular conduction disturbances (Rautaharju et al., 2009). The analysis of the ST level in resting ECG, both ST elevation and depression, is one of the key factors in ACS, where the different changes form the basis for the diagnosis and therapeutic approach (Collet et al., 2021; Ibanez et al., 2018). ST elevation may also be seen in healthy, young individuals, as a benign early repolarization pattern with an elevated J point and upward sloping ST level. However, J-point elevation with a horizontal or downward-sloping ST elevation has been associated with cardiovascular and all-cause mortality (Adler, Rosso, Viskin, Halkin, & Viskin, 2013; Macfarlane et al., 2015; Rollin et al., 2012). In Brugada syndrome, the QRS complex in lead V1 shows a right bundle branch block type morphology, the ST segment is

elevated, and the T wave is inverted in the corresponding lead (Brugada & Brugada, 1992). Brugada syndrome is associated with ventricular fibrillation and sudden cardiac death (Priori et al., 2013; Viskin et al., 2000).

A classification system for ECG abnormalities in resting ECG, including ST depression, was introduced by Blackburn et al. in 1960 (Blackburn, Keys, Simonson, Rautaharju, & Punsar, 1960), nowadays known as the Minnesota Code. In the original publication, the authors found ST depression in 26 of 100 participants with previous anterior myocardial infarction, compared to 0.4% of apparently healthy railroad employees. However, ST depression was also found in 20% of patients with pulmonary emphysema, who had no CHD at autopsy. Since that, many studies dealing with ST depression have used the Minnesota Code for the classification of the ST level, most commonly referred to as 4.1-2 (-3) for major, and 4.3-4 for minor ST changes (Table 3).

Among a large group of middle-aged men, major ST depression was associated with increased CHD mortality rates during five-year follow-up, but this was seen only among symptomatic participants (Rose, Baxter, Reid, & McCartney, 1978). Later Rabkin et al. observed that among apparently healthy men, major ST depression or T-wave abnormality was associated with increased rates of sudden death (Rabkin, Mathewson, & Tate, 1982). In a Belgian population-based study, major ST depression was associated with all-cause, cardiovascular, and CHD mortality in both sexes (De Bacquer, De Backer, Kornitzer, & Blackburn, 1998). In their study, after multivariate adjustment, ST depression was associated with the highest risk for all studied endpoints, especially cardiovascular mortality (risk ratio 4.71 [95% CI 3.30 – 6.72], compared with other ECG abnormalities: T-wave abnormality, arrhythmias, bundle branch blocks, left ventricular hypertrophy (ECG-LVH), and left axis deviation. Other population-based studies have also found major ST depression to be associated with worse outcome and risk for cardiovascular disease (Larsen et al., 2002; Möller, Zethelius, Sundström, & Lind, 2007).

Isolated minor ST changes likewise seem to have an adverse effect on outcome, although most earlier studies combined minor ST and T-wave abnormalities (Minnesota codes 4.3-4 and 5.3-4 [Table 3]) (Kumar & Lloyd-Jones, 2007). Among middle-aged men without known CHD, isolated minor ST/T changes were associated with increased mortality due to myocardial infarction or CHD, and also with cardiovascular and all-cause mortality, during a 29-year follow-up (Daviglus et al., 1999). The risk was pronounced when ST/T changes were found repeatedly. A larger population-based study among both sexes found that combined minor ST/T changes were associated with CHD-related, cardiovascular and total mortality

without interaction with sex (Greenland et al., 2003). However, in their study, isolated minor ST changes were not statistically significantly associated with any of the endpoints after multivariate adjustment.

Table 3. Minnesota Code criteria for ST depression and T-wave abnormality (Prineas, Crow, & Blackburn, 1982).

ST depression at J point (not coded in the presence of Wolf-Parkinson-White pattern, left bundle branch block, right bundle branch block or intraventricular block).	
4.1.1	ST depression ≥ 2.0mm and ST segment horizontal or downward sloping in any of leads I, aVL, V1 - V6, II, aVF.
4.1.2	ST depression ≥ 1.0mm but < 2.0mm, and ST segment horizontal or downward sloping in any of leads I, aVL, V1 - V6, II, aVF.
4.2	ST depression ≥ 0.5mm and < 1.0mm and ST segment horizontal or downward sloping in any of leads I, aVL, V1 - V6, II, aVF.
4.3	No ST depression as much as 0.5mm, but ST segment downward sloping and segment or T-wave nadir ≥ 0.5mm below P-R baseline in lead I, aVL, V2 – V6, II.
4.4	ST depression ≥ 1.0mm and ST segment upward sloping or U-shaped, in any of leads I, aVL, V1 - V6, II.
T-wave abnormality (not coded in the presence of Wolf-Parkinson-White pattern, left bundle branch block, right bundle branch block or intraventricular block).	
5.1	T amplitude negative 5.0mm or more in any of leads I, II or V2 - V6, or in lead aVL when R amplitude is ≥ 5.0mm, or in lead aVF when QRS is mainly upright.
5.2	T amplitude negative or diphasic with negative phase at least 1.0mm but not as deep as 5.0mm in leads I, II or V2 - V6, or in lead aVL when R amplitude is ≥ 5.0mm, or in lead aVF when QRS is mainly upright.
5.3	T amplitude zero, negative or diphasic with less than 1.0 mm negative phase in leads I, II or V3 - V6, or in lead aVL when R amplitude is ≥ 5.0mm.
5.4	T amplitude positive and T/R amplitude ratio < 1/20 in any of leads I, aVL, II or V3 - V6, and R wave amplitude must be ≥ 10.0mm.

In earlier studies, the relative risks for cardiovascular and CHD mortality have been pronounced among participants with major compared to minor ST changes (Kumar & Lloyd-Jones, 2007). Rasmussen et al. found in a large population study that ST depression in the lateral precordial leads was associated with cardiovascular death in a "dose-response" manner (P. V. Rasmussen et al., 2014). Among American Indians, a decreasing ST level in leads V5 – V6 was associated with increasing left ventricular mass and increased prevalence of anatomic LVH, as well as with new-onset heart

failure when divided into quartiles and pooled for a change of 10μV (Okin et al., 2002, 2007). In a Finnish population-based study by Anttila et al., ST depression as a continuous parameter was associated with cardiovascular death in the lateral lead group in women (Anttila et al., 2010).

In addition to the magnitude of ST depression as a clinically relevant factor, the localization of ST depression can also influence patient outcome. Zarafshar et al. found that the association with cardiovascular death was seen only in the lateral lead group in a large population-based study (Zarafshar et al., 2013). However, studies considering ST level as a continuous parameter are rare and the prognostic significance of the localization of the ST-level changes has not been well established.

2.1.5 T wave

Changes in the T wave reflect changes in ventricular repolarization. According to expert recommendations, an inverted T wave is a normal finding in leads III, aVR, aVL, and V1 in adults. In other leads the T wave is normally upright/positive. T-wave inversion is the term used for a T wave descending below the isoelectric level in the ECG. As for the ST segment, T-wave abnormalities may be primary, not induced by changes in depolarization, or secondary, due to alterations in ventricular depolarization. (Rautaharju et al., 2009)

There are different theories to describe the electrophysiological background of T-wave changes. One of these theories is presented in the following: The ventricular myocardium consists of three layers, of which epicardium is the outer layer, the endocardium the inner layer, and M cells are located between these two. The voltage recorded by the surface ECG electrode between the epicardium and the M cells is positive and the voltage between the endocardium and the M cells is negative. Normally the repolarization phase in the myocardium is shortest in the epicardium, and slightly longer in the endocardium, which creates a positive summation vector seen in the surface ECG as a positive T wave. The repolarization phase of the myocardium is vulnerable for ion concentration changes, which may be caused e.g., by changes in the body temperature, electrolyte concentrations, autonomic nervous system, and pH, as well as drugs and hypoxia. The ion channel density is different in the three layers of the ventricular myocardium. If the repolarization phase in the endocardium becomes shorter than in the epicardium because of the changes in ion concentrations, the T wave becomes negative. (Mäkijärvi, Nikus, Raatikainen, Parikka, & Aro, 2019b; Yan & Antzelevitch, 1998)

As mentioned above, myocardial ischemia is an important cause of a primary repolarization abnormalities. In ACS, T-wave inversions may occur in the acute stage, together with ST depression, or as isolated "post-ischemic" T-wave inversions, which last for days or even weeks after the acute phase. Besides CHD, primary T-wave inversion may be present in various conditions including perimyocarditis, acute or chronic pulmonary hypertension, cardiomyopathies, alcoholism, stroke, use of certain drugs, hypokalemia, post tachycardia, hyperventilation, cardiac memory, and in athletes. (Bayés de Luna et al., 2014)

Like ST depression, T-wave inversions have been classified according to the Minnesota Code in many studies (Table 3). Nevertheless, the prevalence of T-wave inversion has varied between different studies, probably depending on the study population and exclusion criteria. The prevalence of T-wave inversions (Minnesota Codes 5.1-3) in general population, both sexes combined, has varied between 1.6% – 5.3%, rising to 13.2% (Minnesota Codes 5.1-4) among American men with a slightly higher mean age than in many other studies (Table 4). The prevalence of T-wave inversions has been pronounced among women, and seems to increase with age in both sexes (De Bacquer et al., 1998; Larsen et al., 2002). It should be noted that most studies so far have reported the prevalence in populations without prior overt CHD.

Inverted T waves have been associated with CHD-related, cardiovascular, sudden arrhythmic, and all-cause mortality, and also with incident ACS, incident CHD, and incident major Q/QS waves in studies on general population. Table 4 shows examples of studies on the prognostic significance of T-wave abnormalities in general population. Apart from classifying T-wave inversions according to the Minnesota Code, two studies studied the T-wave level as a continuous parameter; a decreasing T-wave level in leads I and V5 and in the lateral lead group, was associated with cardiovascular mortality (Anttila et al., 2010; Yamazaki, Myers, & Froelicher, 2005). De Bacquer et al. concluded that the prognostic significance of T-wave inversions was similar between sexes, although for women the results did not reach statistical significance for all endpoints (De Bacquer et al., 1998). In addition to T-wave inversions, minor T-wave abnormalities (Minnesota Codes 5.3-4) have also been associated with adverse prognosis, and also the morphology of the T wave has had prognostic value (Porthan et al., 2013). In a large population-based study from the United States, minor T-wave abnormalities were associated with cardiovascular and CHD mortality when analyzed with both sexes combined (Greenland et al., 2003). However, in a more specific analysis, the adverse prognosis was significant only among men, even though the interaction term was insignificant between sex and T-wave abnormalities.

Table 4. Examples of studies on the prevalence and prognostic significance of T-wave inversion in general population.

Reference	Population characteristics	Diagnostic criteria	Prevalence (%)	Age at baseline (years)	Number of participants	Follow-up (years)	Prognostic significance, multivariate-adjusted RR/HR/OR (95% CI)
(De Bacquer et al., 1998)	Belgian	MC 5.1-3	women: 9.3, men: 6.1	women: mean 48.1 (SD 12.9), men: 48.7 (13.3)	9,954	10+	Mortality: RR 1.37 (1.13–1.66) CVD mortality: RR 2.47 (1.83–3.32) CHD mortality: RR 1.97 (1.30–3.00)
(Larsen et al., 2002)	Danish	MC 5.1-3	5.3	25-74	11,634	21	MI: RR 1.30 (1.07–1.59) CHD: RR 1.45 (1.26–1.67) CVD mortality: RR 1.54 (1.34–1.76)[a]
(Yamazaki et al., 2005)	US men[b]	MC 5.1-4	13.2	mean 53.6 (SD 14.0)	27,335	6	Continuous in lead I: CVD mortality: HR 0.71 (0.68–0.74)
(Möller, Byberg, Sundström, & Lind, 2006)	Swedish men	MC 5.1-4	5.6	50	2,314	20	Major Q-QS pattern (Minnesota 1.1): OR 3.11 (1.18–8.17)
(Möller et al., 2007)	Swedish men	MC 5.1-3	5.9	mean 49.6 (SD 0.6)	2,322	32	Mortality: RR 1.79 (1.44–2.22) CVD mortality: RR 2.75 (2.11–3.59)
(Anttila et al., 2010)	Finnish	Continuous by lead group	ND	30+	5,613	median 6.0, IQ 5.9-6.1	CVD mortality: Anterior HR=NS, Lateral HR=S, Inferior HR=NS, Lead V5 HR=S
(Aro et al., 2012)	Finnish	T wave ≤ 0.1mV, in leads other than aVR, aVL, III and V1	V1-V3 0.5, other leads 0.7	mean 44.0 (SD 8.5)	10,899	mean 30 (SD 11)	V1-V3: Mortality: RR 0.95 (0.64–1.41) cardiac mortality: RR 1.18 (0.61–2.27) SAD: RR 0.76 (0.19–3.06) Other leads: Mortality: RR 1.65 (1.28 –2.14) cardiac mortality: RR 2.65 (1.86–3.78) SAD: RR 3.16 (1.86–5.36)
(Rautaharju, Menotti, Blackburn, Parapid, & Kircanski, 2012)	International, men	MC 5.1-3	1.6	mean 49.3 (SD 5.59)	8,713	40	CHD mortality: HR 1.51 (1.12–2.05)

(Bakhoya, Kurl, & Laukkanen, 2014)	Finnish men	MC 5.1-3	3.6	mean 53, range 42-61	1,997	20	ACS: RR 2.23 (1.57–3.15)
(Laukkanen et al., 2014)	Finnish men	MC 5.1-3	2.4	mean 53, range 42-61	1,951	20	Mortality: HR 1.78 (1.22–2.59)
(Kurl, Mäkikallio, & Laukkanen, 2015)	Finnish men	MC 5.1-3	3.1	mean 53, range 42-61	1,814	21	Mortality: HR 1.41 (1.00–2.02) CVD mortality: HR 2.18 (1.40–3.38) CHD mortality: HR 2.62 (1.57–4.36)

ACS=Acute Coronary Syndrome, CHD=Coronary Heart Disease, CI=Confidence Interval, CVD=Cardiovascular Disease, HR=Hazard Ratio, IQ=Interquartile range, MC=Minnesota Code, MI=Myocardial Infarction, ND=No Data Available, NS=Statistically Non-significant Association, OR=Odds Ratio, RR=Risk Ratio, S=Statistically Significant Association, SAD=Sudden Arrhythmic Death, SD=Standard Deviation, US=United States

[a]Among participants aged 35-74 years

[b]Numbers reported among patients without atrial fibrillation, diagnostic Q waves, ST depression (0.5mm), left ventricular hypertrophy, QRS duration >120ms, left bundle branch block, right bundle branch block, and intraventricular conduction delay at baseline.

Some acute and non-acute etiologies are known to cause T-wave inversions in different anatomical locations. Negative T waves in the anterior leads may accompany arrhythmogenic cardiomyopathy and the takotsubo syndrome (Bayés de Luna et al., 2014). In pulmonary embolism, inverted T waves may appear in the inferior and/or anterior lead groups (Hayden et al., 2002). In ACS, the location of the postischemic T-wave inversions usually reflects the site of the ischemia during the acute phase (Bayés de Luna et al., 2014). The ECG strain pattern associated with LVH causes T-wave inversions together with ST depression in the lateral leads. The strain pattern has also been associated with adverse prognosis (Inoue et al., 2017), as discussed more in detail above in Chapter 2.1.4 "ST segment".

Some studies have also reported prognostic significance of the location of the T-wave inversions in general-population samples. In a Finnish population study, anterior T-wave inversions in leads V1 through V3 were not associated with adverse prognosis (Aro et al., 2012). However, T-wave inversion in other leads (excluding aVR, aVL and III) was associated with cardiac and all-cause mortality, and with sudden arrhythmic death. Lower T-wave level as a continuous variable was associated with cardiovascular mortality in women in an earlier study of the Finnish Health 2000 population, but this was seen only in the lateral lead group (I, aVL, and V5-V6), as well as separately in lead V5 (Anttila et al., 2010). In a study on patients with diabetes mellitus (DM) inverted T waves were associated with all-cause and cardiovascular mortality, and congestive heart failure in the lateral and inferior lead groups, and also with major CHD in the lateral lead group (Mould et al., 2021). However, anterior T-wave inversions (in leads V2 ─ V5) were not associated with increased risk for any of the studied endpoints. Despite these studies, the prognostic significance of the location of inverted T waves has not been well established in general population.

2.2 Atrial cardiomyopathy

Atrial cardiomyopathy was defined as "any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations" in an expert consensus publication (Goette et al., 2016). The same expert consensus classified atrial cardiomyopathy according to the underlying histopathology into four groups: cardiomyocyte-dependent (class I), fibroblast-dependent (II), cardiomyocyte- and fibroblast-dependent (III), and non-collagen deposits (IV). Examples of diseases primarily

affecting cardiomyocytes include lone AF and DM, diseases primarily affecting fibroblasts include aging and smoking, while chronic heart failure, HTA, and valvular heart diseases can cause both of these alterations. Pathologies underlying class IV changes include amyloidosis, fatty infiltration (obesity), inflammatory processes, and granulomatosis.

The myocardial responses to the abovementioned, underlying diseases include atrial cardiomyocyte hypertrophy and contractile dysfunction, arrhythmogenic changes in cardiomyocyte ion-channel and transporter function, atrial fibroblast proliferation, hyperinnervation, and thrombogenic changes (Goette et al., 2016). These changes result in electrophysiological and structural changes in the atrial myocardial tissue, called atrial remodeling. One of the main hallmarks of atrial remodeling is fibrosis. It is clear that fibroblast activation, as a result of atrial injury, leads to interstitial fibrosis (Hirsh et al., 2015). Although cardiomyocytes do not directly synthesize collagen, they can influence structural remodeling by interacting with neighboring fibroblasts (Burstein & Nattel, 2008).

Atrial cardiomyopathy and atrial remodeling affect atrial structure and function, both electrical and mechanical, making the atria more susceptible to arrhythmias and thrombus formation. The term "atrial cardiomyopathy" was initially used to describe the process of atrial remodeling associated with AF (Zipes, 1997), but nowadays it is known that atrial cardiomyopathy can exist with or without AF. Furthermore, AF can be the cause for atrial cardiomyopathy. Ongoing AF itself causes changes in ion channels, and also generates interstitial fibrosis, leading to the vicious circle in AF ("AF begets AF") (Bisbal, Baranchuk, Braunwald, Bayés de Luna, & Bayés-Genís, 2020).

The classical theory of AF-related thromboembolism was based on stasis formation in the left atrial appendage, further supported by the fact that successful closure or surgical removal of the left atrial appendage reduced the risk for thromboembolism (Onalan & Crystal, 2007). However, studies have failed to show a temporal association between AF and ischemic stroke (Hirsh et al., 2015). Atrial cardiomyopathy is proposed to be one of the key elements between the pathophysiological changes of the atria, AF and cardiac thromboembolic ischemic stroke (Figure 6). In a study on patients with cryptogenic stroke, the amount of fibrosis in magnetic resonance imaging was greater than that in patients with an identified cause for stroke and comparable to those with AF (Fonseca et al., 2018). Fibrosis-related P-wave abnormalities underlying impaired atrial electromechanics were associated with incident stroke without known AF (Skov et al., 2018), as discussed more in detail in the Chapter 2.1.3 "P wave". Another study showed that

the left atrial emptying fraction measured with magnetic resonance imaging was inversely associated with increased risk of incident ischemic cerebrovascular events in participants without known AF (Habibi et al., 2019). A study investigating the morphology of the left atrial appendage in patients with AF found that participants with a certain, "chicken wing", left atrial appendage morphology were 79% less likely to have a stroke/transient ischemic attack (TIA) history (Di Biase et al., 2012).

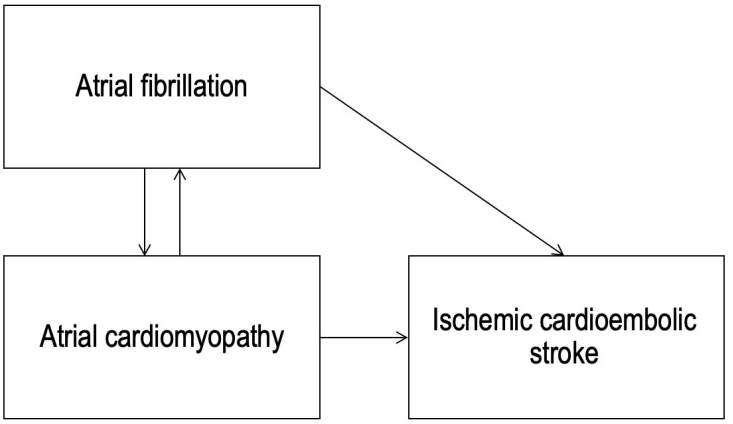

Figure 6. Relationship between atrial cardiomyopathy, atrial fibrillation, and ischemic cardioembolic stroke.

2.3 Atrial fibrillation

AF was first described over 100 years ago (Lewis, 1909). It is the most common sustained cardiac arrhythmia with very high clinical significance and with an increasing incidence (Chugh et al., 2014). AF is associated with increased morbidity and mortality and resulting in high AF-related health care costs (Magnani, Rienstra, et al., 2011).

In AF, the atrial contractions are irregular and rapid (450 – 600 beats per minute). The diagnosis is based on the ECG (or other form of the rhythm recording) registered during the arrhythmia. According to the guidelines, the electrocardiographic characteristics of AF include irregularly irregular R-R intervals, absence of repeating P waves, and irregular atrial activations (Hindricks et al., 2021). The minimum duration required for the diagnosis of AF is throughout an entire standard 12-lead ECG or a 30-sec rhythm tracing. In subclinical AF, e.g., detected by cardiac implantable electronic devices, a longer duration of AF is considered an

indication for anticoagulant therapy. The required AF duration in this situation is still under debate. AF is further classified into paroxysmal, persistent, long-standing persistent and permanent divided by the AF presentation, duration, and spontaneous termination (Hindricks et al., 2021). An ECG example of AF is presented in Figure 7.

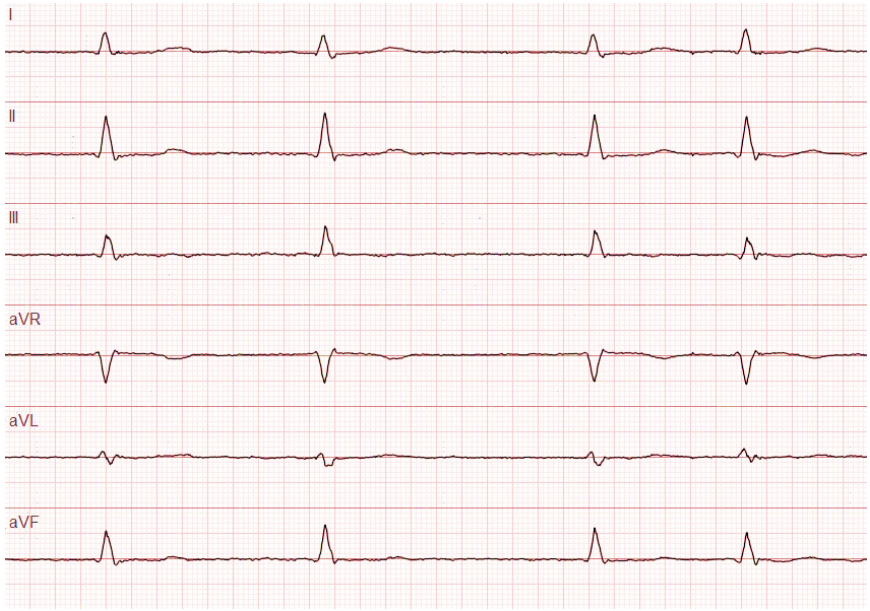

Figure 7. An ECG (limb leads) example of AF. The QRS complexes are irregular and there are no visible P waves. The paper speed is 50mm/s and a calibration of 10mm/mV is used.

The estimated prevalence of AF in adults over 55 years was 1.8% in the European Union in 2010, and the prevalence was projected to more than double by 2060 (Krijthe et al., 2013). In 2010 the estimated age-adjusted prevalence rates of AF globally were 596.2 (95% uncertainty interval 558.4 – 636.7) per 100,000 men and 373.1 (347.9 – 402.2) per 100,000 women. The incidence rates of AF in the global population have increased in recent decades from 60.7 (49.2 – 78.5) per 100,000 person-years in men and 43.8 (35.9 – 55.0) in women in 1990 to 77.5 (65.2 – 95.4) in men and 59.5 (49.9 – 74.9) in women in 2010 (Chugh et al., 2014). The increasing rates have mainly been explained by population aging, longer survival following AF onset, and improved awareness of the disease (Schnabel et al., 2015).

Risk factors for AF include age, heart failure, valvular heart disease, myocardial infarction, HTA, DM, obesity, obstructive sleep apnea, metabolic syndrome, and smoking (Benjamin et al., 2009). The risk factors lead to changes in atrial pressure,

volume, and electrical conditions, and initiate atrial remodeling. Research has also shown a strong association between AF and fibrosis (Burstein & Nattel, 2008), and atrial cardiomyopathy is strongly related to AF development (Hirsh et al., 2015). The concepts of atrial remodeling and atrial cardiomyopathy, and the pathophysiology underlying these changes are discussed more in detail in Chapter 2.2 "Atrial cardiomyopathy".

AF is independently associated with risk of stroke (Wolf et al., 1991), mortality (Benjamin et al., 1998), and dementia (Santangeli et al., 2012). A nearly five-fold risk of stroke was reported in patients with AF (Wolf et al., 1991). A simple explanation for the associated risk has been the stasis and thrombus formation because of the irregular and ineffective contractions resulting in abnormal left atrial blood flow. However, the association seems to be more complex. In patients with AF and no concomitant heart disease or other risk factors ("lone AF"), the risk of stroke is similar to that in patients without AF (Jahangir et al., 2007). Additionally, patients with paroxysmal AF are at risk of stroke even when they have sinus rhythm (Disertori et al., 2013). The fibrotic substrate, AF associated stasis, and inflammatory processes seem to be separate but inter-related mechanisms in the thromboembolism process (Hirsh et al., 2015).

The prediction of an individual's stroke risk is based on the estimation of the cumulative risk factor profile. The CHA_2DS_2-VASc (congestive heart failure, HTA, age $\geq$ 75 years, DM, previous stroke/TIA, vascular disease, age 65 – 74 years, sex [women]) score is used to estimate the benefit an individual derives from anticoagulation therapy over the general risk of bleeding (Lip & Halperin, 2010). In patients with AF and CHA_2DS_2-VASc score $\geq$ 1 in men and $\geq$ 2 in women, oral anticoagulation therapy should be considered (Hindricks et al., 2021). However, other comorbidities and the risk of bleeding must also be evaluated, for which different risk prediction scores can be used, including the HAS-BLED score (HTA, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (> 65 years), and drugs/alcohol concomitantly) (Pisters et al., 2010).

Warfarin anticoagulation therapy lowered the relative risk of AF associated with stroke and total mortality by 64% and 26% respectively (Hart, Pearce, & Aguilar, 2007). The direct oral anticoagulants have a better safety profile than warfarin, they are at least as effective in stroke prevention and are the preferred choice of oral anticoagulant (Connolly et al., 2009; Giugliano et al., 2013; Granger et al., 2011; Hindricks et al., 2021; Patel et al., 2011). Therefore, AF should be diagnosed at an early stage and patients with an increased AF risk should be identified.

2.4 Ischemic stroke

The term stroke is widely used to refer to a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause, including cerebral infarction and intracerebral or subarachnoid hemorrhage. Ischemic stroke, which is discussed in this dissertation, is defined as an episode of neurological dysfunction caused by cerebral, spinal, or retinal cell death attributable to ischemia. Focal arterial ischemia with transient symptoms (lasting <24 hours) and without evidence of infarction, is considered a TIA. (Sacco et al., 2013)

The age-standardized incidence of ischemic stroke in population-based studies has varied from 3.4 to 5.2 / 1,000 person years, and the age-standardized prevalence of stroke for people aged ≥ 65 has varied 4.6 – 7.3% (Feigin, Lawes, Bennett, & Anderson, 2003). Stroke is the fourth common cause of death worldwide, accounting for approximately 12% of all deaths, and of these half result from an ischemic stroke ("Global, Regional, and National Age–Sex Specific All-Cause and Cause-Specific Mortality for 240 Causes of Death, 1990–2013," 2015). Besides being a relatively common cause of death, the costs of the acute treatment and rehabilitation of stroke are significant. In Finland, the estimated proportion of total health care costs caused by stroke is 7% (Meretoja et al., 2011).

In a large international study, the most important risk factors for stroke were HTA, current smoking, obesity, dietary factors, and low physical activity, which accounted for more than 80% of the global risk of all strokes (O'Donnell et al., 2010). The diagnosis of ischemic stroke includes symptoms compatible with cerebral infarction and imaging findings with computerized tomography and/or magnetic resonance imaging with or without contrast or perfusion imaging. The acute treatment is based on rapid intravenous fibrinolysis and/or mechanical thrombectomy for selected patients and medical treatment with antiplatelet agents or anticoagulants according to etiology, as well as effective secondary prevention and rehabilitation. (Powers et al., 2019)

2.4.1 Cardioembolic stroke and embolic stroke of undetermined source

Ischemic stroke is classically divided according to etiology into large artery atherosclerosis, cardioembolism, small-vessel occlusion, other determined etiology, and stroke of undetermined etiology (cryptogenic stroke) (Adams et al., 1993). In a study from Germany, cardioembolism was the most common (25.6%) cause of

stroke, followed by large-artery atherosclerosis (20.9%) and microangiopathy (20.5%) (Grau et al., 2001). In that study, cardioembolic stroke was also associated with the highest mortality and worst functional outcome after 90 days, and also resulted in the most severe acute neurological deficit.

In an international study, AF was the most common (9%) reason for ischemic stroke of cardiac etiology (O'Donnell et al., 2010). The other main risk factors for cardioembolic stroke include systolic heart failure, recent myocardial infarction, patent foramen ovale, aortic arch atheroma, prosthetic heart valves and infective endocarditis (Kamel & Healey, 2017). Cardioembolic stroke, as opposed to other ischemic subtypes, can be diagnosed by the presence of a typical clinical presentation and neuroimaging profile, evidence of a high-risk cardiac source, and the exclusion of a large-artery plaque.

The etiology of ischemic stroke remains unknown in almost a quarter of ischemic cases, i.e., it is cryptogenic (Grau et al., 2001). The most widely used classification system of subtypes of ischemic stroke, "The Trial of Org 10172 in Acute Stroke Treatment", classifies cryptogenic stroke in situations where the diagnostic assessment is incomplete, no cause is found despite extensive assessment or no cause could be established because more than one cause was found (Adams et al., 1993). Lately, a more precise classification for cryptogenic stroke was proposed: embolic stroke of undetermined source (ESUS), where clinical and radiological findings point towards embolism, but the embolic source could not be identified despite sufficient examinations (Hart et al., 2014). Suggested causes for ESUS are minor-risk cardioembolic sources, such as aortic valve stenosis and atrial structural abnormalities, undiagnosed paroxysmal AF, cancer, arteriogenic emboli and paradoxical embolism. There is also evidence that a thrombogenic atrial substrate, such as atrial cardiomyopathy, can lead to atrial thromboembolism even in the absence of AF (Kamel & Healey, 2017).

2.5 Coronary heart disease

The estimated global prevalence of CHD was 2.2% in 2016, while in the United States, the prevalence in 2009-2012 was 7.6% in men and 5.0% in women (Bauersachs et al., 2019). In Finland, the prevalence of CHD in the 2010s was 14.3% in men and 7.1% in women in a population aged ≥ 50 years (Koponen, Borodulin, Lundqvist, Sääksjärvi, & Koskinen, 2018). The prevalence increases rapidly with age and men tend to develop CHD ten years earlier than women. Furthermore, CHD is

the third most frequent cause of death worldwide ("Global, Regional, and National Age–Sex Specific All-Cause and Cause-Specific Mortality for 240 Causes of Death, 1990–2013," 2015).

In CHD, atherosclerosis of the epicardial coronary arteries impairs blood flow, resulting in an imbalance between myocardial oxygen demand and supply. Atherosclerosis is a process where cholesterol particles, mainly low-density lipoprotein (LDL) cholesterol, accumulate in the inner (intimal) wall of an artery. In the intima, LDL particles undergo several reactions such as oxidation and glycation. The modified LDL induces inflammatory processes, e.g., involvement of phagocytic leucocytes. The extracellular lipid that accumulates in the intima form the classic, lipid-rich core of the atherosclerotic plaque. (Guyton & Klemp, 1996; Libby, Aikawa, & Scho, 2000; Libby & Theroux, 2005; Malekmohammad, Bezsonov, & Rafieian-Kopaei, 2021)

Atherosclerotic lesions can be divided into two categories. Stenotic lesions have smaller lipid cores, more fibrosis, more calcification, and a thick fibrous cap. They produce symptoms during exertion or psychological stress, typically chest pain (angina pectoris) or shortness of breath, related to decreased blood flow, also known as chronic coronary syndrome. Non-stenotic lesions generally tend to have large lipid cores and thin, fibrous caps susceptible to rupture, and thrombosis. Non-stenotic plaques do not usually result in symptoms, except for acute plaque rupture leading to ACS. In ACS, disrupted plaques provoke thrombosis in several ways, of which platelet activation and activation of the coagulation cascade are the most important. (Libby & Theroux, 2005)

CHD-related chest pain is characterized as a constricting discomfort in the front of the chest or in the neck, jaw, shoulder, or arm. In chronic coronary syndrome, in contrast to ACS, the symptoms appear or become more severe only with increased levels of exertion (Knuuti, 2020). The first clinical manifestation of CHD may be stress- or effort-induced angina pectoris, but also acute myocardial infarction, silent ischemia, or even sudden cardiac death.

The traditional risk factors for CHD include increasing age, male sex, HTA, hypercholesterolemia, smoking, family history and DM (D'Agostino, Grundy, Sullivan, & Wilson, 2001). The preferred diagnostic method for chronic CHD is based on pre-test probability and clinical likelihood of CHD after evaluation of risk factors and symptoms. Resting 12-lead ECG can provide additional information; pathological Q waves, ST-segment and T-wave changes increase the probability of CHD. Treatment for chronic CHD is based on anti-thrombotic and anti-ischemic medication, life-style management, management of risk factors, and

revascularization for selected patients (Knuuti, 2020). The prognosis of CHD varies depending on risk factors and symptoms. In the Euro Heart Survey of chronic CHD the annual incidence of death and non-fatal myocardial infarction was 1.5% and 1.4% respectively (Daly et al., 2006).

2.5.1 ECG changes in acute coronary syndrome

ACS can be divided into two categories based on the ECG findings: ST-elevation myocardial infarction and non-ST-elevation ACS, which is further divided into non-ST elevation myocardial infarction and unstable angina (Collet et al., 2021; Ibanez et al., 2018). In case of an acute total occlusion of a coronary artery, the first manifestation in the ECG are tall, peaked T waves, followed by ST elevation in the corresponding leads (Figure 8) which is determined by the location of the ischemia (Bayés de Luna et al., 2014). Later, pathological Q waves may develop in the same leads. The Q waves are thought to represent infarcted tissue, with no electrical activity. The formation of pathological Q waves requires a relatively large amount of infarcted tissue, thus a small infarction may not result in Q waves (Nable & Brady, 2009). Negative T waves often accompany pathological Q waves. Persistent negative T waves more than one year after the infarction in the leads with Q waves represented transmural infarction consisting of a thin fibrotic layer at autopsy, whereas positive T waves indicated non-transmural infarction with viable myocardium (Maeda et al., 1996). Furthermore, persistent T-wave inversions after ST-elevation myocardial infarction have been associated with worse prognosis and larger infarct size (Lancellotti, Gérard, Kulbertus, & Piérard, 2002; Reindl et al., 2017). Inverted T waves without pathological Q waves in ACS are a result of coronary artery reperfusion (Figure 8) (Alsaab et al., 2014; Bayés de Luna et al., 2014).

If the coronary artery is not totally occluded, the ECG often shows ST-segment depression, often accompanied with inverted T waves (Bayés de Luna et al., 2014). ST depression is considered to be the typical ECG manifestation of subendocardial ischemia (Price & Janes, 1943). However, ECG in the setting of non-ST elevation myocardial infarction may be normal in up to 30% of cases (Collet et al., 2021). In non-ST elevation myocardial infarction, ST depression has been associated with increased mortality, and larger amount and wider extent of the ST depression has been associated with worse prognosis (Kaul et al., 2001). In a study exploring the significance of the localization of the ST depression in patients suffering their first myocardial infarction, ST depression in the lateral leads was associated with

increased in-hospital death after multivariate adjustment, while ST depression in other leads was not (Barrabés, Figueras, Moure, Cortadellas, & Soler-Soler, 2000). The prognostic significance of the localization of the ECG abnormalities in non-ST elevation myocardial infarction was also found in another study; ST depression with T-wave inversion in ≥ 2 leads in V4 – V6 was independently associated with one-year mortality, as was also the sum of ST depression (Atar et al., 2007). However, studies on the significance of isolated T-wave inversions in ACS without ST elevation have yielded contradictory results. T-wave inversion has been associated with adverse prognosis only in studies including multiple (≥ 5 – 6) leads with inverted T waves (Collet et al., 2021).

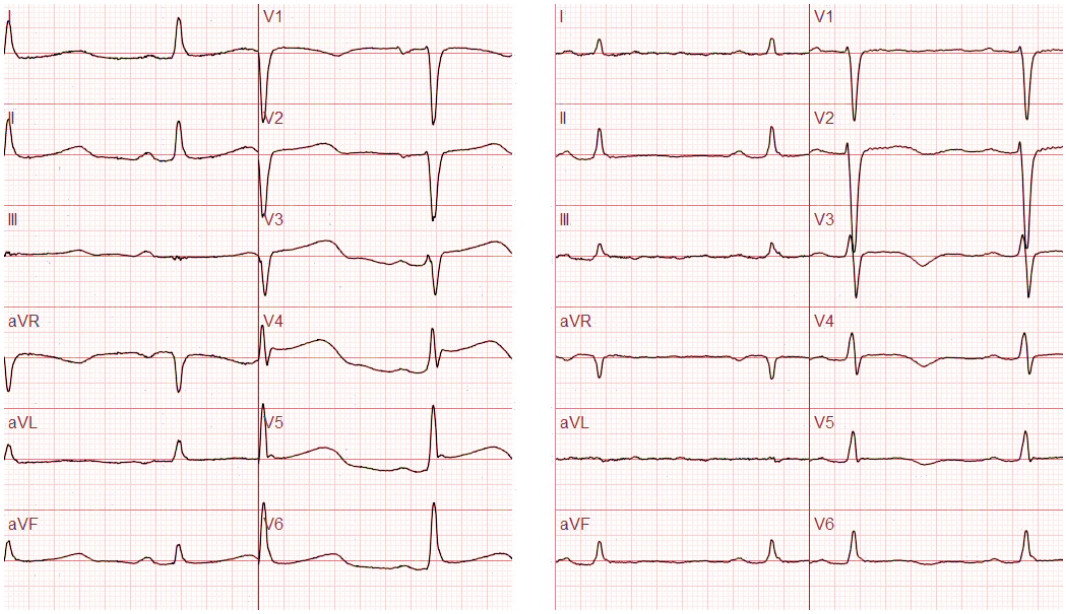

Figure 8. Two ECGs from the same patient representing different stages of ischemia. On the left, signs of acute ST-elevation infarction in the anterolateral leads (V2-V6). The patient had an occlusion of the mid-segment of the left anterior descending coronary artery. The right-sided ECG was recorded two days later, showing post-ischemic T-wave inversions in the same leads as the ST elevations in the first ECG.

2.5.2 Resting ECG in chronic coronary heart disease

Recording a 12-lead resting ECG is recommended when CHD is suspected, even though it is frequently encountered normal in patients with chronic CHD (Knuuti, 2020). Some ECG findings are indicative of prevalent CHD and are associated with

increased risk for incident CHD. In patients with known or suspected chronic CHD, major ECG abnormalities (large Q/QS waves, ECG-LVH, complete bundle branch block or intraventricular block, AF, atrial flutter or major ST/T changes) were found in 37.4% of patients (Kaolawanich, Thongsongsang, Songsangjinda, & Boonyasirinant, 2021). In the same study, the presence of a major ECG abnormality was associated with an approximately threefold increased likelihood of myocardial ischemia in patients with an intermediate pretest probability of obstructive CHD detected by adenosine stress cardiac magnetic resonance imaging.

In patients without known CHD, pathological Q waves in the ECG are considered a sign of unrecognized myocardial infarction and are therefore associated with underlying CHD. However, the sensitivity of pathological Q waves defined by the Minnesota Code (Prineas et al., 1982) has been only modest with reasonable specificity (Sandler, Pinnow, & Lindsay, 2004). Furthermore, in a study by Wasserman et al. (1982), 14.2% of diagnostic Q waves normalized during approximately three years of follow up after myocardial infarction (Wasserman et al., 1982). Another ECG pattern especially associated with anterior myocardial infarction is low R-wave amplitude extending from the right into the mid- or left precordial leads. This so-called poor R-wave progression (PRWP) is caused by loss of anterior depolarization forces (DePace et al., 1983). Although PRWP was associated with cardiac mortality in general population, both with and without associated CHD (Schröder et al., 2022), PRWP was not useful for the detection of anterior infarction in patients undergoing a cardiac stress test (Gami, Holly, & Rosenthal, 2004).

The association between resting ECG abnormalities and incident CHD in participants without known CHD has frequently been studied. In the Copenhagen City Heart Study on general population, ECG-LVH, ST depression with negative T waves and T-wave inversion were independently associated with myocardial infarction and incident CHD (Larsen et al., 2002). ST depression and T-wave inversion have been associated with increased risk for cardiac mortality and incident CHD in numerous previous population-based studies without known underlying CHD as discussed earlier in Chapters 2.1.4 “ST segment” and 2.1.5 “T wave”.

3 AIMS OF THE STUDY

The main aims of the present study on general population were to evaluate the prevalence, characteristics, and prognostic significance of the electrocardiographic parameters IAB, PTF, T-wave inversion, and of the ST level in different lead groups.

The specific aims were:

- To study the prevalence of IAB and the associated risk for AF, stroke, CHD, dementia and all-cause mortality in general population and to explore the significance of different definitions of IAB (Study I).

- To establish the prognostic role of the level of the ST segment and of the ST slope separately in three different anatomical lead groups (anterior, lateral, and inferior) in general population using total mortality as an endpoint (Study II).

- To explore the prognostic significance of T-wave inversion in three different anatomical lead groups (anterior, lateral, and inferior) in general population using new diagnosis of CHD and total mortality as outcomes (Study III).

- To examine longitudinal changes and risk factors for IAB and PTF, to re-evaluate the findings of the Study I on the associated risks of partial and advanced IAB to develop AF using two ECGs from two different timepoints, and to study the associated risk of PTF for AF development with similar methods (Study IV).

4 PARTICIPANTS

4.1 The Health 2000 Survey (Studies I-IV)

The Health 2000 Survey was carried out in Finland in the years 2000-2001. This random-sample nationwide study consisted of 8,028 individuals aged over 30 years, of whom 79% (6,354 individuals) participated in the health examination, which included a structured examination by a physician, health interviews, series of laboratory tests, and ECG recordings. The Health 2000 population was designed to cover a nationally representative population sample of the Finnish population.

The Health 2000 Survey was prospectively designed for public health research and for health monitoring. The main aim of the survey was to gather information on the most important health problems of the Finnish population, their causes and treatment as well as on the population's functional and working capacity. The special emphasis was on cardiovascular and respiratory diseases, musculoskeletal and mental disorders, and oral health. The fieldwork was conducted by five teams in 80 study areas all over the country. Participants aged 80+ were oversampled with a double sampling fraction. The precise methods of the Health 2000 Survey have been published elsewhere (Heistaro, 2008).

4.2 The Health 2011 Survey (Study IV)

The Health 2011 Survey was a re-examination of the Health 2000 Survey, to which all Health 2000 participants who were still alive and living in Finland with contact details on 6 July 2011 were invited. The participation rate of the invited individuals was 73.5% (number of individuals [n] = 5,903), and 59.0% (n = 4,729) participated in the Health 2011 health examination. The methods of the Health 2011 Survey were aimed to be as similar as possible to the Health 2000 Survey to ensure comparability of the two studies. More detailed descriptions of the methods of the Health 2011 survey has been published elsewhere (Lundqvist & Mäki-Opas, 2016).

5 METHODS

5.1 ECG analysis

During the Health 2000 and 2011 health examinations, a standard 12-lead resting ECG in supine position was recorded from each subject with GE MAC 5000 or MAC 5500 electrocardiographs (Freiburg, Germany and Milwaukee, WI, USA). ECGs were stored electronically and printed at a paper speed of 50mm/s and calibration of 10mm/mV. The ECG data were sent for further analysis to the Social Insurance Institution's research center in Turku, where the ECGs were analyzed with Magellan software (Marquette Electronics Inc, Milwaukee, WI, USA). The Marquette 12SL algorithm uses median complexes of the 10-second ECG tracing and the onset of QRS as the isoelectric line. The durations and amplitudes of different parts of the waves in the 12-lead ECG were automatically measured, and the measurement points were checked and corrected when needed. The duration of different waves was measured from the earliest onset in any lead to the latest offset in any lead. A wave crossing the baseline level constituting an area of ≥ 160μVms represented a separate wave. Two investigators at the Institute of Cardiology, Kaunas Medical Academy, Lithuania blinded to the clinical data performed the Minnesota coding (Prineas et al., 1982) for Health 2000 ECGs. The repeatability of the Minnesota Code was ascertained by a repeat analysis of 200 ECGs.

5.1.1 Definition of IAB (Studies I and IV)

We defined biphasic morphology as follows: the amplitude of the initial part of the P wave ≥ 20μV and the amplitude of the terminal part ≤ –20μV. We defined advanced IAB as P-wave duration ≥ 120ms combined with biphasic P waves in at least two inferior leads (II, III, aVF) and partial IAB as P-wave duration ≥ 120ms without biphasic morphology in Study I (Table 5) and maximally one biphasic inferior lead in Study IV. In Study I we also categorized subjects with P-wave duration ≥ 120ms and two or three leads with biphasic P waves in the inferior leads not fulfilling the above-mentioned amplitude criteria as "minor advanced IAB

(minor-aIAB)". In order to establish the significance of the number of biphasic inferior leads, we categorized subjects with one inferior biphasic lead and P-wave duration ≥ 120ms as "1 BIF". To establish the significance of the duration of biphasic P waves, we added a category "2 BIF < 120ms", defined as P-wave duration < 120ms and two or three inferior biphasic leads. ECGs with P-wave duration < 120ms and no more than one biphasic inferior lead were classified as normal. In Study IV all ECGs with P-wave duration < 120ms were classified as normal.

Table 5. IAB groups used in Study I according to P-wave duration and number of biphasic leads in the inferior lead group (leads II, III, aVF).

IAB group	P-wave duration	Number of biphasic leads (amplitude ≥ 20µV)	Number of minor biphasic leads (amplitude < 20µV)
Advanced IAB	≥ 120ms	2-3	0-1
1 BIF	≥ 120ms	1	0-2
Minor-aIAB	≥ 120ms	0	2-3
Partial IAB	≥ 120ms	0	0-1
2 BIF < 120ms	< 120ms	2-3	0-1
Normal	< 120ms	0	0-3

IAB=Interatrial Block

5.1.1.1 Validation of the definition of IAB

To check the validity of the definition of the biphasic morphology, manual comparison blinded to the clinical outcome was performed on 25 randomly selected ECGs defined as advanced IAB and also on 100 ECGs defined as partial IAB. For this purpose, digitalized ECGs with a zoom of 20mm/mV and 100mm/s recording speed were used. One (4%) ECG in the advanced IAB group showed no positive-negative morphology in the inferior leads and was thus a false positive. Among ECGs defined as partial IAB, 11 (11%) ECGs showed positive-negative morphology in one inferior lead, but in none (0%) was the morphology positive-negative in two or more inferior leads.

5.1.2 Definition of PTF (Study IV)

We defined PTF as the area (amplitude x length) of the terminal negative part of the biphasic P wave in lead V1 ≥ −6mVms (Eranti et al., 2014).

5.1.2.1 Validation of the definition of PTF

In order to validate the definition of PTF, we manually reviewed and measured 25 randomly selected ECGs with PTF and 50 ECGs without, blinded to the clinical data and PTF status. For this, digitalized ECGs with a zoom of 20mm/mV and 100mm/s recording speed were used. In 72/75 (96.0%) ECGs the manual classification matched the computerized classification. In three ECGs with computer calculated PTF, the area of the negative end of the P wave in lead V1 was > −6mVms with manual measurement and classified as normal. However, in all three cases the P waves were defined as biphasic both in manual and computerized analysis.

5.1.3 ST level and the lead groups (Study II)

The following three lead groups were used in the study: anterior (leads V1 − V4), lateral (aVL, I, V5 − V6), and inferior (II, aVF, III). In addition, lead V5 was included as a single lead. ST levels were measured at the J point and 80ms after the J point (J + 80ms). The lead with the lowest ST level in a particular lead group was used for analysis. An additional parameter "J_{alt}J + 80ms" was also created and it was defined as the lower ST level of the J point and J + 80ms measurement points.

5.1.3.1 ST slope

ST slope was defined as the difference between the ST level at J + 80ms and J point. If the absolute value of the difference between the measurement points at J + 80ms and the J point was ≤ 0.5mm, the ST segment was classified as horizontal. If the measurement point J + 80ms was > 0.5mm higher than the J point, the ST slope was labeled as positive (upward-sloping ST segment). Finally, if the measurement point J + 80ms was > 0.5mm lower than the J point, the ST slope was classified as negative (downward-sloping ST segment).

5.1.4 Definition of T-wave inversion and lead groups (Study III)

The T wave was considered inverted when the T-wave amplitude was < 0μV. If the T wave was biphasic, the lowest part of the wave indicated the level. The T waves were grouped into lead groups: anterior (V2, V3, V4), lateral (I, aVL, V5 ─ V6,) and inferior (II, aVF). If a lead group contained at least one negative T wave, the lead group was classified as having T-wave inversion. Participants with negative T waves in more than one lead group were classified into a separate group ("multiple locations"). The T waves in leads III, aVL, and V1 were tested separately before being assigned to their respective lead groups because an inverted T wave in these leads is considered normal but the T waves in these leads can also be affected by different disease processes. Lead aVR was not included in the analyses, as the T wave is normally negative in that lead.

5.2 Phenotype data collection

Trained study personnel conducted the Health 2000 health interviews, following a structured detailed written instruction to gather information about pre-existent diseases. Examining physicians conducted another structured interview and a physical examination. We included data on prevalent diseases from the Care Register for Health Care (CRHC) maintained by the National Institute for Health and Welfare. CRHC contains data on all inpatient episodes in Finland at the individual level since 1969 and on outpatients since 1998. The accuracy of the register has been validated previously (Sund, 2012). Information on medication at baseline was gathered by checking the study participants' personal health insurance cards for entitlements to drug reimbursements and by interviewing the study participants about prescription and non-prescription medicines. In addition, data on drug purchases since 1995 and special drug reimbursements since 1964 were gathered from a separate registry (Statistics on reimbursements for prescription medicines: The Social Insurance Institution of Finland).

Height and weight were measured, and BMI was calculated. Blood pressure was measured from the right arm with a standard mercury manometer (Mercuro 300; Speidel & Keller, Jungingen, Germany). An average of two measurements was taken, of which the first was measured after rest for at least five minutes in sitting position. In Studies I and II HTA was defined as blood pressure ≥ 140/90mmHg. In Studies III and IV a previous diagnosis of HTA in the CRHC (ICD-10 [international

classification of diseases, 10th revision] I10, ICD-9/8 401) or entitlement to special drug reimbursements for HTA were also included.

Heart rate was obtained from the ECGs. ECG-LVH was defined by Minnesota Code criteria 3.1, 3.3 or 3.4 (Prineas et al., 1982). In Study IV, the Cornell voltage criteria calculated from ECG were also included into the definition of ECG-LVH. Wide QRS was defined as the length of the QRS complex in the ECG ≥ 120ms. Intraventricular conduction disorder (IVCD) was defined by Minnesota Code criteria 7.1-8. Smoking was determined as a daily use of cigarettes at the time of the interview. Information about chronic obstructive pulmonary disease (COPD) was gathered during the health interview.

Classification of myocardial infarction required either a diagnosis by the examining physician, large Q waves in the resting ECG or a history of myocardial infarction in the CRHC ICD codes I21-I22 (ICD-10) or 410 (ICD-8/9). In Studies I and II the classification of CHD required at least one of the following: diagnosed angina pectoris, myocardial infarction, percutaneous coronary intervention (PCI) or bypass surgery by examining physician or diagnosed PCI or bypass surgery in the health interview, ICD codes I20-25 (ICD-10) or 410-14 (ICD-8/9) in the CRHC and entitlement to drug reimbursements for CHD. For Studies III and IV, the intervention code for coronary artery revascularization in CRHC was also included.

Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, LDL cholesterol (in Study II), triglyceride and plasma glucose concentrations were determined from venous blood samples with a clinical chemistry analyzer (Olympus, AU400, Hamburg, Germany). For Studies I, III and IV LDL cholesterol was calculated using the Friedewald formula. Diagnosis of DM at baseline included fasting serum glucose ≥ 7mmol/l or a history of taking of oral glucose lowering agents or insulin injections (World Health Organization & International Diabetes Federation, 2006).

5.3 Exclusion criteria

From all four studies, we excluded subjects with missing ECG data in 2000 (n = 55). Of these, the recording was not successful in 36 participants with entries such as "difficult to move," "wheelchair", "denial", "leg/hand amputated", "in geriatric chair", "massive hernia", "plaster in leg/ hand". In the further process, 19 ECGs were lost (diskette lost [9], coupling error [4], data reading failure [5], unspecific reason [1]).

Study I: We excluded subjects with ECGs showing supraventricular tachyarrhythmias according to Minnesota Code 8.4.1 (n = 6), all prevalent AF and atrial flutter (n = 204), paced rhythm (Minnesota Code 6.8, n = 4) and ectopic rhythm defined as totally negative P waves in the inferior leads (II, III, aVF) in computer analysis (n = 24). Participants with prior diagnosis of study endpoints (stroke or TIA [n = 143], CHD [n = 435] or dementia [n = 451]) were excluded from analysis considering particular endpoints. In addition, subjects with incident AF (n = 538) were excluded from the analysis when studying IAB as an independent risk factor for stroke and TIA.

Study II: We excluded subjects with either large Q/QS waves in ECG using Minnesota Codes 1.1-3 (n = 127), IVCD (Minnesota Code 7, n = 565), Wolf-Parkinson-White pattern (Minnesota Code 6.4, n = 1) or paced rhythm (Minnesota Code 6.8, n = 4) from the analysis.

Study III: We excluded subjects with Q/QS waves in ECG according to the Minnesota Codes 1.1-3 (n = 127), IVCD (Minnesota Code 7, n = 565), Wolf-Parkinson-White pattern (Minnesota Code 6.4, n = 1), paced rhythm (Minnesota Code 6.8, n = 4) or left ventricular hypertrophy in the ECG (Minnesota Codes 3.1, 3.3 and 3.4, n = 820) from the analysis. In the analysis using CHD as an endpoint, we also excluded prevalent CHD as defined earlier in the Chapter 5.2 "Phenotype data collection".

Study IV: We excluded subjects with prevalent AF or atrial flutter diagnosed from baseline study ECGs or registries (n = 204), ectopic atrial rhythm defined as totally negative P waves in the inferior leads (II, III, and aVF) in computer analysis in both ECGs (2000 and 2011) (n = 31) and those with a heart rate over 120 beats per minute (n = 6) in both ECGs, leaving 6,058 participants. In the analyses where we studied the association between different clinical variables and incident P-wave abnormalities, we included only participants with ECGs available at both timepoints and no incident AF before 2011 (n = 3,224). From these analyses we also excluded participants with any P-wave abnormality (partial IAB, advanced IAB or PTF) at baseline (n = 494) and any other P-wave abnormality than that studied one in 2011. In the analysis of factors associated with evolving P-wave abnormalities, we included only participants with IAB (n = 958) or PTF (n = 131) in either of the study ECGs.

5.4 Follow-up

The data on mortality and causes of death were gathered from the Causes of Death Register maintained by Statistics Finland. This contains 100% of deaths of Finnish citizens in Finland and almost 100% abroad. Information on the incident diseases were obtained from the CRHC. In addition, data on drug purchases and special drug reimbursements were gathered from a separate registry (Statistics on reimbursements for prescription medicines: The Social Insurance Institution of Finland). Databases were linked using a personal identity code. The follow-up lasted until the end of 2015.

5.4.1 Study endpoints

The study endpoints in Study I were AF, stroke and TIA, CHD, dementia, and mortality due to any cause. In Study II, the endpoint was mortality due to any cause, in Study III, mortality and CHD, and in Study IV, AF.

We defined AF as ICD code I48 (revision 10), 4273 (9) or 42792 (8) in the CRHC and Causes of Death Register, entitlement to drug reimbursement for dronedarone or direct oral anticoagulants with diagnostic code (ICD-10) I48 or entitlement to special drug reimbursements for AF.

For prevalent and incident stroke and TIA, we included ICD-10 codes I63-64 and G45 (not I63.6 or G45.4), ICD-9 codes 4330-31A, 4339-41A, 4349A, and 435-36, and ICD-8 codes 433-435 in the CRHC and Causes of Death Register.

Classification of incident CHD included ICD codes I20-25 (ICD-10) in the CRHC, entitlement to drug reimbursements for CHD and ICD codes I21-25, I46, R96, R98 (ICD-10) in the Causes of Death Register. In Study III, we also included the intervention code for coronary artery revascularization from CRHC in the definition of CHD.

Dementia was defined as ICD-10 codes F00-F03, G30, ICD-9 codes 290, 3310, 4378A, and ICD-8 code 290 in the CRHC and in the Causes of Death Register, entitlement to drug reimbursements for donepezil, galantamine, memantine, rivastigmine or tacrine or purchases of anti-dementia drugs.

5.5 Statistical analyses

Comparisons in variables were calculated with either one-way ANOVA, unpaired T-test, Kruskal-Wallis, Chi-square, or Fisher's exact test as appropriate. In Studies I, II, and III Cox proportional hazard models were constructed separately for different endpoints. In Study III (for the CHD endpoint), the analyses were performed using the Fine-Gray proportional subdistribution hazards model treating death as a competing risk. The proportional hazard assumptions were checked visually from Kaplan-Meier curves (Studies I-III) or from cumulative incidence function curves (Study III). Analyses were performed with SPSS and R. Statistical significance was based on two-sided $p<0.05$.

Study I: AF, stroke and TIA were used as primary endpoints and CHD, dementia, and mortality as secondary endpoints. Only the first diagnosis per disease was considered. The categories advanced IAB and partial IAB were compared to normal P waves (P-wave duration < 120ms with zero or one biphasic inferior P wave), and minor-aIAB, 1 BIF and 2 BIF < 120ms were included as a sensitivity analysis (Table 5). We used the following parameters for multivariate adjusting: age, sex, BMI, HDL cholesterol, LDL cholesterol, heart rate, HTA, DM, CHD, and ECG-LVH. To establish the prevalence of different IAB groups at population level, SPSS Complex samples design was used. We also tested the difference between weighted and unweighted Cox proportional hazard models with SPSS Complex samples design, and we found no clinically relevant differences between the two models. All Cox proportional hazard models were presented in unweighted form.

Study II: All analyses were conducted separately for men and women. ST levels were treated as continuous variables. The normality of the distribution of ST-segment levels was estimated with Q-Q plots and histograms. The linearity of the association of ST level and mortality was checked in a spline model. After visual inspection the association did not significantly differ from linear. Hence, we did not test the linearity in other ways. Cox proportional hazard models were constructed separately for minimum ST levels and ST slopes in every lead group and at all measurement points. Total mortality was used as an endpoint. Regarding ST slope, the three categories (upward-sloping, horizontal, downward-sloping) were used and positive slope was used as reference. For ST levels, HRs were scaled for a change of 1.0mm. The following parameters were used for multivariate adjusting: age, BMI, HDL cholesterol, LDL cholesterol, HTA, DM and CHD. Another model was also constructed where known CHD was excluded from the multivariate adjustment.

Study III: Because the T wave may normally be positive or negative in leads III, aVL, and V1 (Rautaharju et al., 2009), we tested the prognosis for each of these leads separately with unadjusted Cox proportional hazard models using both total mortality and CHD as endpoints. After this analysis, we included leads with detrimental prognosis in the lead groups. In these analyses, T-wave inversions in other leads were not excluded as there was no isolated T-wave inversion in III, aVL, or V1. Only the first diagnosis of CHD was considered. The four mutually exclusive groups (anterior, lateral, inferior, and multiple locations) were compared to ECGs with no T-wave inversions (excluding aVR, V1, and III). Both hazard models were constructed with and without adjustment for age and for multivariate analysis for age, sex, BMI, HDL cholesterol, LDL cholesterol, regular smoking, heart rate, HTA, DM, and CHD (not for CHD as an endpoint). In addition, to test for a possible confounding effect of the ST level, we performed a sensitivity analysis including the amplitude of the ST level at the J point (as dichotomous variable $\geq 0\mu V$ or $< 0\mu V$) in the multivariate adjustment. From a clinical point of view, the results of this sensitivity analysis did not differ significantly from the results without ST-level adjustment. Therefore, the results with ST-level adjustment were not included. The interaction was tested between different lead groups and sex for both endpoints and between lead groups and CHD for mortality in unadjusted Cox models. No significant sex-related interactions were observed and all the analyses were performed without sex stratification. The interaction term between lead groups and CHD was significant. Therefore, we performed the mortality analysis also after dividing the data by CHD.

Study IV: Lost to follow-up analysis between participants participating in the re-examination versus those who did not, was calculated with unpaired T-test or Chi-square test. The associations between clinical factors and incident P-wave abnormalities were analyzed using binomial logistic regression adjusted by age and multivariate adjustment comparing subjects who developed new P-wave abnormality with those who did not develop P-wave abnormality (=reference). To study the risk factors for temporal change of P-wave abnormalities, binomial logistic regression was used among participants with IAB (partial and advanced) and PTF in either ECG. In these analyses, participants with retained/worsened P-wave abnormalities were compared to participants with improvement in P-wave abnormality (=reference). Multivariate-adjusted models included all the parameters studied as covariates. To study the prognostic significance of IAB and PTF for the development of new AF in the follow-up period, we used Cox regression analysis with time-varying covariates at the two different time points (2000 and 2011). We

used the following parameters from 2000 for multivariate adjustment: age, sex, BMI, HDL cholesterol, LDL cholesterol, HTA, DM, CHD, smoking, and ECG-LVH. Proportional hazard assumption was tested with Schoenfeld residuals and no violation of the assumption was observed.

5.6 Ethical considerations

The project plan of the Health 2000 and 2011 Surveys received favorable opinions in the Ethical Committee for Research in Epidemiology and Public Health of the Hospital District of Helsinki and Uusimaa. Written informed consent forms were handed out and signed by the study participants separately at the home interview and at the health examination.

The research plan of this study received favorable opinions from the evaluation group of Health 2000 and 2011 in June 2017. This study was based only on the registry data and hence did not require a separate statement from the ethics committee.

The National Institute for Health and Welfare delivered only the data specified in the research plan to the researchers. Written consent about the confidentiality was signed by the personnel participating in the study. Under no circumstances did outsiders have access to the data.

6 RESULTS

6.1 Baseline characteristics of the study population

6.1.1 Participants with IAB and PTF (Studies I and IV)

The baseline characteristics of Studies I and IV divided by IAB groups are presented in Table 6. The participants with IAB morphology were more often men, older, and had larger proportions of the co-morbidities studied and ECG abnormalities than did the participants with normal ECGs, except for COPD, and participants in group "2 BIF < 120ms" had lower prevalence of myocardial infarction. Participants with IAB were also taking the medications studied more often, except for angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor antagonists (ARB) in Study IV. In general, their laboratory profiles were also worse or equal compared to participants with normal ECGs.

Compared to participants with partial IAB, those with advanced IAB were older and more often men. They also had more of the diseases studied and more ECG abnormalities, were more often taking all the medications studied, had higher BMI, larger waist circumference and lower heart rate. They also tended to have lower HDL cholesterol, LDL cholesterol, total cholesterol, and higher uric acid levels.

Participants with PTF (Study IV), compared to participants without PTF, were older, had higher BMI, were more often hypertensive, had higher LDL cholesterol, more often had ECG-LVH, IVCD and beta blocker in use (Table 7). The groups did not differ significantly in terms of sex, smoking habits, diabetes, CHD, HDL cholesterol, wide QRS, and use of ACEI/ARB.

Table 6. Baseline characteristics of Studies I and IV by IAB groups. Regarding Study I, all participants (n = 6,066) are included and for the Study IV, all participants who attended both Health 2000 and 2011 Surveys (n = 3,224).

		Normal		**Advanced IAB**		**Partial IAB**		**Minor-aIAB**		**1 BIF**		**2 BIF < 120ms**		
Variable	Study	Mean/ Median/ n	SD/ Q_1-Q_3/ (%)	Mean/ Median/ n	SD/ Q_1-Q_3/ (%)	Mean/ Median/ n	SD/ Q_1-Q_3/ (%)	Mean/ Median/ n	SD/ Q_1-Q_3/ (%)	Mean/ Median/ n	SD/ Q_1-Q_3/ (%)	Mean/ Median/ n	SD/ Q_1-Q_3/ (%)	p value
n	I	4887	(80.6)	63	(1.0)	585	(9.6)	18	(0.3)	264	(4.4)	249	(4.1)	
	IV	2778	(86.2)	20	(0.6)	426	(13.2)							
Age	I	51.0	14.3	67.4	12.6	55.0	14.0	64.6	12.3	57.5	14.8	58.3	15.5	<0.001
	IV	47.3	11.0	56.2	10.5	51.2	11.5							<0.001
Men	I	2123	(43.4)	36	(57.1)	309	(52.8)	9	(50.0)	156	(59.1)	96	(45.0)	<0.001
	IV	1151	(41.4)	16	(80.0)	244	(57.3)							<0.001
BMI (kg/m^2)	I	26.7	4.6	29.2	4.6	27.5	4.6	29.2	5.2	28.4	4.6	27.2	4.4	<0.001
	IV	26.3	4.3	29.8	5.1	27.5	4.4							<0.001
Regular smoking	I	1087	(22.3)	9	(14.3)	125	(21.4)	3	(16.7)	40	(15.2)	58	(23.4)	0.065
	IV	525	(19.0)	6	(30.0)	83	(19.5)							0.446
HTA	I	1944	(39.8)	38	(60.3)	288	(49.2)	13	(72.2)	144	(54.5)	121	(48.6)	<0.001
	IV	959	(34.6)	11	(55.0)	186	(43.7)							<0.001
DM	I	253	(5.2)	11	(17.5)	41	(7.0)	2	(11.1)	27	(10.2)	35	(14.1)	<0.001
	IV	77	(2.8)	3	(15.0)	18	(4.2)							0.009
ECG-LVH	I	667	(13.6)	15	(23.8)	93	(15.9)	4	(22.2)	56	(21.2)	50	(20.1)	<0.001
	IV	464	(16.7)	5	(25.0)	91	(21.4)							0.041
CHD	I	298	(6.1)	17	(27.0)	57	(9.7)	5	(27.8)	32	(12.1)	26	(10.4)	<0.001
	IV	81	(2.9)	3	(15.0)	21	(4.9)							0.004
HDL (mmol/l)	I	1.3	0.4	1.2	0.4	1.3	0.3	1.3	0.3	1.3	0.3	1.3	0.4	0.001

	IV	1.4	0.4	1.2	0.3	1.3	0.3							0.001
LDL (mmol/l)	I	3.8	1.2	3.6	1.4	3.9	1.1	4.2	1.2	3.6	1.4	3.9	1.3	0.027
	IV	3.8	1.1	3.5	1.4	4.0	1.1							0.003
Waist (cm)	I	91.8	13.3	100.6	12.1	95.1	13.0	101.1	16.3	97.9	13.4	93.6	12.4	<0.001
Heart rate/min	I	63.6	10.7	59.7	10.2	62.5	11.0	62.3	10.0	61.7	10.9	62.8	9.9	0.001
COPD	I	58	(1.2)	1	(1.6)	6	(1.0)	0	(0.0)	5	(1.9)	5	(2.0)	0.554
MI	I	112	(2.3)	8	(12.7)	23	(3.9)	2	(11.1)	13	(4.9)	5	(2.0)	<0.001
Total chol. (mmol/l)	I	5.9	1.1	5.8	1.4	6.0	1.0	6.1	1.2	6.1	1.2	6.2	1.1	0.001
Triglycerides (mmol/l)	I	1.3	1.0-1.8	1.4	1.1-2.2	1.4	1.0-1.9	1.3	1.0-2.0	1.5	1.1-2.0	1.4	1.0-2.0	<0.001
CRP (mg/l)	I	0.7	0.3-1.8	0.7	0.3-2.5	0.7	0.3-1.8	1.1	0.5-3.6	0.9	0.4-2.1	1.2	0.4-3.1	<0.001
Uric acid (µmol/l)	I	294.8	79.0	335.4	97.2	312.4	77.7	324.7	76.3	331.2	83.5	311.9	85.6	<0.001
Wide QRS	IV	46	(1.7)	1	(5.0)	23	(5.4)							<0.001
IVCD	IV	175	(6.3)	3	(15.0)	55	(12.9)							<0.001
Medication:														
Beta blocker	I	556	(11.4)	23	(36.5)	114	(19.5)	9	(50.0)	68	(25.8)	46	(18.5)	<0.001
	IV	201	(7.2)	5	(25.0)	63	(14.8)							<0.001
CCB	I	239	(4.9)	9	(14.3)	50	(8.5)	6	(33.3)	25	(9.5)	19	(7.6)	<0.001
Digitalis	I	29	(0.6)	4	(6.3)	7	(1.2)	2	(11.1)	4	(1.5)	3	(1.2)	<0.001
ACEI/ARB	I	328	(6.7)	11	(17.5)	58	(9.9)	3	(16.7)	32	(12.1)	27	(10.8)	<0.001
	IV	144	(5.2)	2	(10.0)	24	(5.6)							0.592

ACEI=Angiotensin-converting Enzyme Inhibitor, ARB=Angiotensin II Receptor Antagonist, BIF=Biphasic, BMI=Body Mass Index, CCB=Calcium Channel Blocker, CHD=Coronary Heart Disease, COPD=Chronic Obstructive Pulmonary Disease, DM=Diabetes Mellitus, ECG-LVH=Left Ventricular Hypertrophy in ECG, HDL=High-density Lipoprotein Cholesterol, HTA=Hypertension, IAB=Interatrial Block, IVCD=Intraventricular Conduction Disease, LDL=Low-density Lipoprotein Cholesterol, MI=Myocardial Infarction, n=Number, SD=Standard Deviation, Total chol.=Total Cholesterol, Q_1-Q_3=Quartiles

Table 7. Baseline characteristics of the included Health 2000 and 2011 Survey participants (n = 3,224) by PTF status.

Variable	No PTF		PTF		
	Mean/n	SD/(%)	Mean/n	SD/(%)	p value
n	3132	(97.1)	92	(2.9)	
Age	47.6	11.0	56.4	12.1	<0.001
Men	1368	(43.7)	43	(46.7)	0.560
BMI (kg/m^2)	26.4	4.3	27.5	4.6	0.019
Smoking	592	(19.0)	22	(23.9)	0.235
HTA	1101	(35.2)	55	(59.8)	<0.001
DM	93	(3.0)	5	(5.4)	0.202
CHD	100	(3.2)	5	(5.4)	0.224
HDL (mmol/l)	1.4	0.4	1.4	0.4	0.735
LDL (mmol/l)	3.8	1.1	4.2	1.3	0.001
ECG-LVH	526	(16.8)	34	(37.0)	<0.001
Wide QRS	66	(2.1)	4	(4.3)	0.138
IVCD	217	(6.9)	16	(17.4)	<0.001
Beta blocker	252	(8.0)	17	(18.5)	<0.001
ACEI/ARB	166	(5.3)	4	(4.3)	1.000

ACEI=Angiotensin-converting Enzyme Inhibitor, ARB=Angiotensin II Receptor Antagonist, BMI=Body Mass Index, CHD=Coronary Heart Disease, DM=Diabetes Mellitus, ECG-LVH=Left Ventricular Hypertrophy in ECG, HDL=High-density Lipoprotein Cholesterol, HTA=Hypertension, IVCD=Intraventricular Conduction Disease, LDL=Low-density Lipoprotein Cholesterol, n=Number, SD=Standard Deviation, PTF=P-Terminal Force

6.1.1.1 Participants not attending the Health 2011 Survey (Study IV)

Reasons for non-participation in the follow-up Health 2011 Survey were death between the study timepoints (n=670), and decision not to attend the re-examination (n=836); in addition, no ECG was available for 960 subjects from the follow-up study – of these, 879 did not attend the health examination and 81 had no ECG recording for unknown reasons. Compared with the subjects who participated in both the Health 2000 Survey and the re-examination in 2011, the non-participants of the re-examination, were more likely to be male, older, have higher BMI, lower HDL cholesterol, more often HTA, DM, CHD, ECG-LVH, IVCD and QRS ≥ 120ms, use of beta blockers and ACEI/ARB and to be active smokers. The results

of the lost to follow-up analysis are presented in the original publication, Study IV, Appendix 1, Table 1.

6.1.2 Characteristics of survivors and non-survivors by sex (Study II)

The baseline characteristics of the participants of Study II by sex and outcome are presented in Table 8. In women non-survivors and survivors differed significantly with respect to all the parameters studied. In men the differences between survivors and non-survivors were not as obvious as in women. In men the non-survivors were, as anticipated, older, had larger waist circumference, higher heart rate, more often prevalent co-morbidities, lower LDL cholesterol, higher C-reactive protein, higher levels of uric acid and were more often taking the medications studied than were survivors.

Table 8. Baseline characteristics of the Health 2000 Survey participants by outcome and sex.

	Men					Women				
	Survivors		Non-Survivors			Survivors		Non-Survivors		
Variable	Mean/ Median/ n	SD/ Q_1-Q_3/ (%)	Mean/ Median/ n	SD/ Q_1-Q_3/ (%)	p value	Mean/ Median/ n	SD/ Q_1-Q_3/ (%)	Mean/ Median/ n	SD/ Q_1-Q_3/ (%)	p value
n	1972	(80.2)	487	(19.8)		2596	(82.4)	555	(17.6)	
Age	47.2	10.9	64.4	13.5	<0.001	48.7	12.0	72.6	12.2	<0.001
BMI (kg/m^2)	27.1	4.0	27.1	4.5	0.773	26.5	5.0	28.0	5.0	<0.001
Waist (cm)	97.3	11.1	99.3	12.3	0.002	87.3	13.1	93.2	12.6	<0.001
Heart rate/min	61.7	10.7	65.7	12.9	<0.001	63.6	10.2	66.9	11.8	<0.001
Regular smoking	533	(27.1)	150	(30.9)	0.092	472	(18.3)	59	(10.7)	<0.001
COPD	18	(0.9)	19	(3.9)	<0.001	19	(0.7)	18	(3.2)	<0.001
HTA	832	(42.2)	297	(61.0)	<0.001	828	(32.0)	367	(66.5)	<0.001
DM	103	(5.2)	69	(14.2)	<0.001	79	(3.0)	81	(14.6)	<0.001
LVH	419	(21.2)	95	(19.5)	0.406	201	(7.7)	105	(18.9)	<0.001
CHD	76	(3.8)	95	(19.5)	<0.001	73	(2.8)	132	(23.8)	<0.001
MI	21	(1.1)	36	(7.4)	<0.001	11	(0.4)	30	(5.4)	<0.001
Tot. chol.	6.0	1.1	5.9	1.2	0.056	5.8	1.1	6.2	1.2	<0.001
HDL	1.2	0.3	1.2	0.4	0.543	1.5	0.4	1.3	0.4	<0.001
LDL	3.9	1.0	3.7	1.1	0.002	3.6	1.0	3.9	1.1	<0.001
Triglyc.	1.5	1.1-2.2	1.4	1.1-2.0	0.478	1.2	0.9-1.6	1.5	1.1-2.0	<0.001
CRP (mg/l)	0.7	0.33-1.6	1.2	0.4-3.1	<0.001	0.7	0.2-1.9	1.1	0.4-3.1	<0.001
Uric acid	337.5	69.0	348.9	81.7	0.005	258.2	65.7	310.0	86.3	<0.001
Beta blocker	158	(8.0)	116	(23.8)	<0.001	300	(11.6)	172	(31.0)	<0.001
CCB	71	(3.6)	54	(11.1)	<0.001	109	(4.2)	87	(15.7)	<0.001
Digitalis	9	(0.5)	19	(3.9)	<0.001	8	(0.3)	43	(7.7)	<0.001
ACEI/ ARB	124	(6.3)	72	(14.8)	<0.001	155	(6.0)	92	(16.6)	<0.001

ACEI=Angiotensin-converting Enzyme Inhibitor, ARB=Angiotensin II Receptor Antagonist, BMI=Body Mass Index, CCB=Calcium Channel Blocker, CHD=Coronary Heart Disease, COPD=Chronic Obstructive Pulmonary Disease, CRP=C-Reactive Protein, DM=Diabetes Mellitus, HDL=High-density Lipoprotein Cholesterol (mmol/l), HTA=Hypertension, LDL=Low-density Lipoprotein Cholesterol (mmol/l), LVH=Left Ventricular Hypertrophy in ECG, MI=Myocardial Infarction, n=Number, SD=Standard Deviation, Tot. chol.=Total Cholesterol (mmol/l), Triglyc.=Triglycerides (mmol/l), Uric acid: µmol/l, Waist=Waist Circumference, Q_1-Q_3=Quartiles

6.1.3 Participants with T-wave inversion (Study III)

Participants with any T-wave inversion were older and more often had HTA and CHD than did participants without T-wave inversion (Table 9). Regarding other baseline characteristics, those with T-wave inversions differed according to its location. Participants with anterior T-wave inversion and T-wave inversions in many locations were more likely to be women, while participants with lateral or inferior T-wave inversion were more likely to be men, compared to participants without T-wave inversions. Participants with anterior T-wave inversions had higher HDL cholesterol, lower heart rate, and less frequently DM than participants in other groups. Participants with lateral T-wave inversion weighed less and were more often active smokers than participants in the other groups. Participants with T-wave inversions in many locations were oldest, had highest proportions of the co-morbidities studied and the highest heart rate.

Table 9. Baseline characteristics of the Health 2000 Survey participants by lead group with T-wave inversions (n = 4,793).

	No TWI		**Anterior TWI**		**Lateral TWI**		**Inferior TWI**		**Multiple TWI**		
Variable	Mean/ n	SD/ (%)	Mean/ n	SD/ (%)	Mean/ n	SD/ (%)	Mean/ n	SD/ (%)	Mean/ n	SD/ (%)	p value
n	3852	(80.4)	60	(1.3)	440	(9.2)	303	(6.3)	138	(2.9)	
Age	49.5	13.3	53.7	16.9	58.1	14.9	56.2	14.0	68.9	13.6	<0.001
Men	1577	(40.9)	7	(11.7)	197	(44.8)	129	(42.6)	38	(27.5)	<0.001
BMI (kg/m^2)	26.9	4.6	27.4	5.2	26.4	5.4	28.9	4.9	28.7	6.0	<0.001
Heart rate/min	63.5	10.5	61.5	11.6	64.9	12.6	63.8	11.7	65.2	13.7	0.014
Regular smoking	868	(22.6)	10	(16.9)	121	(27.6)	42	(13.9)	16	(11.7)	<0.001
HTA	1482	(38.6)	24	(40.0)	237	(54.0)	175	(57.9)	97	(70.3)	<0.001
DM	170	(4.4)	2	(3.3)	50	(11.4)	21	(6.9)	25	(18.1)	<0.001
CHD	151	(3.9)	3	(5.0)	67	(15.2)	31	(10.2)	47	(34.1)	<0.001
HDL (mmol/l)	1.3	0.4	1.4	0.4	1.3	0.4	1.2	0.3	1.2	0.4	<0.001
LDL (mmol/l)	3.8	1.2	3.7	1.1	3.8	1.2	3.8	1.2	3.7	1.4	0.924

BMI=Body Mass Index, CHD=Coronary Heart Disease, DM=Diabetes Mellitus, HDL=High-density Lipoprotein Cholesterol, HTA=Hypertension, LDL=Low-density Lipoprotein Cholesterol, n=Number, SD=Standard Deviation, TWI=T-Wave Inversion

6.2 Prevalence and characteristics of ECG abnormalities

6.2.1 Prevalence of IAB and PTF (Studies I and IV)

Prevalence of IAB and its subgroups and PTF are shown in Table 10. In Study I we also calculated the weighted prevalence, i.e., corrected the oversampling of participants ≥ 80 years old. The weighted prevalence on the population level without exclusion criteria is presented in Table 10. In Study I, the prevalence was calculated among Health 2000 participants and in Study IV among participants attending both Health 2000 and 2011 Surveys.

Table 10. Prevalence of different ECG abnormalities (Studies I, III, IV) and weighted prevalence of IAB and its subgroups among all participants (no exclusion criteria) (Study I) at baseline.

ECG abnormality	Prevalence %	Weighted prevalence %
Advanced IAB		
Study I	1.0	1.0
Study IV	0.6	
Partial IAB		
Study I	9.6	9.9
Study IV	13.2	
Minor-aIAB	0.3	0.3
1 BIF	4.4	4.3
2 BIF < 120ms	4.1	4.0
PTF	2.9	
T-wave inversion	19.6	
Anterior	1.3	
Lateral	9.2	
Inferior	6.3	
Many locations	2.9	

aIAB=Advanced Interatrial Block, BIF=Biphasic, IAB=Interatrial Block, PTF=P-Terminal Force

6.2.2 Temporal changes in the prevalence of IAB and PTF (Study IV)

The rate of reversal to normal of the ECG parameters studied was 47.4% for partial IAB, 40.0% for advanced IAB, and 79.3% for PTF. Tables 11 and 12 show the proportions of temporal changes in IAB and PTF for participants attending both the Health 2000 and 2011 Surveys.

Table 11. Prevalence and proportions of different IAB groups of participants attending both the Health 2000 and 2011 Surveys divided by year (Study IV).

	2011					
	Normal		pIAB		aIAB	
2000	n	%	n	%	n	%
Normal	2266	81.6	477	17.2	35	1.3
pIAB	202	47.4	213	50.0	11	2.6
aIAB	8	40.0	7	35.0	5	25.0

aIAB=Advanced Interatrial Block, n=Numbers of Participants, pIAB=Partial Interatrial Block

Table 12. Prevalence and proportions of different PTF groups of participants attending both the Health 2000 and 2011 Surveys divided by year (Study IV).

	2011			
	No PTF		PTF	
2000	n	%	n	%
No PTF	3093	98.8	39	1.2
PTF	73	79.3	19	20.7

n=Number of Participants, PTF=P-Terminal Force

6.2.3 Risk factors for incident P-wave abnormalities and for temporal change of P-wave morphology (Study IV)

Age, male sex, higher BMI, HTA, and medication with beta blockers or ACEI/ARB were associated with increased risk of developing new partial IAB during the 11-year follow-up, while higher HDL cholesterol was associated with lower risk. Of these, age, sex, higher BMI, and use of beta blockers were independent risk factors in multivariable adjusted analyses. After multivariate adjustment, higher age, LDL cholesterol, ECG-LVH, and use of ACEI/ARB were independently associated with

increased risk of developing new advanced IAB. Only age and prolonged QRS ≥ 120ms were associated with increased risk of developing new PTF, and in the multivariate-adjusted model only age reached statistical significance. Of the parameters studied, smoking, diabetes, CHD, and IVCD did not affect the risk of developing new P-wave abnormality. The independent risk factors of developing incident P-wave abnormality and their HRs are presented in Figure 9. All other parameters studied and their corresponding HRs are presented in the original Study IV, Table 2.

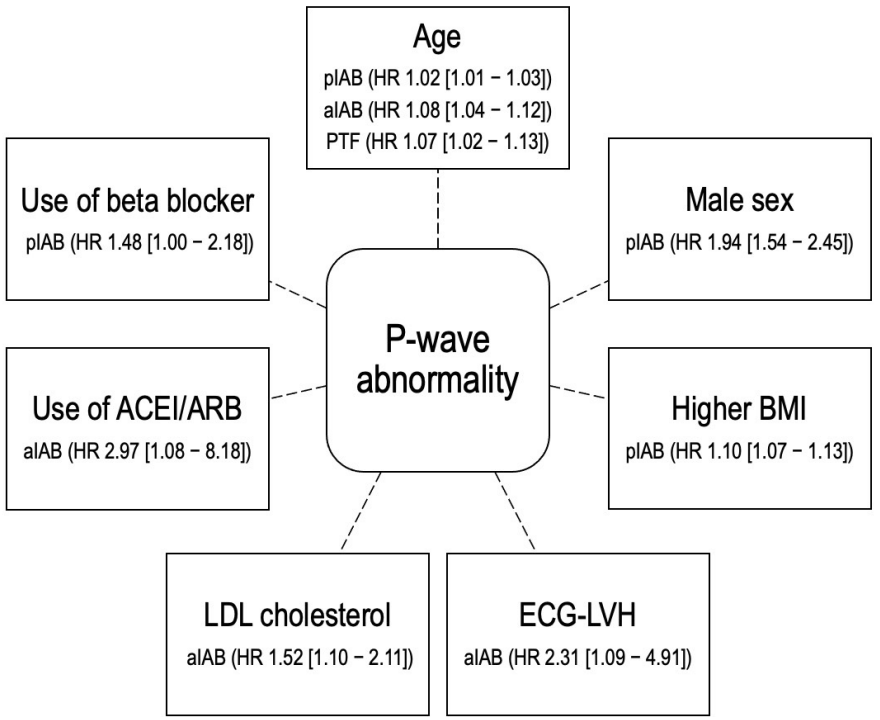

Figure 9. Risk factors for developing incident P-wave abnormality (advanced or partial interatrial block or P-terminal force) after multivariate adjustment and their hazard ratios (HR) and 95% confidence intervals. ACEI=Angiotensin-converting Enzyme Inhibitor, aIAB=Advanced Interatrial Block, ARB=Angiotensin II Receptor Antagonist, BMI=Body Mass Index, ECG-LVH=Left Ventricular Hypertrophy in ECG, LDL=Low-density Lipoprotein, pIAB=Partial Interatrial Block, PTF=P-Terminal Force.

Among participants with partial or advanced IAB in either ECGs (2000 or 2011), higher BMI (HR 1.08 [95% CI 1.04 – 1.12] $p < 0.001$) and HTA (HR 1.81 [95% CI 1.30 – 2.51], $p < 0.001$) were associated with the risk for worsened or persistent IAB

status in the age-adjusted model, and also after multivariate adjustment (higher BMI [HR 1.07 [95% CI 1.02 – 1.12] p = 0.002] and HTA (HR 1.47 [95% CI 1.02 – 2.11], p = 0.037). Higher HDL cholesterol (HR 0.63 [95% CI 0.41 – 0.98], p = 0.040) and CHD (HR 0.47 [95% CI 0.24 – 0.94], p = 0.032) were associated with improved IAB status in the age-adjusted model. Among participants with PTF, only age (HR 1.04 [95% CI 0.01 – 1.08], p = 0.012 with no adjustment and HR 1.04 [95% CI 1.00 – 1.09], p = 0.036 for multivariate adjustment) was associated with the risk for having persistent/evolving PTF. None of the other variables studied (sex, smoking, diabetes, LDL cholesterol, ECG-LVH, wide QRS, IVCD, use of betablockers, and ACEI/ARB) was associated with increased risk of temporal change in P-wave abnormalities.

6.2.4 Amplitude of ST level and prevalence of ST slope by lead groups and sex (Study II)

Mean ST levels at the measurement point $J_{alt}J$ + 80ms are shown in Table 13. Non-survivors, both men and women, had relatively lower ST levels in every lead group, and women tended to have slightly lower ST levels than men. Non-survivors had a higher proportion of negative ST slopes, especially women. Negative ST slope was a fairly rare finding with a prevalence of 0.1% to 5.4% in the different lead groups.

Table 13. Mean ST levels ($J_{alt}J$ + 80ms) and standard deviation and percentages of different ST slope groups by sex and outcome.

	Men			Women		
Variable	**Survivors** (n=1975)	**Non-Survivors** (n=487)	p value	**Survivors** (n=2596)	**Non-Survivors** (n=555)	p value
ST segment, mean (mm) (SD)						
anterior	0.01 (0.54)	-0.10 (0.43)	<0.001	-0.13 (0.27)	-0.29 (0.40)	<0.001
lateral	-0.04 (0.26)	-0.20 (0.32)	<0.001	-0.20 (0.32)	-0.32 (0.38)	<0.001
inferior	-0.11 (0.34)	-0.16 (0.28)	<0.001	-0.09 (0.24)	-0.16 (0.32)	<0.001
V5	0.20 (0.38)	-0.05 (0.42)	<0.001	0.01 (0.27)	-0.22 (0.43)	<0.001
ST slope, percentages (positive/horizontal/negative)						
anterior	58.9 / 40.9 / 0.2	60.4 / 40.6 / 0.2	0.846	44.1 / 55.8 / 0.1	46.7 / 52.6 / 0.7	0.003
lateral	21.3 / 72.2 / 0.5	19.9 / 78.4 / 1.6	0.026	8.9 / 90.4 / 0.7	6.8 / 87.7 / 5.4	<0.001
inferior	4.1 / 93.1 / 2.8	6.2 / 92.0 / 1.8	0.080	3.0 / 96.0 / 1.0	7.0 / 91.0 / 2.0	<0.001
V5	63.6 / 36.1 / 0.3	43.3 / 55.9 / 0.8	<0.001	20.7 / 79.2 / 0.1	13.9 / 82.7 / 3.4	<0.001

n=Number, SD=Standard Deviation

6.2.5 T-wave inversion by lead group (Study III)

6.2.5.1 Forming lead groups

We tested the prognostic significance of T-wave inversion separately for leads III, aVL, and V1 using both mortality and CHD as endpoints before inclusion into lead groups. Negative T waves in leads III and V1 were associated with lower risk of CHD and mortality, hence these leads were not included in any lead group. For lead III, unadjusted HR was 0.84 (95% CI 0.74 – 0.97, p = 0.015) for mortality and HR 0.87 (95% CI 0.72 – 1.04, p = 0.113) for CHD and for V1 HR was 0.61 (95% CI 0.53 – 0.70, p < 0.001) for mortality and HR 0.59 (95% CI 0.49 – 0.71, p < 0.001) for CHD. T-wave inversion in lead aVL was associated with higher mortality risk (HR 3.33 [95% CI 2.84–3.90, p < 0.001]) and also with a higher risk for a new CHD (HR 3.05 [95% CI 2.45 – 3.81, p < 0.001]), hence lead aVL was included in the lateral lead group. The final lead groups were anterior (V2, V3, V4), lateral (I, aVL, V5, V6), and inferior (II, aVF).

6.2.5.2 Prevalence and amplitude of negative T waves

The prevalence of T-wave inversion in total and by lead groups was presented earlier in Table 10. Anterior T-wave inversion was a rare finding compared to other lead groups. However, anterior T-wave inversions tended to be slightly deeper than negative T waves in the other single lead groups. T-wave inversions, when present in multiple leads groups, were deeper than if T-wave inversion was seen only in one lead group. The minimum amplitudes of negative T waves are presented in Figure 10.

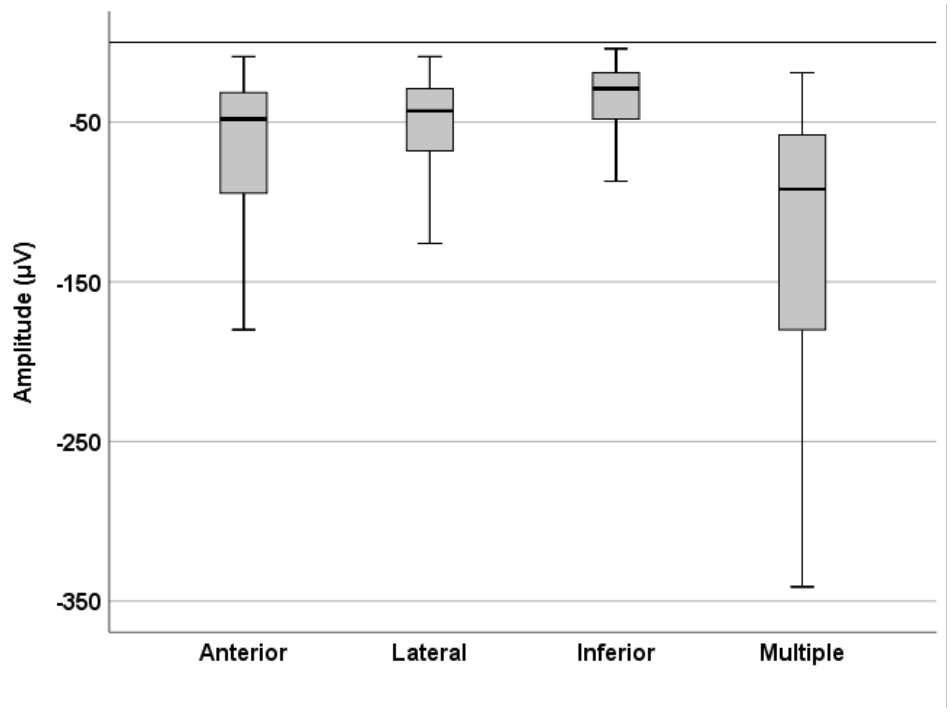

Figure 10. Minimum amplitudes of negative T waves in box plot analysis by lead groups. Outliers have been removed. The figure was originally published in the original publication Study III, Figure 1.

6.3 Prognostic significance of ECG abnormalities

6.3.1 Outcome of the Health 2000 participants

In Study I, there were 538 (8.9%) incident AF cases. The corresponding numbers for stroke and TIA were 434 and 7.3%, for CHD 678 and 12.1%, for dementia 451 and 7.5% and for total mortality 1,159 and 19.1%. In Study IV there were 536 (8.8%) incident AF diagnoses, the difference between Studies I and IV is explained by slightly different exclusion criteria. The mortality rates in Study II were 19.8% (n = 487) for men and 17.6% (n = 555) for women. In Study III, there were 489 (10.9%) new CHD diagnoses and 842 (17.6%) deaths during the follow-up.

6.3.2 Prognostic significance of IAB and PTF (Studies I and IV)

The age-adjusted and multivariate-adjusted HRs and their 95% CIs for partial and advanced IAB, and PTF are presented in Table 14. Partial and advanced IAB were associated with increased risk of AF in both Studies I and IV, and advanced IAB seemed to be associated with higher risk than partial IAB. In Study IV, PTF was not associated with AF neither in the age-adjusted nor in multivariate-adjusted analysis. The follow-up time for AF in Study I was 13.42 (SD 3.74) years.

Advanced IAB was associated with stroke and TIA in both age- and multivariate-adjusted analyses. The same was also true after exclusion of participants with incident AF during follow-up with HR 2.39 (95% CI 1.30 – 4.42, p = 0.005) in the age-adjusted and HR 2.22 (95% CI 1.20 – 4.13, p = 0.012) in multivariate-adjusted analysis. The mean follow-up time for stroke and TIA was 13.56 (SD 3.62) years.

Partial IAB was associated with incident CHD in both age- and multivariate-adjusted analysis, whilst there was no statistically significant association between advanced IAB and CHD. Neither partial nor advanced IAB were associated with dementia or mortality in the analyses.

In the subgroup analyses, where we studied the definition of IAB with three different IAB subgroups "Minor-aIAB", "1 BIF", and "2 BIF < 120ms", only the group "1 BIF" was associated with AF in the age-adjusted model (HR 1.56 [95% CI 1.14 – 2.14], p = 0.006). None of the other groups was statistically significantly associated with the studied endpoints.

Table 14. Prognostic significance of IAB, PTF and T-wave inversion by lead group (Studies I, III and IV) by different endpoints. Partly unpublished data.

Endpoint and ECG parameter	Number of diagnoses/ participants (%)	Hazard Ratio (95% CI)			
		Age adjusted	p value	Multivariate adjusted	p value
Atrial fibrillation					
Advanced IAB (Study I)	18/63 (28.6)	2.11 (1.30-3.40)	0.002	1.63 (1.00-2.65)	0.048
Advanced IAB (Study IV)	19/64 (29.7)	1.96 (1.23-3.11)	0.004	1.72 (1.07-2.75)	0.024
Partial IAB (Study I)	83/585 (14.2)	1.55 (1.22-1.97)	<0.001	1.39 (1.09-1.77)	0.008
Partial IAB (Study IV)	129/862 (15.0)	1.42 (1.16-1.73)	0.001	1.28 (1.04-1.58)	0.020
PTF	34/231 (14.7)	1.06 (0.74-1.53)	0.740	1.06 (0.73-1.54)	0.747
Stroke and TIA					
Advanced IAB	17/58 (29.3)	2.29 (1.40-3.74)	0.001	2.09 (1.27-3.44)	0.004
Partial IAB	47/569 (8.3)	0.94 (0.69-1.28)	0.686	0.93 (0.68-1.27)	0.647
CHD					
Advanced IAB	12/45 (26.7)	1.20 (0.68-2.14)	0.526	1.09 (0.61-1.94)	0.763
Partial IAB	90/526 (17.1)	1.30 (1.04-1.62)	0.024	1.26 (1.01-1.58)	0.045
T-wave inversion					
Anterior	11/57 (19.3)	1.72 (0.90-3.30)	0.100	2.37 (1.20-4.68)	0.013
Lateral	80/373 (21.4)	1.78 (1.38-2.30)	<0.001	1.65 (1.27-2.15)	<0.001
Inferior	39/272 (14.3)	1.22 (0.87-1.73)	0.250	1.11 (0.78-1.58)	0.560
Many locations	34/91 (37.4)	2.06 (1.40-3.03)	<0.001	2.18 (1.49-3.21)	<0.001
All-cause mortality					
Advanced IAB	34/63 (54.9)	1.09 (0.77-1.54)	0.634	1.10 (0.78-1.56)	0.592
Partial IAB	125/585 (21.4)	0.87 (0.72-1.05)	0.134	0.88 (0.73-1.06)	0.185
T-wave inversion					
Anterior	13/60 (21.7)	1.04 (0.60-1.80)	0.893	1.36 (0.76-2.41)	0.302
Lateral	164/440 (37.3)	1.77 (1.48-2.11)	<0.001	1.51 (1.26-1.81)	<0.001
Inferior	67/303 (22.1)	1.09 (0.84-1.40)	0.530	1.14 (0.88-1.47)	0.328
Many locations	78/138 (56.5)	1.53 (1.20-1.95)	<0.001	1.49 (1.16-1.92)	0.002
Dementia					
Advanced IAB	14/63 (22.2)	1.11 (0.65-1.91)	0.694	1.11 (0.64-1.93)	0.717
Partial IAB	49/584 (8.4)	0.84 (0.62-1.13)	0.253	0.85 (0.63-1.15)	0.295

CHD=Coronary Heart Disease, CI=Confidence Interval, IAB=Interatrial Block, PTF=P-Terminal Force, TIA=Transient Ischemic Attack

6.3.3 Prognostic significance of ST level as a continuous variable and ST slope by lead group and sex (Study II)

The mean follow-up time in Study II was 13.7 (SD 3.3.) years. Lower ST level as a continuous parameter was associated with mortality in every lead group at all measurement points and in both genders in crude analysis. Adverse outcome was most evident in the lateral lead group at J + 80ms with HR 0.13 (95% CI 0.11 – 0.15, $p < 0.001$) in women and HR 0.21 (95% CI 0.17 – 0.25, $p < 0.001$) in men for a change of 1.0mm. Figure 11 shows the linearity of the unadjusted association of lateral ST levels and mortality at the measurement point $J_{alt}J$ + 80ms. After adjustment for age, only the lateral leads, at all measurement points in both genders, and the measurement point J + 80ms and $J_{alt}J$ + 80ms in the anterior leads and V5 in women retained their statistical significance for increased mortality. After multivariate adjustment, lower ST levels were associated with higher mortality rates in the lateral leads in both genders at all measurement points and in V5 at $J_{alt}J$ + 80ms in men. The multivariate-adjusted HRs are shown in Table 15.

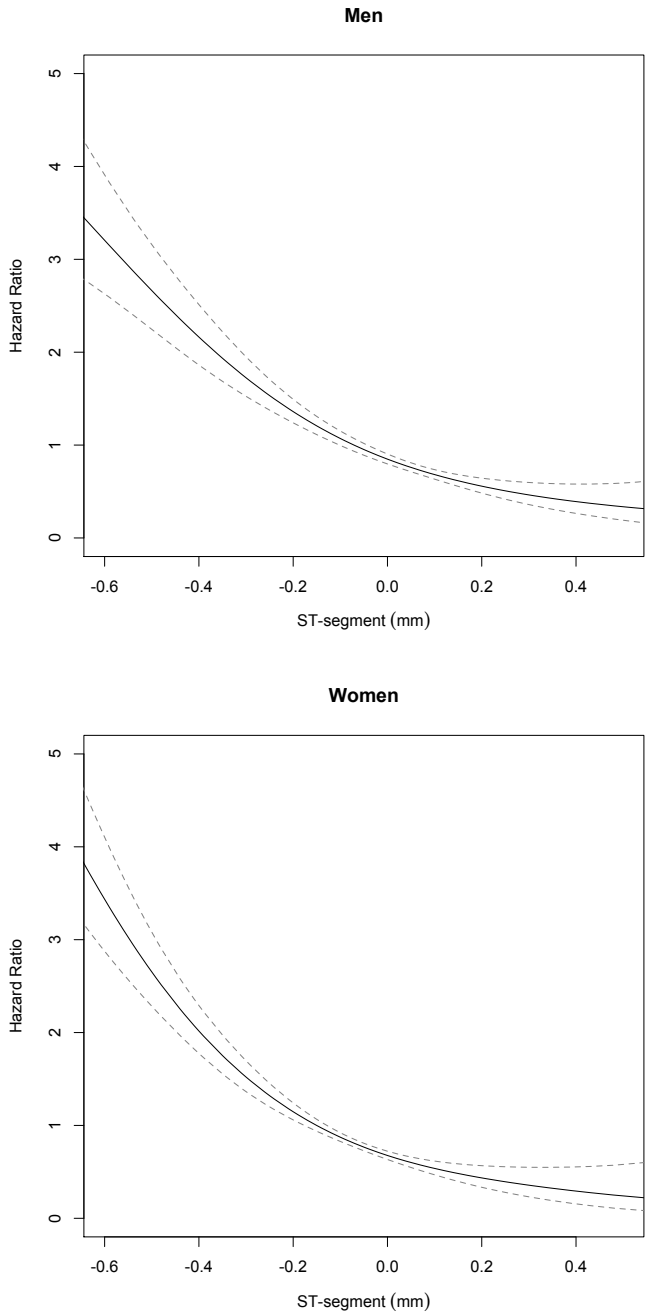

Figure 11. Unadjusted hazard ratios between ST segment and mortality at the measurement point $J_{alt}J$ + 80ms in the lateral leads for men and women. The figure was originally published in the original publication Study II, Figure 2.

Table 15. Multivariate-adjusted Cox regression analysis for ST level as a continuous variable, scaled for a change of 1.0mm, for total mortality.

	Men		Women	
	Hazard Ratio (95 % CI)	p value	Hazard Ratio (95 % CI)	p value
Anterior				
J point	1.06 (0.85-1.30)	0.621	0.93 (0.72-1.20)	0.557
J + 80	1.11 (0.90-1.36)	0.318	0.85 (0.68-1.05)	0.134
J_{alt}J + 80	1.05 (0.85-1.30)	0.641	0.90 (0.70-1.15)	0.411
Lateral				
J point	0.70 (0.54-0.91)	0.008	0.70 (0.53-0.91)	0.009
J + 80	0.64 (0.49-0.84)	0.002	0.61 (0.48-0.78)	<0.001
J_{alt}J + 80	0.69 (0.53-0.89)	0.005	0.68 (0.54-0.87)	0.002
Inferior				
J point	1.12 (0.85-1.48)	0.433	0.96 (0.72-1.29)	0.781
J + 80	1.09 (0.78-1.52)	0.611	0.93 (0.68-1.26)	0.625
J_{alt}J + 80	1.16 (0.86-1.57)	0.323	0.93 (0.69-1.26)	0.639
V5				
J point	0.80 (0.63-1.01)	0.057	0.85 (0.67-1.08)	0.190
J + 80	0.85 (0.71-1.03)	0.094	0.84 (0.69-1.03)	0.086
J_{alt}J + 80	0.79 (0.63-1.00)	0.046	0.83 (0.67-1.05)	0.116

CI=Confidence Interval, J + 80=J point + 80ms, J_{alt}J + 80=Lower of J point or J + 80

Parameters used in multivariate adjustment: Age, Body Mass Index, Coronary Heart Disease, Diabetes, High-density Lipoprotein Cholesterol, Hypertension, Low-density Lipoprotein Cholesterol

A downward sloping ST segment, negative ST slope, in the lateral leads was associated with higher mortality rates in both genders. This was most notable in lead V5, HR for women was 15.09 (95% CI 9.11 – 24.99, $p < 0.001$), and for men 3.69 (95% CI 1.37 – 9.92, $p = 0.010$). In women, a negative ST slope was also associated with increased mortality in the anterior leads, while a horizontal ST, compared with upward sloping ST, was associated with better outcome when present in the inferior leads (HR 0.44 [95% CI 0.32 – 0.62, $p < 0.001$]) and with worse outcome when present in lead V5 (HR 1.51 [95% CI 1.19 – 1.92, $p = 0.001$]). Also in men, a horizontal slope in V5 was associated with worse outcome (HR 2.11 [95% CI 1.76 – 2.52, $p < 0.001$]). However, after adjusting for age, a downward sloping ST segment did not affect outcome in men in any lead groups. In women, a downward sloping or horizontal slope was associated with worse outcome in the lateral leads as did a descending slope in V5. After multivariate adjustment, ST slope lost its statistical significance for predicting mortality in all lead groups in both genders.

6.3.3.1 Significance of ECG-LVH and CHD for the prognostic significance of ST level

After the exclusion of the subjects with ECG-LVH from the multivariate-adjusted analyses, the mortality risk of lower ST levels in the lateral leads increased in men. The same was true for V5 both at the J point and $J_{alt}J$ + 80ms: HR 0.69 (95% CI 0.51 – 0.92, p = 0.011) and HR 0.70 (95% CI 0.52 – 0.94, p = 0.019) respectively. However, the effect of excluding ECG-LVH patients was opposite in women, where only the measurement point, J + 80ms, retained its statistical significance in the lateral leads. On the other hand, excluding subjects with CHD from multivariate adjustment had no clear influence on the results. There was one exception: in lead V5 in women, the ST level at J + 80ms proved to be associated with worse outcome (HR 0.81 [95% CI 0.67 – 0.98, p = 0.033]) compared to multivariate adjusted analysis with CHD. Regarding the anterior and inferior lead groups, excluding ECG-LVH subjects or adjustment for associated CHD did not influence the prognostic significance of ST levels.

Regarding ST slope, exclusion of subjects with ECG-LVH had no significant effect on multivariate-adjusted results. However, ST slope in the lateral leads proved to be a risk marker for all-cause mortality in women when CHD was excluded from the multivariate adjustment model (HR 1.70 [95% CI 1.04 – 2.78, p = 0.036] compared to HR 1.62 [95% CI 0.99 – 2.66, p = 0.056] in the multivariate-adjusted model with CHD).

6.3.4 Prognostic significance of T-wave inversion by lead group (Study III)

The median follow-up time for CHD in Study III was 15.2 years (interquartile range [IQ] 14.9 – 15.3) and for mortality 15.1 (IQ 14.9 – 15.2) years. T-wave inversions were associated with CHD in all lead groups in crude analysis. The cumulative incidence function curves for CHD are presented in Figure 12. In the multivariate-adjusted model, T-wave inversions in the anterior, lateral, and multiple lead groups were associated with new diagnosis of CHD (Table 14). T-wave inversion in the inferior lead group was not associated with CHD after adjustment with age.

Regarding mortality, negative T waves in all but the anterior lead groups were associated with adverse prognosis in crude analysis. After age-adjustment, only the lateral lead group and T-wave inversions in multiple lead groups retained their statistical significance, which was also the case in the multivariate-adjusted model (Table 14).

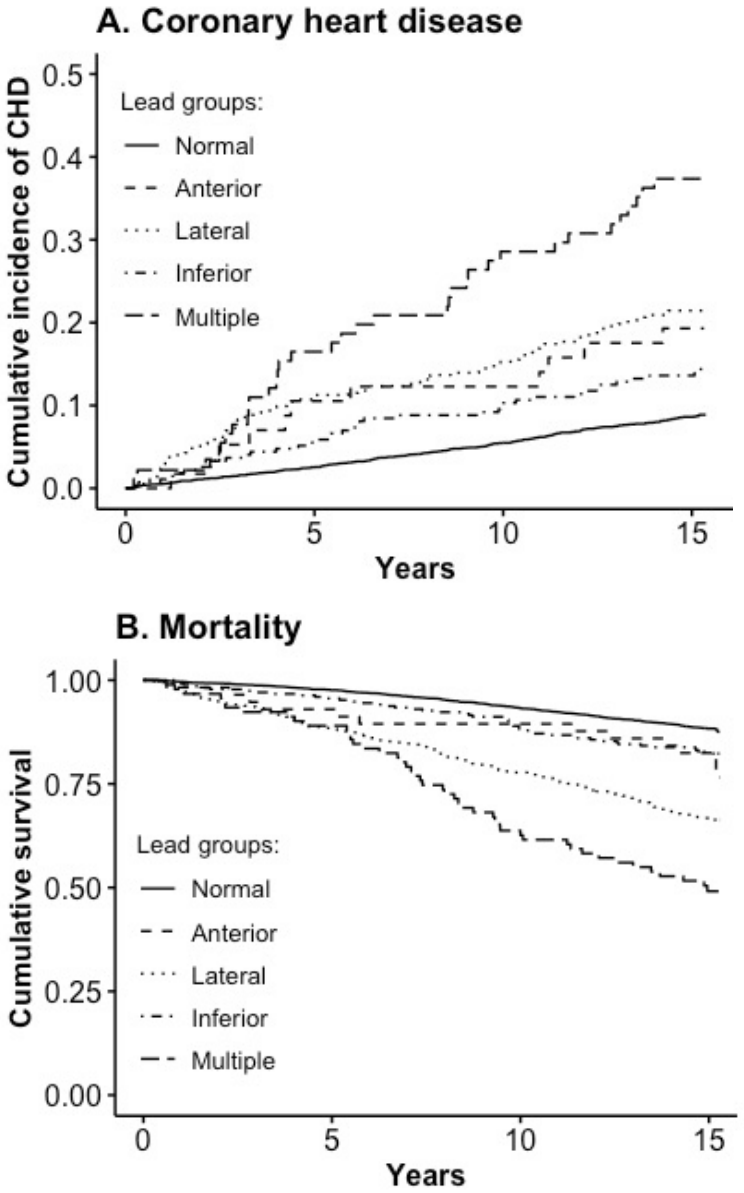

Figure 12. (A.) Cumulative incidence function curves for CHD and (B.) Kaplan-Meier survival curves for mortality in participants without known CHD at baseline based on T-wave inversions in the different lead groups. Number of participants at baseline: Normal = 3852, Anterior = 60, Lateral = 440, Inferior = 303, Multiple = 138. The figure was originally published in the original publication, Study III, Figure 2.

6.3.4.1 Significance of sex, CHD, and ST level for the prognostic significance of T-wave inversions

We tested the significance of sex in an interaction analysis for both CHD and mortality, and observed no sex-related interactions. In addition, to test for a possible confounding effect of the ST level, we conducted a sensitivity analysis, where we included the amplitude of the ST level at the J point as dichotomous variable in the multivariate-adjusted model. From a clinical point of view the results did not differ significantly from the results without ST-level adjustment. On the contrary, for mortality as an endpoint, the interaction term for CHD was significant, and therefore we also performed the analysis after dividing the subjects by CHD status. In participants with CHD, only T-wave inversions in multiple lead groups were associated with increased mortality (HR 1.55 [95% CI 1.03 – 2.34], $p = 0.035$). No statistically significant increase in mortality was seen in any of the single lead groups, or regarding multiple locations after adjustment with age. In participants without known CHD, the results did not greatly differ from the whole study population. In crude analysis, all except the anterior lead group were associated with increased mortality (Figure 12). In age- and multivariate-adjusted models, the lateral lead group and T-wave inversion in many locations were associated with mortality. The HRs were somewhat more pronounced in this analysis compared to the analysis of the whole population (HR in the lateral lead group after age adjustment 1.84 [95% CI 1.50 – 2.25], $p < 0.001$ and after multivariate adjustment 1.59 [95% CI 1.29 – 1.96], $p < 0.001$, and in multiple locations HR 1.65 [95% CI 1.21 – 2.26], $p = 0.002$ and 1.72 [95% CI 1.26 – 2.36], $p = 0.001$ respectively).

7 DISCUSSION

7.1 Main findings of the study

In this study, we investigated two resting ECG parameters related to atrial changes, IAB and PTF, as well as two parameters related to repolarization abnormalities, ST-level and T-wave inversion, in a prospective random-sample Finnish population study. We gained further knowledge about their prevalence, characteristics, and prognostic significance.

The prevalence of advanced IAB was 1% and of partial IAB around 10%. The prevalence of PTF was studied among participants attending both the original and the follow-up study 11 years later and was 2.9%. IAB and PTF were labile ECG abnormalities, as the reversion rate to normal between these two study points varied from 40.0% to 79.3%. The independent risk factors for developing incident P-wave abnormality 11 years later included higher age, male sex, higher BMI, ECG-LVH, LDL cholesterol, and use of ACEI/ARB and beta blockers.

Both advanced and partial IAB were associated with increased risk of developing new AF, and advanced IAB was associated with increased risk of stroke/TIA, also when incident AF was excluded. On the contrary, only partial IAB was associated with increased risk for a new diagnosis of CHD. Neither of these ECG abnormalities was associated with increased risk for all-cause mortality or dementia. PTF was not associated with increased risk of AF in our study population.

The mean ST level of the population was close to baseline, as the level varied from –0.32mm to 0.01mm when divided by sex, lead group and outcome. Women and non-survivors tended to have slightly lower ST levels than men and survivors. Of the participants 19.6% had negative T wave in at least one lead group. The prevalence was lowest in the anterior lead group (1.3%) and highest in the lateral lead group (9.2%).

Of the different lead groups only lower lateral ST level was associated with increased mortality and the risk increased nearly linearly with lowering ST levels. Lateral and anterior T-wave inversions were associated with increased risk of incident CHD, and lateral T-wave inversion was also associated with increased total

mortality. Inferior lower ST level or T-wave inversion was not associated with any of the endpoints.

7.2 Participants with ECG abnormalities

Regarding the study participants in Studies I, III and IV, we divided the Health 2000 population's baseline characteristics according to the ECG abnormalities studied. In general, participants with ECG abnormalities were older than participants without them in all these studies, and there was a tendency for higher prevalence of men among participants with ECG abnormalities. There was one clear exception; women had decidedly more anterior T-wave inversions than men (this issue will be discussed later).

In general, participants with ECG abnormalities had a greater burden of cardiovascular disease and risk factors, including HTA, DM, CHD, and ECG-LVH. We found no significant effect of COPD or smoking on the P-wave parameters studied, although pulmonary disease may result in remodeling of the right side of the heart. In Study III, in most of the lead groups, smoking was less common in subjects with T-wave inversion than among participants without T-wave inversion.

As atrial fibrosis is considered important in IAB, it is logical that age is a contributing factor in conduction disease development (Baranchuk et al., 2018). In a large population study, the prevalence of negative T wave also increased by age (Larsen et al., 2002). Pulmonary emphysema associated with COPD can lead to downward position of the heart. This could potentially lead to an overestimation of the prevalence of PTF (Chhabra et al., 2013) and anterior T-wave inversions. However, we found no support for this in our population. It must be remembered, however, that smoking and COPD, used in our study, are not true surrogates for emphysema. Also, we did not study P-wave amplitudes; a P-wave amplitude ≥ 2.5mm in the inferior leads ("P pulmonale") has been associated with COPD.

In general, in our study, participants with abnormal ECG parameters (IAB, PTF, and T-wave inversion) seemed to share an unfavorable cardiovascular risk profile. In these studies, we also reported the prognostic significance of ECG abnormalities after multivariate adjustment with traditional cardiovascular risk factors to clarify the role of the ECG abnormality as an independent risk factor. However, as stated before (Greenland et al., 2003), from a clinical point of view, the ECG parameters studied must be evaluated in association with the risk profile of the patient, and for that reason, age-adjusted HRs could also be of use.

7.3 Prevalence of ECG abnormalities in general population

7.3.1 Prevalence of interatrial block and P-terminal force

The prevalence of advanced IAB has not previously been explored in a Finnish population. In our Study I, the prevalence of advanced IAB was 1.0% in the study population *per se*, and also 1.0% when reflected to the whole Finnish population in weighted analysis. In the Study IV, the prevalence was 0.6%. In that study, the analysis included participants attending both the Health 2000 and 2011 Surveys, i.e., participants who developed AF or died between the study time points were excluded, which explains the difference from the prevalence in our studies. In two large population-based studies, the prevalence of advanced IAB was 0.5% (O'Neal, Zhang, et al., 2016; Skov et al., 2018). The slight difference could be explained by the different definition of advanced IAB. In the two other studies, the definition required biphasic P waves in all the inferior leads, whereas in our study the definition also included participants with biphasic P waves in 2/3 inferior leads. In the study by Skov et al. (2018) the population consisted of patients, with ECG recording based on the judgement by a general physician, whereas our study and the study by O'Neal et al. (2016) were prospective random sample studies.

The prevalence of partial IAB was 9.6% in Study I and 13.2% in Study IV. The difference is largely explained by the fact that in Study I, we formed two other groups "Minor-aIAB" and "1 BIF", which were included as partial IAB in Study IV. In earlier studies, the prevalence of partial IAB has varied widely depending on the definition and populations studied. In the study by Skov et. al., the prevalence of partial IAB was 16% (Skov et al., 2018). Their population consisted of somewhat older participants (50-90 years), but otherwise the definition of partial IAB was well comparable to that in our Study I.

In our study, the prevalence of PTF was 2.9%. In other Finnish population-based studies, the prevalence of manually evaluated PTF ≤ –6mVms was 1.2% in middle-aged subjects (Eranti et al., 2014), and around 4% among participants 30+ years (Eranti et al., 2020). When using the PTF definition ≤ –4mVms, the prevalence has been higher in former studies varying 7.5% – 15.2% (Eranti et al., 2014; Kamel et al., 2015; Lehtonen et al., 2017).

7.3.1.1 Temporal changes of interatrial block and P-terminal force

Unexpectedly, the reversion rate to normal of the P-wave abnormalities studied was quite high in our population. Nearly half of those who had partial IAB at baseline had a normal P-wave duration 11 years later, and three quarters of those who had advanced IAB at baseline had partial IAB or normal P-wave duration at follow-up. Furthermore, 79.3% of participants with PTF at baseline no longer had this P-wave abnormality 11 years later. Lehtonen et al. studied P-wave duration, PTF with an area < –4mVms and P-wave axis in the same study population and observed similar tendencies (Lehtonen et al., 2017). Apart from these studies, the labile nature of P-wave abnormalities has not been well documented in general population.

We hypothesized that the rate of participants with partial IAB developing into advanced IAB would be higher considering the expected further development of the conduction disease (Ariyarajah, Kranis, Apiyasawat, & Spodick, 2007). However, in our study only 2.6% of participants with partial IAB at baseline had advanced IAB in 2011. As the timeline between our study ECGs was fairly long (11 years), it is possible that many of the vulnerable participants with partial IAB developed AF between the study points, directly or through advanced IAB.

One possible explanation for the variability of the P-wave abnormalities in our study could be effective treatment of the diseases associated with the ECG abnormalities. It was previously shown in hypertensive patients, that treatment shortened the maximal P-wave duration (Aizawa, Sato, & Akazawa, 2019), and in acutely ill cardiac patients (acute myocardial infarction in the majority), decrease in left ventricular filling pressures resulted in many cases in regression of PTF (Heikkilä et al., 1973). However, it is also possible that the fluctuation is due to confounding factors related to serial measurement of the ECGs, such as change of categories of participants with borderline P-wave abnormalities, misplacement of the V1 electrode, and simply measurement error (M. U. Rasmussen et al., 2019). However, we consider misplacement of ECG electrodes a rather unlikely confounding factor in a prospective study with trained study personnel. The participants with the most advanced atriopathy at baseline had an increased likelihood of developing AF or dying during the follow-up period and were therefore excluded from the analysis.

Unfortunately, the number of subjects with temporal changes of P-wave abnormalities was too low to enable analysis of the prognostic significance of the normalization of P-wave pathologies. Our study findings, a high rate of reversal to normal from pathologic P-wave morphology, should be confirmed in larger

populations and the prognostic significance of the phenomenon should be evaluated.

7.3.2 Prevalence of T-wave inversion by lead groups

The prevalence of negative T waves in at least one lead group was 19.6% in this study. In many earlier studies, T-wave inversions have been defined by Minnesota Codes 5.1-3 (Table 3). By this definition the age-standardized prevalence of T-wave inversion was 9.3% in women and 6.1% in men in a Belgian population-based study, and 5.3% in the Copenhagen City Heart Study (De Bacquer et al., 1998; Larsen et al., 2002). The Minnesota Code definition 5.1-3 includes minor T-wave inversions (amplitude > –1.0mm) only in leads I, V3-V6, aVL (when R amplitude is ≥ 5.0mm) and II, which is one explanation for the slightly higher prevalence of T-wave inversions in our study.

The prevalence of anterior T-wave inversions was 1.3% in this study. The prevalence of anterior T-wave inversions (in all the leads V1 – V3) was 0.5% in a Finnish population-based study (Aro et al., 2012). In their study, the prevalence of anterior T-wave inversions was much higher among women than among men, which was also the case in this study. The same phenomenon was also seen in another study among young asymptomatic participants with a mean age of 21.7 (SD 5.4) years (Malhotra et al., 2017). In their population, the prevalence of anterior T-wave inversions (V1 – V4 ≤ –0.1mV) was 4.3% in women and 1.4% in men. One explanation for the sex difference could be that the benign, persistent juvenile T-wave pattern is more frequent in women than in men (B. M. Walsh & Smith, 2015).

The prevalence of lateral and inferior T-wave inversions in this study were 9.2% and 6.3%. We found no studies against which to compare the prevalence of the T-wave inversions in these lead groups in general population.

7.4 Characteristics of ECG abnormalities in general population

7.4.1 Definition of interatrial block

There are no established diagnostic criteria for the amplitudes of the initial and terminal parts of biphasic P waves. We chose a cut-off of 20μV because changes below this magnitude were not recognized in a reproducible manner on enlarged

conventional ECG recordings ("Recommendations for Measurement Standards in Quantitative Electrocardiography. The CSE Working Party," 1985). Regarding P-wave duration, 120ms is the established cut-off for IAB (Bayés de Luna et al., 2012), although earlier studies also used 110ms.

To study the definition of advanced IAB more in detail, we decided to introduce additional subgroups in Study I. We divided the IAB categories further into "Minor-aIAB", which included participants with advanced IAB morphology but with an amplitude of the initial and terminal part of the P wave between -19μV and 19μV, "1 BIF", which included participants with only one biphasic P wave in the inferior leads, and "2 BIF < 120ms", which included participants with advanced IAB morphology, but P-wave duration < 120ms. In general, the baseline characteristics of these subgroups were quite similar to those with advanced and partial IAB groups. However, only the subgroup "1 BIF" was associated with increased risk for AF in the age-adjusted model and none of the other groups was statistically significantly associated with the studied endpoints. Based on the definition, the prognostic significance of the groups "Minor-aIAB" and "1 BIF" should have been at least similar with the group partial IAB. This was not the case, and it is probable that the results rather reflect the somewhat small sizes of the groups than a true finding related to the definition of IAB. In a much larger population, IAB with only one biphasic inferior lead was associated with AF and stroke (Skov et al., 2018). However, it should be noted that the presence of a biphasic P wave in lead III only is a normal finding (Bayés de Luna, Baranchuk, Alberto Escobar Robledo, et al., 2017). The negative hemifield of lead III starts at +30 degrees, which does not represent caudo-cranial activation of the left atrium.

Only few studies investigating P-wave morphology independently of P-wave duration have been presented. Holmqvist et al. found that P-wave morphology was an independent risk factor for AF and non-sudden cardiac death in patients with congestive heart failure and a history of myocardial infarction (Holmqvist et al., 2010). However, the P-wave duration in their study population was quite long (unfiltered 145 ± 19 ms). We studied participants with two or three inferior biphasic leads and P-wave duration < 120ms as a separate group "2 BIF < 120ms" but observed no significant increase in HRs compared to normal P waves. In young patients with high atrial septal aneurysm or septal defect, the electrical stimulus may be unable to cross the upper part of the septum but may depolarize the left atrium with caudo-cranial activation. In these cases, a biphasic morphology may be seen in the inferior lead but the P-wave duration is less than 120ms (Bayés de Luna, Baranchuk, Alberto Escobar Robledo, et al., 2017).

Finally, atypical patterns of advanced IAB have also been described by Bayés de Luna et al. (Bayés de Luna et al., 2018). The criterion includes cases of P-wave duration ≥ 120ms with three different morphologies of inferior P waves (Table 1). In our study, the type 1 and 2 atypical patterns were included in the definition of advanced IAB.

7.4.2 Risk factors for interatrial block and P-terminal force

To the best of our knowledge, this was the first study to investigate the risk factors for incident advanced IAB. The factors associated with incident advanced IAB after adjusting for potential confounding factors were higher age and LDL cholesterol, ECG-LVH and use of ACEI/ARB medication. The corresponding risk factors for partial IAB were age, male sex, higher BMI, and use of beta blockers. An earlier study including patients from a general hospital, showed similar results: participants with prolonged P-wave duration ≥ 110ms were more likely to have HTA, DM, CHD or hypercholesterolemia (Ariyarajah, Apiyasawat, Moorthi, & Spodick, 2006).

As the reversion rate of P-wave abnormalities was quite high in our study, we also considered factors potentially affecting the improvement, or persistence/progression of the P-wave abnormalities. In this analysis, after multivariate adjustment, the factors associated with persistence/progression of IAB were higher BMI and HTA. On the other hand, higher HDL cholesterol and CHD were associated with improvement of IAB, but this was seen only in age-adjusted analysis.

The association between IAB status and HTA or higher BMI is not surprising. HTA may increase left atrial pressure and volume by elevating the left ventricular end-diastolic pressure and has been linked to atrial interstitial fibrosis and conduction disturbances (Staerk, Sherer, Ko, Benjamin, & Helm, 2017). Also, obesity leads to left atrial remodeling, including increased atrial fibrosis, fatty infiltration and conduction slowing. The mechanisms behind these changes include hemodynamic factors, cardiometabolic abnormalities, hormones, and inflammatory processes (Lavie, Pandey, Lau, Alpert, & Sanders, 2017). Conversely, medication with ACEI/ARB has been speculated to be preventive for IAB, at least according to the results from AF patients (Chhabra, Devadoss, Chaubey, & Spodick, 2014). Furthermore, antihypertensive treatment with losartan was effective in reducing left ventricular mass according to ECG-LVH (Wachtell et al., 2007). However, in our study, ACEI/ARB were associated with increased risk of incident advanced IAB.

The most probable explanation for the association may be that the use of these medications generally reflects more severe overall cardiovascular risk.

The observed effect on improvement of IAB status in patients with CHD is somewhat unexpected. Possible explanations for this borderline significant observation could be better treatment of other cardiovascular risk factors thanks to the diagnosis. Other potential explanations are a type II error or simply survival bias since the prevalence of CHD at baseline was higher among participants with partial and advanced IAB, which could result in higher mortality and a higher dropout rate between the study points of these subjects.

Only age and wide QRS complex were associated with risk of incident PTF. It is likely that there are additional, so far unknown, factors leading to the development of P-wave abnormalities, which also explain part of the AF burden in the population. For example, multiple genetic loci have been associated with prolonged P-wave duration (Weng et al., 2020). In addition, susceptibility to inflammation and fibrosis in the atria may differ markedly between subjects and diet may also play a role (Nicholls et al., 2020; Pääkkö et al., 2018).

Many of the risk factors identified, especially hypercholesterolemia, HTA, and obesity, are modifiable. In future studies, it would be important to explore whether the treatment of risk factors in patients with P-wave abnormalities could reduce the risk of AF. For that purpose, larger populations are needed.

7.4.3 Level of ST segment and prevalence of ST slope in resting ECG

A Scottish study defined the normal reference rates for ST amplitudes at J point separately for all ECG leads divided by age group and sex among participants without apparent cardiovascular disease (Macfarlane, 2001). In that study the ST levels decreased with age and were lower in women than in men, and this was most evident in the precordial leads. In the study by Macfarlane et al., the minimum mean ST segment in the age group ≥ 50 years in the anterior leads (V1 – V4) was 0.4mm (SD 0.4) in men and 0.1mm (SD 0.3) in women, in the lateral leads (I, aVL, V5 – V6) 0.0mm (SD 0.2) in men and 0.0mm (SD 0.01) in women, and in the inferior leads (II, III, aVF) 0.1mm (SD 0.2) in men and 0.0mm (SD 0.2) in women. In other words, ST depression, when present, was minimal.

In our study, the mean ST levels also tended to be lower in women than in men. We presented the mean ST levels among survivors and non-survivors by sex at the measurement point $J_{alt}J$ + 80ms (Table 13). In our population, the ST levels were

slightly deeper than in the previously cited study (Macfarlane, 2001). In our study, the mean ST levels varied in different lead groups and the values varied from 0.01mm (SD 0.54) in the anterior leads among surviving men to –0.32mm (SD 0.38) in the lateral lead group among women in the non-survival group.

A difference between men and women was also observed in a large population study among participants with otherwise normal ECGs (Zarafshar et al., 2013). In that study, the median ST level at the J point in the precordial leads varied between 4 – 29μV in men and –5 – 9μV in women. In the limb leads, the lowest median ST levels were 9μV for both men and women.

Regarding ST slope, we found negative ST slope to be a fairly uncommon finding with a prevalence of 0.1% to 5.4% in the different lead groups. Non-survivors tended to have a higher proportion of negative ST slopes than survivors, especially in women. The prevalence of upward sloping ST segment was highly pronounced in the anterior lead group (44.1% – 60.4%) compared to other lead groups (3.0% – 21.3%). The difference could be explained by the early repolarization pattern, which is most frequent in the anterior leads. The estimated prevalence of early repolarization pattern has been 1% – 9% in general population (Benito, Guasch, Rivard, & Nattel, 2010). However, the ECG parameter used in our study, upward sloping ST segment, is not identical with early repolarization, thus the prevalence rates are not comparable. In fact, we found no studies on other study populations dealing with the issue of prevalence of ST slope regardless of ST level.

7.5 Prognostic significance of ECG abnormalities in general population

7.5.1 Prognostic significance of interatrial block

In both Studies I and IV, advanced and partial IAB were associated with increased risk of AF. Many studies in general population (O'Neal, Zhang, et al., 2016; Skov et al., 2018), as well as in many different clinical scenarios (Baranchuk et al., 2018), have come to the same conclusion. In both of our studies, the HRs were higher among participants with advanced than with partial IAB; this was also shown in a large population study in which the risk seemed to increase with the number of affected biphasic inferior leads (Skov et al., 2018).

In Study I, we found that advanced IAB was associated with an increased risk of stroke or TIA. This is also in line with the findings of earlier population-based studies (O'Neal, Kamel, et al., 2016; Skov et al., 2018). In our study, partial IAB was not associated with increased risk of stroke, which was also the case in the study by Skov et al. (Skov et al., 2018). It has been hypothesized that progressive worsening of interatrial conduction would lead to progression from partial IAB to advanced IAB over time. In a study by Ariyarajah et al., the progression time from partial to advanced IAB was shorter than from a normal P wave to advanced IAB (Ariyarajah et al., 2007). This offers at least two potential explanations for the fact that advanced, but not partial IAB, is associated with risk for stroke or TIA. One possible explanation is that partial IAB is associated with less atrial remodeling and thereby with less risk for thromboembolic substrates. The other potential explanation is simply related to time: if advanced IAB develops later than partial IAB, there is more time for an embolic stroke event to occur.

In Study I, we found that the associated risk of participants with advanced IAB of developing stroke or TIA persisted also after exclusion of participants with incident AF. Furthermore, the HRs were approximately of the same magnitude as in the analysis with participants with incident AF, with a more than two-fold risk. Also, in the ARIC study, the associated risk of developing ischemic stroke remained after adjusting for incident AF (O'Neal, Kamel, et al., 2016). Our findings seem to support the theory that advanced IAB is a marker of atrial cardiomyopathy (Hirsh et al., 2015). It must be pointed, however, that in our study, data on prevalent and incident AF were mainly collected from national registers, and it is possible that some AF paroxysms diagnosed in primary care were not included in our analysis. In addition, some subclinical paroxysmal AF in the study population may have influenced the results, which could not be controlled for.

To the best of our knowledge, Study I was the first study to show the associated risk between IAB and incident CHD in general population. Given the pathophysiology of IAB and CHD, it is unlikely that IAB would be an intermediate step in CHD development. However, it is possible that the association found is attributable to the similar risk profiles of CHD and IAB. Another possible explanation is that IAB reflects underlying myocardial ischemia, especially in the atrial region. In earlier studies, IAB has been associated with more severe and diffuse CHD and occlusion of atrial branches during percutaneous coronary intervention (Alexander et al., 2018, 2017; Álvarez-García Jesús et al., 2016). However, as stated before, this was a novel finding with a borderline significance, and the results should be replicated in other populations.

As IAB has been associated with increased risk of all the diseases mentioned above, it is not surprising that prolonged P-wave duration and advanced IAB have been associated with cardiovascular and all-cause mortality (Magnani, Gorodeski, et al., 2011; Skov et al., 2018). However, this was not the case in our study. It is possible that our population was too small to show statistically significant differences.

In a study among centenarians, dementia was more frequent in participants with IAB than in individuals with normal P waves (Martínez-Sellés et al., 2016). We found no association between IAB and incident dementia. Our analysis included dementia diagnosis in general. In order to further study the association between IAB and incident dementia, restricting the analysis to dementia with signs of vascular changes might yield more information.

7.5.2 Prognostic significance of P-terminal force

We found no increased risk of AF among participants with PTF. In general, PTF is a more commonly recognized P-wave abnormality than IAB, and is considered a useful risk marker for AF occurrence (Huang et al., 2020). However, there has been some conflicting results regarding the association between PTF and AF, also in earlier studies. A former Finnish population-based study showed that the association between PTF and AF was found only with a PTF cut-off of ≤ –6mVms (Eranti et al., 2014). Based on this, and because normal reference values for PTF may reach down to –5.9mVms, we chose the cutoff point –6mVms in our study (Soliman et al., 2013). Nevertheless, we did not manage to find statistically significant associations.

It was recently shown that in addition to block in the Bachmann's bundle region, further conduction disturbances may occur in the posterior left atrium. This was seen as the development of a severely prolonged amplified P wave, lacking the biphasic morphology in the inferior leads (Müller-Edenborn et al., 2020). Our study did not include amplified P waves, and it is possible that some cases with extensive atrial conduction disturbances presenting with a short positive initial part and a long low-amplitude terminal part of the P wave were classified as having normal P waves. Another possible explanation for the lack of associated risk of PTF for AF is misplacement of ECG electrode V1 (M. U. Rasmussen et al., 2019). However, we consider this is a rather unlikely confounding factor in our prospective study with trained study personnel. In this study, we were unable to review the placement of

the ECG electrodes when PTF was found, which would be recommendable in future studies.

7.5.3 Prognostic significance of ST level as a continuous variable and ST slope by lead group in men and women in resting ECG

In Study II, we found that lower ST level as a continuous parameter was independently associated with mortality in the lateral lead group regardless of prevalent CHD. The associated risk showed an almost linear association with lower lateral ST levels (Figure 11). In women, the associated risk seemed to be largely caused by ECG-LVH, but in men the effect of excluding participants with ECG-LVH was the opposite; the HRs were more pronounced. The increased risk of lower ST level was also seen in the anterior lead group in women after age-adjustment but was diminished in the multivariate-adjusted model. In the inferior lead group, and in the anterior lead group in men, lower ST levels were not associated with increased risk of mortality after age adjustment.

A large population-based study examining the ST level among different lead groups found similar results (Zarafshar et al., 2013). In that study ST depression in lateral lead group (I, V4 – V6) was associated with cardiovascular mortality, while ST elevation was associated with lower risk. They found no associated risk for mortality in the anterior or inferior leads. A study on the same Health 2000 population, but with a shorter follow-up, found that lower lateral ST levels were associated with cardiovascular mortality, but this was found only in women (Anttila et al., 2010). This suggests that in men death related to lower ST level occurs later than in women. However, the methodology in these two studies was also slightly different and it is possible that, apart from follow-up time, the difference in results can be attributed to the different confounding factors used in multivariate-adjustment and the different endpoint used.

In the very large population-based Copenhagen ECG Study, Rasmussen et al. studied the ST level separately for different precordial leads divided into groups based on the amplitude of the ST segment (P. V. Rasmussen et al., 2014). In their study, ST depression in leads V2 – V6 in older men (≥65 years), and in leads V1 and V4 – V6 in men <65 years was associated with increased cardiovascular death. In women, this was also the case for leads V2 – V6. The ST depressions seemed to be associated with increased risk of cardiovascular death in a "dose-responsive" manner. In that study, ST elevation in lead V1 seemed to be associated with increased

cardiovascular death in both genders in both age groups. Also, in many former population-based studies classifying ST depression according to the Minnesota Code criteria, major ST depression was associated with worse outcome and risk for cardiovascular disease and minor ST changes also had an adverse effect on prognosis (Badheka et al., 2012; Daviglus et al., 1999; Greenland et al., 2003; Kumar & Lloyd-Jones, 2007; Larsen et al., 2002; Möller et al., 2007).

In our study, in women, the adverse prognosis seemed to be largely related to ECG-LVH, but in men, given that adjusting for known CHD had little influence on the results, other etiologies must be considered. In a population-based study of adults ≥ 65 years old, minor ST-segment changes were associated with cardiovascular mortality, but not with non-fatal myocardial infarction (Kumar et al., 2008). The authors suggested that arrhythmia could be behind this finding. Sympathetic activity is also known to cause ST depression in healthy subjects and it is a known risk factor for cardiac death and arrhythmias (Quyyumi, Wright, & Fox, 1983; Toivonen, Helenius, & Viitasalo, 1997). In the large MESA study by Inoue et al., cardiac magnetic resonance imaging showed that left ventricular scar was associated with the strain pattern in ECG, but not with ECG-LVH, and they hypothesized the mechanisms underlying the strain pattern to be silent subendocardial and mid-wall ischemia (Inoue et al., 2017). It should be pointed out that the ST level is not normally affected by stable CHD and in an earlier study, minor ST-segment and T-wave abnormalities were not associated with presence of coronary artery calcium in participants free from clinical CHD at baseline (J. A. Walsh et al., 2013). Fibrotic tissue (scar) may be an important background factor in left ventricular remodeling in patients with the strain pattern, not necessarily induced by ischemia, but by chronic left ventricular volume and/or pressure overload.

We studied the significance of ST slope regardless of the ST level and found no increase in risk after adjusting for potential confounding factors. However, when excluding CHD from the multivariate-adjusted model, descending ST slope in the lateral leads in women was associated with increased mortality. This finding suggests that in women, CHD should be suspected in patients with a descending ST slope in the lateral leads. Lauer et al. studied preoperative ST slope as a quantitative parameter in patients undergoing coronary artery bypass grafting and found that negative ST slope was associated with increased mortality (Lauer, Martino, Ishwaran, & Blackstone, 2007).

7.5.3.1 Gender differences

In earlier ECG studies, men have been overrepresented compared to women, but lately sex differences in the diagnosis and prognosis of cardiovascular disease have been noticed in preventive cardiology. Regarding ST depression, in earlier studies, as well as in our study, women have had a slightly lower ST level than men. The prognostic significance of ST depression has been similar in both genders, especially when it comes to minor changes (De Bacquer et al., 1998, 1998; Kumar & Lloyd-Jones, 2007; Rautaharju et al., 2006). The earlier study on the same population found significant gender differences when studying continuous ST level, and in that study the increase in risk was found only in women (Anttila et al., 2010). Our study seems to be more in line with previous studies, as we found no significant sex differences between the multivariate-adjusted results.

However, regarding ECG-LVH the sexes differed significantly with respect to the prognostic significance of lower lateral ST levels. In women, after excluding subjects with ECG-LVH, only the J + 80ms measurement point retained its power as a negative prognostic marker for all-cause death. For male subjects, excluding those with ECG-LVH, it tended to strengthen the effect of lower lateral ST levels on mortality. We have no definite explanation for this sex difference. In our population, there was a higher proportion of subjects with ECG-LVH in the female non-survivor group than in the survivor group, while there was no statistically significant difference in men. In an earlier population study, the prevalence of voltage-only ECG-LVH increased with age in women but decreased in men, which could be one possible explanation for the gender difference observed (Larsen et al., 2002).

7.5.4 Prognostic significance of T-wave inversion by lead group

In Study III, we studied the prognosis of T-wave inversions in different lead groups for CHD and total mortality. We observed that negative T waves in the lateral leads were associated with increased risk for both endpoints, and anterior T-wave inversions for CHD. T-wave inversions simultaneously in multiple lead groups were also associated with increased risk of CHD and mortality. However, the increased mortality risk was seen only in participants without CHD at baseline. We tested the significance of sex for prognosis in interaction analysis and found no sex-related interactions.

Inverted T waves and minor T-wave abnormalities in general have been associated with incident CHD and cardiovascular mortality in many population-based studies (Bakhoya et al., 2014; Greenland et al., 2003; Larsen et al., 2002; Laukkanen et al., 2014; Rautaharju et al., 2012). A negative T wave in the right precordial leads is a normal condition in children, but in adults, only T-wave inversion in V1 is a clearly normal finding (Rautaharju et al., 2009). Negative T waves in the anterior leads may accompany arrhythmogenic cardiomyopathy and the takotsubo syndrome (Bayés de Luna et al., 2014). However, negative T waves in the anterior leads were not associated with cardiovascular or total mortality in a population study, or with cardiomyopathy in a study among young athletes and non-athletes (Aro et al., 2012; Malhotra et al., 2017). Our study seems to support these findings in general population, as we found no increased risk for mortality among participants with anterior T-wave inversions.

On the contrary, anterior T-wave inversion, as well as T-wave inversion in the lateral leads was associated with increased risk of incident CHD. The same was seen in the category of T-wave inversions in multiple locations. In ACS, T-wave inversions may occur in the acute stage together with ST-segment deviation as a sign of myocardial ischemia. Isolated "post-ischemic" T-wave inversions may persist for weeks after the acute phase. The location of the post-ischemic T-wave inversions in 12-lead ECG usually reflects the site of the ischemia during the acute stage of the disease process. After myocardial infarction, T-wave inversions often accompany pathological Q waves, but they may also appear in isolation. We excluded subjects with Q/QS waves in their ECG, but it is possible that the association found between T-wave inversions and CHD reflect underlying ischemia or unrecognized myocardial infarction, and thus undiagnosed CHD. (Bayés de Luna et al., 2014)

After ST-elevation myocardial infarction, persistent T-wave inversions have been associated with worse prognosis and greater infarct size (Lancellotti et al., 2002; Reindl et al., 2017). In our study, in participants with known CHD at baseline, T-wave inversions did not seem to be significantly associated with mortality. The exclusion of individuals with Q/QS waves in their ECG can be one explanation for this finding. In addition, the prevalence of CHD at baseline was low, and it is possible that the groups were too small to enable the detection of statistically significant differences.

The "strain pattern" in resting ECG, ST depression with asymmetric, downward sloping ST segment, and T-wave inversion in the lateral ECG leads, is a marker of anatomical LVH and was associated with all-cause mortality, systolic dysfunction, and myocardial scar in a population study (Inoue et al., 2017). We excluded

participants with ECG-LVH from the Study III. However, it is possible that some participants with the LVH-related strain pattern not fulfilling the ECG-LVH criteria (Minnesota Codes 3-1, 3-3 and 3-4) were included in the analysis. In fact, in a study by Inoue et al., the associated risk of lateral strain for myocardial infarction, cardiovascular events, mortality, and heart failure was seen independently of ECG-LVH (Inoue et al., 2017).

In addition, T-wave inversions may be present in various conditions, including perimyocarditis, acute or chronic pulmonary hypertension, cardiomyopathies, alcoholism, stroke, certain drugs, and hypokalemia. As this was a population study, many of these diagnoses are unlikely reasons for the adverse prognosis of inverted T waves discovered on population level. The possible impact of undetected left ventricular dysfunction and cardiomyopathies on the study findings could not be explored due to lack of imaging data.

Inferior T-wave inversion was not associated with incident CHD or total mortality, after adjusting for age. This may be explained at least in part by the fact that the direction of the T wave in the extremity leads is dependent on body habitus. In lean individuals with right axis deviation in the frontal plane, the T wave in leads II and aVF is normally positive, but T-wave inversion in lead aVF may be present (Bayés de Luna, 2012).

7.5.5 Significance of the location of decreased ST level and T-wave inversion

Many population-based studies have investigated the prognostic significance of ST depression and T-wave inversion based on Minnesota coding neglecting the location of the ECG abnormality. However, according to the present study, it seems that there are striking differences in the prognostic significance of these ECG abnormalities depending on the location of the change in general population. Other studies have also come to the same conclusion (Anttila et al., 2010; Aro et al., 2012; Zarafshar et al., 2013), as discussed above.

The repolarization abnormalities, ST depression, and T-wave inversion found in the lateral lead group seemed to be the most alarming finding. In Study II, this was the only lead group associated with increased mortality with lower ST levels. In Study III, lateral T-wave inversions were associated with CHD and total mortality.

Regarding the anterior lead group, the adverse prognosis was seen only for T-wave inversion with CHD as the endpoint. When present in the inferior lead group,

the repolarization abnormalities studied were not associated with neither CHD nor mortality in either of the studies, and thus proved to be a benign phenomenon. However, it has to be pointed out that in Study III, the adverse prognosis was seen for both of the studied endpoints in the group with T-wave inversions in multiple locations. Therefore, conclusions based on this study cannot be made in situations where inferior T-wave inversions accompany T-wave inversions in other lead groups.

7.6 Clinical implications and future directions

ECG is the most performed cardiovascular diagnostic test in clinical practice. Even though screening asymptomatic healthy people with ECG is not recommended, ECG recording is included in the diagnostic workup of many cardiac diseases and is used in association with certain cardiovascular risk factors. Whenever an ECG is recorded, it should be carefully and systematically interpreted. Incidental findings are common, and it is important to distinguish between possibly benign findings and ECG abnormalities, which may indicate the presence of a disease.

Despite the known associations of IAB and PTF with AF and stroke, there are no IAB-specific guidelines on how to deal with diagnosed IAB or PTF in the ECG, neither are there recommendations for therapeutic interventions for these P-wave abnormalities. In a population study, IAB improved risk prediction of AF at the individual level when added to a conventional risk model (Skov et al., 2018). In general population, the main future potential clinical importance of IAB lies in the early detection of patients at risk for ischemic stroke and possible prevention of these cases. In this study, advanced IAB was associated with increased risk of stroke and TIA, also after exclusion of incident AF. Moreover, other studies have suggested IAB and PTF to be markers of atrial cardiomyopathy and increased thrombogenicity. Based on this, early anticoagulation therapy for patients with advanced IAB and other cardiovascular risk factors has been proposed (Bayés de Luna, Baranchuk, Martínez-Sellés, & Platonov, 2017). However, according to this study, P-wave abnormalities in general population are highly labile findings. Before studies dealing with anticoagulation therapy in IAB patients are performed, the findings of this study should be replicated, likewise the prognostic significance of reversal of P-wave abnormalities.

Apart from general population, P-wave abnormalities could be used in risk stratification in certain subpopulations such as in patients with cryptogenic stroke

and for patients undergoing ablation therapy for atrial flutter or AF (Baranchuk et al., 2018; Cotter et al., 2011; Gul et al., 2017). For these purposes, future prospective and further randomized controlled trials are required.

In this study, we also gained new insights into the risk factors of IAB and PTF. Furthermore, we found that HTA and BMI may affect the progression of IAB, while higher HDL cholesterol could have beneficial effects. All these are modifiable risk factors. Future studies should evaluate whether treatment of these risk factors in patients with IAB could reduce the risk of AF and stroke.

As earlier pointed out, IAB is associated with an unfavorable cardiovascular risk profile and increased risk of cardiovascular disease. Therefore, when IAB is found in the ECG, it seems relevant to explore the patient's cardiovascular risk factor profile and also check for possible cardiovascular symptoms. This could enable early diagnostic and therapeutic interventions in cardiovascular diseases.

In this study, we also gained important insight into the prognostic significance of the location of repolarization abnormalities; the prognostic significance of ST-segment deviation, as well as T-wave inversion differs markedly between different lead groups. Based on this study and prior knowledge, isolated T-wave inversion in the inferior leads in asymptomatic patients without clinical signs of cardiovascular disease, seems to be a benign finding requiring no further examination. However, in the case of lateral ST depression or T-wave inversion in the lateral, or multiple lead groups, ruling out heart disease should be considered. Yet since negative T wave was a relatively common finding in general population, studies on the prognostic significance and cost effectiveness of further intervention, e.g., cardiology consultation based on these ECG findings would be required before drawing firm conclusions.

7.7 Study limitations and strengths

Resting ECG is a standardized laboratory test, of which the prognostic value is generalizable globally. The Health 2000 and 2011 Surveys are relatively large samples representative of Finnish population with white ethnicity in the majority, as well as with good healthcare access and quality (Fullman et al., 2018). Thus, the results may not be applicable to other populations. The study design of the Health 2000 and 2011 Surveys was prospective, which increases the validity of the baseline data compared to studies with retrospective approach. Despite the size of the cohort, many of the groups studied proved to be small because of the low prevalence of

ECG findings in general population (advanced IAB, PTF, negative ST slope and isolated T-wave inversion). This may have led to missed associations, as well as decreasing the positive predictive value of the associations found (Ioannidis, 2005). However, because the prevalence of ECG abnormalities studied in general population was not established beforehand, *a priori* power analysis would not really have been feasible. In Studies I, II and IV, we also had a relatively high number of statistical comparisons, and therefore borderline significances should be evaluated with caution, and preferably replicated in future studies. However, most of the main results of this study are consistent with the prior hypotheses, which increases the positive predictive value of the results (Ioannidis, 2005). The long follow-up time up to 15 years led to a relatively high number of reported endpoints, which we consider to be a strength of our study.

We had no imaging data from the population, nor had we access to the health records of the study participants, which are limitations very typical in large population studies. E.g., echocardiographic data could have revealed anatomical LVH, which would have been a benefit in Studies II and III. In these studies, we defined ECG-LVH according to the Minnesota coding (3.1, 3.3, and 3.4), and it is possible that some participants with anatomical LVH were included in the analysis. Some participants took medication e.g., for HTA, hypercholesterolemia, DM, and CHD, which may have influenced the results. It was not possible to take all medication into account in the analyses and, in addition, our information on the medications of the study participants was incomplete.

In Study II, we studied continuous instead of categorical variables, which enhances the sensitivity to detect subtle differences. We consider the use of continuous variables to be a strength because this topic has rarely been evaluated before. Inclusion of lead groups for ST and T-wave analyses is important, because the prognostic information clearly differs between the different locations, and the topic has not been extensively studied before from this standpoint.

Study IV included two ECGs 11 years apart, which is a strength of our study. However, we must consider the possibility that the participants with the most severe P-wave changes did not attend the follow-up survey because of death or study exclusion due to AF between the study time points, which may have led to a selection bias. As in all PTF studies, the lead placement of the electrode V1 plays a major role. In this study, we were unable to review the placement of the ECG electrodes when PTF was found, which is a limitation. However, the ECGs were obtained for research purposes by trained study personnel, which should have reduced the risk of misplacement of the electrodes.

7.7.1 Computerized ECG analysis

Historically, the standard ECG recording format has been paper. However, digitalized ECG recording has now become the dominant ECG format. Digitalized ECG recording enables automatic measurements, leading to computer-generated diagnostic statements (Kligfield et al., 2007). The performance of some programs has been almost as accurate as cardiologists, and it was reported that computer-assisted ECG interpretation can decrease the analysis time by up to 28% for experienced readers (Schläpfer & Wellens, 2017). Despite that, there is evidence that physician over-reading of computer-based ECGs is required, and the interpretation of the ECG by an experienced cardiologist is still considered the golden standard (Kligfield et al., 2007).

This study was based on computerized ECG analysis. The ECGs were recorded and stored electronically, as well as in paper form and the ECG data were further analyzed with computer software (Magellan, Marquette Electronics Inc, Milwaukee, WI, USA). The durations and amplitudes of different parts of the waves in the 12-lead ECG were automatically measured and the measurement points were checked and corrected if needed.

We consider that computer-based automatic measurements may help to alleviate possible difficulties in interpretation because of wandering baseline and disturbing artifacts. Automatic measurements may help to identify the end of the waves, which may be difficult in manual analysis. As the golden standard for ECG interpretation is manual, comparisons of the accuracy of the computer-based calculations are made against manual interpretation. It has been recognized that computerized ECG intervals are generally longer than manually reviewed, at least considering the QT interval (Schläpfer & Wellens, 2017). In manual ECG interpretation, intra- and interobserver variability may also play a role (A. Murray et al., 1994). However, the repeatability of automated measurements is excellent.

In our study, variation in ST level and T-wave amplitudes was small. In Study II, HRs were scaled for differences of 1mm. However, our data suggests that smaller changes also have a prognostic effect. Our definition of IAB was based on the amplitudes $\geq 20\mu V$ of the different parts of the P wave. Computerized measurement of the ECG abnormalities is useful to perform reliable measurements in case of minor changes. Also, the diagnosis of PTF based on the measurements of the area of the terminal part of the P wave in V1 may be difficult without computer-based calculations.

It is known that high-pass filtering in the ECG recording can affect the ST level in the ECG and can produce artifactual ST deviations. The recommendations for the filter used have been as low as 0.05Hz, but this requirement can be extended to 0.67Hz for some newer digital filters (Kligfield et al., 2007). In this study high-pass filter 0.16Hz was used. According to the GE's validation document, the Marquette 12SL program can use high-pass filter at 0.32Hz without inducing artifacts to the ST-level or T-wave measurements, and thus the filter should not have disrupted the low frequency components of the ECGs (*Marquette 12SL ECG Analysis Program Statement of Validation and Accuracy*, 2007). The low-pass filter was set at 150Hz as recommended (Kligfield et al., 2007). However, if the participant had significant muscular tremors that disrupted the recording, the filter was lowered to 40Hz.

7.7.2 Validity of Finnish registries and definition of endpoints

The different endpoints of the Studies were gathered from Finnish registries; from the Causes of Death Register and the CRHC. In addition, data on drug purchases and special drug reimbursements were gathered from a separate registry (Statistics on reimbursements for prescription medicines: The Social Insurance Institution of Finland). In addition, the definitions of prevalent diseases included data on the abovementioned registries. The CRHC contains data on all inpatient episodes in Finland at the individual level since 1969 and on outpatients since 1998 in the special health care.

Regarding AF, there are no studies so far on the validity of the Finnish registries. In general, the completeness and accuracy of the CRHC has varied from satisfactory to very good (Sund, 2012). However, according to the treatment recommendations for AF (Hindricks et al., 2021), it is possible that some individuals were treated only in primary or private health care and thus were not included in this study. In general, the uncertain coverage of the AF diagnosis is a limitation of our study. It is also possible that subclinical paroxysmal AF in the study population may have influenced the results of Studies I and IV, which could not be controlled for.

The term CHD (coronary heart disease) was used in this study to refer to all ischemic heart disease. To some extent, the medical literature uses the term "coronary artery disease" to refer to obstructive ischemic heart disease confirmed by imaging. Our study was partly based on registry data and most probably includes participants with wide diagnostic criteria for ischemic heart disease. Hence, we did not distinguish between these terms. Furthermore, the European Society of

Cardiology prefers the term "chronic coronary syndrome" in chronic situations to distinguish from ACS.

The diagnosis of acute myocardial infarction and fatal CHD in CRHC and Causes of Death Register has proved to be highly predictive of a true major coronary event (Rapola et al., 1997). Also, the wider definition of CHD in these registries corresponded to a diagnosis found in a coronary disease primary prevention trial in Finland (Pietila, Tenkanen, Manttari, & Manninen, 1997). In addition to these registries the endpoint of CHD included participants entitled to drug reimbursements for CHD and the code for coronary artery revascularization in the CRHC. We estimate that the diagnosis on CHD in our study covers a sufficient majority of the diagnosed cases of CHD in the study population.

A validation study for stroke found that the validity of the Finnish registries was fairly good, although for ischemic strokes, the sensitivity and positive predictive value were inferior to those for subarachnoid and intracerebral hemorrhage (Tolonen et al., 2007). For dementia diagnoses, the registries had very good accuracy, but the sensitivity was low (Solomon et al., 2014). The use of data on drug reimbursements in addition to other registries, also implemented in this study, improved positive predictive value and sensitivity. However, underestimation of dementia occurrence may have caused an underestimation of associations with IAB and could be one reason for not finding any association between IAB and dementia.

8 CONCLUSIONS

In this study, we gained further insight into four ECG parameters, IAB, PTF, ST level and T-wave inversions, regarding their prevalence, characteristics, and prognostic significance in general population. The main findings and conclusions of this study are:

- The prevalence of advanced IAB in the Finnish population is 1% and of partial IAB around 10%.

- Partial and advanced IAB are associated with increased risk of AF in general population.

- Advanced IAB is associated with increased risk of stroke and TIA in general population, also independently of incident AF, which could indicate that IAB is a marker of atrial cardiomyopathy and increased atrial thrombogenicity.

- Traditional modifiable risk factors, including HTA, higher BMI and hypercholesterolemia are associated with incident IAB in the ECG or with the progression/persistence of IAB.

- IAB and PTF are labile ECG abnormalities in general population and the prognostic significance of the reversion of P-wave abnormalities should be investigated in further studies.

- The location of the repolarization abnormalities in the ECG has a major effect on the prognostic significance.

    - Lower lateral ST level is associated with increased mortality and lateral T-wave inversion is associated with increased risk of mortality and CHD.

- The adverse prognosis of lower lateral ST level in women is likely caused by ECG-LVH, while in men other etiologies should be suspected.

- Anterior T-wave inversion is associated with increased risk of CHD, but not with mortality, indicating that CHD should be suspected in case of anterior T-wave inversion.

- Inferior repolarization abnormality (lower ST level and T-wave inversion) proved to be a benign phenomenon in this study.

9 REFERENCES

Adams, H. P., Bendixen, B. H., Kappelle, L. J., Biller, J., Love, B. B., Gordon, D. L., & Marsh, E. E. (1993). Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*, *24*(1), 35–41. doi: 10.1161/01.STR.24.1.35

Adler, A., Rosso, R., Viskin, D., Halkin, A., & Viskin, S. (2013). What Do We Know About the "Malignant Form" of Early Repolarization? *Journal of the American College of Cardiology*, *62*(10), 863–868. doi: 10.1016/j.jacc.2013.05.054

Aizawa, Y., Sato, T., & Akazawa, K. (2019). Prevalence, significance and reversal of abnormal P-wave indices in hypertension: A review and meta-analysis. *Journal of Electrocardiology*, *53*, 13–17. doi: 10.1016/j.jelectrocard.2018.12.008

Alexander, B., Baranchuk, A., Haseeb, S., van Rooy, H., Kuchtaruk, A., Hopman, W., … Johri, A. M. (2018). Interatrial block predicts atrial fibrillation in patients with carotid and coronary artery disease. *Journal of Thoracic Disease*, *10*(7), 4328–4334. doi: 10.21037/jtd.2018.06.53

Alexander, B., MacHaalany, J., Lam, B., van Rooy, H., Haseeb, S., Kuchtaruk, A., … Baranchuk, A. (2017). Comparison of the Extent of Coronary Artery Disease in Patients With Versus Without Interatrial Block and Implications for New-Onset Atrial Fibrillation. *The American Journal of Cardiology*, *119*(8), 1162–1165. doi: 10.1016/j.amjcard.2016.12.032

Alsaab, A., Hira, R. S., Alam, M., Elayda, M., Wilson, J. M., & Birnbaum, Y. (2014). Usefulness of T Wave Inversion in Leads With ST Elevation on the Presenting Electrocardiogram to Predict Spontaneous Reperfusion in Patients With Anterior ST Elevation Acute Myocardial Infarction. *The American Journal of Cardiology*, *113*(2), 270–274. doi: 10.1016/j.amjcard.2013.09.018

Álvarez-García Jesús, Vives-Borrás Miquel, Gomis Pedro, Ordoñez-Llanos Jordi, Ferrero-Gregori Andreu, Serra-Peñaranda Antoni, & Cinca Juan. (2016). Electrophysiological Effects of Selective Atrial Coronary Artery Occlusion in Humans. *Circulation*, *133*(23), 2235–2242. doi: 10.1161/CIRCULATIONAHA.116.021700

Anttila, I., Nikus, K., Kähönen, M., Jula, A., Reunanen, A., Salomaa, V., … Nieminen, T. (2010). Prognostic implications of quantitative ST-segment characteristics and T-wave amplitude for cardiovascular mortality in a general population from the Health 2000 Survey. *Annals of Medicine*, *42*(7), 502–511. doi: 10.3109/07853890.2010.505932

Apiyasawat, S., Thomas, A. J., & Spodick, D. H. (2005). Interatrial block during exercise tolerance tests as an additional parameter for the diagnosis of ischemic heart disease. *Journal of Electrocardiology*, *38*(4), 150–153. doi: 10.1016/j.jelectrocard.2005.06.027

Ariyarajah, V., Apiyasawat, S., Moorthi, R., & Spodick, D. H. (2006). Potential Clinical Correlates and Risk Factors for Interatrial Block. *Cardiology*, *105*(4), 213–218. doi: 10.1159/000091642

Ariyarajah, V., Kranis, M., Apiyasawat, S., & Spodick, D. H. (2007). Potential factors that affect electrocardiographic progression of interatrial block. *Annals of Noninvasive Electrocardiology*, *12*(1), 21–26.

Ariyarajah, V., Mercado, K., Apiyasawat, S., Puri, P., & Spodick, D. H. (2005). Correlation of Left Atrial Size With P-Wave Duration in Interatrial Block. *Chest*, *128*(4), 2615–2618. doi: 10.1378/chest.128.4.2615

Aro, A. L., Anttonen, O., Tikkanen, J. T., Junttila, M. J., Kerola, T., Rissanen, H. A., … Huikuri, H. V. (2012). Prevalence and prognostic significance of T-wave inversions in right precordial leads of a 12-lead electrocardiogram in the middle-aged subjects. *Circulation*, *125*(21), 2572–2577. doi: 10.1161/CIRCULATIONAHA.112.098681

Asad, N., & Spodick, D. H. (2003). Prevalence of interatrial block in a general hospital population. *The American Journal of Cardiology*, *91*(5), 609–610. doi: 10.1016/S0002-9149(02)03320-9

Atar, S., Fu, Y., Wagner, G. S., Rosanio, S., Barbagelata, A., & Birnbaum, Y. (2007). Usefulness of ST Depression With T-Wave Inversion in Leads V4 to V6 for Predicting One-Year Mortality in Non–ST-Elevation Acute Coronary Syndrome (from the Electrocardiographic Analysis of the Global Use of Strategies to Open Occluded Coronary Arteries IIB Trial). *The American Journal of Cardiology*, *99*(7), 934–938. doi: 10.1016/j.amjcard.2006.11.039

Bacharova, L., & Wagner, G. S. (2015). The time for naming the Interatrial Block Syndrome: Bayes Syndrome. *Journal of Electrocardiology*, *48*(2), 133–134. doi: 10.1016/j.jelectrocard.2014.12.022

Bachmann, G. (1916). THE INTER-AURICULAR TIME INTERVAL. *American Journal of Physiology-Legacy Content*. (world). doi: 10.1152/ajplegacy.1916.41.3.309

Bakhoya, V. N., Kurl, S., & Laukkanen, J. A. (2014). T-wave inversion on electrocardiogram is related to the risk of acute coronary syndrome in the general population. *European Journal of Preventive Cardiology*, *21*(4), 500–506. doi: 10.1177/2047487312460022

Baranchuk, A. (Ed.). (2017). *Interatrial block and supraventricular arrhythmias. Chapter 1, pages 1-16*. (2017th ed.). Minneapolis, Minnesota, USA: Cardiotext publishing, Minneapolis, Minnesota.

Baranchuk, A., Alexander, B., Cinier, G., Martinez-Selles, M., Tekkesin, A. I., Elousa, R., & De Luna, A. B. (2018). Bayés' syndrome: Time to consider early anticoagulation? *Northern Clinics of Istanbul*, *5*(4), 370–378. doi: 10.14744/nci.2017.60251

Barold, S. S. (2003). Willem Einthoven and the Birth of Clinical Electrocardiography a Hundred Years Ago. *Cardiac Electrophysiology Review*, *7*(1), 99–104.

Barrabés, J. A., Figueras, J., Moure, C., Cortadellas, J., & Soler-Soler, J. (2000). Prognostic significance of ST segment depression in lateral leads I, aVL, V5 and V6 on the admission electrocardiogram in patients with a first acute myocardial infarction without ST segment elevation. *Journal of the American College of Cardiology*, *35*(7), 1813–1819. doi: 10.1016/S0735-1097(00)00630-6

Bauersachs, R., Zeymer, U., Brière, J.-B., Marre, C., Bowrin, K., & Huelsebeck, M. (2019). Burden of Coronary Artery Disease and Peripheral Artery Disease: A Literature Review. *Cardiovascular Therapeutics*, *2019*, 1–9. doi: 10.1155/2019/8295054

Bayés de Luna, A. (Ed.). (2012). *Clinical Electrocardiography: A Textbook. Chapter 7, pages 67—94*. (Vol. 2012). West Sussex, UK: Wiley-Blackwell.

Bayés de Luna, A. (2019). Willem Einthoven and the ECG. *European Heart Journal*, *40*(41), 3381–3383. doi: 10.1093/eurheartj/ehz721

Bayés de Luna, A., Baranchuk, A., Alberto Escobar Robledo, L., Massó van Roessel, A., & Martínez-Sellés, M. (2017). Diagnosis of interatrial block. *Journal of Geriatric Cardiology : JGC*, *14*(3), 161–165. doi: 10.11909/j.issn.1671-5411.2017.03.007

Bayés de Luna, A., Baranchuk, A., Martínez-Sellés, M., & Platonov, P. G. (2017). Anticoagulation in patients at high risk of stroke without documented atrial fibrillation. Time for a paradigm shift? *Annals of Noninvasive Electrocardiology*, *22*(1), e12417. doi: 10.1111/anec.12417

Bayés de Luna, A., Escobar-Robledo, L. A., Aristizabal, D., Weir Restrepo, D., Mendieta, G., Massó van Roessel, A., … Baranchuk, A. (2018). Atypical advanced interatrial blocks: Definition and electrocardiographic recognition. *Journal of Electrocardiology*, *51*(6), 1091–1093. doi: 10.1016/j.jelectrocard.2018.09.004

Bayés de Luna, A., Platonov, P., Cosio, F. G., Cygankiewicz, I., Pastore, C., Baranowski, R., … Spodick, D. (2012). Interatrial blocks. A separate entity from left atrial enlargement: A consensus report. *Journal of Electrocardiology*, *45*(5), 445–451. doi: 10.1016/j.jelectrocard.2012.06.029

Bayés de Luna, A., Zareba, W., Fiol, M., Nikus, K., Birnbaum, Y., Baranowski, R., … Wellens, H. (2014). Negative T Wave in Ischemic Heart Disease: A Consensus Article. *Annals of Noninvasive Electrocardiology*, *19*(5), 426–441. doi: 10.1111/anec.12193

Benito, B., Guasch, E., Rivard, L., & Nattel, S. (2010). Clinical and Mechanistic Issues in Early Repolarization. *Journal of the American College of Cardiology*, *56*(15), 1177–1186. doi: 10.1016/j.jacc.2010.05.037

Benjamin, E. J., Chen, P.-S., Bild, D. E., Mascette, A. M., Albert, C. M., Alonso, A., … Wyse, D. G. (2009). Prevention of Atrial Fibrillation: Report From a National Heart, Lung, and Blood Institute Workshop. *Circulation*, *119*(4), 606–618. doi: 10.1161/CIRCULATIONAHA.108.825380

Benjamin, E. J., Wolf, P. A., D'Agostino, R. B., Silbershatz, H., Kannel, W. B., & Levy, D. (1998). Impact of Atrial Fibrillation on the Risk of Death: The Framingham Heart Study. *Circulation*, *98*(10), 946–952. doi: 10.1161/01.CIR.98.10.946

Birnbaum, Y. (2003). The electrocardiogram in ST elevation acute myocardial infarction: Correlation with coronary anatomy and prognosis. *Postgraduate Medical Journal*, *79*(935), 490–504. doi: 10.1136/pmj.79.935.490

Bisbal, F., Baranchuk, A., Braunwald, E., Bayés de Luna, A., & Bayés-Genís, A. (2020). Atrial Failure as a Clinical Entity. *Journal of the American College of Cardiology*, *75*(2), 222–232. doi: 10.1016/j.jacc.2019.11.013

Blackburn, H., Keys, A., Simonson, E., Rautaharju, P., & Punsar, S. (1960). The Electrocardiogram in Population Studies: A Classification System. *Circulation*, *21*(6), 1160–1175. doi: 10.1161/01.CIR.21.6.1160

Brugada, P., & Brugada, J. (1992). Right bundle branch block, persistent ST segment elevation and sudden cardiac death: A distinct clinical and electrocardiographic syndrome. *Journal of the American College of Cardiology*, *20*(6), 1391–1396. doi: 10.1016/0735-1097(92)90253-J

Burch, G. E. (1978). History of precordial leads in electrocardiography. *European Journal of Cardiology*, *8*(2), 207–236.

Burstein, B., & Nattel, S. (2008). Atrial Fibrosis: Mechanisms and Clinical Relevance in Atrial Fibrillation. *Journal of the American College of Cardiology*, *51*(8), 802–809. doi: 10.1016/j.jacc.2007.09.064

Chen, L. Y., Ribeiro, A. L. P., Platonov, P. G., Cygankiewicz, I., Soliman, E. Z., Gorenek, B., … Baranchuk, A. (2022). P-Wave Parameters and Indices: A Critical Appraisal of Clinical Utility, Challenges, and Future Research—A Consensus Document Endorsed by the International Society of Electrocardiology and the International Society for Holter and Noninvasive Electrocardiology. *Circ Arrhythm Electrophysiol*, *2022;15:e010435*. doi: 10.1161/CIRCEP.121.010435

Chhabra, L., Chaubey, V., Kothagundla, C., Bajaj, Kaul, S., & Spodick. (2013). P-wave indices in patients with pulmonary emphysema: Do P-terminal force and interatrial block have confounding effects? *International Journal of Chronic Obstructive Pulmonary Disease*, (2013:8), 245–250. doi: 10.2147/COPD.S45127

Chhabra, L., Devadoss, R., Chaubey, V. K., & Spodick, D. H. (2014). Interatrial Block in the Modern Era. *Current Cardiology Reviews*, *10*(3), 181–189. doi: 10.2174/1573403X10666140514101748

Chugh, S. S., Havmoeller, R., Narayanan, K., Singh, D., Rienstra, M., Benjamin, E. J., … Murray, C. J. L. (2014). Worldwide Epidemiology of Atrial Fibrillation: A Global Burden of Disease 2010 Study. *Circulation*, *129*(8), 837–847. doi: 10.1161/CIRCULATIONAHA.113.005119

Collet, J.-P., Thiele, H., Barbato, E., Barthélémy, O., Bauersachs, J., Bhatt, D. L., … Siontis, G. C. M. (2021). 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *European Heart Journal*, *42*(14), 1289–1367. doi: 10.1093/eurheartj/ehaa575

Connolly, S. J., Ezekowitz, M. D., Yusuf, S., Eikelboom, J., Oldgren, J., Parekh, A., … Wallentin, L. (2009). Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *New England Journal of Medicine*, *361*(12), 1139–1151. doi: 10.1056/NEJMoa0905561

Cotter, P. E., Martin, P. J., Pugh, P. J., Warburton, E. A., Cheriyan, J., & Belham, M. (2011). Increased Incidence of Interatrial Block in Younger Adults with Cryptogenic Stroke and Patent Foramen Ovale. *Cerebrovascular Diseases Extra*, *1*(1), 36–43. doi: 10.1159/000327346

Crinion, D., & Baranchuk, A. (2020). Algorithms to Identify Accessory Pathways' Location on the 12-Lead Electrocardiogram. *Cardiac Electrophysiology Clinics*, *12*(4), 465–474. doi: 10.1016/j.ccep.2020.08.007

D'Agostino, R. B., Grundy, S., Sullivan, L. M., & Wilson, P. (2001). Validation of the Framingham Coronary Heart Disease Prediction Scores: Results of a Multiple Ethnic Groups Investigation. *JAMA*, *286*(2), 180. doi: 10.1001/jama.286.2.180

Daly, C. A., De Stavola, B., Sendon, J. L. L., Tavazzi, L., Boersma, E., Clemens, F., … Fox, K. M. (2006). Predicting prognosis in stable angina—results from the Euro heart survey of stable angina: Prospective observational study. *BMJ*, *332*(7536), 262–267. doi: 10.1136/bmj.38695.605440.AE

Daviglus, M. L., Liao, Y., Greenland, P., Dyer, A. R., Liu, K., Xie, X., … Stamler, J. (1999). Association of Nonspecific Minor ST-T Abnormalities With Cardiovascular Mortality: The Chicago Western Electric Study. *JAMA*, *281*(6), 530–536. doi: 10.1001/jama.281.6.530

De Bacquer, D., De Backer, G., Kornitzer, M., & Blackburn, H. (1998). Prognostic value of ECG findings for total, cardiovascular disease, and coronary heart disease death in men and women. *Heart*, *80*(6), 570–577.

DePace, N. L., Colby, J., Hakki, A.-H., Manno, B., Horowitz, L. N., & Iskandrian, A. S. (1983). Poor R wave progression in the precordial leads: Clinical implications for the

diagnosis of myocardial infarction. *Journal of the American College of Cardiology*, *2*(6), 1073–1079. doi: 10.1016/S0735-1097(83)80332-5

Di Biase, L., Santangeli, P., Anselmino, M., Mohanty, P., Salvetti, I., Gili, S., … Gaita, F. (2012). Does the Left Atrial Appendage Morphology Correlate With the Risk of Stroke in Patients With Atrial Fibrillation? *Journal of the American College of Cardiology*, *60*(6), 531–538. doi: 10.1016/j.jacc.2012.04.032

Dilaveris, P. E., Gialafos, E. J., Sideris, S. K., Theopistou, A. M., Andrikopoulos, G. K., Kyriakidis, M., … Toutouzas, P. K. (1998). Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. *American Heart Journal*, *135*(5), 733–738. doi: 10.1016/S0002-8703(98)70030-4

Disertori, M., Franzosi, M. G., Barlera, S., Cosmi, F., Quintarelli, S., Favero, C., … Latini, R. (2013). Thromboembolic event rate in paroxysmal and persistent atrial fibrillation: Data from the GISSI-AF trial. *BMC Cardiovascular Disorders*, *13*, 28. doi: 10.1186/1471-2261-13-28

Einthoven, W. (1903). Die galvanometrische Registrirung des menschlichen Elektrokardiogramms, zugleich eine Beurtheilung der Anwendung des Capillar-Elektrometers in der Physiologie. *Pflüger, Archiv für die Gesammte Physiologie des Menschen und der Thiere*, *99*(9–10), 472–480. doi: 10.1007/BF01811855

Eranti, A., Aro, A. L., Kerola, T., Anttonen, O., Rissanen, H. A., Tikkanen, J. T., … Huikuri, H. V. (2014). Prevalence and Prognostic Significance of Abnormal P Terminal Force in Lead V_1 of the ECG in the General Population. *Circulation: Arrhythmia and Electrophysiology*, *7*(6), 1116–1121. doi: 10.1161/CIRCEP.114.001557

Eranti, A., Carlson, J., Kenttä, T., Holmqvist, F., Holkeri, A., Haukilahti, M. A., … Platonov, P. G. (2020). Orthogonal P-wave morphology, conventional P-wave indices, and the risk of atrial fibrillation in the general population using data from the Finnish Hospital Discharge Register. *EP Europace*, *22*(8), 1173–1181. doi: 10.1093/europace/euaa118

Eyer, K. (2015). Support for a mechanico-electrical source of the "U" wave. *Journal of Electrocardiology*, *48*(1), 31–32. doi: 10.1016/j.jelectrocard.2014.11.003

Feigin, V. L., Lawes, C. M., Bennett, D. A., & Anderson, C. S. (2003). Stroke epidemiology: A review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. *The Lancet Neurology*, *2*(1), 43–53. doi: 10.1016/S1474-4422(03)00266-7

Fonseca, A. C., Alves, P., Inácio, N., Marto, J. P., Viana-Baptista, M., Pinho-e-Melo, T., … Almeida, A. G. (2018). Patients With Undetermined Stroke Have Increased Atrial Fibrosis: A Cardiac Magnetic Resonance Imaging Study. *Stroke*, *49*(3), 734–737. doi: 10.1161/STROKEAHA.117.019641

Franz, M. R., Bargheer, K., Rafflenbeul, W., Haverich, A., & Lichtlen, P. R. (1987). Monophasic action potential mapping in human subjects with normal electrocardiograms: Direct evidence for the genesis of the T wave. *Circulation*, *75*(2), 379–386. doi: 10.1161/01.CIR.75.2.379

Froelicher, V. F., & Myers, J. (2000). *Exercise and the Heart* (Vol. 2000). Pennsylvania, Philadelphia: W.B.Saunders Co.

Fullman, N., Yearwood, J., Abay, S. M., Abbafati, C., Abd-Allah, F., Abdela, J., … Lozano, R. (2018). Measuring performance on the Healthcare Access and Quality Index for 195 countries and territories and selected subnational locations: A systematic analysis from the Global Burden of Disease Study 2016. *The Lancet*, *391*(10136), 2236–2271. doi: 10.1016/S0140-6736(18)30994-2

Gami, A. S., Holly, T. A., & Rosenthal, J. E. (2004). Electrocardiographic poor R-wave progression: Analysis of multiple criteria reveals little usefulness. *American Heart Journal*, *148*(1), 80–85. doi: 10.1016/j.ahj.2004.02.005

Giugliano, R. P., Ruff, C. T., Braunwald, E., Murphy, S. A., Wiviott, S. D., Halperin, J. L., … Antman, E. M. (2013). Edoxaban versus Warfarin in Patients with Atrial Fibrillation. *New England Journal of Medicine*, *369*(22), 2093–2104. doi: 10.1056/NEJMoa1310907

Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013. (2015). *The Lancet*, *385*(9963), 117–171. doi: 10.1016/S0140-6736(14)61682-2

Goette, A., Kalman, J. M., Aguinaga, L., Akar, J., Cabrera, J. A., Chen, S. A., … Nattel, S. (2016). EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: Definition, characterization, and clinical implication. *Europace*, *18*(10), 1455–1490. doi: 10.1093/europace/euw161

Goldberger, E. (1942). The aVl, aVr, and aVf leads: A simplification of standard lead electrocardiography. *American Heart Journal*, *24*(3), 378–396. doi: 10.1016/S0002-8703(42)90821-4

Granger, C. B., Alexander, J. H., McMurray, J. J. V., Lopes, R. D., Hylek, E. M., Hanna, M., … Wallentin, L. (2011). Apixaban versus Warfarin in Patients with Atrial Fibrillation. *New England Journal of Medicine*, *365*(11), 981–992. doi: 10.1056/NEJMoa1107039

Grau, A. J., Weimar, C., Buggle, F., Heinrich, A., Goertler, M., Neumaier, S., … Diener, H.-C. (2001). Risk Factors, Outcome, and Treatment in Subtypes of Ischemic Stroke: The German Stroke Data Bank. *Stroke*, *32*(11), 2559–2566. doi: 10.1161/hs1101.098524

Greenland, P., Xie, X., Liu, K., Colangelo, L., Liao, Y., Daviglus, M. L., … Stamler, J. (2003). Impact of minor electrocardiographic ST-segment and/or T-wave abnormalities on cardiovascular mortality during long-term follow-up. *The American Journal of Cardiology*, *91*(9), 1068–1074. doi: 10.1016/S0002-9149(03)00150-4

Gul, E. E., Pal, R., Caldwell, J., Boles, U., Hopman, W., Glover, B., … Baranchuk, A. (2017). Interatrial block and interatrial septal thickness in patients with paroxysmal atrial fibrillation undergoing catheter ablation: Long-term follow-up study. *Annals of Noninvasive Electrocardiology*, *22*(4), e12428. doi: 10.1111/anec.12428

Guyton, J. R., & Klemp, K. F. (1996). Development of the Lipid-Rich Core in Human Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *16*(1), 4–11. doi: 10.1161/01.ATV.16.1.4

Habibi, M., Zareian, M., Ambale Venkatesh, B., Samiei, S., Imai, M., Wu, C., … Lima, J. A. C. (2019). Left Atrial Mechanical Function and Incident Ischemic Cerebrovascular Events Independent of AF. *JACC: Cardiovascular Imaging*, *12*(12), 2417–2427. doi: 10.1016/j.jcmg.2019.02.021

Hart, R. G., Diener, H.-C., Coutts, S. B., Easton, J. D., Granger, C. B., O'Donnell, M. J., … Connolly, S. J. (2014). Embolic strokes of undetermined source: The case for a new clinical construct. *The Lancet Neurology*, *13*(4), 429–438. doi: 10.1016/S1474-4422(13)70310-7

Hart, R. G., Pearce, L. A., & Aguilar, M. I. (2007). Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation. *Annals of Internal Medicine*, *146*(12), 857–867. doi: 10.7326/0003-4819-146-12-200706190-00007

Hayden, G. E., Brady, W. J., Perron, A. D., Somers, M. P., & Mattu, A. (2002). Electrocardiographic T-wave inversion: Differential diagnosis in the chest pain patient. *The American Journal of Emergency Medicine*, *20*(3), 252–262. doi: 10.1053/ajem.2002.32629

Heikkilä, J., Hugenholtz, P. G., & Tabakin, B. S. (1973). Prediction of left heart filling pressure and its sequential change in acute myocardial infarction from the terminal force of the P wave. *Heart*, *35*(2), 142–151. doi: 10.1136/hrt.35.2.142

Heistaro, S. (Ed.). (2008). *Methodology report: Health 2000 survey*. Helsinki, Finland: Publications of the National Public Health Institute B26/2008. Retrieved from https://urn.fi/URN:NBN:fi-fe201204193320

Hindricks, G., Potpara, T., Dagres, N., Arbelo, E., Bax, J. J., Blomström-Lundqvist, C., … Zakirov, N. U. (2021). 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *European Heart Journal*, *42*(5), 373–498. doi: 10.1093/eurheartj/ehaa612

Hirsh, B. J., Copeland-Halperin, R. S., & Halperin, J. L. (2015). Fibrotic Atrial Cardiomyopathy, Atrial Fibrillation, and Thromboembolism: Mechanistic Links and Clinical Inferences. *Journal of the American College of Cardiology*, *65*(20), 2239–2251. doi: 10.1016/j.jacc.2015.03.557

Holmqvist, F., Platonov, P. G., McNitt, S., Polonsky, S., Carlson, J., Zareba, W., & Moss, A. J. (2010). Abnormal P-Wave Morphology Is a Predictor of Atrial Fibrillation Development and Cardiac Death in MADIT II Patients. *Annals of Noninvasive Electrocardiology*, *15*(1), 63–72. doi: 10.1111/j.1542-474X.2009.00341.x

Huang, Z., Zheng, Z., Wu, B., Tang, L., Xie, X., Dong, R., … Liu, J. (2020). Predictive value of P wave terminal force in lead V1 for atrial fibrillation: A meta-analysis. *Annals of Noninvasive Electrocardiology*, *25*(e12739). doi: 10.1111/anec.12739

Ibanez, B., James, S., Agewall, S., Antunes, M. J., Bucciarelli-Ducci, C., Bueno, H., … Gale, C. P. (2018). 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *European Heart Journal*, *39*(2), 119–177. doi: 10.1093/eurheartj/ehx393

Inoue, Y. Y., Soliman, E. Z., Yoneyama, K., Ambale-Venkatesh, B., Wu, C. O., Sparapani, R., … Ashikaga, H. (2017). Electrocardiographic Strain Pattern Is Associated With Left Ventricular Concentric Remodeling, Scar, and Mortality Over 10 Years: The Multi-Ethnic Study of Atherosclerosis. *Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease*, *6*(e006624). doi: 10.1161/JAHA.117.006624

Ioannidis, J. P. A. (2005). Why Most Published Research Findings Are False. *PLoS Medicine*, *2*(8), e124. doi: 10.1371/journal.pmed.0020124

Jahangir, A., Lee, V., Friedman, P. A., Trusty, J. M., Hodge, D. O., Kopecky, S. L., … Gersh, B. J. (2007). Long-Term Progression and Outcomes With Aging in Patients With Lone Atrial Fibrillation: A 30-Year Follow-Up Study. *Circulation*, *115*(24), 3050–3056. doi: 10.1161/CIRCULATIONAHA.106.644484

Jairath, U. C., & Spodick, D. H. (2001). Exceptional prevalence of interatrial block in a general hospital population. *Clinical Cardiology*, *24*(8), 548–550. doi: 10.1002/clc.4960240805

Josephson, M. E., Horowitz, L. N., Waxman, H. L., Cain, M. E., Spielman, S. R., Greenspan, A. M., … Ezri, M. D. (1981). Sustained ventricular tachycardia: Role of the 12-lead

electrocardiogram in localizing site of origin. *Circulation*, *64*(2), 257–272. doi: 10.1161/01.CIR.64.2.257

Kamel, H., & Healey, J. S. (2017). Cardioembolic Stroke. *Circulation Research*, (120), 514–526. doi: https://doi.org/10.1161/CIRCRESAHA.116.308407

Kamel, H., O'Neal, W. T., Okin, P. M., Loehr, L. R., Alonso, A., & Soliman, E. Z. (2015). Electrocardiographic left atrial abnormality and stroke subtype in the atherosclerosis risk in communities study. *Annals of Neurology*, *78*(5), 9.

Kamel, H., Soliman, E. Z., Heckbert, S. R., Kronmal, R., Longstreth, W. T., Nazarian, S., & Okin, P. M. (2014). P-Wave Morphology and the Risk of Incident Ischemic Stroke in the Multi-Ethnic Study of Atherosclerosis. *Stroke*, *45*(9), 2786–2788. doi: 10.1161/STROKEAHA.114.006364

Kaolawanich, Y., Thongsongsang, R., Songsangjinda, T., & Boonyasirinant, T. (2021). Clinical values of resting electrocardiography in patients with known or suspected chronic coronary artery disease: A stress perfusion cardiac MRI study. *BMC Cardiovascular Disorders*, *21*(1), 621. doi: 10.1186/s12872-021-02440-5

Kaul, P., Fu, Y., Chang, W.-C., Harrington, R. A., Wagner, G. S., Goodman, S. G., … Armstrong, P. W. (2001). Prognostic value of ST segment depression in acute coronary syndromes: Insights from PARAGON-A applied to GUSTO-IIb11Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network (PARAGON-A); Global Use of Strategies To Open occluded arteries in acute coronary syndromes (GUSTO-IIb). *Journal of the American College of Cardiology*, *38*(1), 64–71. doi: 10.1016/S0735-1097(01)01307-9

Klabunde, R. E. (2017). Cardiac electrophysiology: Normal and ischemic ionic currents and the ECG. *Advances in Physiology Education*, *41*(1), 29–37. doi: 10.1152/advan.00105.2016

Kligfield, P., Gettes, L. S., Bailey, J. J., Childers, R., Deal, B. J., Hancock, E. W., … Wagner, G. S. (2007). Recommendations for the Standardization and Interpretation of the Electrocardiogram: Part I: The Electrocardiogram and Its Technology: A Scientific Statement From the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society *Endorsed by the International Society for Computerized Electrocardiology*. *Circulation*, *115*(10), 1306–1324. doi: 10.1161/CIRCULATIONAHA.106.180200

Knuuti, J. (2020). 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Russian Journal of Cardiology*, *25*(2), 119–180. doi: 10.15829/1560-4071-2020-2-3757

Koponen, P., Borodulin, K., Lundqvist, A., Sääksjärvi, K., & Koskinen, S. (2018). *Health, functional capacity and welfare in Finland – FinHealth 2017 study*. National Institute for Health and Welfare (THL).

Krijthe, B. P., Kunst, A., Benjamin, E. J., Lip, G. Y. H., Franco, O. H., Hofman, A., … Heeringa, J. (2013). Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *European Heart Journal*, *34*(35), 2746–2751. doi: 10.1093/eurheartj/eht280

Kumar, A., & Lloyd-Jones, D. M. (2007). Clinical Significance of Minor Nonspecific St-segment and T-wave Abnormalities in Asymptomatic Subjects: A Systematic Review. *Cardiology in Review*, *15*(3), 133–142. doi: 10.1097/01.crd.0000249382.65955.14

Kumar, A., Prineas, R. J., Arnold, A. M., Psaty, B. M., Furberg, C. D., Robbins, J., & Lloyd-Jones, D. M. (2008). Prevalence, prognosis and implications of isolated minor non-specific ST-segment and T-wave abnormalities in older adults: Cardiovascular health study. *Circulation*, *118*(25), 2790–2796. doi: 10.1161/CIRCULATIONAHA.108.772541

Kurl, S., Mäkikallio, T. H., & Laukkanen, J. A. (2015). T-wave inversion and mortality risk. *Annals of Medicine*, *47*(1), 69–73. doi: 10.3109/07853890.2014.985703

Lancellotti, P., Gérard, P. L., Kulbertus, H. E., & Piérard, L. A. (2002). Persistent negative T waves in the infarct-related leads as an independent predictor of poor long-term prognosis after acute myocardial infarction. *The American Journal of Cardiology*, *90*(8), 833–837. doi: 10.1016/S0002-9149(02)02703-0

Larsen, C. T., Dahlin, J., Blackburn, H., Scharling, H., Appleyard, M., Sigurd, B., & Schnohr, P. (2002). Prevalence and prognosis of electrocardiographic left ventricular hypertrophy, ST segment depression and negative T-wave. The Copenhagen City Heart Study. *European Heart Journal*, *23*(4), 315–324. doi: 10.1053/euhj.2001.2774

Lauer, M. S., Martino, D., Ishwaran, H., & Blackstone, E. H. (2007). Quantitative Measures of Electrocardiographic Left Ventricular Mass, Conduction, and Repolarization, and Long-Term Survival After Coronary Artery Bypass Grafting. *Circulation*, *116*(8), 888–893. doi: 10.1161/CIRCULATIONAHA.107.698019

Laukkanen, J. A., Di Angelantonio, E., Khan, H., Kurl, S., Ronkainen, K., & Rautaharju, P. (2014). T-Wave Inversion, QRS Duration, and QRS/T Angle as Electrocardiographic Predictors of the Risk for Sudden Cardiac Death. *The American Journal of Cardiology*, *113*(7), 1178–1183. doi: 10.1016/j.amjcard.2013.12.026

Lavie, C. J., Pandey, A., Lau, D. H., Alpert, M. A., & Sanders, P. (2017). Obesity and Atrial Fibrillation Prevalence, Pathogenesis, and Prognosis. *Journal of the American College of Cardiology*, *70*(16), 2022–2035. doi: 10.1016/j.jacc.2017.09.002

Lehtonen, A. O., Langén, V. L., Porthan, K., Kähönen, M., Nieminen, M. S., Jula, A. M., & Niiranen, T. J. (2018). Electrocardiographic predictors of atrial fibrillation in nonhypertensive and hypertensive individuals: *Journal of Hypertension*, *36*(1), 000–000. doi: 10.1097/HJH.0000000000001760

Lehtonen, A. O., Langén, V. L., Puukka, P. J., Kähönen, M., Nieminen, M. S., Jula, A. M., & Niiranen, T. J. (2017). Incidence rates, correlates, and prognosis of electrocardiographic P-wave abnormalities – a nationwide population-based study. *Journal of Electrocardiology*, *50*(6), 925–932. doi: https://doi.org/10.1016/j.jelectrocard.2017.07.004

Lehtonen, A. O., Puukka, P., Varis, J., Porthan, K., Tikkanen, J. T., Nieminen, M. S., … Niiranen, T. J. (2016). Prevalence and prognosis of ECG abnormalities in normotensive and hypertensive individuals. *Journal of Hypertension*, *34*(5), 959–966. doi: 10.1097/HJH.0000000000000882

Lewis, T. (1909). REPORT CXIX. AURICULAR FIBRILLATION: A COMMON CLINICAL CONDITION. *BMJ*, *2*(2552), 1528–1528. doi: 10.1136/bmj.2.2552.1528

Libby, P., Aikawa, M., & Scho, U. (2000). Cholesterol and atherosclerosis. *Biochimica et Biophysica Acta*, (1529), 299–309.

Libby, P., & Theroux, P. (2005). Pathophysiology of Coronary Artery Disease. *Circulation*, *111*(25), 3481–3488. doi: 10.1161/CIRCULATIONAHA.105.537878

Lip, G. Y. H., & Halperin, J. L. (2010). Improving Stroke Risk Stratification in Atrial Fibrillation. *The American Journal of Medicine*, *123*(6), 5.

Liu, G., Tamura, A., Torigoe, K., Kawano, Y., Shinozaki, K., Kotoku, M., & Kadota, J. (2013). Abnormal P-wave terminal force in lead V1 is associated with cardiac death or hospitalization for heart failure in prior myocardial infarction. *Heart and Vessels*, *28*(6), 690–695. doi: 10.1007/s00380-012-0307-9

Lundqvist, A., & Mäki-Opas, T. (Eds.). (2016). *Health 2011 Survey – Methods*. Tampere, Finland: Juvenes Print. Retrieved from https://urn.fi/URN:ISBN:978-952-302-669-8

Macfarlane, P. W. (2001). Age, sex, and the ST amplitude in health and disease. *Journal of Electrocardiology*, *34*(4), 235–241. doi: 10.1054/jelc.2001.28906

Macfarlane, P. W., Antzelevitch, C., Haissaguerre, M., Huikuri, H. V., Potse, M., Rosso, R., … Yan, G.-X. (2015). The Early Repolarization Pattern. *Journal of the American College of Cardiology*, *66*(4), 470–477. doi: 10.1016/j.jacc.2015.05.033

Maeda, S., Imai, T., Kuboki, K., Chida, K., Watanabe, C., & Ohkawa, S.-I. (1996). Pathologic implications of restored positive T waves and persistent negative T waves after Q wave myocardial infarction. *Journal of the American College of Cardiology*, *28*(6), 1514–1518. doi: 10.1016/S0735-1097(96)00338-5

Magnani, J. W., Gorodeski, E. Z., Johnson, V. M., Sullivan, L. M., Hamburg, N. M., Benjamin, E. J., & Ellinor, P. T. (2011). P wave duration is associated with cardiovascular and all-cause mortality outcomes: The National Health and Nutrition Examination Survey. *Heart Rhythm*, *8*(1), 93–100. doi: 10.1016/j.hrthm.2010.09.020

Magnani, J. W., Lopez, F. L., Soliman, E. Z., Maclehose, R. F., Crow, R. S., & Alonso, A. (2012). P Wave Indices, Obesity, and the Metabolic Syndrome: The Atherosclerosis Risk in Communities Study. *Obesity*, *20*(3), 666–672. doi: 10.1038/oby.2011.53

Magnani, J. W., Rienstra, M., Lin, H., Sinner, M. F., Lubitz, S. A., McManus, D. D., … Benjamin, E. J. (2011). Atrial fibrillation: Current knowledge and future directions in epidemiology and genomics. *Circulation*, *124*(18), 1982–1993. doi: 10.1161/CIRCULATIONAHA.111.039677

Magnani, J. W., Zhu, L., Lopez, F., Pencina, M. J., Agarwal, S. K., Soliman, E. Z., … Alonso, A. (2015). P-wave indices and atrial fibrillation: Cross-cohort assessments from the Framingham Heart Study (FHS) and Atherosclerosis Risk in Communities (ARIC) study. *American Heart Journal*, *169*(1), 53-61.e1. doi: 10.1016/j.ahj.2014.10.009

Maheshwari, A., Norby, F. L., Soliman, E. Z., Koene, R. J., Rooney, M. R., O'Neal, W. T., … Chen, L. Y. (2017). Abnormal P-Wave Axis and Ischemic Stroke: The Atherosclerosis Risk In Communities Study. *Stroke*, *48*(8), 2060–2065. doi: 10.1161/STROKEAHA.117.017226

Mäkijärvi, M., Nikus, K., Raatikainen, P., Parikka, H., & Aro, A. (2019a). *EKG. Chapter 7, pages 254-259*. Helsinki, Finland: Duodecim.

Mäkijärvi, M., Nikus, K., Raatikainen, P., Parikka, H., & Aro, A. (Eds.). (2019b). *EKG. Chapter 13, pages 464-465*. Helsinki, Finland: Duodecim.

Malekmohammad, K., Bezsonov, E. E., & Rafieian-Kopaei, M. (2021). Role of Lipid Accumulation and Inflammation in Atherosclerosis: Focus on Molecular and Cellular Mechanisms. *Frontiers in Cardiovascular Medicine*, *8*, 707529. doi: 10.3389/fcvm.2021.707529

Malhotra, A., Dhutia, H., Gati, S., Yeo, T.-J., Dores, H., Bastiaenen, R., … Sharma, S. (2017). Anterior T-Wave Inversion in Young White Athletes and Nonathletes. *Journal of the American College of Cardiology*, *69*(1), 1–9. doi: 10.1016/j.jacc.2016.10.044

Marquette 12SL ECG Analysis Program Statement of Validation and Accuracy. (2007). GE Healthcare.

Martínez-Sellés, M., Massó-van Roessel, A., Álvarez-García, J., García de la Villa, B., Cruz-Jentoft, A. J., Vidán, M. T., … Bayes de Luna, A. (2016). Interatrial block and atrial arrhythmias in centenarians: Prevalence, associations, and clinical implications. *Heart Rhythm*, *13*(3), 645–651. doi: 10.1016/j.hrthm.2015.10.034

Maseri, A., Parodi, O., Severi, S., & Pesola, A. (1976). Transient transmural reduction of myocardial blood flow demonstrated by thallium-201 scintigraphy, as a cause of variant angina. *Circulation*, *54*(2), 280–288. doi: 10.1161/01.CIR.54.2.280

Meretoja, A., Kaste, M., Roine, R. O., Juntunen, M., Linna, M., Hillbom, M., … Häkkinen, U. (2011). Direct Costs of Patients With Stroke Can Be Continuously Monitored on a National Level: Performance, Effectiveness, and Costs of Treatment Episodes in Stroke (PERFECT Stroke) Database in Finland. *Stroke*, *42*(7), 2007–2012. doi: 10.1161/STROKEAHA.110.612119

Möller, C. S., Byberg, L., Sundström, J., & Lind, L. (2006). T wave abnormalities, high body mass index, current smoking and high lipoprotein (a) levels predict the development of major abnormal Q/QS patterns 20 years later. A population-based study. *BMC Cardiovascular Disorders*, *6*(10). doi: 10.1186/1471-2261-6-10

Möller, C. S., Zethelius, B., Sundström, J., & Lind, L. (2007). Persistent ischaemic ECG abnormalities on repeated ECG examination have important prognostic value for cardiovascular disease beyond established risk factors: A population-based study in middle-aged men with up to 32 years of follow-up. *Heart*, *93*(9), 1104–1110. doi: 10.1136/hrt.2006.109116

Morris, J. J., Estes, E. H., Whalen, R. E., Thompson, H. K., & Mcintosh, H. D. (1964). P-Wave Analysis in Valvular Heart Disease. *Circulation*, *29*(2), 242–252. doi: 10.1161/01.CIR.29.2.242

Mould, S. J., Soliman, E. Z., Bertoni, A. G., Bhave, P. D., Yeboah, J., & Singleton, M. J. (2021). Association of T-wave abnormalities with major cardiovascular events in diabetes: The ACCORD trial. *Diabetologia*, *64*(3), 504–511. doi: 10.1007/s00125-020-05337-8

Müller-Edenborn, B., Chen, J., Allgeier, J., Didenko, M., Moreno-Weidmann, Z., Neumann, F.-J., … Jadidi, A. (2020). Amplified sinus-P-wave reveals localization and extent of left atrial low-voltage substrate: Implications for arrhythmia freedom following pulmonary vein isolation. *EP Europace*, *22*(2), 240–249. doi: 10.1093/europace/euz297

Murray, A., McLaughlin, N. B., Bourke, J. P., Doig, J. C., Furniss, S. S., & Campbell, R. W. (1994). Errors in manual measurement of QT intervals. *Heart*, *71*(4), 386–390. doi: 10.1136/hrt.71.4.386

Murray, C. J., & Lopez, A. D. (1997). Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *The Lancet*, *349*(9064), 1498–1504. doi: 10.1016/S0140-6736(96)07492-2

Nable, J. V., & Brady, W. (2009). The evolution of electrocardiographic changes in ST-segment elevation myocardial infarction. *The American Journal of Emergency Medicine*, *27*(6), 734–746. doi: 10.1016/j.ajem.2008.05.025

Nicholls, S. J., Lincoff, A. M., Garcia, M., Bash, D., Ballantyne, C. M., Barter, P. J., … Nissen, S. E. (2020). Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk: The STRENGTH Randomized Clinical Trial. *JAMA*, *324*(22), 2268–2280. doi: 10.1001/jama.2020.22258

Ninios, I., Pliakos, C., Ninios, V., Karvounis, H., & Louridas, G. (2007). Prevalence of Interatrial Block in a General Population of Elderly People. *Annals of Noninvasive Electrocardiology*, *12*(4), 298–300. doi: 10.1111/j.1542-474X.2007.00178.x

O'Donnell, M. J., Xavier, D., Liu, L., Zhang, H., Chin, S. L., Rao-Melacini, P., … Yusuf, S. (2010). Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): A case-control study. *The Lancet*, *376*(9735), 112–123. doi: 10.1016/S0140-6736(10)60834-3

Okin, P. M., Devereux, R. B., Fabsitz, R. R., Lee, E. T., Galloway, J. M., & Howard, B. V. (2002). Quantitative assessment of electrocardiographic strain predicts increased left ventricular mass: The strong heart study. *Journal of the American College of Cardiology*, *40*(8), 1395–1400. doi: 10.1016/S0735-1097(02)02171-X

Okin, P. M., Devereux, R. B., Nieminen, M. S., Jern, S., Oikarinen, L., Viitasalo, M., … Dahlöf, B. (2001). Relationship of the electrocardiographic strain pattern to left ventricular structure and function in hypertensive patients: The LIFE study. *Journal of the American College of Cardiology*, *38*(2), 514–520. doi: 10.1016/S0735-1097(01)01378-X

Okin, P. M., Devereux, R. B., Nieminen, M. S., Jern, S., Oikarinen, L., Viitasalo, M., … Dahlöf, B. (2004). Electrocardiographic Strain Pattern and Prediction of Cardiovascular Morbidity and Mortality in Hypertensive Patients. *Hypertension*, *44*(1), 48–54. doi: 10.1161/01.HYP.0000132556.91792.6a

Okin, P. M., Oikarinen, L., Viitasalo, M., Toivonen, L., Kjeldsen, S. E., Nieminen, M. S., … Devereux, R. B. (2009). Prognostic Value of Changes in the Electrocardiographic Strain Pattern During Antihypertensive Treatment: The Losartan Intervention for End-Point Reduction in Hypertension Study (LIFE). *Circulation*, *119*(14), 1883–1891. doi: 10.1161/CIRCULATIONAHA.108.812313

Okin, P. M., Roman, M. J., Lee, E. T., Galloway, J. M., Best, L. G., Howard, B. V., & Devereux, R. B. (2007). Usefulness of Quantitative Assessment of Electrocardiographic ST Depression for Predicting New-Onset Heart Failure in American Indians (from the Strong Heart Study). *The American Journal of Cardiology*, *100*(1), 94–98. doi: 10.1016/j.amjcard.2007.02.059

Onalan, O., & Crystal, E. (2007). Left Atrial Appendage Exclusion for Stroke Prevention in Patients With Nonrheumatic Atrial Fibrillation. *Stroke*, *38*(2), 624–630. doi: 10.1161/01.STR.0000250166.06949.95

O'Neal, W. T., Kamel, H., Zhang, Z.-M., Chen, L. Y., Alonso, A., & Soliman, E. Z. (2016). Advanced interatrial block and ischemic stroke: The Atherosclerosis Risk in Communities Study. *Neurology*, *87*(4), 352–356. doi: https://doi.org/10.1212/wnl.0000000000002888

O'Neal, W. T., Zhang, Z.-M., Loehr, L. R., Chen, L. Y., Alonso, A., & Soliman, E. Z. (2016). Electrocardiographic Advanced Interatrial Block and Atrial Fibrillation Risk in the General Population. *The American Journal of Cardiology*, *117*(11), 1755–1759. doi: 10.1016/j.amjcard.2016.03.013

Pääkkö, T. J. W., Perkiömäki, J. S., Silaste, M.-L., Bloigu, R., Huikuri, H. V., Kesäniemi, Y. A., & Ukkola, O. H. (2018). Dietary sodium intake is associated with long-term risk of new-onset atrial fibrillation. *Annals of Medicine*, *50*(8), 694–703. doi: 10.1080/07853890.2018.1546054

Park, J.-K., Park, J., Uhm, J.-S., Joung, B., Lee, M.-H., & Pak, H.-N. (2016). Low P-wave amplitude (<0.1 mV) in lead I is associated with displaced inter-atrial conduction and

clinical recurrence of paroxysmal atrial fibrillation after radiofrequency catheter ablation. *Europace*, *18*(3), 384–391. doi: 10.1093/europace/euv028

Park, K.-M., Kim, Y.-H., & Marchlinski, F. E. (2012). Using the Surface Electrocardiogram to Localize the Origin of Idiopathic Ventricular Tachycardia. *Pacing and Clinical Electrophysiology*, *35*(12), 1516–1527. doi: 10.1111/j.1540-8159.2012.03488.x

Patel, M. R., Mahaffey, K. W., Garg, J., Pan, G., Singer, D. E., Hacke, W., … the ROCKET AF Steering Committee. (2011). Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. *New England Journal of Medicine*, *365*(10), 883–891. doi: 10.1056/NEJMoa1009638

Perkiomaki, J. S., Zareba, W., Greenberg, H. M., & Moss, A. J. (2002). Usefulness of standard electrocardiographic parameters for predicting cardiac events after acute myocardial infarction during modern treatment era. *The American Journal of Cardiology*, *90*(3), 205–209. doi: 10.1016/S0002-9149(02)02455-4

Pietila, K., Tenkanen, L., Manttari, M., & Manninen, V. (1997). How to Define Coronary Heart Disease in Register-based Follow-up Studies: Experience from the Helsinki Heart Study. *Annals of Medicine*, *29*(3), 253–259. doi: 10.3109/07853899708999343

Pisters, R., Lane, D. A., Nieuwlaat, R., de Vos, C. B., Crijns, H. J. G. M., & Lip, G. Y. H. (2010). A Novel User-Friendly Score (HAS-BLED) To Assess 1-Year Risk of Major Bleeding in Patients With Atrial Fibrillation. Chest, 138(5), 1093–1100. doi: 10.1378/chest.10-0134

Platonov, P. G. (2012). P-Wave Morphology: Underlying Mechanisms and Clinical Implications. *Annals of Noninvasive Electrocardiology*, *17*(3), 161–169. doi: 10.1111/j.1542-474X.2012.00534.x

Porthan, K., Viitasalo, M., Toivonen, L., Havulinna, A. S., Jula, A., Tikkanen, J. T., … Oikarinen, L. (2013). Predictive value of electrocardiographic T-wave morphology parameters and T-wave peak to T-wave end interval for sudden cardiac death in the general population. *Circulation: Arrhythmia and Electrophysiology*, *6*(4), 690–696. doi: 10.1161/CIRCEP.113.000356

Powers, W. J., Rabinstein, A. A., Ackerson, T., Adeoye, O. M., Bambakidis, N. C., Becker, K., … on behalf of the American Heart Association Stroke Council. (2019). Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*, *50*, e344–e418. doi: 10.1161/STR.0000000000000211

Price, R. K., & Janes, L. R. (1943). A CASE OF SUBENDOCARDIAL INFARCTION. *Heart*, *5*(3), 134–138. doi: 10.1136/hrt.5.3.134

Prineas, R. J., Crow, R. S., & Blackburn, H. W. (1982). *The Minnesota Code Manual of Electrocardiographic Findings* (June, 1982). Littleton, MA: John Wright-PSG, Inc.

Priori, S. G., Wilde, A. A., Horie, M., Cho, Y., Behr, E. R., Berul, C., … Tracy, C. (2013). HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes. *Heart Rhythm*, *10*(12), 1932–1963. doi: 10.1016/j.hrthm.2013.05.014

Quyyumi, A. A., Wright, C., & Fox, K. (1983). Ambulatory electrocardiographic ST segment changes in healthy volunteers. *British Heart Journal*, *50*(5), 460–464.

Rabkin, S. W., Mathewson, F. L., & Tate, R. B. (1982). The electrocardiogram in apparently healthy men and the risk of sudden death. *Heart*, *47*(6), 546–552. doi: 10.1136/hrt.47.6.546

Rapola, J. M., Virtamo, J., Korhonen, P., Haapakoski, J., Hartman, A. M., Edwards, B. K., & Heinonen, O. P. (1997). Validity of diagnoses of major coronary events in national registers of hospital diagnoses and deaths in Finland. *European Journal of Epidemiology*, *13*(2), 133–138. doi: 10.1023/A:1007380408729

Rasmussen, M. U., Fabricius-Bjerre, A., Kumarathurai, P., Larsen, B. S., Domínguez, H., Kanters, J. K., & Sajadieh, A. (2019). Common source of miscalculation and misclassification of P-wave negativity and P-wave terminal force in lead V1. *Journal of Electrocardiology*, *53*, 85–88. doi: 10.1016/j.jelectrocard.2019.01.088

Rasmussen, P. V., Nielsen, J. B., Pietersen, A., Graff, C., Lind, B., Struijk, J. J., … Holst, A. G. (2014). Electrocardiographic Precordial ST-Segment Deviations and the Risk of Cardiovascular Death: Results From the Copenhagen ECG Study. *Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease*, *3*(e000549). doi: 10.1161/JAHA.113.000549

Rautaharju, P. M., Ge, S., Nelson, J. C., Marino Larsen, E. K., Psaty, B. M., Furberg, C. D., … Chaves, P. H. M. (2006). Comparison of Mortality Risk for Electrocardiographic Abnormalities in Men and Women With and Without Coronary Heart Disease (from the Cardiovascular Health Study). *The American Journal of Cardiology*, *97*(3), 309–315. doi: 10.1016/j.amjcard.2005.08.046

Rautaharju, P. M., Menotti, A., Blackburn, H., Parapid, B., & Kircanski, B. (2012). Isolated negative T waves as independent predictors of short-term and long-term coronary heart disease mortality in men free of manifest heart disease in the Seven Countries Study. *Journal of Electrocardiology*, *45*(6), 717–722. doi: 10.1016/j.jelectrocard.2012.07.006

Rautaharju, P. M., Surawicz, B., & Gettes, L. S. (2009). AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram. *Journal of the American College of Cardiology*, *53*(11), 982–991. doi: 10.1016/j.jacc.2008.12.014

Recommendations for measurement standards in quantitative electrocardiography. The CSE Working Party. (1985). *European Heart Journal*, *6*(10), 815–825.

Reindl, M., Reinstadler, S. J., Feistritzer, H.-J., Niess, L., Koch, C., Mayr, A., … Metzler, B. (2017). Persistent T-wave inversion predicts myocardial damage after ST-elevation myocardial infarction. *International Journal of Cardiology*, *241*, 76–82. doi: 10.1016/j.ijcard.2017.03.164

Rollin, A., Maury, P., Bongard, V., Sacher, F., Delay, M., Duparc, A., … Ruidavets, J.-B. (2012). Prevalence, Prognosis, and Identification of the Malignant Form of Early Repolarization Pattern in a Population-Based Study. *The American Journal of Cardiology*, *110*(9), 1302–1308. doi: 10.1016/j.amjcard.2012.06.033

Rose, G., Baxter, P. J., Reid, D. D., & McCartney, P. (1978). Prevalence and prognosis of electrocardiographic findings in middle-aged men. *Heart*, *40*(6), 636–643. doi: 10.1136/hrt.40.6.636

Sacco, R. L., Kasner, S. E., Broderick, J. P., Caplan, L. R., Connors, J. J. (Buddy), Culebras, A., … Vinters, H. V. (2013). An Updated Definition of Stroke for the 21st Century: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*, *44*(7), 2064–2089. doi: 10.1161/STR.0b013e318296aeca

Sandler, L. L., Pinnow, E. E., & Lindsay, J. (2004). The accuracy of electrocardiographic Q waves for the detection of prior myocardial infarction as assessed by a novel standard

of reference: Accuracy of Q waves for the detection of prior MI. *Clinical Cardiology*, *27*(2), 97–100. doi: 10.1002/clc.4960270212

Santangeli, P., Di Biase, L., Bai, R., Mohanty, S., Pump, A., Cereceda Brantes, M., … Natale, A. (2012). Atrial fibrillation and the risk of incident dementia: A meta-analysis. *Heart Rhythm*, *9*(11), 1761-1768.e2. doi: 10.1016/j.hrthm.2012.07.026

Schläpfer, J., & Wellens, H. J. (2017). Computer-Interpreted Electrocardiograms. *Journal of the American College of Cardiology*, *70*(9), 1183–1192. doi: 10.1016/j.jacc.2017.07.723

Schnabel, R. B., Yin, X., PhilimonGona, Larson, M. G., Beiser, A. S., McManus, D. D., … Levy, D. (2015). Fifty-Year Trends in Atrial Fibrillation Prevalence, Incidence, Risk Factors, and Mortality in the Community. *Lancet (London, England)*, *386*(9989), 154–162. doi: 10.1016/S0140-6736(14)61774-8

Schröder, L. C., Holkeri, A., Eranti, A., Haukilahti, M. A. E., Kerola, T., Kenttä, T. V., … Aro, A. L. (2022). Poor R-wave progression as a predictor of sudden cardiac death in the general population and subjects with coronary artery disease. *Heart Rhythm*, *19*(6), 952–959. doi: 10.1016/j.hrthm.2022.02.010

Skov, M. W., Ghouse, J., Kühl, J. T., Platonov, P. G., Graff, C., Fuchs, A., … Nielsen, J. B. (2018). Risk Prediction of Atrial Fibrillation Based on Electrocardiographic Interatrial Block. *Journal of the American Heart Association*, *7*(11), e008247. doi: 10.1161/JAHA.117.008247

Soliman, E. Z., Alonso, A., Misialek, J. R., Jain, A., Watson, K. E., Lloyd-Jones, D. M., … Heckbert, S. R. (2013). Reference ranges of PR duration and P-wave indices in individuals free of cardiovascular disease: The Multi-Ethnic Study of Atherosclerosis (MESA). *Journal of Electrocardiology*, *46*(6), 702–706. doi: 10.1016/j.jelectrocard.2013.05.006

Solomon, A., Ngandu, T., Soininen, H., Hallikainen, M. M., Kivipelto, M., & Laatikainen, T. (2014). Validity of dementia and Alzheimer's disease diagnoses in Finnish national registers. *Alzheimer's & Dementia*, *10*(3), 303–309. doi: 10.1016/j.jalz.2013.03.004

Staerk, L., Sherer, J. A., Ko, D., Benjamin, E. J., & Helm, R. H. (2017). Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes. *Circulation Research*, *120*(9), 1501–1517. doi: 10.1161/CIRCRESAHA.117.309732

Standardisation of precordial leads: Joint recommendations of the Cardiac Society of Great Britain and Ireland and the American Heart Association. (1938). *The Lancet*, *231*(5969), 221–222. doi: 10.1016/S0140-6736(00)93227-6

Sund, R. (2012). Quality of the Finnish Hospital Discharge Register: A systematic review. *Scandinavian Journal of Public Health*, *40*(6), 505–515. doi: 10.1177/1403494812456637

Sykes, A. H. (1987). A D Waller and the electrocardiogram, 1887. *BMJ*, *294*(6584), 1396–1398. doi: 10.1136/bmj.294.6584.1396

Tiffany Win, T., Ambale Venkatesh, B., Volpe, G. J., Mewton, N., Rizzi, P., Sharma, R. K., … Tereshchenko, L. G. (2015). Associations of electrocardiographic P-wave characteristics with left atrial function, and diffuse left ventricular fibrosis defined by cardiac magnetic resonance: The PRIMERI Study. *Heart Rhythm*, *12*(1), 155–162. doi: 10.1016/j.hrthm.2014.09.044

Toivonen, L., Helenius, K., & Viitasalo, M. (1997). Electrocardiographic Repolarization During Stress From Awakening on Alarm Call. *Journal of the American College of Cardiology*, *30*(3), 774–779. doi: 10.1016/S0735-1097(97)00222-2

Tolonen, H., Salomaa, V., Torppa, J., Sivenius, J., Immonen-Räihä, P., Lehtonen, A., & Finstroke, R. (2007). The validation of the Finnish Hospital Discharge Register and

Causes of Death Register data on stroke diagnoses. *European Journal of Cardiovascular Prevention & Rehabilitation*, *14*(3), 380–385. doi: 10.1097/01.hjr.0000239466.26132.f2

Viskin, S., Fish, R., Eldar, M., Zeltser, D., Lesh, M. D., Glick, A., & Belhassen, B. (2000). Prevalence of the Brugada sign in idiopathic ventricular fibrillation and healthy controls. *Heart*, *84*(1), 31–36. doi: 10.1136/heart.84.1.31

Wachtell, K., Okin, P. M., Olsen, M. H., Dahlöf, B., Devereux, R. B., Ibsen, H., … Thygesen, K. (2007). Regression of Electrocardiographic Left Ventricular Hypertrophy During Antihypertensive Therapy and Reduction in Sudden Cardiac Death: The LIFE Study. *Circulation*, *116*(7), 700–705. doi: 10.1161/CIRCULATIONAHA.106.666594

Walsh, B. M., & Smith, S. W. (2015). "Persistent Juvenile" T-Wave Pattern May Not Be Persistent: Case Series and Literature Review. *The Journal of Emergency Medicine*, *49*(6), e165–e172. doi: 10.1016/j.jemermed.2015.06.064

Walsh, J. A., Prineas, R., Soliman, E. Z., Liu, K., Ning, H., Daviglus, M. L., & Lloyd-Jones, D. M. (2013). Association of isolated minor non-specific ST-segment and T-wave abnormalities with subclinical atherosclerosis in a middle-aged, biracial population: Coronary Artery Risk Development in Young Adults (CARDIA) study. *European Journal of Preventive Cardiology*, *20*(6), 1035–1041. doi: 10.1177/2047487312460017

Wasserman, A. G., Bren, G. B., Ross, A. M., Richardson, D. W., Hutchinson, R. G., & Rios, J. C. (1982). Prognostic implications of diagnostic Q waves after myocardial infarction. *Circulation*, *65*(7), 1451–1455. doi: 10.1161/01.CIR.65.7.1451

Weng, L.-C., Hall, A. W., Choi, S. H., Jurgens, S. J., Haessler, J., Bihlmeyer, N. A., … Lubitz, S. A. (2020). Genetic Determinants of Electrocardiographic P-Wave Duration and Relation to Atrial Fibrillation. *Circulation: Genomic and Precision Medicine*, *13*(5), 387–395. doi: 10.1161/CIRCGEN.119.002874

Wilson, F. N., Johnston, F. D., Macleod, A. G., & Barker, P. S. (1934). Electrocardiograms that represent the potential variations of a single electrode. *American Heart Journal*, *9*(4), 447–458. doi: 10.1016/S0002-8703(34)90093-4

Wolf, P. A., Abbott, R. D., & Kannel, W. B. (1991). Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. *Stroke*, *22*(8), 983–988. doi: 10.1161/01.STR.22.8.983

World Health Organization & International Diabetes Federation. (2006). *Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: Report of a WHO/IDF consultation*. Retrieved from http://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/

Yamazaki, T., Myers, J., & Froelicher, V. F. (2005). Prognostic importance of isolated T-wave abnormalities. *The American Journal of Cardiology*, *95*(2), 300–304. doi: 10.1016/j.amjcard.2004.08.099

Yan, G.-X., & Antzelevitch, C. (1998). Cellular Basis for the Normal T Wave and the Electrocardiographic Manifestations of the Long-QT Syndrome. *Circulation*, *98*(18), 1928–1936. doi: 10.1161/01.CIR.98.18.1928

Zarafshar, S., Wong, M., Singh, N., Aggarwal, S., Adhikarla, C., & Froelicher, V. F. (2013). Resting ST Amplitude: Prognosis and Normal Values in an Ambulatory Clinical Population. *Annals of Noninvasive Electrocardiology*, *18*(6), 519–529. doi: 10.1111/anec.12066

Zipes, D. P. (1997). Atrial Fibrillation: A Tachycardia-Induced Atrial Cardiomyopathy. *Circulation*, *95*(3), 562–564. doi: 10.1161/01.CIR.95.3.562

PUBLICATIONS

PUBLICATION I

The prevalence and prognostic significance of interatrial block in the general population

Istolahti Tiia, Eranti Antti, Huhtala Heini, Lyytikäinen Leo-Pekka, Kähönen Mika, Lehtimäki Terho, Eskola Markku, Anttila Ismo, Jula Antti, Bayés de Luna Antoni, Nikus Kjell, Hernesniemi Jussi

Annals of Medicine, 52:3-4, 63-73
DOI: 10.1080/07853890.2020.1731759

The prevalence and prognostic significance of interatrial block in the general population.

Running head: Interatrial block in the general population.

Tiia Istolahti[a,b], Antti Eranti[c], Heini Huhtala[d], Leo-Pekka Lyytikäinen[a,e,f], Mika Kähönen[a,g], Terho Lehtimäki[a,f], Markku Eskola[a,e], Ismo Anttila[h], Antti Jula[i], Antoni Bayés de Luna[j], Kjell Nikus[a,e], Jussi Hernesniemi[a,e]

[a]Faculty of Medicine and Health Technology, Tampere University, and Finnish Cardiovascular Research Center, Tampere, Finland
[b]Department of Internal Medicine, Vaasa Central Hospital, Vaasa, Finland
[c]Heart Center, Central Hospital of North Karelia, Joensuu, Finland
[d]Faculty of Social Sciences, Tampere University, Tampere, Finland
[e]Heart Center, Department of Cardiology, Tampere University Hospital, Tampere, Finland
[f]Department of Clinical Chemistry, Fimlab Laboratories, Tampere, Finland
[g]Department of Clinical Physiology, Tampere University Hospital, Tampere, Finland
[h]Department of Emergency Services, Seinäjoki Central Hospital, Seinäjoki, Finland
[i]National Institute for Health and Welfare, Helsinki, Finland
[j]Cardiovascular Research Foundation, Cardiovascular ICCC-Program, Research Institute Hospital de la Santa Creu i Sant Pau, IIB-Sant Pau, Barcelona, Spain

Corresponding author: Tiia Istolahti, Department of Internal Medicine, Vaasa Central Hospital, Hietalahdenkatu 2-4, 65100 Vaasa, Finland. E-mail address: tiia.istolahti@tuni.fi.

Key words: Interatrial block, ECG, population study, atrial fibrillation, mortality

Abstract

Introduction Partial and advanced interatrial block (IAB) in the ECG represents inter-atrial conduction delay. IAB is associated with atrial fibrillation (AF) and stroke in the general population.
Material and methods A representative sample of Finnish subjects (n=6 354) aged over 30 years (mean 52.2 years, SD 14.6) underwent a health examination including a 12-lead ECG. Five different IAB groups based on automatic measurements were compared to normal P waves using multivariate-adjusted Cox proportional hazard model. Follow-up lasted up to 15 years.
Results The prevalence of advanced and partial IAB was 1.0% and 9.7%, respectively. In the multivariate model, both advanced (hazard ratio [HR] 1.63 [95% CI 1.00 - 2.65]) and partial IAB (HR 1.39 [1.09 - 1.77]) were associated with increased risk of AF. Advanced IAB was associated with increased risk of stroke or transient ischemic attack (TIA) independently of associated AF (HR 2.22 [1.20 - 4.13]). Partial IAB was also associated with increased risk of being diagnosed with coronary heart disease (HR 1.26 [1.01 - 1.58]).
Discussion IAB is a rather frequent finding in the general population. IAB is a risk factor for AF and is associated with an increased risk of stroke or TIA independently of associated AF.

Key messages

1. Both partial and advanced interatrial block are associated with increased risk of atrial fibrillation in the general population.
2. Advanced interatrial block is an independent risk factor for stroke and transient ischemic attack.
3. The clinical significance of interatrial block is dependent on the subtype classification.

Introduction

Interatrial block (IAB) is a distinct electrocardiographic (ECG) pattern that has been studied with growing interest since it was first described in 1979 by Bayés de Luna (1). IAB is caused by conduction delay between the right and left atrium, probably resulting from local fibrosis. When the conduction through the Bachmann's bundle is blocked, the electrical activation to the left atrium takes an alternative route through the lower parts of the interatrial septum resulting in caudo-cranial activation in the left atrium. (2) This is reflected in the surface ECG as a biphasic morphology of the P wave in the inferior leads (II, III, aVF). This together with a P-wave duration ≥ 120 ms is considered as advanced IAB (Fig. 1). P-wave duration ≥ 120 ms with normal P-wave morphology is defined as partial IAB, and delayed conduction via the interatrial septum through Bachmann's bundle is considered as the background pathology for this ECG phenomenon. (3)

Both advanced (4) and partial IAB are risk factors for atrial fibrillation (AF) in the general population (5,6). The association between IAB and AF is called Bayés' syndrome (7). It has also been suggested that IAB is an independent risk factor for ischemic stroke (8) and cardiovascular and all-cause mortality (5,9). In some studies IAB was associated with dementia (10) and coronary heart disease (CHD) (11,12), but data concerning other endpoints than AF is limited. The clinical relevance of IAB lies on the associated risk of AF and the importance of early prevention of stroke by timely anticoagulation therapy. Some authors even suggested anticoagulation therapy based on IAB without a diagnosis of AF (13). Data on the prevalence, prognostic significance and diseases associated with IAB is sparse.

The primary aims of the study were to explore the prevalence of IAB and the risk for AF and stroke associated with this ECG manifestation in the general population. Secondary aims were to study: 1) the risk of IAB for CHD, dementia and all-cause mortality, 2) the significance of the number of inferior leads with biphasic P waves, and 3) the significance of the duration and amplitudes of biphasic inferior P waves.

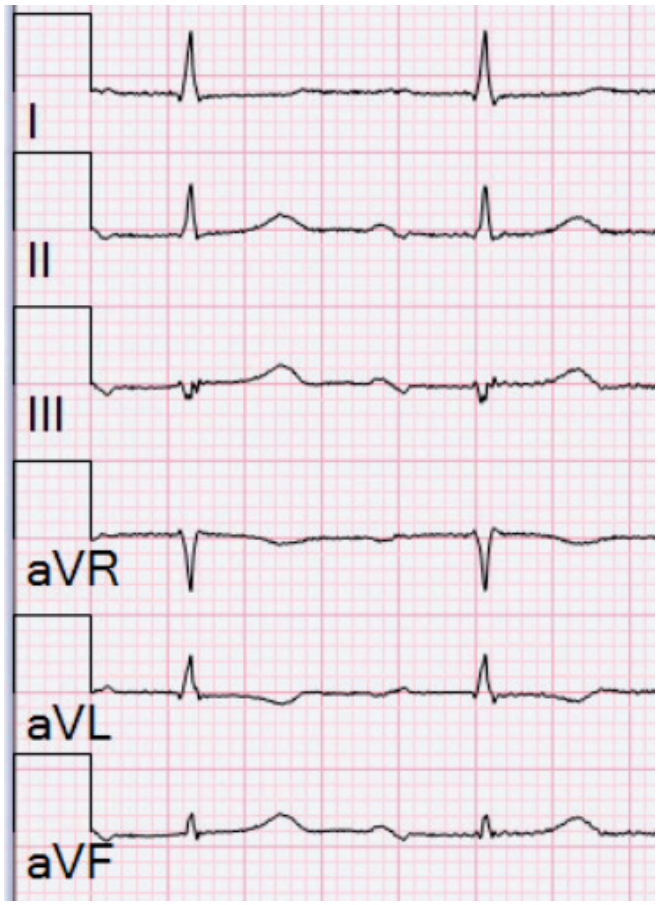

Figure 1. Limb leads of an ECG with advanced interatrial block. P-wave duration is 140 ms and the P wave is biphasic in the inferior leads (II, III, aVF). The paper speed is 25mm/s and calibration of 10mm/mV is used.

Materials and Methods

Study population

The Health 2000 survey was carried out in 2000-2001. This population-based nationwide study consisted of 8028 individuals aged over 30 years, of whom 79 % (6354 individuals) participated in the health examination, which included a structured examination by a physician, health interviews, series of laboratory tests and ECG recordings. The Health 2000 population was designed to cover a nationally representative population sample of the Finnish population. Participants aged 80+ were oversampled with a double sampling fraction. More detailed descriptions of the methods of the Health 2000 survey have been published previously (14). Ethical approval for the Health 2000 study was obtained from Ethical Committee for Research in Epidemiology and Public Health at the Hospital District of Helsinki and Uusimaa (HUS).

ECG registration and analysis

During the health examination, a standard 12-lead resting ECG in supine position was recorded from each subject with Marquette Hellige MAC 5000 electrocardiographs (Freiburg, Germany and Milwaukee, WI, USA). ECGs were stored electronically and printed at a paper speed of 50 mm/s. The ECG data were sent for further analysis to the Social Insurance Institution's research center in Turku, where the ECGs were analyzed with Magellan software (Marquette Electronics Inc, Milwaukee, WI, USA). The Marquette 12SL algorithm uses median complexes of the 10-second ECG tracing and the onset of QRS as the isoelectric line. P-wave durations and amplitudes of different parts of the P wave were automatically measured, the measurement points were checked and corrected if needed. The duration was measured from the earliest onset in any lead to the latest offset in any lead. A wave crossing the baseline level constituting an area of ≥160 μVms represented a separate wave. Two investigators at the Institute of Cardiology, Kaunas Medical Academy, Lithuania, blinded to the clinical data performed the Minnesota coding (15). The repeatability of the Minnesota Code was ascertained by a repeat analysis of 200 ECGs.

Definition of IAB

Figure 2 shows the different ECG categories. We defined biphasic morphology as follows: the amplitude of the initial part of the P wave ≥ 20uV and the amplitude of the terminal part ≤ -20uV. We defined advanced IAB as P-wave duration ≥ 120 ms combined with biphasic P waves in at least two inferior leads (II, III, aVF) and partial IAB as P-wave duration ≥ 120 ms without biphasic morphology. We categorized subjects with P-wave duration ≥ 120 ms and two or three leads with biphasic P waves in the inferior leads not fulfilling the above-mentioned amplitude criteria as "minor-aIAB". In order to establish the significance of the number of biphasic inferior leads, we categorized subjects with one inferior biphasic lead and P-wave duration ≥ 120ms as "1 BIF". To establish the significance of the duration of biphasic P waves, we added a category "2 BIF < 120 ms", which was defined as P-wave duration < 120 ms and two or three inferior biphasic leads. ECGs with a P-wave duration < 120 ms and maximally one biphasic inferior lead were classified as normal.

To check the validity of the definition of the biphasic morphology, manual comparison blinded to the clinical outcome was performed from 25 randomly selected ECGs defined as advanced IAB, as well as 100 ECGs defined as partial IAB. For this purpose, digitalized ECGs with a zoom of 20 mm/mV and 100 mm/sec were used. In the advanced IAB group, in one ECG (4%) the inferior leads were not positive-negative. Among ECGs defined as partial IAB, 11 (11%) ECGs showed positive-negative morphology in one inferior lead, but in none (0%) was the morphology positive-negative in two or more inferior leads.

Amount of biphasic inferior leads	**P-wave duration**	
	< 120 ms	≥ 120 ms
0	Normal	pIAB
1		1 BIF
Minor* 2 or 3		Minor-aIAB
2 or 3	2 BIF < 120 ms	aIAB

Figure 2. Definitions of different IAB-groups in our study. *Biphasic P waves not fulfilling the amplitude criterion (± 20 uV) were called "minor". pIAB=Partial Interatrial Block, BIF=Biphasic, aIAB=Advanced Interatrial Block.

Study covariates

Trained study personnel performed the health interview, and they followed a structural detailed written instruction to gather information about pre-existent diseases. Examining physicians performed another structured interview and physical examination. We included data on prevalent diseases from the Care Register for Health Care (CRHC) maintained by the National Institute for Health and Welfare. CRHC contains data of all inpatient episodes in Finland at the individual level since year 1969 and on outpatients since 1998. The accuracy of the register has been validated previously (16). Information about medication at baseline were gathered by checking the study participants' personal health insurance cards for rights of drug reimbursements and by interviewing the study participants about prescription and non-prescription medicines.

Height, weight and waist circumference were measured and body mass index (BMI) was calculated. Blood pressure was measured from the right arm with a standard mercury manometer (Mercuro 300; Speidel & Keller, Jungingen, Germany). An average of two measurements was used, of which the first one was measured after rest for at least 5 minutes in sitting position. Arterial hypertension

(HTA) was defined as blood pressure ≥ 140/90. Heart rate was obtained from the ECGs. Smoking was determined as a daily use of cigarettes at the time of the interview. For the diagnosis of chronic obstructive pulmonary disease (COPD), information gathered during the health interview was used. Left ventricular hypertrophy in the ECG (ECG-LVH) was defined by Minnesota code criteria 3-1, 3-3 or 3-4 (15). Classification of myocardial infarction required either a diagnosis by the examining physician, large Q waves in the resting ECG or a history of myocardial infarction in the CRHC ICD-codes I21-I22 (ICD10) or 410 (ICD8/9).

Serum total cholesterol, high-density lipoprotein cholesterol (HDL), triglyceride and plasma glucose concentrations were determined enzymatically (Roche Diagnostics, GmbH, Mannheim, Germany for HDL and Olympus System Reagent, Hamburg, Germany for total cholesterol, triglycerides and glucose) from venous blood samples with a clinical chemistry analyzer (Olympus, AU400, Hamburg, Germany). Low density lipoprotein cholesterol (LDL) was calculated using the Friedewald formula. The diagnosis of diabetes mellitus (DM) at baseline included fasting serum glucose (fS-Gluc) ≥ 7 or a history of use of oral glucose lowering agents or insulin injections (17).

Follow-up and study endpoints

The data for mortality and causes of death were gathered from the Causes of Death register maintained by Statistics Finland. It contains 100% of deaths of Finnish citizens in Finland and almost 100% abroad. Information on the incident diseases were obtained from the CRHC. In addition, data on drug purchases since year 1995 and special drug reimbursements since year 1964 were gathered from a separate registry (Statistics on reimbursements for prescription medicines: The Social Insurance Institution of Finland). Databases were linked using a personal identity code. The follow-up lasted until the end of the year 2015. The study endpoints were a new diagnosis of AF, ischemic stroke or transient ischemic attack (TIA), dementia, CHD and all-cause mortality. The endpoints were tested separately.

We defined AF as ICD-codes I48 (version 10), 4273 (9) or 42792 (8) in the CRHC and Causes of Death register, right for drug reimbursement for dronedarone or direct oral anticoagulants with diagnose-code (ICD-10) I48 or right for special drug reimbursements for AF. For prevalent and incident stroke and TIA, we included the ICD-10-codes I63-64 and G45 (not I63.6 or G45.4), ICD-9-codes 4330-31A,

4339-41A, 4349A and 435-36, and ICD-8-codes 433-435 in the CRHC and Causes of Death register. Classification of prevalent CHD required at least one of the following: diagnosed angina pectoris, myocardial infarction, percutaneous coronary intervention (PCI) or bypass surgery by examining physician or diagnosed PCI or bypass surgery in the health interview, ICD-codes I20-25 (ICD-10) or 410-14 (ICD8/9) in the CRHC or the right for drug reimbursements for CHD. For the diagnosis of incident CHD, we also included ICD-codes I21-25, I46, R96, R98 (ICD-10) and 410-414, 798 (not 7980A) (ICD-8/9) in the Causes of Death register. We defined dementia as ICD-10 codes F00-F03, G30, ICD-9-codes 290, 3310, 4378A, and ICD-8-code 290 in the CRHC and in the Causes of Death register, right for drug reimbursements for donepezil, galantamine, memantine, rivastigmine or tacrine or purchases for anti-dementia drugs.

Exclusion criteria

We excluded subjects with missing ECG data (number of participants (n) = 55). Of those, the recording was not successful in 36 participants with entries such as “difficult to move,” “wheelchair”, “denial”, “leg/hand amputated”, “in geriatric chair”, “massive hernia”, “plaster in leg/ hand”. In the further process, 19 ECGs were lost (diskette lost [9], coupling error [4], data reading failure [5], unspecific reason [1]). We also excluded subjects with ECGs showing supraventricular tachyarrhythmias according to Minnesota-code 8-4-1 (n=6), all prevalent atrial fibrillation and atrial flutter as defined previously (n=204), paced rhythm (Minnesota-code 6-8, n=4) and ectopic rhythm defined as totally negative P waves in the inferior leads (II, III, aVF) in computer analysis (n=24) leaving 6066 individuals in the final study sample. Participants with prior diagnosis of study endpoints (stroke or TIA [n=143], CHD [n=435] or dementia [n=451]) were excluded from analysis considering particular endpoint. In addition, subjects with incident AF (n=538) were excluded from the analysis when studying IAB as an independent risk factor for stroke and TIA.

Statistical analyses

Comparisons in variables were calculated with either one-way ANOVA, Kruskal-Wallis, Chi-square or Fisher’s exact test as appropriate. Cox proportional hazard models were constructed separately for different endpoints. AF and stroke and TIA were used as primary endpoints and CHD, dementia and mortality as secondary endpoints. Only the first diagnosis per disease was considered.

Advanced IAB and partial IAB were compared to normal P waves (P duration < 120ms with zero or one biphasic inferior P wave), and minor-aIAB, 1 BIF and 2 BIF < 120 ms were included as sensitivity analysis. We used the following parameters for multivariate adjusting: age, sex, BMI, HDL, LDL, heart rate, HTA, DM, CHD and ECG-LVH. To establish the prevalence of different IAB groups on the population level, SPSS Complex samples design was used. We tested also the difference between weighted and unweighted Cox proportional hazard models with SPSS Complex samples design, and we found no clinically relevant differences between the two models. All Cox proportional hazard models are presented in unweighted form. All analyses were performed with SPSS 25. Statistical significance was based on $p<0.05$.

Results

The final study sample consisted of 6066 participants free of AF at baseline. The mean age of the participants was 52.2 (standard deviation [SD] 14.6) years. Table 1 shows the baseline characteristics of the study population. Table 2 shows the population-corrected prevalence of different IAB groups separately for sinus rhythm and without exclusion criteria. Participants within the different categories of IAB were significantly older than participants with normal P waves and age increased with IAB severity. Participants with IAB were more often men and more often had co-morbidities. The use of all studied medications was more frequent in the subjects with IAB. ECG-LVH was more prevalent in the categories with biphasic morphology.

IAB and the risk of adverse events

During a mean follow-up period of 13.42 (SD 3.74) years, there were 538 incident diagnoses of AF. Table 3 shows the age-adjusted and multi-adjusted hazard ratios (HR) for different endpoints and numbers of incident diseases. Advanced IAB, partial IAB and 1 BIF increased the risk for incident AF in the age-adjusted model. The increase in risk was most evident in the advanced IAB group and similar between the partial IAB and 1 BIF -groups. In a multi-adjusted model, advanced IAB and partial IAB increased the risk for AF. The category 1 BIF lost its statistical significance after multivariate adjustment. Minor-aIAB or 2 BIF <120 ms had no prognostic significance regarding incident AF with HRs close to one.

Table 1. Baseline characteristics of the Health 2000 Survey participants

	aIAB		Minor-aIAB		1 BIF		pIAB		2 BIF < 120ms		Normal		
Variable	Mean/ Median/ N	SD/ Q_1-Q_3/ (%)	Mean/ Median/ N	SD/ Q_1-Q_3/ (%)	Mean/ Median/ N	SD/ Q_1-Q_3/ (%)	Mean/ Median/ N	SD/ Q_1-Q_3/ (%)	Mean/ Median/ N	SD/ Q_1-Q_3/ (%)	Mean/ Median/ N	SD/ Q_1-Q_3/ (%)	p value
N	63	(1.0%)	18	(0.3%)	264	(4.4%)	585	(9.6%)	249	(4.1%)	4887	(80.6%)	
Age	67.4	12.6	64.6	12.3	57.5	14.8	55.0	14.0	58.3	15.5	51.0	14.3	<0.001
Men	36	(57.1%)	9	(50.0%)	156	(59.1%)	309	(52.8%)	96	(45.0%)	2123	(43.4%)	<0.001
BMI (kg/m^2)	29.2	4.6	29.2	5.2	28.4	4.6	27.5	4.6	27.2	4.4	26.7	4.6	<0.001
Waist circumf-erence (cm)	100.6	12.1	101.1	16.3	97.9	13.4	95.1	13.0	93.6	12.4	91.8	13.3	<0.001
Heart rate/min	59.7	10.2	62.3	10.0	61.7	10.9	62.5	11.0	62.8	9.9	63.6	10.7	0.001
Regular smoking	9	(14.3%)	3	(16.7%)	40	(15.2%)	125	(21.4%)	58	(23.4%)	1087	(22.3%)	0.065
COPD	1	(1.6%)	0	(0.0%)	5	(1.9%)	6	(1.0%)	5	(2.0%)	58	(1.2%)	0.554
Hypertension	38	(60.3%)	13	(72.2%)	144	(54.5%)	288	(49.2%)	121	(48.6%)	1944	(39.8%)	<0.001
Diabetes	11	(17.5%)	2	(11.1%)	27	(10.2%)	41	(7.0%)	35	(14.1%)	253	(5.2%)	<0.001
LVH	15	(23.8%)	4	(22.2%)	56	(21.2%)	93	(15.9%)	50	(20.1%)	667	(13.6%)	<0.001
CHD	17	(27.0%)	5	(27.8%)	32	(12.1%)	57	(9.7%)	26	(10.4%)	298	(6.1%)	<0.001
Myocardial infarction	8	(12.7%)	2	(11.1%)	13	(4.9%)	23	(3.9%)	5	(2.0%)	112	(2.3%)	<0.001
Total cholesterol (mmol/L)	5.8	1.4	6.1	1.2	6.1	1.2	6.0	1.0	6.2	1.1	5.9	1.1	0.001
HDL (mmol/L)	1.2	0.4	1.3	0.3	1.3	0.3	1.3	0.3	1.3	0.4	1.3	0.4	0.001
LDL (mmol/L)	3.6	1.4	4.2	1.2	3.8	1.3	3.9	1.1	3.9	1.3	3.8	1.2	0.027
Triglycerides (mmol/L)	1.4	1.1-2.2	1.3	1.0-2.0	1.5	1.1-2.0	1.4	1.0-1.9	1.4	1.0-2.0	1.3	1.0-1.8	<0.001
CRP (mg/L)	0.7	0.3-2.5	1.1	0.5-3.6	0.9	0.4-2.1	0.7	0.3-1.8	1.2	0.4-3.1	0.7	0.3-1.8	<0.001
Uric acid (µmol/L)	335.4	97.2	324.7	76.3	331.2	83.5	312.4	77.7	311.9	85.6	294.8	79.0	<0.001
Medication:													
Beta-blocker	23	(36.5%)	9	(50.0%)	68	(25.8%)	114	(19.5%)	46	(18.5%)	556	(11.4%)	<0.001
CCB	9	(14.3%)	6	(33.3%)	25	(9.5%)	50	(8.5%)	19	(7.6%)	239	(4.9%)	<0.001
Digitalis	4	(6.3%)	2	(11.1%)	4	(1.5%)	7	(1.2%)	3	(1.2%)	29	(0.6%)	<0.001
ACEI/ARB	11	(17.5%)	3	(16.7%)	32	(12.1%)	58	(9.9%)	27	(10.8%)	328	(6.7%)	<0.001

aIAB=Advanced Interatrial Block, BIF=Biphasic, pIAB=Partial Interatrial Block, BMI=Body Mass Index, COPD=Chronic Obstructive Pulmonary Disease, LVH=Left Ventricular Hypertrophy, CHD=Coronary Heart Disease, HDL=High-density Lipoprotein, LDL=Low-density Lipoprotein, CCB=Calcium Channel Blocker, ACEI=Angiotensin-converting Enzyme Inhibitor, ARB=Angiotensin II Receptor Antagonist, SD=Standard Deviation, N=Number, Q_1-Q_3=Quartiles

Table 2. Prevalence of different IAB groups: weighted Health 2000 population.

	In sinus rhythm* (%)	All (no exclusion criteria) (%)
aIAB	1.0	1.0
Minor-aIAB	0.3	0.3
1 BIF	4.4	4.3
pIAB	9.7	9.9
2 BIF <120 ms	4.0	4.0

*and no previous diagnosis of atrial fibrillation.
aIAB=Advanced interatrial block, BIF=Biphasic, pIAB= Partial interatrial block

Advanced IAB proved to be a significant risk marker for stroke and TIA both in age-adjusted and multi-adjusted models. The other IAB categories were even associated with lower risk than the control group, although the difference was not statistically significant. When participants with incident AF during the follow-up were excluded, advanced IAB increased the risk for stroke and TIA independently in the age-adjusted (HR 2.39 [95 % confidence interval [CI] 1.30 - 4.42, p=0.005]) and in the multi-adjusted model (HR 2.22 [1.20 - 4.13, p=0.012]). The mean follow-up time for stroke and TIA was 13.56 (SD 3.62) years.

Partial IAB showed a borderline significance for CHD after multivariate adjustment. In addition, advanced IAB and minor-aIAB seemed to increase the risk for CHD, but the difference was not statistically significant. Despite the increased risk for AF, stroke/TIA and CHD, none of the IAB groups was associated with increased all-cause mortality. In addition, none of the IAB categories predicted dementia.

Table 3. Cox proportional hazard analysis for different endpoints according to P-wave morphology compared to normal P waves.

Endpoint (N, %)	Events/1000 person-years	Hazard Ratio (95% CI)			
		Age adjusted	p value	Multivariate adjusted*	p value
Atrial fibrillation (538, 8.9%)	**6.6**				
aIAB	28.5	2.11 (1.30-3.40)	0.002	1.63 (1.00-2.65)	0.048
Minor-aIAB	13.5	1.20 (0.39-3.74)	0.754	0.99 (0.32-3.10)	0.988
1 BIF	13.4	1.56 (1.14-2.14)	0.006	1.28 (0.93-1.76)	0.129
pIAB	10.9	1.55 (1.22-1.97)	<0.001	1.39 (1.09-1.77)	0.008
2 BIF <120 ms	10.3	1.16 (0.80-1.66)	0.436	1.08 (0.75-1.56)	0.687
Stroke and TIA (434, 7.3%)	**5.4**				
aIAB	30.0	2.29 (1.40-3.74)	0.001	2.09 (1.27-3.44)	0.004
Minor-aIAB	8.8	0.84 (0.21-3.35)	0.799	0.79 (0.20-3.20)	0.746
1 BIF	7.0	0.91 (0.59-1.40)	0.658	0.84 (0.55-1.29)	0.427
pIAB	6.2	0.94 (0.69-1.28)	0.686	0.93 (0.68-1.27)	0.647
2 BIF <120 ms	5.8	0.70 (0.44-1.13)	0.146	0.64 (0.40-1.03)	0.067
CHD (678, 12.1%)	**8.9**				
aIAB	24.5	1.20 (0.68-2.14)	0.526	1.09 (0.61-1.94)	0.763
Minor-aIAB	24.6	1.50 (0.56-4.03)	0.416	1.40 (0.52-3.76)	0.508
1 BIF	11.7	0.93 (0.66-1.31)	0.680	0.80 (0.57-1.13)	0.212
pIAB	13.0	1.30 (1.04-1.62)	0.024	1.26 (1.01-1.58)	0.045
2 BIF <120 ms	13.4	1.01 (0.73-1.41)	0.950	0.91 (0.65-1.27)	0.572
Dementia (451, 7.5%)	**5.5**				
aIAB	20.4	1.11 (0.65-1.91)	0.694	1.11 (0.64-1.93)	0.717
Minor-aIAB	0.0	No events		No events	
1 BIF	10.6	1.11 (0.79-1.57)	0.557	1.13 (0.80-1.60)	0.480
pIAB	6.2	0.84 (0.62-1.13)	0.253	0.85 (0.63-1.15)	0.295
2 BIF <120 ms	9.2	0.95 (0.65-1.38)	0.772	0.92 (0.63-1.36)	0.688
Death (1159, 19.1%)	**13.9**				
aIAB	45.4	1.09 (0.77-1.54)	0.634	1.10 (0.78-1.56)	0.592
Minor-aIAB	21.8	0.77 (0.32-1.86)	0.561	0.65 (0.24-1.73)	0.388
1 BIF	19.2	0.86 (0.67-1.10)	0.238	0.86 (0.67-1.10)	0.234
pIAB	15.6	0.87 (0.72-1.05)	0.134	0.88 (0.73-1.06)	0.185
2 BIF <120 ms	23.8	1.01 (0.80-1.28)	0.910	1.04 (0.82-1.31)	0.770

N=Number of participants, CI=Confidence interval, aIAB=Advanced interatrial block, BIF=Biphasic, pIAB=Partial interatrial block, CHD=Coronary heart disease.

*Age, Sex, Body mass index, Coronary heart disease, Hypertension, Diabetes, High-density lipoprotein, Low-density lipoprotein, Heart rate, ECG Left ventricular hypertrophy

Discussion

In a population study, where we used weighting adjustment and included individuals aged 30+, without a diagnosis of AF at baseline, the prevalence of advanced IAB was 1.0% and partial IAB was 9.7%, respectively. Both advanced and partial IAB were predictors of incident AF during long-term follow-up and advanced IAB also increased the risk of stroke or TIA after multivariate adjustment independently of associated AF. Partial IAB also seemed to associate with increased risk for CHD, but the association was no longer significant when adjusted for multiple testing. We found no association between IAB and all-cause mortality or dementia. The ECG categories with less advanced signs of IAB had no significant predictive value.

Prevalence of IAB

In the Atherosclerosis Risk in Communities (ARIC) study of 45 to 64 year old male and female subjects (mean age 54 years [± 5.8 y]) 0.5% had advanced IAB at baseline (4). Similar prevalence was found in the Copenhagen ECG study of 152 759 individuals aged 50 to 90 years (5). In the geriatric population of Ariyarajah et al, the prevalence of advanced IAB was around 6% (18) and the prevalence was even higher in 80 subjects older than 100 years in a study of Martínez-Sellés et al (10). They found advanced IAB in 26% and partial IAB in 20%, but they did not exclude participants with pre-existing AF (25%). In the Copenhagen ECG study, subjects with advanced IAB were much older than those without IAB, but there was only a two-year age difference between those with partial IAB and no IAB. We made similar observations: subjects with advanced IAB were more than 16 years older than those without IAB, but the difference between subjects with partial IAB and no IAB was only four years. As atrial fibrosis is considered important in IAB, it is logical that age is a contributing factor in conduction disease development. The mean age in our study (52.2 years [SD 14.6]) was close to the mean age in the ARIC-study, but we noticed a slightly higher prevalence of advanced IAB (1.0%). The difference is likely explained by the different definition of advanced IAB; we included also ECGs with two biphasic inferior leads.

IAB and AF

The association between IAB and supraventricular arrhythmias, mainly AF, the Bayés' syndrome, has been demonstrated in many different clinical scenarios (19). In the present population study, there was a clear association between advanced IAB and incident AF. With age-adjustment, the risk of a new AF diagnosis during long-term follow-up was about twofold, and after multi-variate adjustment, the risk was still more than 1.5-fold. In the ARIC study, there was a threefold increased risk for AF in individuals with advanced IAB (4). The very large Copenhagen ECG study (5) showed that IAB improves risk prediction of AF when added to a conventional risk model. The highest effect of IAB on the absolute risk of AF was observed in individuals aged 60 to 70 years with baseline cardiovascular disease.

Previous studies are contradictory concerning the increase in risk between advanced and partial forms of IAB. In the REgistre GIroní del COR (REGICOR) population-based (mean age 74.3 years [± 7.4]) cohort, a P wave longer than 110 milliseconds increased the risk of AF during 7.12 years of follow-up, but advanced IAB morphology did not provide an additional AF risk beyond that of P-wave duration (20). However, in the Copenhagen ECG study (5) the risk seemed to increase with the number of affected biphasic inferior leads. In our study also partial IAB was associated with incident AF, but the risk of a new AF diagnosis was lower than for advanced IAB. The multi-variate adjusted HR 1.39 (1.09 - 1.77) for partial IAB was close to the corresponding HR of 1.25 (1.19 - 1.30) in the Copenhagen ECG study (5). The smaller CIs in the Copenhagen ECG study probably reflect their much larger study population.

IAB and cerebrovascular event

As in the previous population study by Skov et al (5), we found that advanced, but not partial IAB, was associated with increased stroke risk. Ariyarajah and Spodick hypothesized that progressive worsening of interatrial conduction via the Bachmann Bundle in partial IAB may lead to advanced IAB over time (21). They found support for their hypothesis in another study, where the progression time from partial to advanced IAB was shorter than from normal P wave to advanced IAB (22). This offers two potential explanations for the fact that the advanced, but not partial IAB, seems to be associated with risk for stroke or TIA. One possible explanation is that partial IAB is associated with

less atrial remodeling and thereby with less risk for thromboembolic substrates. The other potential explanation is simply related to time: if advanced IAB develops later than partial IAB, there is more time for an embolic stroke event to happen.

The pathophysiology between the association of AF and stroke is not completely understood. In patients with AF and no concomitant heart disease or other risk factors, the risk of stroke is similar to the risk in patients without AF (23), and also patients with paroxysmal AF are at risk of stroke even when in sinus rhythm (24). It has been suggested that chronic atrial injury may lead to increased thrombogenicity of the atria and atrial fibrosis could be a sign of this pathophysiology (25). Our study seems to support the possibility that mechanisms other than AF-induced thrombus from the left atrium could cause the increased risk, as advanced IAB was associated with stroke or TIA without prevalent and incident AF. It is important to identify diagnostic markers of thrombogenic atria, such as IAB, and target therapies to patients with increased risk of cardioembolic stroke. Some authors have proposed anticoagulation therapy in the elderly with high risk of advanced IAB and AF even before a clinical diagnosis of AF (13). Propensity score matching and randomized controlled trials could help to support this hypothesis.

IAB and CHD

Surprisingly in this study, only partial, but not advanced IAB, seemed to associate with incident CHD before accounting for multiple testing in the analyses. It should be pointed out that subjects with advanced IAB more often had CHD or a history of myocardial infarction at baseline, and the proportion of diagnosed CHD increased with the severity of IAB. Alexander et al. (26) found that among patients, who underwent coronary angiography and carotid ultrasonography, the existence of either partial or advanced IAB was associated with more severe CHD and greater carotid intima-media thickness. Álvarez-García et al. (27) demonstrated that patients, who had occlusion of the atrial branches during percutaneous coronary intervention, had three times greater incidence of new-onset IAB and they had also a greater post-procedure increase in P-wave duration than in those without occlusion. In addition, the rate of incident intra-atrial conduction delay was much higher in patients with atrial branch occlusion. According to Apiyasawat et al. (11) IAB appeared more often in patients with CHD during an exercise stress test. Additionally, including IAB to the results of the exercise test improved sensitivity to detect CHD. A previous study of Alexander et al. found an

association between diffuse coronary atherosclerosis and IAB (12) and the authors stated that their findings support the concept that IAB may be the result of persistent atrial ischemia.

The present study is the first to report a possible association between IAB and incident CHD. Due to the number of hypotheses tested, this finding could be a false positive or due to the fact that IAB shares risk factors with CHD, including HTA, diabetes and hypercholesterolemia (28). It is also possible that undiagnosed cases of CHD could have influenced the results despite the wide definition of CHD in our study. However, more studies are needed to replicate this finding.

Mortality

We did not find an association between IAB and all-cause mortality in our population study. In a population study of Magnani et al. (9) prolonged P-wave duration was independently associated with cardiovascular mortality. The association with all-cause mortality was not significant when individuals with known cardiovascular disease were excluded. In the Copenhagen ECG study (5), advanced IAB with two or three biphasic inferior leads was associated with increased all-cause mortality. It is possible that our study population was too small to detect the effect on all-cause mortality.

Dementia

Atrial fibrillation is independently associated with increased risk of dementia (29), but data of the association between IAB and dementia is limited. Martínes-Sellés et al. (10) found that dementia was more frequent among centenarians with IAB compared to individuals with normal P waves, and the association was stronger among participants with advanced than for those with partial IAB. We found no association between IAB and incident dementia. Our analysis included dementia diagnoses in general. In order to study further the association between IAB and incident dementia, restricting analysis only to dementia with signs of vascular changes could give us more information.

Definition of interatrial block

Investigators have used different methods to define biphasic P waves. We decided to use computer-based measurements. Manual analysis of the P-wave morphology may be difficult because of small P-wave amplitudes, wandering baseline and disturbing artifacts. It may also be difficult to get a reliable picture of the end of the P wave because of frequent changes of the PR level. Automatic measurements may help to correct for these factors and the repeatability of automated measurements is excellent. Nonetheless manual ECG measurements may give comparable results, if performed after tracing vertical lines to define the interval between the earliest and the latest detection of atrial depolarization in the frontal leads. After tracing these two vertical lines, the measurement should preferably be performed with calipers or method calculators (2). Regarding P-wave duration, 120 ms is the established cut-off for IAB (3), although earlier studies also used 110 ms.

There are no established diagnostic criteria for the amplitudes of the initial and terminal parts of biphasic P waves. We chose a cut-off of 20 µV, because changes below this magnitude were not recognized in a reproducible manner on enlarged conventional ECG recordings (30). In our study in the group with amplitudes below 20 µV (minor-aIAB group), the baseline characteristics were quite similar to those with advanced IAB, but HRs for different endpoints were more comparable with the partial IAB group than the advanced IAB group. Thereby, it seems that the amplitude of the biphasic aspects of the P waves matter. As we found only 18 subjects fulfilling these criteria, it is difficult to draw firm conclusions.

There are only few studies investigating P-wave morphology independently of P-wave duration. Holmqvist et al. found that P-wave morphology was an independent risk factor for FA and non-sudden cardiac death in patients with congestive heart failure and a history of myocardial infarction (31). However, the P-wave duration in their study population was quite long (unfiltered 145 ± 19 ms). We studied participants with two or three inferior biphasic leads and P-wave duration < 120 ms as a separate group, but we did not notice any significant increase in HRs compared to normal P waves. In young patients with high atrial septal aneurysm or septal defect, the electrical stimulus may not be able to cross the upper part of the septum but may depolarize the left atrium with

caudo-cranial activation. In these cases, a biphasic morphology may be seen in the inferior leads but the P-wave duration is less than 120 ms (2).

Interestingly, in our study prolonged P-wave duration with one biphasic inferior lead (1 BIF) was not associated with AF and CHD, while prolonged P-wave duration without biphasic morphology (partial IAB) was. In the much larger population reported by Skov et al., IAB with only one biphasic inferior lead was associated with AF and stroke (5). It should be pointed out that the presence of a biphasic P wave only in lead III is a normal finding (2). The negative hemifield of lead III starts at +30°, which does not represent caudo-cranial activation of the left atrium. The caudocranial activation occurs when the final part of the biphasic P wave falls in the negative hemifield of aVF. The criteria for advanced IAB used in different studies present slight differences, however in all of them aVF presents final negativity as an expression of caudo-cranial activation of the LA, which is the hallmark of the diagnosis of advanced IAB. It is possible that lead specific analysis would have revealed differences in prognosis between different leads (32).

An atypical pattern of advanced IAB has also been described by Bayés de Luna et al. (32). The criterion includes cases of P-wave duration ≥ 120 ms with three different morphologies in inferior P waves. In type 1 and 2, there is a biphasic P wave in leads III and aVF and in lead II an isodiphasic (type 1) or biphasic (type 2) final component of the otherwise positive P wave. Type 3 presents biphasic P wave in lead II and is isodiphasic with final negativity in III and aVF. In our study atypical patterns type 1 and 2 were included in the definition of advanced IAB.

Study limitations and strengths

This study was a follow-up study of a large population cohort consisting of individuals aged 30+ with predominant white ethnicity. Our study results may not apply to populations of other ethnicities. Only the baseline ECG was used for analysis, but on the other hand, this represents the clinical situation, where therapeutic decisions have to be made. The long follow-up time up to 15 years resulted in a relatively high number of events. Data of prevalent and incident AF were mainly collected from national registers, but it is possible that some AF paroxysms diagnosed in primary care were not included in our analysis. It is also possible that subclinical paroxysmal AF in the study

population may have influenced the results, which was not possible to control for. Also lack of echocardiographic data about the size of atria could be considered as a limitation of the study.

The results of the present study are based on an exploratory analysis with multiple comparisons made between the exposure and outcome variables. However, given the *a priori* information of the possibly significant association between IAB with AF and cerebrovascular events, it is unlikely our observations are false positives. Supporting this, even after considering a stringent Bonferroni correction for twenty-five independent associations that were tested, the main results would be statistically significant ($p<0.05$).

Conclusions

IAB is a relatively common ECG finding in the general population. We were able to strengthen the results of previous studies showing that IAB is a risk factor for AF in the general population. In addition, advanced IAB proved to be a stronger risk marker than partial IAB. Advanced IAB was associated with increased risk of stroke or TIA independently of associated AF or other cardiovascular risk factors. In contrast, partial IAB did not increase the risk of stroke or TIA.

Finally, our study highlights the importance of the definition of advanced IAB: two (but not one) inferior biphasic leads increased the risk of AF and stroke or TIA, outcome was dependent on the cut-off values of the amplitude of the P-wave deflections and on P-wave duration.

Acknowledgements

We thank the investigators, staff and participants of the Health 2000 survey. A. S. Havulinna, V. Salomaa and the National Institute of Health and Welfare for their work on coding endpoints.

Disclosure of interest

The authors report no conflicts of interest.

Source of funding

This work was supported by the Doctoral Programme in Medicine and Life Sciences, Faculty of Medicine and Health Technology, Tampere University; the Finnish Medical Foundation; grants from Finska Läkaresällskapet; The Academy of Finland (grant 322098); Competitive State Research Financing of the Expert Responsibility area of Tampere; Finnish Foundation for Cardiovascular Research; Tampere Tuberculosis Foundation; EU Horizon 2020 (grant 755320 for TAXINOMISIS); Tampere University Hospital Supporting Foundation; and Emil Aaltonen's Foundation.

Word count: 5468

References

1. Bayés de Luna AJ. [Block at the auricular level]. Rev Esp Cardiol. 1979;32(1):5–10.
2. Bayés de Luna A, Baranchuk A, Alberto Escobar Robledo L, Massó van Roessel A, Martínez-Sellés M. Diagnosis of interatrial block. J Geriatr Cardiol JGC. 2017 Mar;14(3):161–5. https://dx.doi.org/10.11909%2Fj.issn.1671-5411.2017.03.007.
3. Bayés de Luna A, Platonov P, Cosio FG, Cygankiewicz I, Pastore C, Baranowski R, et al. Interatrial blocks. A separate entity from left atrial enlargement: a consensus report. J Electrocardiol. 2012 Sep;45(5):445–51. https://doi.org/10.1016/j.jelectrocard.2012.06.029.
4. O'Neal WT, Zhang Z-M, Loehr LR, Chen LY, Alonso A, Soliman EZ. Electrocardiographic Advanced Interatrial Block and Atrial Fibrillation Risk in the General Population. Am J Cardiol. 2016 Jun;117(11):1755–9. https://doi.org/10.1016/j.amjcard.2016.03.013.
5. Skov MW, Ghouse J, Kühl JT, Platonov PG, Graff C, Fuchs A, et al. Risk Prediction of Atrial Fibrillation Based on Electrocardiographic Interatrial Block. J Am Heart Assoc. 2018 Jun 1;7(11):e008247. https://doi.org/10.1161/jaha.117.008247.
6. Lehtonen AO, Langén VL, Puukka PJ, Kähönen M, Nieminen MS, Jula AM, et al. Incidence rates, correlates, and prognosis of electrocardiographic P-wave abnormalities – a nationwide population-based study. J Electrocardiol. 2017 Nov 1;50(6):925–32. https://doi.org/10.1016/j.jelectrocard.2017.07.004.
7. Bacharova L, Wagner GS. The time for naming the Interatrial Block Syndrome: Bayes Syndrome. J Electrocardiol. 2015 Mar;48(2):133–4. https://doi.org/10.1016/j.jelectrocard.2014.12.022.
8. O'Neal WT, Kamel H, Zhang Z-M, Chen LY, Alonso A, Soliman EZ. Advanced interatrial block and

ischemic stroke: The Atherosclerosis Risk in Communities Study. Neurology. 2016 Jul 26;87(4):352–6. https://doi.org/10.1212/wnl.0000000000002888.
9. Magnani JW, Gorodeski EZ, Johnson VM, Sullivan LM, Hamburg NM, Benjamin EJ, et al. P wave duration is associated with cardiovascular and all-cause mortality outcomes: the National Health and Nutrition Examination Survey. Heart Rhythm. 2011 Jan;8(1):93–100. https://doi.org/10.1016/j.hrthm.2010.09.020.
10. Martínez-Sellés M, Massó-van Roessel A, Álvarez-García J, García de la Villa B, Cruz-Jentoft AJ, Vidán MT, et al. Interatrial block and atrial arrhythmias in centenarians: Prevalence, associations, and clinical implications. Heart Rhythm. 2016 Mar;13(3):645–51. https://doi.org/10.1016/j.hrthm.2015.10.034.
11. Apiyasawat S, Thomas AJ, Spodick DH. Interatrial block during exercise tolerance tests as an additional parameter for the diagnosis of ischemic heart disease. J Electrocardiol. 2005 Oct;38(4):150–3. https://doi.org/10.1016/j.jelectrocard.2005.06.027.
12. Alexander B, MacHaalany J, Lam B, van Rooy H, Haseeb S, Kuchtaruk A, et al. Comparison of the Extent of Coronary Artery Disease in Patients With Versus Without Interatrial Block and Implications for New-Onset Atrial Fibrillation. Am J Cardiol. 2017 Apr 15;119(8):1162–5. https://doi.org/10.1016/j.amjcard.2016.12.032.
13. Bayes de Luna A, Martinez-Selles M, Bayes-Genis A, Elosua R, Baranchuk A. Surface ECG interatrial block-guided treatment for stroke prevention: rationale for an attractive hypothesis. BMC Cardiovasc Disord. 2017;17(1):211. https://doi.org/10.1186/s12872-017-0650-y.
14. Heistaro S (ed.). Methodology report: Health 2000 survey. Publications of the National Public Health Institute B26/2008. http://urn.fi/URN:NBN:fi-fe201204193320
15. Prineas RJ, Crow RS, Blackburn HW. The Minnesota Code Manual of Electrocardiographic Findings. June, 1982. Littleton, MA: John Wright-PSG, Inc.
16. Sund R. Quality of the Finnish Hospital Discharge Register: A systematic review. Scand J Public Health. 2012 Aug 1;40(6):505–15. https://doi.org/10.1177/1403494812456637.
17. World Health Organization, International Diabetes Federation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation [Internet]. 2006 [cited 2019 Apr 16]. Available from: http://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/
18. Ariyarajah V, Puri P, Kranis M, Wilner DA, Spodick DH. Prevalence of interatrial block in the Program of All-Inclusive Care for the Elderly (PACE). Am J Geriatr Cardiol. 2006 Jun;15(3):174–7. https://doi.org/10.1111/j.1076-7460.2006.04518.x.
19. Baranchuk A, Alexander B, Cinier G, Martinez-Selles M, Tekkesin AI, Elousa R, et al. Bayés' syndrome: Time to consider early anticoagulation? North Clin Istanb. 2018 May 23;5(4):370–8. https://doi.org/10.14744/nci.2017.60251.
20. Massó-van Roessel A, Escobar-Robledo LA, Dégano IR, Grau M, Sala J, Ramos R, et al. Analysis of the Association Between Electrocardiographic P-wave Characteristics and Atrial Fibrillation in the REGICOR Study. Rev Esp Cardiol Engl Ed. 2017 Oct 1;70(10):841–7. https://doi.org/10.1016/j.rec.2017.02.019.
21. Ariyarajah V, Spodick DH. Progression of partial to advanced interatrial block. J Electrocardiol. 2006 Apr;39(2):177–9. https://doi.org/10.1016/j.jelectrocard.2005.08.016.
22. Ariyarajah V, Kranis M, Apiyasawat S, Spodick DH. Potential factors that affect electrocardiographic progression of interatrial block. Ann Noninvasive Electrocardiol. 2007 Jan;12(1):21–6. https://doi.org/10.1111/j.1542-474X.2007.00134.x.
23. Jahangir A, Lee V, Friedman PA, Trusty JM, Hodge DO, Kopecky SL, et al. Long-Term Progression and Outcomes With Aging in Patients With Lone Atrial Fibrillation: A 30-Year Follow-

Up Study. Circulation. 2007 Jun 19;115(24):3050–6.
https://doi.org/10.1161/CIRCULATIONAHA.106.644484.
24. Disertori M, Franzosi MG, Barlera S, Cosmi F, Quintarelli S, Favero C, et al. Thromboembolic event rate in paroxysmal and persistent atrial fibrillation: Data from the GISSI-AF trial. BMC Cardiovasc Disord. 2013 Apr 15;13:28. https://doi.org/10.1186/1471-2261-13-28.
25. Hirsh BJ, Copeland-Halperin RS, Halperin JL. Fibrotic Atrial Cardiomyopathy, Atrial Fibrillation, and Thromboembolism: Mechanistic Links and Clinical Inferences. J Am Coll Cardiol. 2015 May 26;65(20):2239–51. https://doi.org/10.1016/j.jacc.2015.03.557.
26. Alexander B, Baranchuk A, Haseeb S, van Rooy H, Kuchtaruk A, Hopman W, et al. Interatrial block predicts atrial fibrillation in patients with carotid and coronary artery disease. J Thorac Dis. 2018 Jul;10(7):4328–34. https://doi.org/10.21037/jtd.2018.06.53.
27. Álvarez-García Jesús, Vives-Borrás Miquel, Gomis Pedro, Ordoñez-Llanos Jordi, Ferrero-Gregori Andreu, Serra-Peñaranda Antoni, et al. Electrophysiological Effects of Selective Atrial Coronary Artery Occlusion in Humans. Circulation. 2016 Jun 7;133(23):2235–42.
https://doi.org/10.1161/CIRCULATIONAHA.116.021700.
28. Ariyarajah V, Apiyasawat S, Moorthi R, Spodick DH. Potential Clinical Correlates and Risk Factors for Interatrial Block. Cardiology. 2006;105(4):213–8. https://doi.org/10.1159/000091642.
29. Santangeli P, Di Biase L, Bai R, Mohanty S, Pump A, Cereceda Brantes M, et al. Atrial fibrillation and the risk of incident dementia: A meta-analysis. Heart Rhythm. 2012 Nov;9(11):1761-1768.e2.
https://doi.org/10.1016/j.hrthm.2012.07.026.
30. Recommendations for measurement standards in quantitative electrocardiography. The CSE Working Party. Eur Heart J. 1985 Oct;6(10):815–25.
31. Holmqvist F, Platonov PG, McNitt S, Polonsky S, Carlson J, Zareba W, et al. Abnormal P-Wave Morphology Is a Predictor of Atrial Fibrillation Development and Cardiac Death in MADIT II Patients. Ann Noninvasive Electrocardiol. 2010;15(1):63–72. https://doi.org/10.1111/j.1542-474X.2009.00341.x.
32. Bayés de Luna A, Escobar-Robledo LA, Aristizabal D, Weir Restrepo D, Mendieta G, Massó van Roessel A, et al. Atypical advanced interatrial blocks: Definition and electrocardiographic recognition. J Electrocardiol. 2018 Nov;51(6):1091–3.
https://doi.org/10.1016/j.jelectrocard.2018.09.004.

PUBLICATION II

Long-term prognostic significance of the ST level and ST slope in the 12-lead ECG in the general population

Istolahti Tiia, Nieminen Tuomo, Huhtala Heini, Lyytikäinen Leo-Pekka, Kähönen Mika, Lehtimäki Terho, Eskola Markku, Anttila Ismo, Jula Antti, Rissanen Harri, Nikus Kjell, Hernesniemi Jussi

Journal of Electrocardiology, 58, 176-183
DOI: 10.1016/j.jelectrocard.2019.12.010

Journal of Electrocardiology 58 (2020) 176–183

Contents lists available at ScienceDirect

Journal of Electrocardiology

journal homepage: www.jecgonline.com

Long-term prognostic significance of the ST level and ST slope in the 12-lead ECG in the general population

Tiia Istolahti [a,b,*], Tuomo Nieminen [c], Heini Huhtala [d], Leo-Pekka Lyytikäinen [a,e,f], Mika Kähönen [a,g], Terho Lehtimäki [a,f], Markku Eskola [a,e], Ismo Anttila [h], Antti Jula [i], Harri Rissanen [i], Kjell Nikus [a,e], Jussi Hernesniemi [a,e]

[a] Faculty of Medicine and Health Technology, Tampere University, and Finnish Cardiovascular Research Center, Tampere, Finland
[b] Department of Internal Medicine, Vaasa Central Hospital, Vaasa, Finland
[c] Department of Internal Medicine, Päijät-Häme Central Hospital, Lahti, Finland
[d] Faculty of Social Sciences, Tampere University, Tampere, Finland
[e] Heart Center, Department of Cardiology, Tampere University Hospital, Tampere, Finland
[f] Department of Clinical Chemistry, Fimlab Laboratories, Tampere, Finland
[g] Department of Clinical Physiology, Tampere University Hospital, Tampere, Finland
[h] Department of Emergency Services, Seinäjoki Central Hospital, Seinäjoki, Finland
[i] National Institute for Health and Welfare, Helsinki, Finland

ARTICLE INFO

Keywords:
ST level
ST slope
Population study
Outcome
ECG

ABSTRACT

Background: Even minor ST depression in the electrocardiogram (ECG) is associated with cardiovascular disease and increased mortality. There is limited data on the prognostic significance of ST-level changes in the general population.

Subjects and methods: A random sample of Finnish subjects (n = 6354) aged over 30 years (56.1% women) underwent a health examination including a 12-lead ECG in the Health 2000 survey. The effects of relative ST level as a continuous variable and ST slope (upsloping, horizontal, downsloping) in three different lead groups were analyzed using a multi-adjusted Cox proportional hazard model separately for men and women with total mortality as endpoint.

Results: The follow-up lasted for 13.7 (SD 3.3) years for men and 13.9 (SD 3.1) years for women. Lower lateral ST levels were associated with all-cause mortality in multi-adjusted models in both genders (at J + 80 ms hazard ratio [HR] 0.64 for a change of 1.0 mm [95% confidence interval 0.49–0.84, p = 0.002] for men and HR 0.61 [0.48–0.78, p < 0.001] for women). Associated coronary heart disease had no major influence on the results. Exclusion of subjects with ECG signs of left ventricular hypertrophy from the analyses increased the mortality risk of lower lateral ST levels in men but decreased it in women. For the anterior and inferior lead groups, no statistically significant difference was seen after multivariate adjustment. ST slope was not an independent predictor of mortality after multivariate adjustment.

Conclusion: Lower ST level in the lateral ECG leads is an independent prognostic factor to predict all-cause mortality in the general population.

Introduction

Abnormalities in the electrocardiographic (ECG) ST level reflect abnormalities in ventricular repolarization. In earlier population studies, major ST depression has been associated with worse outcome and risk for cardiovascular disease [1–3], and also minor ST changes had an adverse effect on prognosis [4–7]. In most of the studies, outcome was determined by the magnitude of these ECG changes [4]. Some studies even suggested that ST depression was associated cardiovascular death in a "dose-response" manner [8]. However, there are only few studies examining the ST level as a continuous instead of a categorical variable.

A downsloping ST segment, especially in exercise testing, is considered typical for coronary artery disease [9]. Also, a downward sloping ST segment together with T-wave inversion in the lateral leads, the "strain pattern", is a marker of anatomical left ventricular hypertrophy (LVH) and is associated with increased left ventricular mass and mortality [10]. There is very limited data on the prognostic value of ST slope as

* Corresponding author at: Department of Internal Medicine, Vaasa Central Hospital, Hietalahdenkatu 2-4, 65100 Vaasa, Finland.
E-mail address: tiia.istolahti@tuni.fi (T. Istolahti).

https://doi.org/10.1016/j.jelectrocard.2019.12.010
0022-0736/

a separate ECG parameter (independently of the ST level), especially in the general population.

The prognostic value of ST changes is dependent of the location of the changes within the 12-lead ECG [8,11]. Nevertheless, many authors did not specify the location of ST changes in their analyses. Gender differences in cardiovascular diseases have received attention in preventive cardiology. Previously most of the studies dealing with ST changes included more men than women. Lately, some studies have also focused on women, and it seems that the prognostic significance of these ECG changes is similar in both genders, especially when it comes to minor changes [3,4,12,13].

The aim of this study was to establish the prognostic role of the level of the ST segment and of the ST slope, separately in three different anatomical lead groups, in both men and women in the general population.

Materials and methods

Study population

The study is based on the Health 2000 survey, which was carried out in 2000–2001. The study design has been described more in detail previously [14]. The population-based nationwide study consisted of 8028 individuals aged over 30 years, of whom 79% (6354 individuals) participated in the health examination, which included a structured examination by a physician, series of laboratory tests and an ECG recording. The study was designed to cover a nationally representative population sample of the Finnish population. Individuals aged 80+ were oversampled using double inclusion probabilities. Ethical approval for the Health 2000 study was obtained from the Ethical Committee for Research in Epidemiology and Public Health at the Hospital District of Helsinki and Uusimaa (HUS).

ECG registration, definitions and analysis

During the health examination, a standard 12-lead resting ECG in supine position was recorded from each subject with Marquette Hellige MAC 5000 electrocardiographs (Freiburg, Germany and Milwaukee, WI, USA). ECGs were stored electronically and printed at a paper speed of 50 mm/s. The low-pass filter was set at 150 Hz. If the participant had significant muscular tremors that interfered with the recording, the filter was set at 40 Hz. High-pass filter 0.16 Hz was used. The Marquette 12SL program can use high-pass filter at 0.32 Hz without inducing artifacts to the ST level measurements. The ECG data were sent for further analysis to the Social Insurance Institution's research center in Turku, where ECGs were analyzed with Magellan software (Marquette Electronics Inc., Milwaukee, WI, USA). ST levels and durations and amplitudes of different waves of every single 12-lead ECG were measured. The Marquette 12SL algorithm uses median complexes of the 10-s ECG tracing and uses the onset of QRS as an isoelectric line. The Minnesota coding was performed at the Institute of Cardiology, Kaunas Medical Academy, Lithuania, by two investigators blinded to the clinical data. The repeatability of the Minnesota Code was checked by repeat analysis of 200 ECGs.

The following three lead groups were used in the present study: anterior (leads V1-V4), lateral (aVL, I, V5-V6) and inferior (II, aVF, III). In addition, lead V5 was included as a single lead. ST levels were measured at the J point and 80 ms after the J point (J + 80 ms). The lead with the lowest ST level in a particular lead group was used for analysis. An additional parameter "$J_{at}J$ + 80 ms" was also created, and it was defined as the lower ST level of the J point and J + 80 ms measurement points. ST slope was defined as the difference between the ST level at the J + 80 ms and J point in a single lead. If the absolute value of difference between the measurement point at J + 80 ms and the J point was ≤0.5 mm, the ST segment was classified as horizontal. If the measurement point J + 80 ms was >0.5 mm higher than the J point, the ST slope was labeled as positive (upsloping ST segment). Finally, if the measurement point J + 80 ms was >0.5 mm lower than the J point, the ST slope was classified as negative (downsloping ST segment). The lead with the lowest single measurement at J point or J + 80 ms was selected to represent the lead group. Fig. 1 shows an example of a downsloping ST segment, and also the measurement points: the J point and J + 80 ms.

Follow-up

The data for mortality and follow-up until the end of the year 2015 were gathered from the Causes of Death register maintained by Statistics Finland. It contains 100% of deaths of Finnish citizens in Finland and almost 100% abroad. Databases were linked using a personal identity code. The endpoint of this study was mortality from any cause and the follow-up time was the time between entering the study and time of death or the end of follow up at the end of 2015.

Medication

Information about the prescribed baseline medication was gathered by checking the study participants' personal health insurance cards for rights of drug reimbursements and interviewing the study participants about prescription and non-prescription medicines. The names of the medications were checked from prescriptions or packages. Also, data from a separate registry (Statistics on reimbursements for prescription medicines: The Social Insurance Institution of Finland) was included in the definition of coronary heart disease (CHD).

Definitions of CHD, myocardial infarction, LVH and chronic obstructive pulmonary disease

Trained study personnel performed the health interview, and they followed a structural detailed written instruction to gather information about pre-existent diseases. Examining physicians performed another structured interview and physical examination. Information on CHD was obtained from the Care Register for Health Care maintained by National Institute for Health and Welfare, which contains data of all

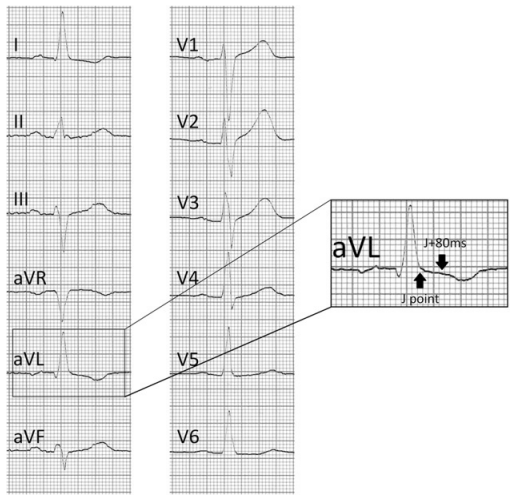

Fig. 1. An ECG example of a 59-year-old male participant who died during the follow-up. The ST segment in lead aVL is downsloping. Compared with the reference line, the level of the J point is −0.15 mm, while the level at the measurement point J + 80 ms is −0.75 mm. The lowest J point in the lateral leads is in V5 (−0.40 mm). The ECG was recorded at 50 mm/s and 10 mm/mV.

inpatient episodes in Finland at the individual level. The accuracy of the registers has been validated previously [15,16].

Classification of CHD required at least one of the following: diagnosed angina pectoris, myocardial infarction, percutaneous coronary intervention (PCI) or bypass surgery by examining physician, diagnosed PCI or bypass surgery in the health interview, ICD-codes 410-414 (ICD8/9) or I20-I25 (ICD10) in the Care Register for Health Care before the reference date of the study, or the right for drug reimbursements for CHD. Classification of myocardial infarction required either a diagnosis of a history of a myocardial infarction by the examining physician, large Q waves in the resting ECG or a history of myocardial infarction in the Care Register for Health Care, ICD-codes 410 (ICD8/9) or I21-I22 (ICD10). LVH was defined by Minnesota code criteria 3-1, 3-3 or 3-4 [17]. For the diagnosis of chronic obstructive pulmonary disease (COPD), information gathered during the health interview was used.

Other measurements and definitions

Height, weight and waist circumference were measured and body mass index (BMI) was calculated. Blood pressure was measured from the right arm with a standard mercury manometer (Mercuro 300; Speidel & Keller, Jungingen, Germany). An average of two measurements was used, of which the first was measured after rest for at least 5 min in sitting position. Hypertension (arterial hypertension, HTA) was defined as a blood pressure ≥ 140/90 at the baseline.

Serum total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglyceride and plasma glucose concentrations were determined enzymatically from venous blood samples with a clinical chemistry analyzer (Olympus, AU400, Hamburg, Germany). The diagnosis of diabetes mellitus (DM) at baseline was determined as fasting serum glucose (fS-Gluc) ≥ 7 or a history of use of oral glucose lowering agents or insulin injections [18].

Exclusion criteria

We excluded subjects with missing ECG data (n = 55). Of those, the recording was unsuccessful in 36 participants with entries such as “difficult to move,” “wheelchair”, “denial”, “leg/hand amputated”, “in geriatric chair”, “massive hernia”, “plaster in leg/hand”. In the further process, 19 ECGs were lost (diskette lost 9, coupling error 4, data reading failure 5, unspecific reason 1). We also excluded subjects with either large Q/QS waves in the ECG using Minnesota codes 1-1, 1-2 and 1-3 (n = 127), left or right bundle branch block or left anterior hemiblock (Minnesota code 7, n = 565), Wolf-Parkinson-White pattern (Minnesota code 6-4, n = 1) or paced rhythm (Minnesota code 6-8, n = 4) from the analysis. Thereby, the final study population consisted of 5613 subjects, of which 2462 were males and 3151 females.

Statistical analysis

All analyses were done separately for men and women. Comparisons in variables were calculated with either *t*-test, Mann-Whitney U or Chi-square tests as appropriate. ST levels were treated as continuous variables. The normality of the distribution of ST-segment levels was estimated with Q-Q plots and histograms. The linearity of the association of ST level and mortality was checked in a spline model. After visual inspection the association did not significantly differ from linear. Hence, we did not test the linearity in other ways. Cox proportional hazard models were constructed separately for minimum ST levels and ST slopes in every lead group and at all measurement points. Total mortality was used as the endpoint. Regarding ST slope, the three previously mentioned categories (upsloping, horizontal, downsloping) were used and the upsloping ST segment was used as reference. For ST levels, hazard ratios (HR) were scaled for a change of 1.0 mm. The following parameters were used for multivariate adjusting: age, BMI, HDL, LDL, HTA, DM and CHD. Another model was also constructed, where known CHD was excluded from the multivariate adjustment. The linearity analyses were done using R and all other analyses were performed with SPSS 25. Statistical significance was based on $p < 0.05$.

Results

Table 1 shows the baseline characteristics and medication of the study population. Compared with survivors, the non-survivors were older and more often had co-morbidities. There was higher proportion of subjects with ECG-LVH in the female non-survivor group compared to the survivor group, while there was no statistically significant difference in male subjects in a similar comparison. The use of all studied medication groups was clearly more frequent among non-survivors than among survivors. Table 2 shows the mean ST levels and the type of ST slope in the three lead groups and lead V5 separately for women and men and for survivors and non-survivors. Non-survivors had relatively lower ST levels in both men and women in every lead group, and women tended to have slightly lower ST levels than men. The variation of the ST levels was quite low as the maximum standard deviation (SD) was 0.54 mm. Non-survivors also had a higher proportion of negative ST slopes, especially in women. However, negative ST slope was a quite rare finding with a prevalence of 0.1% to 5.4% in the population in the different lead groups.

The mean follow-up time was 13.7 years (SD 3.3 years) for men and 13.9 years for women (SD 3.1 years). Of the male subjects, 487 (19.8%) died during follow-up compared to 555 (17.6%) women.

ST level and outcome

Lower ST levels were associated with worse outcome in every lead group at all measurement points and in both genders. Adverse outcome was most evident in the lateral lead group at J + 80 ms with a HR of 0.13 (95% confidence interval [CI] 0.11–0.15, $p < 0.001$) in women and HR 0.21 (CI 0.17–0.25, $p < 0.001$) in men for a change of 1.0 mm. Fig. 2 shows the linearity of the unadjusted association of lateral ST levels and mortality at the measurement point $J_{alt}J + 80$ ms. After adjustment for age, the increase in risk of lower ST levels was diminished in the inferior leads, and also for the anterior leads in men. Lower ST level in the lateral leads at all measurement points in both genders retained its statistical significance for increased mortality after adjusting with age. This was also the case in women at the measurement point J + 80 ms and for $J_{alt}J + 80$ ms in the anterior leads and V5. For all the other measurement points and lead groups, the statistical significance was lost after adjustment for age. After multivariate adjustment, lower ST levels were associated with higher mortality rates in the lateral leads in both genders at all measurement points and in V5 at $J_{alt}J + 80$ ms in men. At all the other measurement points and lead groups, the statistical significance was lost after multivariate adjustment. The multi-adjusted hazard ratios are shown in Table 3.

Significance of ECG-LVH and associated CHD

In multi-adjusted analysis, after the exclusion of the subjects with ECG-LVH, the mortality risk of lower ST levels in the lateral leads increased in men. The same was true for V5 both at the J point and $J_{alt}J + 80$ ms: HR 0.69 (CI 0.51–0.92, $p = 0.011$) and HR 0.70 (CI 0.52–0.94, $p = 0.019$), respectively. However, the effect of excluding ECG-LVH patients was opposite in women, where only the measurement point J + 80 ms retained its statistical significance in the lateral leads. Fig. 3 shows the HRs in the multi-adjusted model in lateral leads separately for men and women after exclusion of subjects with ECG-LVH. On the other hand, excluding subjects with CHD from multivariate adjustment had no clear influence on the results: lower lateral ST levels remained a significant risk factor in both genders (Fig. 3). There was one exception: in lead V5 in women, ST level at J + 80 ms proved to be associated with worse outcome (HR 0.81 [CI 0.67–0.98,

Table 1
Baseline characteristics of the Health 2000 Survey participants.

Variable	Men					Women				
	Survivors		Non-survivors		p value	Survivors		Non-survivors		p value
	Mean/Median/N	SD/Q_1-Q_3/(%)	Mean/Median/N	SD/Q_1-Q_3/(%)		Mean/Median/N	SD/Q_1-Q_3/(%)	Mean/Median/N	SD/Q_1-Q_3/(%)	
N	1975	(80.2%)	487	(19.8%)		2596	(82.4%)	555	(17.6%)	
Age	47.2	10.9	64.4	13.5	<0.001	48.7	12.0	72.6	12.2	<0.001
BMI (kg/m^2)	27.1	4.0	27.1	4.5	0.773	26.5	5.0	28.0	5.0	<0.001
Waist circumference (cm)	97.3	11.1	99.3	12.3	0.002	87.3	13.1	93.2	12.6	<0.001
Heart rate/min	61.7	10.7	65.7	12.9	<0.001	63.6	10.2	66.9	11.8	<0.001
Regular smoking	533	(27.1%)	150	(30.9%)	0.092	472	(18.3%)	59	(10.7%)	<0.001
COPD	18	(0.9%)	19	(3.9%)	<0.001	19	(0.7%)	18	(3.2%)	<0.001
Hypertension	832	(42.2%)	297	(61.0%)	<0.001	828	(32.0%)	367	(66.5%)	<0.001
Diabetes	103	(5.2%)	69	(14.2%)	<0.001	79	(3.0%)	81	(14.6%)	<0.001
LVH	419	(21.2%)	95	(19.5%)	0.406	201	(7.7%)	105	(18.9%)	<0.001
CHD	76	(3.8%)	95	(19.5%)	<0.001	73	(2.8%)	132	(23.8%)	<0.001
Myocardial infarction	21	(1.1%)	36	(7.4%)	<0.001	11	(0.4%)	30	(5.4%)	<0.001
Total cholesterol (mmol/L)	6.0	1.1	5.9	1.2	0.056	5.8	1.1	6.2	1.2	<0.001
HDL (mmol/L)	1.2	0.3	1.2	0.4	0.543	1.5	0.4	1.3	0.4	<0.001
LDL (mmol/L)	3.9	1.0	3.7	1.1	0.002	3.6	1.0	3.9	1.1	<0.001
Triglycerides (mmol/L)	1.5	1.1–2.2	1.4	1.1–2.0	0.478	1.2	0.9–1.6	1.5	1.1–2.0	<0.001
CRP (mg/L)	0.7	0.33–1.6	1.2	0.4–3.1	<0.001	0.7	0.2–1.9	1.1	0.4–3.1	<0.001
Uric acid (μmol/L)	337.5	69.0	348.9	81.7	0.005	258.2	65.7	310.0	86.3	<0.001
Medication										
Beta-blocker	158	(8.0%)	116	(23.8%)	<0.001	300	(11.6%)	172	(31.0%)	<0.001
CCB	71	(3.6%)	54	(11.1%)	<0.001	109	(4.2%)	87	(15.7%)	<0.001
Digitalis	9	(0.5%)	19	(3.9%)	<0.001	8	(0.3%)	43	(7.7%)	<0.001
ACEI/ARB	124	(6.3%)	72	(14.8%)	<0.001	155	(6.0%)	92	(16.6%)	<0.001

BMI = body mass index, COPD = chronic obstructive pulmonary disease, LVH = left ventricular hypertrophy, CHD = coronary heart disease, HDL = high-density lipoprotein, LDL = low-density lipoprotein, CCB = calcium channel blocker, ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor antagonist, SD = standard deviation, N = number, Q_1-Q_3 = quartiles.

p = 0.033]). Regarding the anterior and inferior lead groups, excluding ECG-LVH subjects or adjustment for associated CHD did not influence the prognostic significance of ST levels (data not shown).

ST slope

A downsloping ST segment in the lateral leads was associated with higher mortality rates in both genders. This was most evident in lead V5 in women; 19 out of 22 female study participants with a downsloping ST segment died during the follow-up (HR 15.09 [CI 9.11–24.99, p < 0.001]). The corresponding HR for men was 3.69 (CI 1.37–9.92, p = 0.010). In women, a negative ST slope was also associated with increased mortality in the anterior leads, while a horizontal ST, compared with upsloping ST, was associated with better outcome when present in the inferior leads (HR 0.44 [CI 0.32–0.62, p < 0.001]) and worse outcome when present in V5 (HR 1.51 [CI 1.19–1.92, p = 0.001]). Also, in men, a horizontal slope in V5 was associated with worse outcome (HR 2.11 [CI 1.76–2.52, p < 0.001]). However, after adjusting for age, a downsloping ST segment did not affect outcome in men in any lead groups. In women, a downsloping or horizontal slope was associated with worse outcome in the lateral leads as did also a descending slope in V5. After multivariate adjustment, ST slope lost its statistical significance to predict mortality in all lead groups in both genders (data not shown). Excluding subjects with ECG-LVH did not have any significant effect on the multivariate adjusted results. However, a downsloping ST segment in the lateral leads proved to be a risk marker for all-cause mortality in women, when CHD was excluded from the multivariate adjustment model (HR 1.70 [CI 1.04–2.78, p = 0.036] compared to HR 1.62 [CI 0.99–2.66, p = 0.056] in multivariate adjusted model with CHD).

Table 2
Mean ST (the lowest of J and J + 80 ms (J_{alt} + 80 ms)) levels and standard deviation (SD) and the percentages of different ST slope groups.

Variable	Men			Women		
	Survivors (N = 1975)	Non-survivors (N = 487)	p value	Survivors (N = 2596)	Non-survivors (N = 555)	p value
ST segment, mean (mm) (SD)						
Anterior	0.01 (0.54)	−0.10 (0.43)	<0.001	−0.13 (0.27)	−0.29 (0.40)	<0.001
Lateral	−0.04 (0.26)	−0.20 (0.32)	<0.001	−0.20 (0.32)	−0.32 (0.38)	<0.001
Inferior	−0.11 (0.34)	−0.16 (0.28)	<0.001	−0.09 (0.24)	−0.16 (0.32)	<0.001
V5	0.20 (0.38)	−0.05 (0.42)	<0.001	0.01 (0.27)	−0.22 (0.43)	<0.001
ST slope, percentages (positive/horizontal/negative)						
Anterior	58.9/40.9/0.2	60.4/40.6/0.2	0.846	44.1/55.8/0.1	46.7/52.6/0.7	0.003
Lateral	21.3/72.2/0.5	19.9/78.4/1.6	0.026	8.9/90.4/0.7	6.8/87.7/5.4	<0.001
Inferior	4.1/93.1/2.8	6.2/92.0/1.8	0.080	3.0/96.0/1.0	7.0/91.0/2.0	<0.001
V5	63.6/36.1/0.3	43.3/55.9/0.8	<0.001	20.7/79.2/0.1	13.9/82.7/3.4	<0.001

N = number, SD = standard deviation.

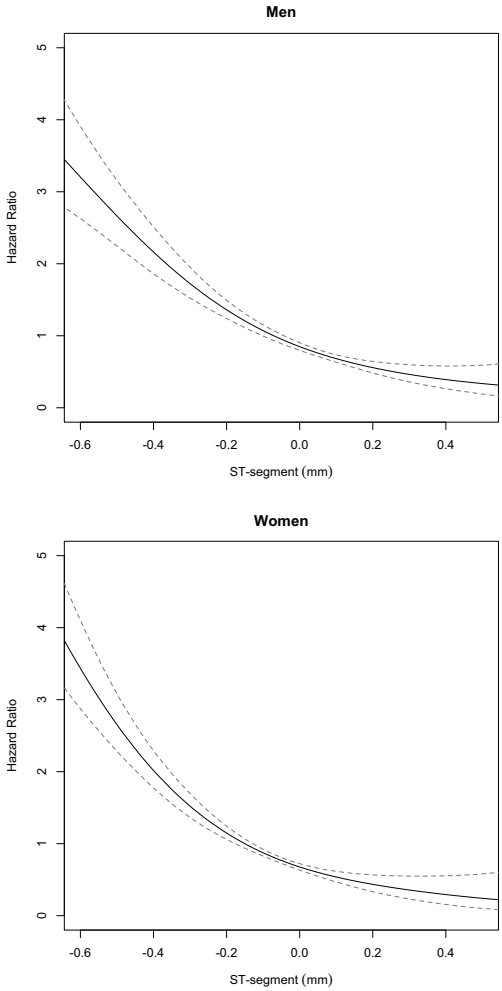

Fig. 2. The unadjusted hazard ratios between ST segment and mortality at measurement point $J_{alt}J + 80$ ms (lower of J point and J + 80 ms) in lateral leads in men and in women among normal ranges of ST-level measurements. The risk for mortality increases along the lower ST levels.

Discussion

Our population study, with a follow-up of nearly 14 years, showed that lower ST level in the lateral ECG leads (I, aVL, V5, V6) as a continuous variable is independently associated with all-cause mortality in both women and men. ST changes in the lateral leads had clearly negative prognostic impact, while anterior or inferior ST level had no prognostic significance after multivariate adjustment. Some previous studies have also reported consistency of prognosis between the genders especially regarding minor, non-specific or "borderline" ST changes in the general population [3,4,12,13]. We found that age has strong impact on the ST level, as was also documented previously [4,5].

All analyses were done separately for men and women because of the previously described gender differences related to the relative ST segment and the T wave in the 12-lead ECG [11]. We also wanted to study gender-specific differences in different lead groups and measurement points. In previous studies, the prevalence of minor ST changes has been greater in women than in men [4]. Also in our study, women had lower mean ST levels than men. In the anterior leads, age seemed to explain the association between lower ST levels and mortality in men, but in women, lower anterior ST levels increased the risk for mortality also after adjusting with age. However, the HRs did not differ significantly between sexes after multivariate adjustment.

Table 3
Mortality of continuous ST levels in different lead groups in men and women, multivariate adjusted[a] Cox regression analysis. Hazard ratios are scaled for a change of 1.0 mm.

	Men		Women	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Anterior				
J point	1.06 (0.85–1.30)	0.621	0.93 (0.72–1.20)	0.557
J + 80 ms	1.11 (0.90–1.36)	0.318	0.85 (0.68–1.05)	0.134
$J_{alt}J$ + 80 ms	1.05 (0.85–1.30)	0.641	0.90 (0.70–1.15)	0.411
Lateral				
J point	0.70 (0.54–0.91)	0.008	0.70 (0.53–0.91)	0.009
J + 80 ms	0.64 (0.49–0.84)	0.002	0.61 (0.48–0.78)	<0.001
$J_{alt}J$ + 80 ms	0.69 (0.53–0.89)	0.005	0.68 (0.54–0.87)	0.002
Inferior				
J point	1.12 (0.85–1.48)	0.433	0.96 (0.72–1.29)	0.781
J + 80 ms	1.09 (0.78–1.52)	0.611	0.93 (0.68–1.26)	0.625
$J_{alt}J$ + 80 ms	1.16 (0.86–1.57)	0.323	0.93 (0.69–1.26)	0.639
V5				
J point	0.80 (0.63–1.01)	0.057	0.85 (0.67–1.08)	0.190
J + 80 ms	0.85 (0.71–1.03)	0.094	0.84 (0.69–1.03)	0.086
$J_{alt}J$ + 80 ms	0.79 (0.63–1.00)	0.046	0.83 (0.67–1.05)	0.116

CI = confidence interval, J + 80 ms = J point + 80 ms, $J_{alt}J$ + 80 ms = lower of J point and J + 80 ms.
[a] Age, body mass index, high-density lipoprotein, low-density lipoprotein, hypertension, diabetes, coronary heart disease.

ECG-LVH produced strikingly different prognostic implications between the genders. In women after excluding subjects with ECG-LVH, only the J + 80 ms measurement point retained its power as a negative prognostic marker for all-cause death after multivariate adjustment. For the male subjects, excluding those with ECG-LVH tended to strengthen the effect of lower lateral ST levels on mortality. Previously, when we studied continuous ST depression and cardiovascular mortality in the same population with shorter follow-up, we found a similar effect of the exclusion of ECG-LVH patients in individuals older than 55 years [11]. The results of our study indicate that the prognostic significance of a lower lateral ST level at the J point in women is, at least to some extent, explained by ECG-LVH. In men, including ECG-LVH into the analyses had an opposite effect, indicating that the adverse prognostic effect of this ECG change is not related to ECG-LVH. We have no definite explanation for this gender difference. In our population, there was a higher proportion of subjects with ECG-LVH in the female non-survivor group compared to the survivor group, while there was no statistically significant difference in men (Table 1). Also, more male than female study participants were excluded from the statistical analyses when studying the effect of ECG-LVH. Considering the large number of study participants, we think that this difference did not have major impact on the results, although this possibility cannot be excluded with certainty. In an earlier population study of Larsen et al. [1], the prevalence of voltage-only ECG-LVH increased with age in women but decreased in men, which could be one possible explanation for the observed gender difference.

Many previous studies have evaluated the significance of ST depression after excluding subjects with known CHD. Interestingly, adjusting for CHD did not have any major influence on our results. The definition of CHD in our study included many alternative (even though relevant) criteria, and the vast majority of subjects with a CHD diagnosis is likely to be covered. Participants with asymptomatic, and thus undiagnosed CHD, could dilute the results. However, it should be kept in mind that the ST level is not normally affected by stable CHD. In a study by Walsh et al., minor ST-segment and T-wave abnormalities were not associated with the presence of coronary artery calcium in participants free of clinical CHD at baseline [19]. Our study results indicate that

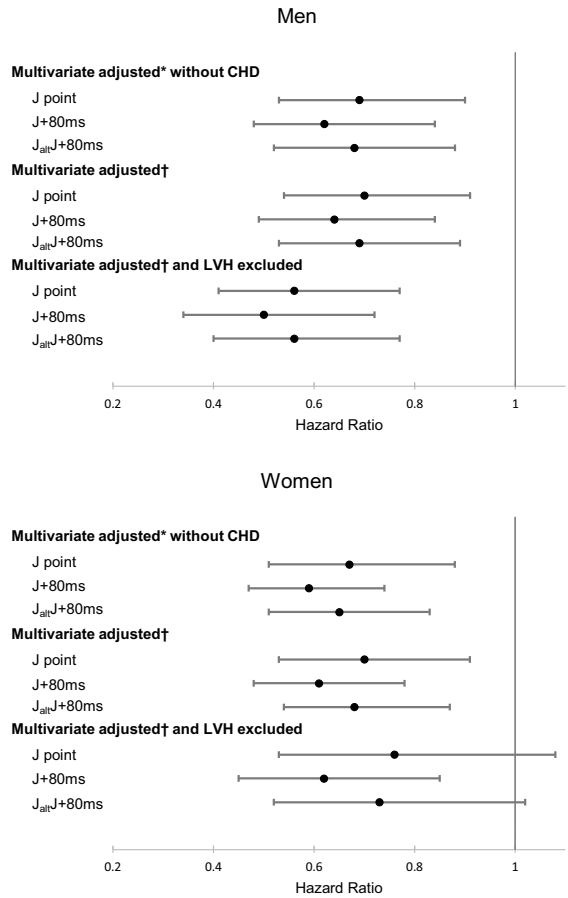

Fig. 3. Hazard ratios of lower lateral ST levels and mortality in different measurement points after multivariate adjustment with† and without* coronary heart disease and after excluding participants with left ventricular hypertrophy. Hazard ratios are scaled for a change of 1.0 mm. CHD = coronary heart disease, LVH = left ventricular hypertrophy, J + 80 ms = J point + 80 ms, J_{alt}J + 80 ms = lower of J point and J + 80 ms. †Age, body mass index, high-density lipoprotein, low-density lipoprotein, hypertension, diabetes, coronary heart disease. *Age, body mass index, high-density lipoprotein, low-density lipoprotein, hypertension, diabetes.

other etiologies may be more important than CHD to explain the prognostic role on changes in the ST level in the lateral ECG leads. In some studies, minor ST segment changes associated with cardiovascular mortality, but not with non-fatal myocardial infarction, indicating that arrhythmias could be one of the causes of the association [20].

Sympathetic activity is known to cause ST depression in healthy subjects, and it is a known risk factor for cardiac death and arrhythmias [21,22]. The use of digoxin, which clearly may affect the ST level and ST slope, was quite rare in this study. In structural heart disease, ECG-LVH often accompanies ST depression. In the present study, the negative prognostic impact of low lateral ST level remained after the exclusion of ECG-LVH in men and also in women at J + 80 ms. Structural heart disease often results in ventricular conduction defects with broad QRS, but this was an exclusion criterion in this study.

The prognostic role of the ST slope

The early repolarization pattern with a horizontal ST segment has been associated with cardiovascular and all-cause mortality, while an elevated J point with upsloping ST segment has not been associated with adverse prognosis in population studies [23,24]. The "strain pattern", ST depression with downsloping ST and T-wave inversion, is a well-recognized marker of anatomical LVH and is associated with larger left ventricular mass and worse outcome in HTA [25,26], and was associated with all-cause mortality, systolic dysfunction, and myocardial scar in multiethnic participants of a population study [10]. To our knowledge, the role of the ST-segment morphology independently of the level of the ST segment has not been established before.

We found that a downsloping ST segment was associated with increased all-cause mortality in the lateral leads (and V5) in both genders and in the anterior leads in women regardless of the level of the ST segment. Interestingly, in our study, a horizontal ST segment in the inferior leads was even associated with a better prognosis than an upsloping ST in women. In V5, the associated mortality increased among the groups in both genders: a horizontal ST segment was associated with higher mortality rates compared to an upsloping ST segment, and a downsloping ST segment was associated with even higher mortality rates. After multivariate adjustment, a downsloping ST segment lost its significance in all lead groups in both genders, but in the multi-adjusted model without CHD, lateral negative slope increased mortality in women. We hypothesize that CHD should be suspected in case of a downsloping ST segment in the lateral leads in women.

Lead groups and measurement points

Most of the previous population studies classified ST changes based on the Minnesota coding, ignoring the location of ST and T-wave changes within the 12-lead ECG. A few studies showed that the prognosis of ST changes vary depending on their location over different lead groups [8,11]. We divided the leads into three anatomical groups, and these carried clearly different prognostic values. Age seemed to explain the adverse prognosis of lower ST levels in the inferior and anterior leads, while lower lateral ST level remained as an independent risk factor for increased mortality also after multivariate adjustment.

The chosen measurement point for ST deviations vary between studies. Our earlier account from the same data with shorter follow-up [11] used three different measurement points. Neither shorter nor the current longer follow-up differentiated HRs between different measurement points. However, the increase in the risk was somewhat more pronounced when using the measurement point J + 80 both in multi-adjusted models and after excluding ECG-LVH.

The variation of the ST level was small, and we used computerized measurements to measure the level of the ST segment. Automatic measurements help to correct for disturbances caused by wandering baseline and improve comparison between different ECGs. In our study HRs were scaled for difference of 1 mm. However, our data suggest that smaller changes have prognostic effect. Computerized measurement of the ST level is necessary to perform reliable measurements in case of minor changes.

Study limitations and strengths

The Health 2000 population is a representative sample of the Finnish population 30 years of age or older. The results may not be applicable to other populations. The long follow-up time up to 15 years resulted in a relatively high mortality rate (19.8% in men and 17.6% in women) for a population study. As our study contained a relatively high number of statistical comparisons, borderline significances should be evaluated with caution. Absence of echocardiographic and magnetic resonance imaging data on LVH is a study limitation typical of a population study.

Continuous instead of categorical variable enhances sensitivity to detect subtle differences. Inclusion of lead groups for ST analyses is important, because the prognostic information clearly differs between the different categories. The lead with the lowest ST level was chosen to represent a lead group. This makes our results easy to implement into clinical practice.

We examined ST slope independently of the level of ST segment. It is possible that the combination of slope with ST depression would have altered the study results. This was not the aim of our study, because the prognostic significance of the lateral “strain pattern” has already been established in the general population, in hypertension and structural heart disease.

Conclusion

Lower levels of the ST segment in the lateral lead group as a continuous variable is associated with increased mortality in the general population independently of gender, other cardiovascular risk factors and CHD. The prognosis is highly dependent on the lead-related spatial region: in the anterior and inferior lead groups, the ST level did not affect prognosis after multivariate adjustment. In women, the prognostic effect of a lower lateral ST level, measured at the J point, is likely explained by ECG-LVH. Regarding the measurement point J + 80 ms and in male individuals, more studies are required to understand the pathophysiology of the phenomenon. A downward slope of the ST segment in the lateral leads was associated with all-cause mortality, but the increased risk seemed to be explained by age and associated CHD.

CRediT authorship contribution statement

Tiia Istolahti: Conceptualization, Methodology, Formal analysis, Writing - original draft. **Tuomo Nieminen:** Conceptualization, Methodology, Writing - review & editing. **Heini Huhtala:** Methodology, Formal analysis. **Leo-Pekka Lyytikäinen:** Software, Writing - review & editing. **Mika Kähönen:** Supervision, Writing - review & editing. **Terho Lehtimäki:** Writing - review & editing. **Markku Eskola:** Writing - review & editing. **Ismo Anttila:** Writing - review & editing. **Antti Jula:** Data curation, Writing - review & editing. **Harri Rissanen:** Resources, Writing - review & editing. **Kjell Nikus:** Conceptualization, Methodology, Writing - original draft, Supervision, Project administration. **Jussi Hernesniemi:** Methodology, Formal analysis, Writing - review & editing, Supervision.

Declaration of competing interest

None.

Acknowledgements

We thank the investigators, staff and participants of the Health 2000 survey.

Source of funding

This work was supported by The Doctoral Programme in Medicine and Life Sciences, Faculty of Medicine and Health Technology, Tampere University; Finnish Medical Foundation; Finska Läkaresällskapet; Academy of Finland (grant 322098); Competitive State Research Financing of the Expert Responsibility area of Tampere; Finnish Foundation for Cardiovascular Research; Tampere Tuberculosis Foundation; EU Horizon 2020 (grant 755320 for TAXINOMISIS); and Tampere University Hospital Supporting Foundation.

References

[1] Larsen CT, Dahlin J, Blackburn H, Scharling H, Appleyard M, Sigurd B, et al. Prevalence and prognosis of electrocardiographic left ventricular hypertrophy, ST segment depression and negative T-wave. The Copenhagen City Heart Study. Eur Heart J 2002;23(4):315–24. https://doi.org/10.1053/euhj.2001.2774 Feb 1.
[2] Möller CS, Zethelius B, Sundström J, Lind L. Persistent ischaemic ECG abnormalities on repeated ECG examination have important prognostic value for cardiovascular disease beyond established risk factors: a population-based study in middle-aged men with up to 32 years of follow-up. Heart 2007;93(9):1104–10. https://doi.org/10.1136/hrt.2006.109116 Sep 1.
[3] Rautaharju PM, Ge S, Nelson JC, Marino Larsen EK, Psaty BM, Furberg CD, et al. Comparison of mortality risk for electrocardiographic abnormalities in men and women with and without coronary heart disease (from the Cardiovascular Health Study). Am J Cardiol 2006;97(3):309–15. https://doi.org/10.1016/j.amjcard.2005.08.046 Feb.
[4] Kumar A, Lloyd-jones DM. Clinical significance of minor nonspecific St-segment and T-wave abnormalities in asymptomatic subjects: a systematic review. Cardiol Rev 2007;15(3):133–42. https://doi.org/10.1097/01.crd.0000249382.65955.14 May 1.
[5] Badheka AO, Rathod A, Marzouka GR, Patel N, Bokhari SSI, Moscucci M, et al. Isolated nonspecific ST-segment and T-wave abnormalities in a cross-sectional United States population and mortality (from NHANES III). Am J Cardiol 2012;110(4):521–5. https://doi.org/10.1016/j.amjcard.2012.04.023 Aug.
[6] Greenland P, Xie X, Liu K, Colangelo L, Liao Y, Daviglus ML, et al. Impact of minor electrocardiographic ST-segment and/or T-wave abnormalities on cardiovascular mortality during long-term follow-up. Am J Cardiol 2003;91(9):1068–74. https://doi.org/10.1016/s0002-9149(03)00150-4 May 1.
[7] Daviglus ML, Liao Y, Greenland P, Dyer AR, Liu K, Xie X, et al. Association of nonspecific minor ST-T abnormalities with cardiovascular mortality: the Chicago Western Electric Study. JAMA 1999;281(6):530–6. https://doi.org/10.1097/00132586-200002000-00057 Feb 10.
[8] Rasmussen PV, Nielsen JB, Pietersen A, Graff C, Lind B, Struijk JJ, et al. Electrocardiographic precordial ST-segment deviations and the risk of cardiovascular death: results from the Copenhagen ECG study. J Am Heart Assoc Cardiovasc Cerebrovasc Dis 2014;3(3). https://doi.org/10.1161/jaha.113.000549 Internet. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4309043/. May 9 [cited 2018 Dec 23].
[9] Froelicher VF, Myers J. Exercise and the heart. vol. 2000. Pennsylvania, Philadelphia: W.B. Saunders Co.

[10] Inoue YY, Soliman EZ, Yoneyama K, Ambale-Venkatesh B, Wu CO, Sparapani R, et al. Electrocardiographic strain pattern is associated with left ventricular concentric remodeling, scar, and mortality over 10 years: the multi-ethnic study of atherosclerosis. J Am Heart Assoc Cardiovasc Cerebrovasc Dis 2017;6(9). https://doi.org/10.1161/jaha.117.006624 Internet. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634304/. Sep 20 [cited 2019 Feb 9].
[11] Anttila I, Nikus K, Kähönen M, Jula A, Reunanen A, Salomaa V, et al. Prognostic implications of quantitative ST-segment characteristics and T-wave amplitude for cardiovascular mortality in a general population from the Health 2000 Survey. Ann Med 2010;42(7):502–11. https://doi.org/10.3109/07853890.2010.505932 Oct 1.
[12] De Bacquer D, De Backer G, Kornitzer M, Myny K, Doyen Z, Blackburn H. Prognostic value of ischemic electrocardiographic findings for cardiovascular mortality in men and women. J Am Coll Cardiol 1998;32(3):680–5. https://doi.org/10.1016/s0735-1097(98)00303-9 Sep 1.
[13] De Bacquer D, De Backer G, Kornitzer M, Blackburn H. Prognostic value of ECG findings for total, cardiovascular disease, and coronary heart disease death in men and women. Heart 1998;80(6):570–7. https://doi.org/10.1136/hrt.80.6.570 Dec.
[14] Heistaro S, editor. Methodology report: Health 2000 survey. Publications of the National Public Health Institute B26/; 2008. http://urn.fi/URN:NBN:fi-fe201204193320.
[15] Sund R. Quality of the Finnish Hospital Discharge Register: a systematic review. Scand J Public Health 2012;40(6):505–15. https://doi.org/10.1177/1403494812456637 Aug 1.
[16] Rapola JM, Virtamo J, Korhonen P, Haapakoski J, Hartman AM, Edwards BK, et al. Validity of diagnoses of major coronary events in national registers of hospital diagnoses and deaths in Finland. Eur J Epidemiol 1997;13(2):133–8 Feb 1.
[17] Prineas RJ, Crow RS, Blackburn HW. The Minnesota code manual of electrocardiographic findings. June Littleton, MA: John Wright-PSG, Inc; 1982.
[18] World Health Organization, International Diabetes Federation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation. Internet. [cited 2019 Apr 16]. Available from http://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/; 2006.
[19] Walsh JA, Prineas R, Soliman EZ, Liu K, Ning H, Daviglus ML, et al. Association of isolated minor non-specific ST-segment and T-wave abnormalities with subclinical atherosclerosis in a middle-aged, biracial population: Coronary Artery Risk Development in Young Adults (CARDIA) study. Eur J Prev Cardiol 2013;20(6):1035–41. https://doi.org/10.1177/2047487312460017 Dec 1.
[20] Kumar A, Prineas RJ, Arnold AM, Psaty BM, Furberg CD, Robbins J, et al. Prevalence, prognosis and implications of isolated minor non-specific ST-segment and T-wave abnormalities in older adults: Cardiovascular Health Study. Circulation 2008;118(25):2790–6. https://doi.org/10.1161/circulationaha.108.772541 Dec 16.
[21] Toivonen L, Helenius K, Viitasalo M. Electrocardiographic repolarization during stress from awakening on alarm call. J Am Coll Cardiol 1997;30(3):774–9. https://doi.org/10.1016/s0735-1097(97)00222-2 Jul.
[22] Quyyumi AA, Wright C, Fox K. Ambulatory electrocardiographic ST segment changes in healthy volunteers. Br Heart J 1983;50(5):460–4. https://doi.org/10.1136/hrt.50.5.460 Nov.
[23] Adler A, Rosso R, Viskin D, Halkin A, Viskin S. What do we know about the "Malignant Form" of early repolarization? J Am Coll Cardiol 2013;62(10):863–8. https://doi.org/10.1016/j.jacc.2013.05.054 Sep.
[24] Rollin A, Maury P, Bongard V, Sacher F, Delay M, Duparc A, et al. Prevalence, prognosis, and identification of the malignant form of early repolarization pattern in a population-based study. Am J Cardiol 2012;110(9):1302–8. https://doi.org/10.1016/j.amjcard.2012.06.033 Nov.
[25] Okin PM, Devereux RB, Nieminen MS, Jern S, Oikarinen L, Viitasalo M, et al. Relationship of the electrocardiographic strain pattern to left ventricular structure and function in hypertensive patients: the LIFE study. J Am Coll Cardiol 2001;38(2):514–20. https://doi.org/10.1016/s1062-1458(01)00566-9 Aug.
[26] Okin PM, Oikarinen L, Viitasalo M, Toivonen L, Kjeldsen SE, Nieminen MS, et al. Prognostic value of changes in the electrocardiographic strain pattern during antihypertensive treatment: the losartan intervention for end-point reduction in hypertension study (LIFE). Circulation 2009;119(14):1883–91. https://doi.org/10.1161/circulationaha.108.812313 Apr 14.

PUBLICATION III

The prognostic significance of T-wave inversion according to ECG lead group during long-term follow-up in the general population

Istolahti Tiia, Lyytikäinen Leo-Pekka, Huhtala Heini, Nieminen Tuomo, Kähönen Mika, Lehtimäki Terho, Eskola Markku, Anttila Ismo, Jula Antti, Rissanen Harri, Nikus Kjell, Hernesniemi Jussi

Annals of Noninvasive Electrocardiology, 26:e12799
DOI: 10.1111/anec.12799

Received: 27 May 2020 | Revised: 14 July 2020 | Accepted: 19 August 2020

DOI: 10.1111/anec.12799

ORIGINAL ARTICLE

WILEY

The prognostic significance of T-wave inversion according to ECG lead group during long-term follow-up in the general population

Tiia Istolahti MD[1,2] | Leo-Pekka Lyytikäinen MD[1,3,4] | Heini Huhtala MSc[5] | Tuomo Nieminen MD, PhD[6] | Mika Kähönen MD, PhD[1,7] | Terho Lehtimäki MD, PhD[1,4] | Markku Eskola MD, PhD[1,3] | Ismo Anttila MD, PhD[8] | Antti Jula MD, PhD[9] | Harri Rissanen MSc[9] | Kjell Nikus MD, PhD[1,3] | Jussi Hernesniemi MD, PhD[1,3]

[1]Faculty of Medicine and Health Technology, Tampere University, and Finnish Cardiovascular Research Center, Tampere, Finland

[2]Department of Internal Medicine, Vaasa Central Hospital, Vaasa, Finland

[3]Heart Center, Department of Cardiology, Tampere University Hospital, Tampere, Finland

[4]Department of Clinical Chemistry, Fimlab Laboratories, Tampere, Finland

[5]Faculty of Social Sciences, Tampere University, Tampere, Finland

[6]Department of Internal Medicine, Päijät-Häme Central Hospital, Lahti, Finland

[7]Department of Clinical Physiology, Tampere University Hospital, Tampere, Finland

[8]Health Services, Lapua, Finland

[9]Finnish Institute for Health and Welfare, Helsinki, Finland

Correspondence
Tiia Istolahti, Faculty of Medicine and Health Technology, Tampere University, and Finnish Cardiovascular Research Center, Tampere, Finland.
Email: tiia.istolahti@tuni.fi

Funding information
This work was supported by the Doctoral Programme in Medicine and Life Sciences, Faculty of Medicine and Health Technology, Tampere University, and Ida Montin Foundation, Finland (for T.I.); the Competitive Research Funding of the Tampere University Hospital (grant X51001), the Finnish Foundation for Cardiovascular Research, the Emil Aaltonen Foundation, Finland, the Tampere Tuberculosis Foundation, EU Horizon 2020 (grant 755320 for TAXINOMISIS and grant 848146 for To Aition); and the Academy of Finland grant 322098 (for T.L).

Abstract

Background: Inverted T waves in the electrocardiogram (ECG) have been associated with coronary heart disease (CHD) and mortality. The pathophysiology and prognostic significance of T-wave inversion may differ between different anatomical lead groups, but scientific data related to this issue is scarce.

Methods: A representative sample of Finnish subjects (n = 6,354) aged over 30 years underwent a health examination including a 12-lead ECG in the Health 2000 survey. ECGs with T-wave inversions were divided into three anatomical lead groups (anterior, lateral, and inferior) and were compared to ECGs with no pathological T-wave inversions in multivariable-adjusted Fine–Gray and Cox regression hazard models using CHD and mortality as endpoints.

Results: The follow-up for both CHD and mortality lasted approximately fifteen years (median value with interquartile ranges between 14.9 and 15.3). In multivariate-adjusted models, anterior and lateral (but not inferior) T-wave inversions associated with increased risk of CHD (HR: 2.37 [95% confidence interval 1.20–4.68] and 1.65 [1.27–2.15], respectively). In multivariable analyses, only lateral T-wave inversions associated with increased risk of mortality in the entire study population

(HR 1.51 [1.26–1.81]) as well as among individuals with no CHD at baseline (HR 1.59 [1.29–1.96]).

Conclusions: The prognostic information of inverted T waves differs between anatomical lead groups. T-wave inversion in the anterior and lateral lead groups is independently associated with the risk of CHD, and lateral T-wave inversion is also associated with increased risk of mortality. Inverted T wave in the inferior lead group proved to be a benign phenomenon.

KEYWORDS

coronary heart disease, electrocardiogram, mortality, population study, T wave

1 | INTRODUCTION

Inverted T waves in the electrocardiogram (ECG) defined by the Minnesota codes 5.1-3 (Prineas et al., 1982) have been associated with ischemic heart disease events as well as cardiovascular and total mortality in former population-based studies (Bakhoya et al., 2014; Larsen et al., 2002; Laukkanen et al., 2014; Rautaharju et al., 2012). The pathophysiology and prognostic significance of T-wave inversion may differ between different anatomical lead groups. According to expert recommendations, an inverted T wave is a normal finding in leads III, aVR, aVL, and V1 in adults (Rautaharju et al., 2009). Inverted T waves in the right precordial leads V1-V3 are typical for arrhythmogenic right ventricular cardiomyopathy (Nasir et al., 2004), but in a population study, they were not associated with cardiovascular or total mortality (Aro et al., 2012). A downsloping ST segment with asymmetric T-wave inversion in the lateral leads, the "strain pattern," is a marker of anatomical left ventricular hypertrophy (LVH) and is associated with increased left ventricular mass and mortality (Inoue et al., 2017). Lower T-wave level as a continuous variable was associated with cardiovascular mortality in women in an earlier study of the Health 2000 population, but this was seen only in the lateral lead group (I, aVL, and V5-V6) (Anttila et al., 2010).

We hypothesized that the pathophysiology and prognostic significance of T-wave inversion differ between different anatomical lead groups of the 12-lead resting ECG. Therefore, in this study, we sought to explore the long-term prognostic significance of T-wave inversion in three different anatomical lead groups (anterior, lateral, and inferior) in the general population using new diagnosis of coronary heart disease (CHD) and total mortality as outcomes.

2 | METHODS

2.1 | Study population

The Health 2000 survey was carried out in 2000–2001 and was designed to cover a nationally representative population sample of the Finnish population. This population-based nationwide study consisted of 8,028 individuals aged over 30 years, of whom 79% (6,354 individuals) participated in the health examination, which included a structured examination by a physician, health interviews, series of laboratory tests, and ECG recordings. Participants aged 80 + were oversampled with a double sampling fraction. More detailed descriptions of the methods of the Health 2000 survey have been published previously (Heistaro, 2008). Ethical approval for the Health 2000 study was obtained from Ethical Committee for Research in Epidemiology and Public Health at the Hospital District of Helsinki and Uusimaa (HUS).

2.2 | Study covariates

Trained study personnel performed the health interview, and they followed a structural detailed written instruction to gather information about pre-existent diseases. Examining physicians performed another structured interview and physical examination. We included data on prevalent diseases from the Care Register for Health Care (CRHC) maintained by the Finnish Institute for Health and Welfare. CRHC contains data of all inpatient episodes in Finland at the individual level since year 1969 and on outpatients since 1998. The accuracy of the register has been validated previously (Sund, 2012). Information about medication at baseline was gathered by checking the study participants' personal health insurance cards for rights of drug reimbursements and by interviewing the study participants about prescription and nonprescription medicines. In addition, data on drug purchases since year 1995 and special drug reimbursements since year 1964 were gathered from a separate registry (Statistics on reimbursements for prescription medicines: The Social Insurance Institution of Finland).

Height and weight were measured, and body mass index (BMI) was calculated. Blood pressure was measured from the right arm with a standard mercury manometer (Mercuro 300; Speidel & Keller). An average of two measurements was used, of which the first one was measured after rest for at least 5 min in sitting position. Arterial hypertension (HTA) was defined as blood pressure ≥140/90, a previous diagnosis of HTA in the CRHC (ICD-10 I10, ICD-9/8 401),

or right for special drug reimbursements for HTA. Heart rate was obtained from the ECGs. Smoking was determined as a daily use of cigarettes at the time of the interview.

Serum high-density lipoprotein (HDL) cholesterol and plasma glucose concentrations were determined enzymatically (Roche Diagnostics, GmbH, Mannheim, Germany, for HDL-cholesterol and Olympus System Reagent, Hamburg, Germany, for glucose) from venous blood samples with a clinical chemistry analyzer (Olympus, AU400, Hamburg, Germany). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. The diagnosis of diabetes mellitus (DM) at baseline included fasting serum glucose (fS-Gluc) ≥7 or a history of use of oral glucose-lowering agents or insulin injections (World Health Organization & International Diabetes Federation, 2006).

A standard 12-lead resting ECG in the supine position was recorded from each subject during the health examination with Marquette Hellige MAC 5000 electrocardiographs (Freiburg, Germany and Milwaukee, WI, USA). ECGs were stored electronically. The ECG data were sent for further analysis to the Social Insurance Institution's research center in Turku, Finland, where the ECGs were analyzed with Magellan software (Marquette Electronics Inc). The Marquette 12SL algorithm uses median complexes of the 10-s ECG tracing using the onset of QRS as the isoelectric line. A wave crossing the baseline level constituting an area of ≥160 μVms represents a separate wave. In addition, the ECGs were Minnesota-coded (Prineas et al., 1982) by two investigators at the Institute of Cardiology, Kaunas Medical Academy, Lithuania, blinded to the clinical data.

2.3 | The definition of T-wave inversion and lead groups

Amplitudes of different parts of the T wave were automatically measured. The T wave was considered negative when the T-wave amplitude was <0 μV. If the T wave was biphasic, the lowest part of the wave indicated the level. T waves were grouped into lead groups: anterior (V2, V3, V4), lateral (I, aVL, V5, V6), and inferior (II, aVF). If a lead group contained at least one negative T wave, the lead group was classified as having T-wave inversion. Participants with negative T waves in more than one lead group were classified into a separate group ("multiple locations"). The T waves in leads III, aVL, and V1 were separately tested before inclusion into their respective lead groups, because an inverted T wave in these leads is considered normal, but the T waves in these leads can also be affected by different disease processes. Lead aVR was not included in the analyses, as the T wave is normally negative in that lead.

2.4 | Follow-up and study endpoints

The data for mortality and causes of death were gathered from the Causes of Death register maintained by Statistics Finland. It contains 100% of deaths of Finnish citizens in Finland and almost 100% abroad. Information on the incident diseases was obtained from the CRHC. Databases were linked using a personal identity code. The follow-up lasted until the end of the year 2015.

The study endpoints were total mortality and a new diagnosis of CHD. The endpoints were tested separately. Classification of prevalent CHD required at least one of the following: diagnosed angina pectoris, myocardial infarction, percutaneous coronary intervention (PCI) or bypass surgery by examining physician or diagnosed PCI or bypass surgery in the health interview, ICD codes I20-25 (ICD-10) or 410–14 (ICD8/9) in the CRHC, the right for drug reimbursements for CHD, or interventional code for coronary artery revascularization in the CRHC. For the diagnosis of incident CHD, we included above-mentioned ICD codes and interventional codes for CHD, ICD codes I21-25, I46, R96, and R98 (ICD-10) in the Causes of Death register, and a new right for drug reimbursements for CHD.

2.5 | Exclusion criteria

We excluded subjects with missing ECG data (number of participants [n] = 55). Of those, the recording was not successful in 36 participants with entries such as "difficult to move," "wheelchair," "denial," "leg/hand amputated," "in geriatric chair," "massive hernia," and "plaster in leg/ hand." In the further process, 19 ECGs were lost (diskette lost [9], coupling error [4], data reading failure [5], and unspecific reason [1]). We also excluded subjects with Q/QS waves in the ECG according to the Minnesota codes (Prineas et al., 1982) 1–1, 1–2, and 1–3 ($n = 127$), left or right bundle branch block or left anterior hemiblock (Minnesota code 7, $n = 565$), Wolff–Parkinson–White pattern (Minnesota code 6–4, $n = 1$), paced rhythm (Minnesota code 6–8, $n = 4$), or left ventricular hypertrophy in the ECG (Minnesota codes 3–1, 3–3, and 3–4, $n = 820$) from the analysis. The final study sample consisted of 4,793 participants. In the analysis where we used CHD as an endpoint, we also excluded prevalent CHD as defined earlier.

2.6 | Statistical analyses

Because the T wave may normally be positive or negative in leads III, aVL, and V1 (Rautaharju et al., 2009), we tested the prognosis for each of these leads separately with unadjusted Cox proportional hazard models using both total mortality and CHD as endpoints. After this analysis, we included leads with detrimental prognosis in the lead groups. In these analyses, T-wave inversions in other leads were not excluded as there was no isolated T-wave inversion in III, aVL, or V1. Comparisons in variables were calculated with one-way ANOVA for continuous variables and chi-square test for categorical variables. Cox proportional hazard models were constructed for total mortality. The Fine–Gray proportional subdistribution hazards model treating death as a competing risk was used to study the association of T-wave inversions with CHD in different lead groups. The proportional hazard assumption was checked visually

TABLE 1 Baseline characteristics of the Health 2000 Survey participants

	No TWI		Anterior TWI		Lateral TWI		Inferior TWI		Multiple TWI		
	n/mean	%/(*SD*)	*n*/ mean	%/(*SD*)	*n*/ mean	%/(*SD*)	*n*/mean	%/(*SD*)	*n*/ mean	%/(*SD*)	*p* Value
N	3,852	80.4%	60	1.3%	440	9.2%	303	6.3%	138	2.9%	
Age	49.5	(13.3)	53.7	(16.9)	58.1	(14.9)	56.2	(14.0)	68.9	(13.6)	<.001
Men	1,577	40.9%	7	11.7%	197	44.8%	129	42.6%	38	27.5%	<.001
BMI (kg/m^2)	26.9	(4.6)	27.4	(5.2)	26.4	(5.4)	28.9	(4.9)	28.7	(6.0)	<.001
Heart rate/min	63.5	(10.5)	61.5	(11.6)	64.9	(12.6)	63.8	(11.7)	65.2	(13.7)	.014
Regular smoking	868	22.6%	10	16.9%	121	27.6%	42	13.9%	16	11.7%	<.001
Hypertension	1,482	38.6%	24	40.0%	237	54.0%	175	57.9%	97	70.3%	<.001
Diabetes	170	4.4%	2	3.3%	50	11.4%	21	6.9%	25	18.1%	<.001
CHD	151	3.9%	3	5.0%	67	15.2%	31	10.2%	47	34.1%	<.001
HDL (mmol/L)	1.3	(0.4)	1.4	(0.4)	1.3	(0.4)	1.2	(0.3)	1.2	(0.4)	<.001
LDL (mmol/L)	3.8	(1.2)	3.7	(1.1)	3.8	(1.2)	3.8	(1.2)	3.7	(1.4)	.924

Abbreviations: BMI, body mass index; CHD, coronary heart disease; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; *N*, number; *SD*, standard deviation; TWI, T-wave inversion.

from the Kaplan–Meier curves for mortality and from cumulative incidence function curves for CHD. Only the first diagnosis of CHD was considered. The four mutually exclusive groups (anterior, lateral, inferior, and multiple locations) were compared to ECGs with no T-wave inversions (excluding aVR, V1, and III). Both hazard models were constructed with and without adjustment for age and for multivariate analysis for age, sex, BMI, HDL-cholesterol, LDL-cholesterol, regular smoking, heart rate, HTA, DM, and CHD (not for CHD as an endpoint). In addition, to test for a possible confounding effect of the ST level, we performed a sensitivity analysis, where we included the amplitude of the ST level at the J point (as dichotomous variable ≥ 0 μV or < 0 μV) in the multivariate adjustment. From a clinical point of view, the results of this sensitivity analysis did not differ significantly from the results without ST-level adjustment. Therefore, the results with the ST-level adjustment are not included. The interaction was tested between different lead groups and sex for both endpoints and between lead groups and CHD for mortality in unadjusted Cox models. No significant sex-related interactions were observed, and all the analyses were performed without sex stratification. The interaction term between lead groups and CHD was significant. Therefore, we performed the mortality analysis also after dividing the data by CHD. Analyses

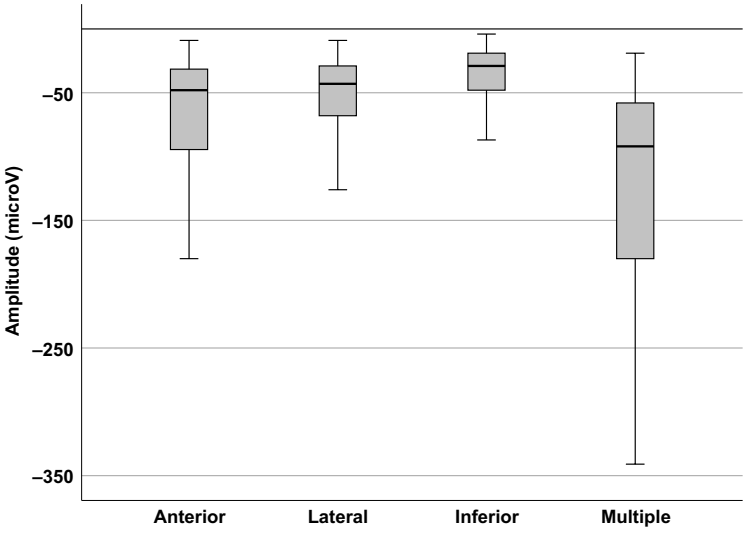

FIGURE 1 Minimum amplitudes of negative T waves in box plot analysis divided by lead groups. Outliers have been removed

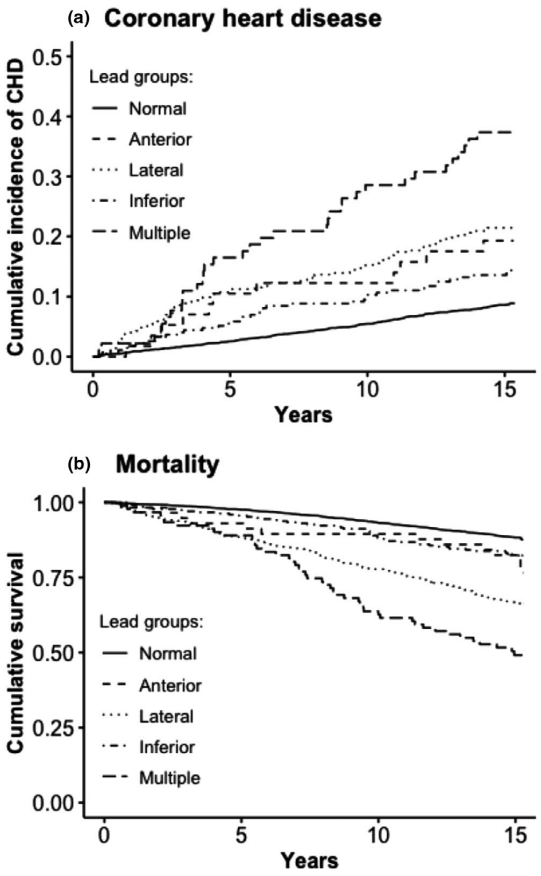

FIGURE 2 (a) Cumulative incidence function curves for coronary heart disease and (b) Kaplan–Meier survival curves for mortality of T-wave inversions in different lead groups in participants without known coronary heart disease at the baseline

were performed using SPSS 25 and R 3.6.3. Statistical significance was based on $p < .05$.

3 | RESULTS

3.1 | Forming ECG lead groups

To form final lead groups, we tested the prognostic significance of T-wave inversion separately for leads III, aVL, and V1 using both mortality and CHD as endpoints, because both a positive and a negative T wave is considered normal in these leads (Rautaharju et al., 2009). Negative T waves in leads III and V1 were associated with lower risk of CHD and mortality, and therefore, these leads were not included in any lead group. For lead III, unadjusted hazard ratio (HR) was 0.84 (95% confidence interval [CI]: 0.74–0.97, $p = .015$) for mortality and 0.87 (0.72–1.04, $p = .113$) for CHD and for V1 HR was 0.61 (0.53–0.70, $p < .001$) for mortality and 0.59 (0.49–0.71, $p < .001$) for CHD. T-wave inversion in lead aVL was associated with higher mortality risk (HR: 3.33 [2.84–3.90, $p < .001$]) as well as a higher risk for a new CHD diagnosis (HR: 3.05 [2.45–3.81, $p < .001$]). Therefore, lead aVL was included in the lateral lead group. Hence, the final lead groups were anterior (V2, V3, V4), lateral (I, aVL, V5, V6), and inferior (II, aVF).

3.2 | Study sample

Table 1 shows the baseline characteristics and the prevalence of T-wave inversions in different lead groups. There were 59.4% women in the study sample versus 40.6% men. T-wave inversion was a rare finding in the anterior lead group with the prevalence of 1.3%. T-wave inversion in the lateral, inferior, and multiple lead groups was found in 9.2%, 6.3%, and 2.9%, respectively. Individuals with inverted T waves were significantly older than those without. Anterior T-wave inversions were far more prevalent among women (88.3%), while lateral and inferior T-wave inversions were slightly less frequent in women than in men. The rate of HTA, DM, and CHD was clearly higher in individuals with inverted T waves in more than one lead group than in those with T-wave inversion in only one lead group or no T-wave inversion.

Figure 1 shows the amplitudes of the inverted T waves. Inverted T waves in the anterior lead group were deeper than those in the lateral or inferior lead groups. Among individuals with T-wave inversions in two or three lead groups, the T waves were much deeper than in those with T-wave inversions only in one lead group.

3.3 | T-wave inversion and incident CHD

There were 489 (10.9%) new CHD diagnoses during the median follow-up time of 15.2 years (interquartile range: 14.9–15.3). T-wave inversions in all lead groups were associated with a new diagnosis of CHD in unadjusted models. Figure 2a shows the cumulative incidence function curves. Table 2 shows the unadjusted and adjusted HRs for the association between T-wave inversion and CHD in the different lead groups. Lateral T-wave inversions, as well as negative T waves in two or more lead groups, were associated with higher risk for a new CHD diagnosis. Regarding anterior T-wave inversion, there was an association between the studied ECG phenomenon and higher CHD rates in crude and multivariate-adjusted analysis. The association between inferior T-wave inversion and CHD was not statistically significant after adjusting for age and after multivariate adjustment.

3.4 | T-wave inversion and total mortality

The median follow-up time for mortality was 15.1 years (14.9–15.2) and 842 (17.6%) individuals died during the follow-up period. T-wave inversions in the lateral (HR 3.29 [2.76–3.92, $p < .001$]) and inferior (HR 1.75 [1.35–2.25, $p < .001$]) lead groups were associated with

TABLE 2 Fine–Gray proportional subdistribution hazards analysis of T-wave inversion by location for CHD

Lead groups	Amount of CHD diagnoses/ participants (%)	Hazard ratio (95% CI) Unadjusted	*p* Value	Age-adjusted	*p* Value	Multivariate-adjusted[a]	*p* Value
Anterior	11/57 (19.3%)	2.36 (1.29–4.33)	.006	1.72 (0.90–3.30)	.100	2.37 (1.20–4.68)	.013
Lateral	80/373 (21.4%)	2.68 (2.09–3.43)	<.001	1.78 (1.38–2.30)	<.001	1.65 (1.27–2.15)	<.001
Inferior	39/272 (14.3%)	1.70 (1.22–2.37)	.002	1.22 (0.87–1.73)	.250	1.11 (0.78–1.58)	.560
Many sites	34/91 (37.4%)	5.12 (3.59–7.30)	<.001	2.06 (1.40–3.03)	<.001	2.18 (1.49–3.21)	<.001

Abbreviations: CHD, coronary heart disease; CI, confidence interval.

[a]Age, sex, diabetes, hypertension, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, heart rate, body mass index, and regular smoking.

TABLE 3 Cox proportional hazard analysis of T-wave inversion by location for mortality in participants with and without known CHD at baseline

Lead groups	Deaths/ participants (%)	Hazard ratio (95% CI) Unadjusted	*p* Value	Age-adjusted	*p* Value	Multivariate-adjusted[a]	*p* Value
Interaction		CHD × lead groups	<.001				
Participants without CHD							
Anterior	11/57 (19.3%)	1.72 (0.94–3.13)	.076	1.08 (0.59–1.97)	.796	1.40 (0.75–2.64)	.293
Lateral	125/373 (33.5%)	3.32 (2.73–4.06)	<.001	1.84 (1.50–2.25)	<.001	1.59 (1.29–1.96)	<.001
Inferior	48/272 (17.6%)	1.56 (1.16–2.10)	.004	1.04 (0.77–1.40)	.813	1.06 (0.78–1.43)	.719
Many sites	46/91 (50.5%)	5.66 (4.18–7.67)	<.001	1.65 (1.21–2.26)	.002	1.72 (1.26–2.36)	.001
Participants with CHD							
Anterior	2/3 (66.7%)	1.57 (0.39–6.40)	.526	0.93 (0.23–3.80)	.924	1.34 (0.33–5.56)	.684
Lateral	39/67 (58.2%)	1.14 (0.78–1.66)	.507	1.41 (0.96–2.08)	.078	1.32 (0.89–1.97)	.174
Inferior	19/31 (61.3%)	1.29 (0.78–2.12)	.324	1.11 (0.68–1.84)	.671	1.33 (0.79–2.23)	.284
Many sites	32/47 (68.1%)	1.55 (1.03–2.34)	.035	1.15 (0.76–1.73)	.503	1.18 (0.76–1.81)	.463

Abbreviations: CHD, coronary heart disease; CI, confidence interval; *N*, number.

[a]Age, sex, diabetes, hypertension, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, heart rate, body mass index, and regular smoking.

higher mortality rates in the crude Cox models. After adjusting for age, the increase in mortality rates was significant only in the lateral leads (HR 1.77 [1.48–2.11, $p < .001$]). This was also the case for multivariate adjustment (HR 1.51 [1.26–1.81, $p < .001$]). The associated risk for mortality was also significant among participants with negative T waves in more than one lead group and of similar magnitude as for participants with only lateral T-wave inversions (HR 1.49 [1.16–1.92, $p = .002$]).

We noticed a significant interaction ($p < .001$) in unadjusted analysis between the lead groups and CHD with regard to the mortality risk during follow-up. We performed these analyses again after dividing the data by existing prevalent CHD and noticed that the adverse prognosis of T-wave inversion in different lead groups was not significant in participants with known CHD. Table 3 shows the HRs in the mortality analyses in individuals with and without known CHD at baseline. Figure 2b shows the cumulative survival rates for negative T waves in different lead groups in participants without known CHD at baseline.

4 | DISCUSSION

The main finding of this population-based study is that the prognostic significance of T-wave inversion differs between the different anatomical lead groups of the 12-lead ECG. Inverted T waves in the anterior and lateral lead groups at baseline were independently associated with a new CHD diagnosis during long-term follow-up. T-wave inversions in the lateral lead group were independently associated with increased mortality. The risk did not differ between the sexes. The results of interaction analyses showed a significantly pronounced mortality risk among subjects with no CHD at baseline. T-wave inversion in the inferior lead group proved to be a benign phenomenon.

4.1 | The prevalence of T-wave inversion

The prevalence of T-wave inversions varies between different studies depending on the population, exclusion criteria, and

definition of T-wave inversion. In a population study of Larsen et al. (Larsen et al., 2002), the prevalence of T-wave inversions increased with age. Also in our study, participants with negative T waves were older than those without (53.7–68.9 versus 49.5 years, $p < .001$). In our study population, T-wave inversions were prevalent in 1.3% (anterior), 9.2% (lateral), and 6.3% (inferior) of the participants. In the BIRNH study (De Bacquer et al., 1998), the age-standardized prevalence of inverted T waves was 9.3% among women and 6.1% among men. Anterior T-wave inversions were found in 2.3% of asymptomatic participants with a mean age of 21.7 years (±5.7) and were more frequent among women and in athletes (Malhotra et al., 2017). In a study by Aro et al. (Aro et al., 2012), the prevalence of anterior T-wave inversions (in all of the leads V1-V3) was 0.5%. In their study, the prevalence of anterior T-wave inversions was much higher among women than among men, and this was the case also in the present study. The prevalence in other leads was opposite between the sexes, as was the case also in our study.

4.2 | The prognostic significance of inverted T waves

Inverted T waves and minor T-wave abnormalities have been associated with incident CHD and cardiovascular mortality in many previous population-based studies (Bakhoya et al., 2014; Greenland et al., 2003; Larsen et al., 2002; Laukkanen et al., 2014; Rautaharju et al., 2012). In the majority of these studies, the location of the T-wave changes was not specified, and the studies included T-wave changes in general. We found that the association between T-wave inversion and CHD was highly dependent on the location of the ECG abnormality and concerned only the anterior and lateral lead groups. In the anterior lead group, we noticed a more than twofold increase in the associated risk to receive a new diagnosis of CHD including acute coronary events, also after adjusting for traditional CHD risk factors. It is possible that inverted T waves in the anterior and lateral lead groups reflect underlying asymptomatic CHD (Luna et al., 2014). The association between T-wave inversion and CHD is highlighted by the fact that in the anterior lead group, the association with worse prognosis was seen only for CHD and not for mortality. After adjusting for age, inferior T-wave inversions were not associated with CHD or total mortality. This may at least partly be explained by the fact that the direction of the T-wave in the extremity leads is dependent on body habitus. In lean individuals with right axis deviation in the frontal plane, the T wave in lead II and aVF is normally positive, but T-wave inversion in lead aVF may be present (Bayés de Luna, 2012).

A negative T wave in the precordial leads (V1-V3) is a normal condition in children, but in adults, of these leads, only in lead V1, T-wave inversion is clearly a normal finding (Rautaharju et al., 2009). Negative T waves in the anterior leads may accompany arrhythmogenic right ventricular cardiomyopathy and Takotsubo syndrome (Luna et al., 2014). In a study of asymptomatic athletes and nonathletes with a mean age of 21.7 years (±5.7), none of the 338 study participants with anterior T-wave inversions had cardiomyopathy and none experienced an adverse event during 2-year follow-up (Malhotra et al., 2017). In a population study of Aro et al., T-wave inversions in leads V1-V3 were not associated with increased risk of cardiovascular or total mortality (Aro et al., 2012). Our study confirms these findings: Inverted T waves in the anterior lead group (V2-V4) were not associated with increased risk of mortality.

The "strain pattern," ST depression with asymmetric, downsloping ST segment, and T-wave inversion in the lateral ECG leads, is a marker of anatomical LVH and is associated with larger left ventricular mass and worse outcome in HTA (Okin et al., 2009); this ECG pattern was associated with all-cause mortality, systolic dysfunction, and myocardial scar in a population study (Inoue et al., 2017). In a study of Inoue et al. (Inoue et al., 2017), the associated risk of myocardial infarction, cardiovascular events, mortality, and heart failure for lateral strain (I, II, aVL, or V3 to V6) was seen independently of ECG-LVH. In their study, left ventricular scar was associated with strain but not with ECG-LVH and they hypothesized that the mechanism underlying the strain pattern would be silent subendocardial and mid-wall ischemia, which could explain the increased risk for adverse cardiovascular events.

In acute coronary syndrome, T-wave inversions can occur in the acute stage together with ST segment deviation as a sign of myocardial ischemia. Isolated "postischemic" T-wave inversions may persist for weeks after the acute phase. After myocardial infarction, T-wave inversions often accompany pathological Q waves, but they may also appear in isolation. The location of the postischemic T-wave inversions within the 12-lead ECG usually reflects the site of the ischemia during the acute phase (Luna et al., 2014), and persistent T-wave inversions after ST-elevation myocardial infarction have been associated with worse prognosis and larger infarct size (Lancellotti et al., 2002; Reindl et al., 2017). In our study, in participants with known CHD at baseline, T-wave inversions did not seem to associate significantly with mortality. The related risk estimate was increased but not as pronounced as among other subjects. We excluded individuals with Q/QS waves in their ECG, which can be one explanation for this finding. In addition, the prevalence of CHD at baseline was low, and it is possible that the groups were too small to enable the detection of statistically significant differences.

In the group with T-wave inversions in more than one lead group, the crude HRs were considerably higher than in individuals with T-wave inversions located to one lead group. The participants with more widespread T-wave inversions were also older and had more comorbidities which explain the decrease in HRs when adjusting for age and other cardiovascular risk factors. Despite the similar multivariate-adjusted HRs compared to some of the groups with T-wave inversions in only one lead group, it is possible that participants with widespread and deep T-wave inversions are at higher risk of adverse events because of the unfavorable risk profile. As we did not analyze the impact of different combinations of

lead groups with inverted T waves, no conclusions can be drawn regarding differences in outcome between combinations of lead groups.

We tested the effect of sex on the prognosis in the interaction analysis and did not find significant interactions. There was also no significant interaction between the sexes in the Copenhagen City Heart Study, where the prognostic impact of inverted T waves on myocardial infarction, ischemic heart disease events, and cardiovascular mortality was studied (Larsen et al., 2002). De Bacquer et al. (De Bacquer et al., 1998) studied the prognosis of inverted T waves separately for men and women and noticed that the adverse effect on all-cause mortality was seen only in men. The relative risk for cardiovascular mortality was slightly higher for women than for men, while the opposite was true for CHD mortality. In a former study of the Health 2000 population, the negative prognostic impact of inverted lateral T waves (as a continuous parameter) on cardiovascular mortality was seen only among women (Anttila et al., 2010).

The changes in the T waves reflect changes in ventricular repolarization and may be present with or without ST deviation. We performed an additional analysis to study the possible confounding of the ST level, but at least in this population study, the polarity of the ST level had no influence on the results. Primary T-wave inversion may be present in various conditions including perimyocarditis, acute or chronic pulmonary hypertension, cardiomyopathies, alcoholism, stroke, certain drugs, and hypokalemia and in athletes. Because this was a population study, stroke and acute pulmonary embolism are very unlikely etiologies of the T-wave inversions.

4.3 | Study limitations and strengths

The Health 2000 population is a representative sample of the Finnish population 30 years of age or older. The results may not be applicable to other populations. The long follow-up time up to 15 years resulted in a relatively high mortality rate (17.6%) for a population study. We excluded participants with LVH based on Minnesota ECG criteria (3–1, 3–3, and 3–4). It is possible that some participants with anatomical LVH were included in this study and vice versa. Lack of echocardiographic data, including LVH data, could be considered as a limitation of the study. We had no access to the health records of the study participants, which is a limitation very typical for a large population study. In general, T-wave alterations in the general population are minor, and therefore, we decided not to further separate the patient groups according to T-wave amplitudes. We used computer-based measurements, which helps to correct for artifacts caused by wandering baseline and some other technical disturbances. However, it has to be pointed out that the smaller magnitudes of T-wave inversion detected in the automated measurements are not possible with naked-eye detection.

Inclusion of lead groups for T-wave analyses is important, because the prognostic information clearly differs between the different lead categories and the prognostic aspects of T-wave inversions have not been extensively studied before from this standpoint. We wanted to study lead groups instead of individual leads, because different disease processes in the heart typically affect more than one ECG lead. Therefore, ECG diagnoses, for example related to CHD, rely on changes in parallel leads. We tested the prognosis for leads III, aVL, and V1 separately before the decision to include any of these leads to their corresponding lead group. This was done because the direction and amplitude of the T wave in these leads may be affected by different disease states although T-wave negativity is considered as normal.

5 | CONCLUSIONS

The present general population study showed that the prognostic information of T-wave changes differs between anatomical lead groups. Lateral T-wave inversion is associated with increased risk of mortality and CHD. Additionally, T-wave inversion in the anterior lead group is independently associated with the risk of CHD, but not mortality, highlighting the need to consider CHD when anterior T-wave inversions are observed. Inverted T wave in the inferior lead group proved to be a benign phenomenon.

ACKNOWLEDGMENTS

We thank the investigators, staff, and participants of the Health 2000 survey, and A. S. Havulinna, V. Salomaa, and the Finnish Institute of Health and Welfare for their work on coding endpoints.

CONFLICT OF INTEREST

The authors report no conflicts of interest.

ETHICS

Ethical approval for the Health 2000 study was obtained from Ethical Committee for Research in Epidemiology and Public Health at the Hospital District of Helsinki and Uusimaa (HUS).

AUTHOR CONTRIBUTIONS

Conceived the study, contributed to methodology, performed the formal analysis, and wrote the original draft of the manuscript: Tiia Istolahti. Developed the software and wrote, reviewed, and edited the manuscript: Leo-Pekka Lyytikäinen. Contributed to methodology and performed the formal analysis: Heini Huhtala. Wrote, reviewed, and edited the manuscript: Tuomo Nieminen. Wrote, reviewed, and edited the manuscript, and supervised the study: Mika Kähönen. Wrote, reviewed, and edited the manuscript: Terho Lehtimäki. Wrote, reviewed, and edited the manuscript: Markku Eskola. Wrote, reviewed, and edited the manuscript: Ismo Anttila. Curated the data and wrote, reviewed, and edited the manuscript: Antti Jula. Collected the resources and wrote, reviewed, and edited the manuscript: Harri Rissanen. Conceived the study, contributed to methodology, wrote the original draft of the manuscript, supervised the study, and administered the project: Kjell Nikus. Contributed to methodology; performed the formal analysis; wrote, reviewed, and edited the manuscript; and supervised the study: Jussi Hernesniemi.

DATA AVAILABILITY STATEMENT

Data are not available due to containing information that could compromise the privacy of research participants.

ORCID

Tiia Istolahti https://orcid.org/0000-0002-3743-4887

REFERENCES

Anttila, I., Nikus, K., Kähönen, M., Jula, A., Reunanen, A., Salomaa, V., … Nieminen, T. (2010). Prognostic implications of quantitative ST-segment characteristics and T-wave amplitude for cardiovascular mortality in a general population from the Health 2000 Survey. *Annals of Medicine*, *42*(7), 502–511. https://doi.org/10.3109/07853890.2010.505932

Aro, A. L., Anttonen, O., Tikkanen, J. T., Junttila, M. J., Kerola, T., Rissanen, H. A., … Huikuri, H. V. (2012). Prevalence and prognostic significance of T-wave inversions in right precordial leads of a 12-lead electrocardiogram in the middle-aged subjects. *Circulation*, *125*(21), 2572–2577. https://doi.org/10.1161/CIRCULATIONAHA.112.098681

Bakhoya, V. N., Kurl, S., & Laukkanen, J. A. (2014). T-wave inversion on electrocardiogram is related to the risk of acute coronary syndrome in the general population. *European Journal of Preventive Cardiology*, *21*(4), 500–506. https://doi.org/10.1177/2047487312460022

De Bacquer, D., De Backer, G., Kornitzer, M., & Blackburn, H. (1998). Prognostic value of ECG findings for total, cardiovascular disease, and coronary heart disease death in men and women. *Heart*, *80*(6), 570–577. https://doi.org/10.1136/hrt.80.6.570

de Luna, A. B., (Ed.). (2012). *Clinical electrocardiography: A textbook*. Chapter 7, pages 67–94. (Vol. *2012*). West Sussex, UK: Wiley-Blackwell.

de Luna, A. B., Zareba, W., Fiol, M., Nikus, K., Birnbaum, Y., Baranowski, R., … Wellens, H. (2014). Negative T wave in ischemic heart disease: a consensus article. *Annals of Noninvasive Electrocardiology*, *19*(5), 426–441. https://doi.org/10.1111/anec.12193

Greenland, P., Xie, X., Liu, K., Colangelo, L., Liao, Y., Daviglus, M. L., … Stamler, J. (2003). Impact of minor electrocardiographic ST-segment and/or T-wave abnormalities on cardiovascular mortality during long-term follow-up. *American Journal of Cardiology*, *91*(9), 1068–1074. https://doi.org/10.1016/S0002-9149(03)00150-4

Heistaro, S. (Ed.). (2008). *Methodology report: Health 2000 survey*. Helsinki, Finland: Publications of the National Public Health Institute B26; 2008. Retrieved from http://urn.fi/URN:NBN:fi-fe20120419 3320

Inoue, Y. Y., Soliman, E. Z., Yoneyama, K., Ambale-Venkatesh, B., Wu, C. O., Sparapani, R., … Ashikaga, H. (2017). Electrocardiographic strain pattern is associated with left ventricular concentric remodeling, scar, and mortality over 10 years: The Multi-Ethnic Study of atherosclerosis. *Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease*, *6*(9), e006624. https://doi.org/10.1161/JAHA.117.006624

Lancellotti, P., Gérard, P. L., Kulbertus, H. E., & Piérard, L. A. (2002). Persistent negative t waves in the infarct-related leads as an independent predictor of poor long-term prognosis after acute myocardial infarction. *American Journal of Cardiology*, *90*(8), 833–837. https://doi.org/10.1016/S0002-9149(02)02703-0

Larsen, C. T., Dahlin, J., Blackburn, H., Scharling, H., Appleyard, M., Sigurd, B., & Schnohr, P. (2002). Prevalence and prognosis of electrocardiographic left ventricular hypertrophy, ST segment depression and negative T-wave. The Copenhagen City Heart Study. *European Heart Journal*, *23*(4), 315–324. https://doi.org/10.1053/euhj.2001.2774

Laukkanen, J. A., Di Angelantonio, E., Khan, H., Kurl, S., Ronkainen, K., & Rautaharju, P. (2014). T-wave inversion, QRS duration, and QRS/T angle as electrocardiographic predictors of the risk for sudden cardiac death. *American Journal of Cardiology*, *113*(7), 1178–1183. https://doi.org/10.1016/j.amjcard.2013.12.026

Malhotra, A., Dhutia, H., Gati, S., Yeo, T.-J., Dores, H., Bastiaenen, R., … Sharma, S. (2017). Anterior T-wave inversion in young white athletes and nonathletes. *Journal of the American College of Cardiology*, *69*(1), 1–9. https://doi.org/10.1016/j.jacc.2016.10.044

Nasir, K., Bomma, C., Tandri, H., Roguin, A., Dalal, D., Prakasa, K., … Calkins, H. (2004). Electrocardiographic features of arrhythmogenic right ventricular dysplasia/cardiomyopathy according to disease severity: A need to broaden diagnostic criteria. *Circulation*, *110*(12), 1527–1534. https://doi.org/10.1161/01.CIR.0000142293.60725.18

Okin, P. M., Oikarinen, L., Viitasalo, M., Toivonen, L., Kjeldsen, S. E., Nieminen, M. S., … Devereux, R. B. (2009). Prognostic value of changes in the electrocardiographic strain pattern during antihypertensive treatment: The Losartan Intervention for End-Point Reduction in Hypertension Study (LIFE). *Circulation*, *119*(14), 1883–1891. https://doi.org/10.1161/CIRCULATIONAHA.108.812313

Prineas, R. J., Crow, R. S., & Blackburn, H. W. (1982). *The Minnesota code manual of electrocardiographic findings* (June, 1982). Littleton, MA: John Wright-PSG Inc.

Rautaharju, P. M., Menotti, A., Blackburn, H., Parapid, B., & Kircanski, B. (2012). Isolated negative T waves as independent predictors of short-term and long-term coronary heart disease mortality in men free of manifest heart disease in the Seven Countries Study. *Journal of Electrocardiology*, *45*(6), 717–722. https://doi.org/10.1016/j.jelectrocard.2012.07.006

Rautaharju, P. M., Surawicz, B., & Gettes, L. S. (2009). AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram. *Journal of the American College of Cardiology*, *53*(11), 982–991. https://doi.org/10.1016/j.jacc.2008.12.014

Reindl, M., Reinstadler, S. J., Feistritzer, H.-J., Niess, L., Koch, C., Mayr, A., … Metzler, B. (2017). Persistent T-wave inversion predicts myocardial damage after ST-elevation myocardial infarction. *International Journal of Cardiology*, *241*, 76–82. https://doi.org/10.1016/j.ijcard.2017.03.164

Sund, R. (2012). Quality of the Finnish Hospital Discharge Register: A systematic review. *Scandinavian Journal of Public Health*, *40*(6), 505–515. https://doi.org/10.1177/1403494812456637

World Health Organization & International Diabetes Federation (2006). *Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: Report of a WHO/IDF consultation*. Retrieved from http://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/

How to cite this article: Istolahti T, Lyytikäinen L-P, Huhtala H, et al. The prognostic significance of T-wave inversion according to ECG lead group during long-term follow-up in the general population. *Ann Noninvasive Electrocardiol*2021; 26:e12799. https://doi.org/10.1111/anec.12799

PUBLICATION IV

Interatrial block and P terminal force in the general population – Longitudinal changes, risk factors and prognosis

Istolahti Tiia, Eranti Antti, Huhtala Heini, Tynkkynen Juho, Lyytikäinen Leo-Pekka, Kähönen Mika, Lehtimäki Terho, Eskola Markku, Anttila Ismo, Jula Antti, Nikus Kjell, Hernesniemi Jussi

Journal of Electrocardiology, 73, 12–20
DOI: 10.1016/j.jelectrocard.2022.04.006

Journal of Electrocardiology 73 (2022) 12–20

Contents lists available at ScienceDirect

Journal of Electrocardiology

journal homepage: www.jecgonline.com

Interatrial block and P terminal force in the general population – Longitudinal changes, risk factors and prognosis

Tiia Istolahti, MD [a,b,*], Antti Eranti, MD, PhD [c], Heini Huhtala, MSc [d], Juho Tynkkynen, MD, PhD [e], Leo-Pekka Lyytikäinen, MD [a,f,g], Mika Kähönen, MD, PhD [a,h], Terho Lehtimäki, MD, PhD [a,g], Markku Eskola, MD, PhD [a,f], Ismo Anttila, MD, PhD [i], Antti Jula, MD, PhD [j], Kjell Nikus, MD, PhD [a,f], Jussi Hernesniemi, MD, PhD [a,f]

[a] *Faculty of Medicine and Health Technology, Tampere University, Finnish Cardiovascular Research Center, Tampere, Finland*
[b] *Department of Cardiology, Vaasa Central Hospital, Vaasa, Finland*
[c] *Heart Center, Central Hospital of North Karelia, Joensuu, Finland*
[d] *Faculty of Social Sciences, Tampere University, Tampere, Finland*
[e] *Department of Radiology, Tampere University Hospital, Tampere, Finland*
[f] *Tays Heart Hospital, Department of Cardiology, Tampere University Hospital, Tampere, Finland*
[g] *Department of Clinical Chemistry, Fimlab Laboratories, Tampere, Finland*
[h] *Department of Clinical Physiology, Tampere University Hospital, Tampere, Finland*
[i] *Department of Internal Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland*
[j] *National Institute for Health and Welfare, Helsinki, Finland*

ARTICLE INFO

Keywords:
Interatrial block
P terminal force
P wave
Atrial fibrillation
ECG

ABSTRACT

Background: Partial and advanced interatrial block (IAB) and P terminal force (PTF) in lead V1 are markers of atrial remodeling and risk factors for atrial fibrillation (AF). There is a lack of information about constancy and possible factors influencing the development of these P-wave abnormalities.
Methods: The study sample consisted of 6058 Finnish participants (mean age 52.16 ± 14.60 years, 45.0% male) from the general population with an ECG taken in a health examination, and from 3224 of these participants, who had a re-examination 11 years later. Risk factors for incident partial and advanced IAB and PTF were studied using binomial logistic regression analysis, and the prognostic significance of these ECG changes for new AF was studied using time-varying Cox regression analysis.
Results: The rate of reversal to normal of the studied ECG parameters were 47.4% for partial IAB, 40.0% for advanced IAB and 79.3% for PTF. Age, male sex, hypertension, higher BMI, higher LDL cholesterol, ECG left ventricular hypertrophy, use of beta blocker, and use of angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist were independently associated with a risk to develop incident P-wave abnormality. Partial IAB was independently associated with increased AF risk (HR 1.28 [95% CI 1.04–1.58]), as was also advanced IAB (HR 1.72 [95% CI 1.07–2.75]).
Conclusion: Traditional cardiovascular risk factors increase the risk of a new P-wave abnormality. Partial and advanced IAB are associated with increased AF risk. Surprisingly, P-wave abnormalities are often reversible during long-term follow-up in the general population.

Background

Partial and advanced interatrial block (IAB) and biphasic P wave with a deep negative terminal deflection in lead V1 (P terminal force, PTF [1]) in the standard 12-lead ECG have been associated with increased risk of atrial fibrillation (AF) in the general population [2–4]. Previous studies have shown a strong association between AF and atrial fibrosis [5], and structural and electrophysiological remodeling are important background factors for AF. Atrial injury and atrial wall stretch lead to activation of fibroblasts and formation of fibrotic atrial cardiomyopathy. IAB and PTF are markers of atrial remodeling. Disrupted interatrial conduction through the atrial septal wall leads to a

* Corresponding author at: Department of Cardiology, Vaasa Central Hospital, Hietalahdenkatu 2-4, 65100 Vaasa, Finland.
E-mail address: tiia.istolahti@tuni.fi (T. Istolahti).

https://doi.org/10.1016/j.jelectrocard.2022.04.006

Available online 27 April 2022

prolongation of the P wave in the surface ECG [6]. In partial IAB, the length of the P wave exceeds 120 ms, and in the advanced form, in addition to P-wave prolongation, the P waves in the inferior leads (II, III and aVF) are biphasic as a result of caudocranial activation of the left atrium [7].

A previous study showed that P-wave abnormalities in the general population can be highly reversible [8]. This raises the question about the clinical significance of reversible P-wave abnormalities and options for therapeutic interventions to prevent atriopathy. In previous studies, the risk factors for P-wave abnormalities have been similar to those linked to AF [8,9], even though there is scarcity of study data. Wider understanding of the factors associated with the development of IAB and PTF could also help to understand mechanisms leading to AF and enable more targeted preventive interventions.

The aims of this study were to examine longitudinal changes and risk factors for P-wave abnormalities, to re-evaluate earlier findings about the associated risks of partial and advanced IAB to develop AF using ECGs from two different time points, as well as to study the associated risk of PTF for AF development with similar methods.

Methods

Study population

This study is based on the Health 2000 and Health 2011 surveys that were carried out in the years 2000–2001 and 2011–2012 in Finland. The Health 2000 population was designed to cover a nationally representative population sample of the Finnish population and consisted of 8028 individuals aged 30+, of whom 79% (6354 individuals) participated in the health examination. The health examination included a structured examination by a physician, health interviews and series of laboratory tests, including ECG recordings. Participants aged 80+ were oversampled with a double sampling fraction.

All participants of the Health 2000 Survey sample, who were alive, living in Finland on July 6th, 2011, had contact details available and had not refused to participate in further surveys, were invited to take part in the Health 2011 Survey. Of the invited subjects, 73.5% ($n = 5903$) participated in the study, and 59.0% ($n = 4729$) participated in the 2011 health examination. To ensure the comparability of the two studies, the aim was to use the same study methodologies in the Health 2011 survey as in the Health 2000 survey, always when possible. More detailed descriptions of the methods of the Health 2000 and 2011 surveys have been published previously [10,11]. Ethical approval for the Health 2000 and 2011 surveys were obtained from the ethical committee at the Hospital District of Helsinki and Uusimaa (HUS).

ECG registration and analysis

During the health examinations, a standard 12-lead resting ECG in supine position was recorded from each subject with GE MAC 5000 or MAC 5500 electrocardiographs (Freiburg, Germany and Milwaukee, WI, USA) at paper speed of 50 mm/s and calibration of 10 mm/mV. The ECG data were sent for further analysis to the Social Insurance Institution's research center in Turku, where the ECGs were analyzed with Magellan software (Marquette Electronics Inc., Milwaukee, WI, USA). The Marquette 12SL algorithm uses median complexes of the 10-s ECG tracing and the onset of QRS is used as the isoelectric line. P-wave durations and amplitudes of different parts of the P wave were automatically measured, the measurement points were checked and corrected if needed. A wave crossing the baseline level constituting an area of ≥160 μVms represented a separate wave. The P-wave duration was measured from the earliest onset in any lead to the latest offset in any lead. Two investigators at the Institute of Cardiology, Kaunas Medical Academy, Lithuania, blinded to the clinical data performed the Minnesota coding [12] for the Health 2000 ECGs. The repeatability of the Minnesota Code was ascertained by a repeat analysis of 200 ECGs.

Definition of P-wave abnormalities

We defined biphasic morphology in the inferior leads (II, III and aVF) as follows: the amplitude of the initial part of the P wave ≥20uV and the amplitude of the terminal part ≤ -20uV. We chose a cut-off of 20 mV, because changes below this magnitude were not recognized in a reproducible manner on enlarged conventional ECG recordings [13]. We defined advanced IAB as P-wave duration ≥120 ms combined with biphasic P waves in at least two inferior leads and partial IAB as P-wave duration ≥120 ms with maximum one biphasic inferior lead. For the purpose of IAB analysis, ECGs with a P-wave duration <120 ms were classified as normal. The validity of the definition was checked and published before [2].

We defined PTF as the area (amplitude x length) of the negative biphasic end of the P wave in lead V1 ≥6 mV x ms as was done in a previous study [4].

In order to validate the definition of PTF, we manually reviewed and measured 25 randomly selected ECGs with PTF and 50 ECGs without, blinded to the clinical data and PTF status. For this purpose, digitalized ECGs with a zoom of 20 mm/mV and 100 mm/s were used. In 72/75 (96.0%) ECGs the manual classification matched the computerized one. In three ECGs with computer-calculated PTF, the area of the negative distal part of the P wave in lead V1 was measured as <6 mV x ms with manual analysis, and therefore the ECG was classified as normal. However, in all of those cases, the P wave was defined as biphasic both in manual and computerized analysis.

Study covariates

Trained study personnel performed the health interview, and they followed a structural detailed written instruction to gather information about pre-existent diseases. Examining physicians performed another structured interview and physical examination in the year 2000. We included data on prevalent diseases from the Care Register for Health Care (CRHC) maintained by the National Institute for Health and Welfare. CRHC contains data of all inpatient episodes in Finland at the individual level since 1969 and on outpatients since 1998. The accuracy of the register has been validated previously [14]. Information about medication was gathered by trained interviewers and in addition, data on drug purchases since 1995 and special drug reimbursements since 1964 were gathered from a separate registry (Statistics on reimbursements for prescription of medicines: The Social Insurance Institution of Finland).

High-density lipoprotein (HDL) cholesterol and plasma glucose concentrations were determined from venous blood samples with a clinical chemistry analyzer (Olympus, AU400, Hamburg, Germany). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. The diagnosis of diabetes mellitus (DM) included fasting serum glucose (fS-Gluc) ≥7 or a history of use of oral glucose lowering agents or insulin injections [15]. Height and weight were measured, and body mass index (BMI) was calculated. Blood pressure was measured from the right arm with a standard mercury manometer (Mercuro 300; Speidel & Keller, Jungingen, Germany). An average of two measurements was used, of which the first one was measured after rest for at least 5 min in sitting position. Arterial hypertension (HTA) was defined as blood pressure ≥140/90, a previous diagnosis of HTA in the CRHC (ICD-10 I10, ICD-9/8 401) or right for special drug reimbursements for HTA. Smoking was determined as a daily use of cigarettes at the time of the interview. Left ventricular hypertrophy in the ECG (ECG-LVH) was defined by Minnesota code criteria 3.1, 3.3 or 3.4 or Cornell voltage criteria calculated from ECG measurements. Wide QRS was defined a QRS-duration ≥120 ms. Intraventricular conduction disorder (IVCD) was defined by Minnesota code criteria 7.1–8. Classification of CHD required at least one of the following: diagnosed percutaneous coronary intervention (PCI) or bypass surgery in the health interview, ICD-codes I20–25 (ICD-10) or 410–14 (ICD8/9) in the

CRHC, the right for drug reimbursements for CHD, interventional code for coronary artery revascularization in the CRHC or diagnosed angina pectoris, myocardial infarction, percutaneous coronary intervention (PCI) or bypass surgery, stated by examining physician.

Follow-up and definition of AF

The data for mortality and causes of death were gathered from the Causes of Death register maintained by Statistics Finland. It contains 100% of deaths of Finnish citizens in Finland and almost 100% abroad. Information on the incident diseases were obtained from the CRHC and information on new drug reimbursements were obtained from The Social Insurance Institution of Finland's separate registry. Databases were linked using a personal identity code.

The endpoint of the study was new-onset AF. We defined AF based on the Minnesota code criteria 8.3 in the ECG at the baseline (year 2000), ICD-codes I48 (version 10), 4273 (9) or 42792 (8) in the CRHC and Causes of Death register, right for drug reimbursement for dronedarone or direct oral anticoagulants with diagnose-code (ICD-10) I48 or right for special drug reimbursements for AF. The follow-up lasted until the end of the year 2015.

Exclusion criteria

From those 6354 participants, who participated in the health examination in the year 2000, we excluded subjects with missing ECG data ($n = 55$). Of them, the recording was not successful in 36 participants, while in 19 subjects, the ECGs were lost during the further process. We excluded subjects with prevalent AF or atrial flutter diagnosed from study ECGs or registries as defined previously ($n = 204$), ectopic atrial rhythm defined as totally negative P waves in the inferior leads (II, III and aVF) in computer analysis in both ECGs (years 2000 and 2011) ($n = 31$) and those with a heart rate over 120 bpm ($n = 6$) in both ECGs leaving 6058 participants. In the analyses, where we studied the association between different clinical variables and incident P-wave abnormalities, we included only participants with ECGs available at both time points and no incident AF before the year 2011 ($n = 3224$) (Fig. 1.). From these analyses we also excluded participants with any P-wave abnormality (pIAB, aIAB or PTF) at baseline ($N = 494$) and any other P-wave abnormality than the studied one in 2011. In the analysis of factors associated with temporal change of P-wave abnormalities, we included only participants with IAB ($n = 958$) or PTF ($n = 131$) in either of the study ECGs.

Statistical analyses

Comparisons of baseline variables was performed with one-way ANOVA, unpaired *t*-test, Chi-square or Fisher's exact test as appropriate. Lost to follow-up analysis between participants, who participated in the re-examination versus those who did not, was calculated with unpaired t-test or Chi-square test. The associations between clinical factors and incident P-wave abnormalities were analyzed using binomial logistic regression adjusted by age and multivariate adjustment comparing subjects who developed new P-wave abnormality to those who did not develop P-wave abnormality (=reference). To study the risk factors for temporal change of P-wave abnormalities, binomial logistic regression was used among participants with IAB (partial and advanced) and PTF in either ECGs. In these analyses, participants with retained/worsened P-wave abnormalities were compared to participants with improvement of the P-wave abnormality (=reference). Multivariate-adjusted models included all the studied parameters as covariates. To study the prognostic significance of IAB and PTF for the development of new AF in the follow-up period, we used Cox regression analysis with time-varying covariates at the two different time points (2000 and 2011). We tested the proportional hazard assumption with Schoenfeld residuals, and no violation of the assumption was observed. In these analyses we used the following parameters from the year 2000 for multivariate adjustment: age, sex, BMI, HDL cholesterol, LDL cholesterol, HTA, DM, CHD, smoking and ECG-LVH. Analyses were performed with SPSS (versions 25 and 27) and R 4.0.3. Statistical significance was based on two-sided $p < 0.05$.

Results

Study sample

The mean age of the included Health 2000 participants with ECGs available at both study time points was 47.86 years (standard deviation [SD] 11.12 years) at baseline. Table 1 shows the baseline characteristics of these participants divided by P-wave pathology. Participants with P-wave abnormalities were significantly older than those without. They were also more likely to have higher BMI, HTA, higher LDL cholesterol, ECG-LVH, IVCD and beta blocker in use. Participants with IAB were also more likely to be men, have DM, CHD, lower HDL cholesterol and wide

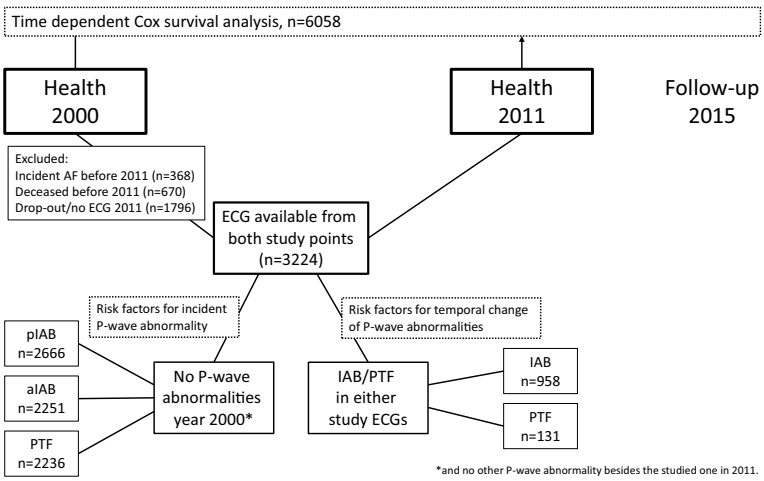

Fig. 1.. There were 6058 eligible Health 2000 participants who were followed until the end of 2015 and new diagnoses of atrial fibrillation were observed. In the analyses, where we studied the association between different clinical variables and incident P-wave abnormalities, we included only participants with ECGs available at both time points. In the analysis of factors associated with temporal change of P-wave abnormalities, we included only participants with IAB or PTF in either of the study ECGs. n=Number of Participants in The Analysis, (n)=Number of Participants per Group, AF=Atrial Fibrillation, pIAB=Partial Interatrial Block, aIAB=Advanced Interatrial Block, IAB=Interatrial Block, PTF=P Terminal Force.

Table 1
Baseline characteristics of the included Health 2000 and 2011 Survey participants ($n = 3224$).

	P wave <120 ms		Partial IAB		Advanced IAB			No PTF		PTF		
	n/mean	%/(SD)	n/mean	%/(SD)	n/mean	%/(SD)	*p* value	n/mean	%/(SD)	n/mean	%/(SD)	p value
N	2778	86.2	426	13.2	20	0.6		3132	97.1	92	2.9	
Age	47.30	(10.95)	51.18	(11.52)	56.20	(10.51)	<0.001	47.61	(10.99)	56.43	(12.10)	<0.001
Men	1151	41.4	244	57.3	16	80.0	<0.001	1368	43.7	43	46.7	0.560
BMI (kg/m^2)	26.30	(4.30)	27.49	(4.42)	29.83	(5.06)	<0.001	26.44	(4.33)	27.52	(4.56)	0.019
Smoking	525	19.0	83	19.5	6	30.0	0.446	592	19.0	22	23.9	0.235
Hypertension	959	34.6	186	43.7	11	55.0	<0.001	1101	35.2	55	59.8	<0.001
Diabetes	77	2.8	18	4.2	3	15.0	0.009	93	3.0	5	5.4	0.202
CHD	81	2.9	21	4.9	3	15.0	0.004	100	3.2	5	5.4	0.224
HDL (mmol/L)	1.37	(0.37)	1.31	(0.34)	1.16	(0.29)	0.001	1.36	(0.37)	1.37	(0.39)	0.735
LDL (mmol/L)	3.76	(1.12)	3.95	(1.07)	3.49	(1.41)	0.003	3.77	(1.11)	4.16	(1.26)	0.001
ECG-LVH	464	16.7	91	21.4	5	25.0	0.041	526	16.8	34	37.0	<0.001
Wide QRS	46	1.7	23	5.4	1	5.0	<0.001	66	2.1	4	4.3	0.138
IVCD	175	6.3	55	12.9	3	15.0	<0.001	217	6.9	16	17.4	<0.001
Beta blocker	201	7.2	63	14.8	5	25.0	<0.001	252	8.0	17	18.5	<0.001
ACEI/ARB	144	5.2	24	5.6	2	10.0	0.592	166	5.3	4	4.3	1.000

BMI = Body Mass Index, CHD = Coronary Heart Disease, HDL = High-density Lipoprotein, LDL = Low-density Lipoprotein, SD = Standard Deviation, n = Number, ECG-LVH = Left Ventricular Hypertrophy in ECG (Minnesota 3.1, 3, 4 and Cornell voltage criteria), IVCD = Intraventricular Conduction Delay, ACEI = Angiotensin-converting Enzyme Inhibitor, ARB = Angiotensin II Receptor Antagonist.

QRS in the ECG. The prevalence of co-morbidities was higher among participants with advanced IAB compared to participants with partial IAB and normal P-wave duration.

Compared with the subjects, who participated in both the Health 2000 study and the re-examination in 2011, the non-participants of the re-examination, were more likely male, were older, had higher BMI, lower HDL cholesterol, more often HTA, DM, CHD, ECG-LVH, IVCD and QRS $\geq$ 120 ms, used beta blockers, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor antagonists (ARB) and were active smokers (Appendix, Table 1). Reasons for non-participation were death between the study time points ($n = 670$), and decision not to attend the re-examination ($n = 836$); in addition, no ECG was available for 960 subjects from the follow-up study — of these 879 did not attend the health examination and 81 had no ECG recording for unknown reasons.

Among those who developed new AF between 2000 and 2011 ($n = 368$), the prevalence of P-wave abnormalities in 2000 was 4.6% for advanced IAB, 24.7% for partial IAB and 6.8% for PTF, and among those who died 2.4%, 16.4% and 7.4%, respectively. The proportions of all included Health 2000 participants divided by the outcome year 2011 are presented in the Appendix (Tables 2 and 3).

The prevalence of P-wave abnormalities

Among participants attending both surveys ($n = 3224$), the prevalence of partial and advanced IAB in the baseline ECG was 13.2% ($n = 426$) and 0.6% ($n = 20$). The prevalence of IAB increased during follow-up and in 2011 the corresponding percentages were 21.6% ($n = 697$) and 1.6% ($n = 51$). P-wave duration was normal (< 120 ms) in both ECGs in 70.3% ($n = 2266$) of the participants; 6.6% ($n = 213$) had partial IAB and 0.2% (n = 5) had advanced IAB in both ECGs. In 16.2% ($n = 523$) of the population interatrial conductivity worsened and in 6.7% ($n = 217$) conductivity improved (Fig. 2).

The prevalence of PTF in the baseline ECG was 2.9% ($n = 92$) and in the 2011 ECG 1.8% ($n = 58$). In total 95.9% ($n = 3093$) of the subjects did not have PTF in either ECGs, 0.6% ($n = 19$) had PTF in both ECGs, and 79.3% ($n = 73$) of those who had PTF at baseline, had normal P waves in 2011. New PTF in the 2011 ECG was detected in 1.2% ($n = 39$) of the subjects. The prevalence and proportions of changed IAB and PTF groups within the population are shown in Figs. 2 and 3.

Risk factors for incident P-wave abnormalities and temporal change of P-wave morphology

Age, male sex, higher BMI, HTA and medication with beta blockers or ACEI/ARB were associated with increased risk to develop new partial IAB during the 11-year follow-up, while higher HDL cholesterol was associated with lower risk (Table 2). Of these, age, sex, higher BMI and use of beta blockers were independent risk factors in multivariable adjusted analyses. The risk factors for the development of new advanced IAB were age, LDL cholesterol, ECG-LVH and the use of ACEI/ARB, and all of these were also independent risk factors after multivariate adjustment. Only age and prolonged QRS over 120 ms were associated with increased risk to develop new PTF and in the multivariate adjusted model only age reached statistical significance.

Among participants with partial or advanced IAB in either ECGs (2000/2011), higher BMI and HTA were associated with the risk for worsened or persistent IAB status after multivariate adjustment (Table 3), while higher HDL cholesterol and CHD were associated with improved IAB status. Among participants with PTF, only age was associated with the risk to have persistent/evolving PTF.

Prognostic significance of IAB and PTF

There were 6058 eligible participants in the year 2000 with a mean age of 52.16 years (SD 14.60 years), and 45.0% were male. Table 4 shows the hazard ratios (HR) and their 95% CIs for the risk of subjects with IAB and PTF to develop new AF. There were 536 subjects with a new AF diagnosis during the follow-up. Both partial and advanced IAB associated with increased risk to develop AF in age adjusted (HR 1.42 [1.16–1.73, $p = 0.001$] for partial IAB and HR 1.96 [1.23–3.11, $p = 0.004$] for advanced IAB) and multivariate adjusted models (HR 1.28 [1.04–1.58, $p = 0.020$] and 1.72 [1.07–2.75, $p = 0.024$]), respectively. PTF was not associated with AF in either analysis (HR 1.06 [0.74–1.53, $p = 0.740$] and HR 1.06 [0.73–1.54, $p = 0.747$]).

Discussion

This prospective, population-based study with long-term follow-up showed that P-wave abnormalities in the 12-lead ECG are often reversible; the rate of normalization of partial or even advanced IAB was surprisingly high. On the other hand, progression from partial to advanced IAB was rare. We could also corroborate previous study findings regarding the increased risk for new AF in subjects with partial or advanced IAB. We also gained new insights into the risk factors for the

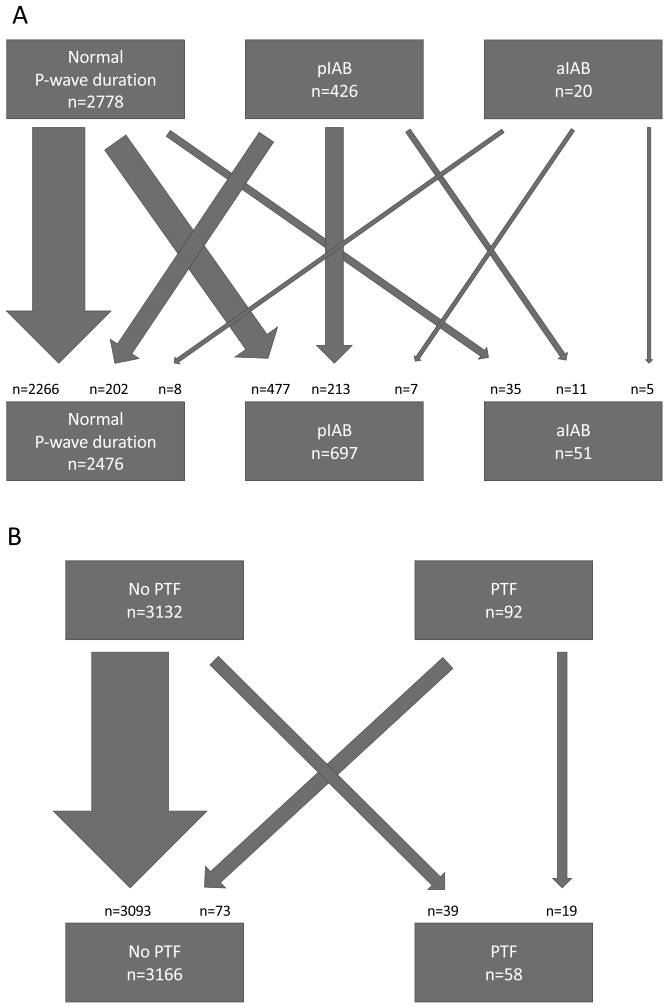

Fig. 2. The prevalence of interatrial block (A) and P-terminal force (B) in 2000 and 2011 and temporal changes within the population. n=Number of participants, pIAB=partial interatrial block, aIAB=advanced interatrial block, PTF=P-terminal force

development of P-wave abnormalities with time.

The reversible nature of P-wave abnormalities

In the present study, nearly half (47.4%) of those, who had partial IAB at baseline, had a normal P-wave duration 11 years later, and 75% of those, who had advanced IAB at baseline, had partial IAB or normal P-wave duration at follow-up. Furthermore, 79.3% of participants with PTF at baseline did no longer have this P-wave abnormality 11 years later. We conclude that IAB and PTF seem to be labile ECG manifestations during long-term follow-up. Similar conclusions were drawn from a previous study, where Lehtonen et al. (2017) [8] studied P-wave duration, PTF ($\geq$ 4 mV x ms) and P-wave axis in the same population. Apart from these studies, the labile nature of P-wave abnormalities has not been well documented in the general population. In hypertensive patients, treatment shortened the maximal P-wave duration [16]. It is not known whether this seemingly favorable change reduces the risk of AF as well. A previous study also showed that in acutely ill cardiac patients (acute myocardial infarction in the majority), there was an association between left ventricular filling pressures and PTF; when pressures dropped to normal, the ECG change returned to normal as well [17]. In the present study, the number of subjects with prevalent P-wave abnormalities was too low to enable analysis of the prognostic significance of the normalization of P-wave pathologies.

It is possible that part of the fluctuation is explained by the change of categories of participants with borderline P-wave abnormalities. It has also been demonstrated that misplacement of the ECG electrode V1 may result in a false ECG diagnosis of PTF based on an increase of the terminal negative area of the biphasic P wave [18]. However, we consider this as a rather unlikely confounding factor in this prospective study with trained study personnel. Also, this analysis included only participants with EGCs available in both study points 11 years apart and no prior AF. It is probable that participants with most advanced atriopathy at baseline developed AF or died during the follow-up and were thus excluded from the analysis.

Fig. 3. The rate of changes of the P-wave morphology, (A) IAB and (B) PTF, in % between the baseline (year 2000) and the follow-up ECG (year 2011). N = Number of participants/group.

Risk factors to develop new or altered P-wave abnormality

We found that age was a major contributing factor to develop any P-wave abnormality. The development of new partial IAB was associated with traditional cardiovascular risk factors such as male sex, higher BMI, HTA and low HDL cholesterol, as well as use of beta blockers or ACEI/ARB medication. An earlier study, which included patients from a general hospital, showed similar results: participants with prolonged P-wave duration ≥110 ms were more likely to have HTA, DM, CHD or hypercholesterolemia [19]. In our study, higher BMI and HTA also associated with worsened IAB status, while higher HDL cholesterol and CHD seemed to be associated with improved IAB status. The observation of the possible association with CHD is rather unexpected. Possible explanations for this borderline significant observation could be a type II error or better treatment of other cardiovascular risk factors thanks to the diagnosis. Another potential explanation is survival bias since the prevalence of CHD at baseline was higher among participants with partial and advanced IAB, which could result in higher mortality and a higher dropout rate between the study points of these subjects. On the contrary, the association between worsened or persistent IAB status and HTA or higher BMI is not surprising. Hypertension may increase left atrial pressure and volume by elevating the left ventricular end-diastolic pressure and has been linked to atrial interstitial fibrosis and conduction disturbances [20]. Obesity leads to left atrial remodeling, including increased atrial fibrosis, fatty infiltration and conduction slowing. Mechanisms behind these changes include hemodynamics, cardiometabolic abnormalities, hormones and inflammatory processes. [21]

In contrast to partial IAB, we found that risk factors to develop new

Table 2
Risk factors to develop new P-wave abnormality. Year 2000 clinical variables and binary logistic regression to develop incident P-wave abnormality year 2011.

	pIAB (Odds Ratio [95% CI]) $n = 448$			aIAB (Odds Ratio [95% CI]) $n = 33$				PTF (Odds Ratio [95% CI]) $n = 18$			
	Adjusted with age	*p*-value	Multivariate adjusted	p-value	Adjusted with age	p-value	Multivariate adjusted	p-value	Adjusted with age	p-value	Multivariate adjusted	p-value
Age	1.03 (1.02–1.04) unadjusted	<0.001	1.02 (1.01–1.03)	<0.001	1.10 (1.07–1.13) unadjusted	0.001	1.08 (1.04–1.12)	<0.001	1.08 (1.04–1.13) unadjusted	<0.001	1.07 (1.02–1.13)	0.008
Male sex	1.91 (1.55–2.34)	<0.001	1.94 (1.54–2.45)	<0.001	1.71 (0.85–3.44)	0.133	1.76 (0.82–3.81)	0.149	0.45 (0.15–1.37)	0.159	0.39 (0.11–1.32)	0.130
BMI (kg/m^2)	1.10 (1.08–1.13)	<0.001	1.10 (1.07–1.13)	<0.001	1.05 (0.97–1.14)	0.260	1.04 (0.94–1.14)	0.484	0.95 (0.84–1.08)	0.416	0.970 (0.85–1.11)	0.662
Smoking	0.87 (0.66–1.15)	0.342	0.89 (0.67–1.19)	0.430	0.43 (0.10–1.84)	0.255	0.41 (0.10–1.80)	0.239	2.45 (0.83–7.21)	0.105	2.95 (0.96–9.08)	0.060
Hypertension	1.60 (1.28–2.00)	<0.001	1.08 (0.84–1.38)	0.559	1.77 (0.81–3.87)	0.150	1.17 (0.50–2.71)	0.723	1.10 (0.40–3.04)	0.853	1.26 (0.39–4.02)	0.698
Diabetes	1.36 (0.79–2.36)	0.268	0.89 (0.50–1.58)	0.687	0.82 (0.11–6.19)	0.845	0.64 (0.08–5.17)	0.673	1.63 (0.21–12.65)	0.640	3.51 (0.39–31.51)	0.262
CHD	0.81 (0.45–1.47)	0.493	0.61 (0.32–1.16)	0.130	0.72 (0.16–3.22)	0.671	1.05 (0.21–5.25)	0.955	0.79 (0.10–6.28)	0.820	0.84 (0.09–8.09)	0.882
HDL (mmol/L)	0.55 (0.41–0.73)	<0.001	1.07 (0.77–1.49)	0.699	0.62 (0.23–1.66)	0.339	0.83 (0.27–2.53)	0.741	2.53 (0.85–7.54)	0.097	2.14 (0.59–7.72)	0.245
LDL (mmol/L)	1.00 (0.91–1.10)	0.971	0.98 (0.89–1.07)	0.645	1.56 (1.14–2.15)	0.006	1.52 (1.10–2.11)	0.012	1.06 (0.68–1.64)	0.794	1.04 (0.65–1.67)	0.867
ECG-LVH	1.20 (0.92–1.57)	0.174	1.16 (0.88–1.53)	0.279	2.39 (1.15–4.98)	0.020	2.31 (1.09–4.91)	0.030	1.48 (0.51–4.31)	0.468	1.50 (0.49–4.66)	0.481
Wide QRS	1.66 (0.81–3.39)	0.164	1.18 (0.53–2.64)	0.685	1.25 (0.15–10.21)	0.835	0.39 (0.03–4.88)	0.465	5.81 (1.21–28.83)	0.028	5.85 (0.67–51.24)	0.111
IVCD	1.34 (0.91–1.99)	0.143	1.27 (0.81–1.99)	0.294	1.67 (0.55–5.04)	0.365	2.32 (0.65–8.26)	0.195	2.75 (0.77–9.83)	0.119	1.64 (0.30–9.06)	0.569
Beta blocker	1.57 (1.10–2.22)	0.012	1.48 (1.00–2.18)	0.049	0.46 (0.11–1.98)	0.295	0.38 (0.08–1.84)	0.229	1.65 (0.45–5.98)	0.448	2.30 (0.56–9.50)	0.250
ACEI/ARB	1.63 (1.09–2.44)	0.017	1.32 (0.85–2.03)	0.213	3.11 (1.23–7.87)	0.017	2.97 (1.08–8.18)	0.035	No events		No events	

pIAB = Partial Interatrial Block, aIAB = Advanced Interatrial Block, PTF=P Terminal Force, CI=Confidence Interval, BMI=Body Mass Index, CHD=Coronary Heart Disease, HDL = High-density Lipoprotein, LDL = Low-density Lipoprotein, ECG-LVH = Left Ventricular Hypertrophy in ECG (Minnesota 3.1, 3, 4 and Cornell voltage criteria), IVCD=Intraventricular Conduction Delay, ACEI = Angiotensin-converting Enzyme Inhibitor, ARB = Angiotensin II Receptor Antagonist. Multivariate adjusted models included all the listed parameters as covariates.

Table 3
Risk factors for temporal change of P-wave abnormalities. Risk factors for year 2000 detected P-wave abnormalities (IAB and PTF) to persist or progress year 2011. Binomial logistic regression. Number of participants in the analysis was 958 for IAB and 131 for PTF.

	IAB (Odds Ratio [95% CI])				PTF (Odds Ratio [95% CI])			
	Adjusted with age	p-value	Multivariate adjusted	p-value	Adjusted with age	p-value	Multivariate adjusted	p-value
Age (unadjusted)	1.01 (1.00–1.03)	0.092	1.01 (0.99–1.02)	0.352	1.04 (1.01–1.08)	0.012	1.04 (1.00–1.09)	0.036
Male sex	0.87 (0.64–1.19)	0.384	0.93 (0.66–1.32)	0.698	1.30 (0.64–2.67)	0.469	1.31 (0.57–2.98)	0.526
BMI (kg/m^2)	1.08 (1.04–1.12)	<0.001	1.07 (1.02–1.12)	0.002	0.98 (0.90–1.07)	0.708	0.97 (0.87–1.07)	0.511
Smoking	1.44 (0.99–2.11)	0.060	0.69 (0.47–1.03)	0.070	1.11 (0.47–2.61)	0.821	1.27 (0.50–3.26)	0.619
Hypertension	1.81 (1.30–2.51)	<0.001	1.47 (1.02–2.11)	0.037	1.16 (0.56–2.39)	0.698	1.35 (0.57–3.20)	0.501
Diabetes	0.73 (0.36–1.49)	0.387	0.58 (0.27–1.22)	0.148	0.44 (0.08–2.47)	0.349	0.31 (0.04–2.61)	0.281
CHD	0.47 (0.24–0.94)	0.032	0.47 (0.22–1.01)	0.053	3.42 (0.66–17.83)	0.144	2.65 (0.32–21.74)	0.364
HDL (mmol/L)	0.63 (0.41–0.98)	0.040	0.82 (0.49–1.38)	0.454	0.83 (0.34–1.99)	0.674	0.83 (0.28–2.47)	0.740
LDL (mmol/L)	1.04 (0.90–1.19)	0.629	0.97 (0.84–1.12)	0.684	0.90 (0.66–1.23)	0.509	0.92 (0.65–1.30	0.644
ECG-LVH	1.46 (0.98–2.18)	0.061	1.45 (0.96–2.19)	0.081	0.59 (0.28–1.28)	0.182	0.46 (0.19–1.14)	0.093
Wide QRS	0.79 (0.38–1.66)	0.538	0.87 (0.37–2.09)	0.761	0.55 (0.11–2.73)	0.467	0.79 (0.12–5.36)	0.806
IVCD	0.85 (0.53–1.38)	0.522	0.88 (0.50–1.53)	0.639	0.62 (0.23–1.70)	0.351	0.68 (0.20–2.29)	0.537
Beta blocker	0.93 (0.59–1.48)	0.764	0.90 (0.52–1.53)	0.691	1.82 (0.73–4.55)	0.201	1.50 (0.44–5.10)	0.517
ACEI/ARB	1.27 (0.68–2.38)	0.452	1.04 (0.54–2.02)	0.906	No events		No events	

IAB = Interatrial Block, PTF = P Terminal Force, CI = Confidence Interval, BMI = Body Mass Index, CHD = Coronary Heart Disease, HDL = High-density Lipoprotein, LDL = Low-density Lipoprotein, ECG-LVH = Left Ventricular Hypertrophy in ECG (Minnesota 3.1, 3, 4 and Cornell voltage criteria), IVCD=Intraventricular Conduction Delay, ACEI = Angiotensin-converting Enzyme Inhibitor, ARB = Angiotensin II Receptor Antagonist. Multivariate-adjusted models included all the listed parameters as covariates.

Table 4
Prognostic significance of IAB and PTF to develop new AF during the follow up period. The Cox regression analysis with time varying covariates at two different time points years 2000 and 2011, with the follow up lasting until 2015.

			Hazard ratio (95% CI)			
	AF diagnoses/participants	%	Adjusted with age	p value	Multivariate adjusted	p value
Normal (P wave <120 ms)	388/5132	7.6	1		1	
Partial IAB	129/862	15.0	1.42 (1.16–1.73)	0.001	1.28 (1.04–1.58)	0.020
Advanced IAB	19/64	29.7	1.96 (1.23–3.11)	0.004	1.72 (1.07–2.75)	0.024
No PTF	502/5827	8.6	1		1	
PTF	34/231	14.7	1.06 (0.74–1.53)	0.740	1.06 (0.73–1.54)	0.747

IAB = Interatrial Block, PTF = P Terminal Force, CI = Confidence Interval, AF = atrial fibrillation. Parameters used in multivariate adjustment: Age, Sex, High-density Lipoprotein Cholesterol, Low-density Lipoprotein cholesterol, Body Mass Index, Hypertension, Diabetes Mellitus, Coronary Heart Disease, Smoking and Left Ventricular Hypertrophy in ECG.

advanced IAB included, in addition to age, ECG-LVH, higher LDL cholesterol and use of ACEI/ARB medication. The association with ACEI/ARB is interesting as they are potential preventive medications for IAB, at least based on results from AF patients [22]. Furthermore, antihypertensive treatment with losartan was effective in reducing left ventricular mass according to ECG-LVH [23]. The most probable explanation for the association may be that the use of these medications generally reflects more severe overall cardiovascular risk. However, there is a lack of prospective studies about the effects of medical therapy to prevent or reverse IAB. Only higher age and wide QRS complex were associated with increased risk to develop new PTF, and only higher age associated with increased risk of new PTF or persistence of the ECG parameter.

Surprisingly, the associations with cardiovascular risk factors and the development of P-wave abnormalities were not particularly strong. Thus, it is likely that there are additional, yet unknown, factors leading to the development of P-wave abnormalities, which also explain part of the AF burden in the population. For example, multiple genetic loci have been associated with prolonged P-wave duration. Furthermore, adding complexity, some of the genetic loci associated with increased P-wave duration have been associated with reduced risk of AF [24]. In addition, the susceptibility to inflammation and fibrosis in the atria may differ markedly between subjects, and diet may also play a role [25,26]. Thus, future effort should be directed to identifying and understanding yet unknown risk factors of atrial cardiomyopathy.

Prognostic significance of IAB and PTF

Like in our earlier study about IAB and its subgroups in the general population [2], we found that partial and advanced IAB were associated with increased risk of AF during long-term follow-up. Many previous studies in the general population [3,27], as well as in many different clinical situations [28], have come to the same conclusion. In our study, the HRs were higher among participants with advanced than with partial IAB; this was also shown in a large population study in which the risk seemed to increase with the number of affected biphasic inferior leads [3].

We did not find any increased risk of AF among participants with PTF. Previous studies also have shown conflicting results regarding the association between PTF and AF [29]. A recent study [30] showed that apart from the classical advanced IAB morphology with conduction disturbances through the Bachmann's bundle, additional conduction disturbance in the posterior left atrium led to development of a severely prolonged amplified P wave, lacking the biphasic morphology in the inferior leads. Our study did not include amplified P waves, and it is possible that some cases with further atrial damage presenting with a short positive initial part and a long low-amplitude terminal part of the P wave were classified as having normal P waves.

A well-grounded hypothesis has been presented suggesting that subjects at high risk of stroke with advanced IAB might benefit of early anticoagulation therapy already before an AF diagnosis [28,31]. Even though we found an association between IAB and increased risk of AF, this study revealed that P-wave abnormalities were highly labile during 11 years follow up. This finding seems to complicate the issue of

therapeutic measures in IAB patients, although the prognostic significance of reversal of P-wave abnormalities remains unknown.

Study limitations and strengths

This was a large population study with 6058 participants at baseline. Nevertheless, some of the groups studied remained small-sized. The study protocol with ECGs 11 years apart is a strength of our study. However, we have to consider the possibility that the participants with the most severe P-wave changes did not attend the follow-up survey, because of death or study exclusion due to AF between the study time points. We used the PTF definition of $\geq$6 mV x ms instead of the more often used $\geq$4 mV x ms, which reduces the risk of PTF overestimation due to misplaced V1 electrodes [18]. However, the possible misplacement of the electrode V1 is a limitation in PTF studies even though we consider it less likely to happen in research circumstances than in clinical practice. We used computer-based measurements of the ECG, as manual analysis of the P-wave morphology may be difficult because of the small P-wave amplitudes, disturbing artefacts and because it may be difficult to get a reliable detection of the end of the P wave. Automatic measurements may help to correct for these factors and the repeatability of automated measurements is excellent. To study the prognostic significance of P-wave abnormalities we used time-varying Cox regression, which allowed us to consider timely changes in the studied ECG variables.

Data of prevalent and incident AF were mainly collected from national registers, but it is possible that some AF paroxysms diagnosed in primary care were not included in our analysis. It is also possible that subclinical paroxysmal AF, which was not possible to control for in the study population, may have influenced the results. Also, as in most studies from the general population, we could not correlate our study results with echocardiographic or other imaging data.

Finally, apart from IAB and PTF, our study did not explore the significance of other P-wave abnormalities, such as P-wave area [32], P-wave axis [33], P-wave voltage [34] and P-wave dispersion [35].

Conclusion

Partial and advanced IAB are risk factors for AF development. The risk factors for new P-wave abnormalities include traditional cardiovascular risk factors such as HTA, higher BMI and higher LDL cholesterol. According to our study results, P-wave abnormalities are highly labile during long-term follow-up in the general population. Therefore, we think that the prognostic significance of normalization of P-wave abnormalities needs to be explored before considering therapeutic interventions based on IAB or PTF.

Funding

The study was financially supported by the Maire Taponen's Foundation; the Ida Montin's Foundation and the Doctoral Programme in Medicine and Life Sciences, Faculty of Medicine and Health Technology, Tampere University (for T.I.); and Competitive Research Funding of the Tampere University Hospital [grant numbers 9M048 and 9N035]; the Finnish Cultural Foundation; the Finnish Foundation for Cardiovascular Research; the Emil Aaltonen Foundation; the Tampere Tuberculosis Foundation; EU Horizon 2020 [grant number 755320 for TAXINOMISIS and grant number 848146 for To Aition], and the Academy of Finland [grant number 322098] (for T.L.).

CRediT authorship contribution statement

Tiia Istolahti: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Antti Eranti:** Conceptualization, Methodology, Writing – review & editing. **Heini Huhtala:** Methodology, Formal analysis. **Juho Tynkkynen:** Methodology, Formal analysis, Writing – review & editing. **Leo-Pekka Lyytikäinen:** Software, Writing – review & editing. **Mika Kähönen:** Writing – review & editing, Supervision. **Terho Lehtimäki:** Writing – review & editing. **Markku Eskola:** Writing – review & editing. **Ismo Anttila:** Writing – review & editing. **Antti Jula:** Data curation, Writing – review & editing. **Kjell Nikus:** Conceptualization, Methodology, Writing – original draft, Supervision, Project administration. **Jussi Hernesniemi:** Conceptualization, Methodology, Formal analysis, Writing – review & editing, Supervision.

Declaration of Competing Interest

None.

Acknowledgements

We thank the investigators, staff, and participants of the Health 2000 and 2011 surveys, and A. S. Havulinna, V. Salomaa, and the Finnish Institute of Health and Welfare for their work on coding endpoints.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jelectrocard.2022.04.006.

References

[1] Morris JJ, Estes EH, Whalen RE, Thompson HK, Mcintosh HD. P-wave analysis in Valvular heart disease. Circulation 1964;29:242–52. https://doi.org/10.1161/01.CIR.29.2.242.
[2] Istolahti T, Eranti A, Huhtala H, Lyytikäinen L-P, Kähönen M, Lehtimäki T, et al. The prevalence and prognostic significance of interatrial block in the general population. Ann Med 2020:1–11. https://doi.org/10.1080/07853890.2020.1731759.
[3] Skov MW, Ghouse J, Kühl JT, Platonov PG, Graff C, Fuchs A, et al. Risk prediction of atrial fibrillation based on electrocardiographic interatrial block. J Am Heart Assoc 2018;7:e008247. https://doi.org/10.1161/JAHA.117.008247.
[4] Eranti A, Aro AL, Kerola T, Anttonen O, Rissanen HA, Tikkanen JT, et al. Prevalence and prognostic significance of abnormal P terminal force in Lead V_1 of the ECG in the general population. Circ Arrhythm Electrophysiol 2014;7:1116–21. https://doi.org/10.1161/CIRCEP.114.001557.
[5] Hirsh BJ, Copeland-Halperin RS, Halperin JL. Fibrotic atrial cardiomyopathy, atrial fibrillation, and thromboembolism: mechanistic links and clinical inferences. J Am Coll Cardiol 2015;65:2239–51. https://doi.org/10.1016/j.jacc.2015.03.557.
[6] Bayés de Luna A, Platonov P, Cosio FG, Cygankiewicz I, Pastore C, Baranowski R, et al. Interatrial blocks. A separate entity from left atrial enlargement: a consensus report. J Electrocardiol 2012;45:445–51. https://doi.org/10.1016/j.jelectrocard.2012.06.029.
[7] Bayés de Luna A, Baranchuk A, Alberto Escobar Robledo L, Massó van Roessel A, Martínez-Sellés M. Diagnosis of interatrial block. J Geriatr Cardiol JGC 2017;14:161–5. https://doi.org/10.11909/j.issn.1671-5411.2017.03.007.
[8] Lehtonen AO, Langén VL, Puukka PJ, Kähönen M, Nieminen MS, Jula AM, et al. Incidence rates, correlates, and prognosis of electrocardiographic P-wave abnormalities – a nationwide population-based study. J Electrocardiol 2017;50:925–32. https://doi.org/10.1016/j.jelectrocard.2017.07.004.
[9] Benjamin EJ, Chen P-S, Bild DE, Mascette AM, Albert CM, Alonso A, et al. Prevention of atrial fibrillation: report from a National Heart, Lung, and Blood Institute workshop. Circulation 2009;119:606–18. https://doi.org/10.1161/CIRCULATIONAHA.108.825380.
[10] Heistaro S. Methodology report: health 2000 surveyB26. Helsinki, Finland: Publications of the National Public Health Institute; 2008. Available from, http://urn.fi/URN:NBN:fi-fe201204193320.
[11] Lundqvist A, Mäki-Opas T. Health 2011 survey – methods [cited 2021 Jul 1]; Available from: https://www.julkari.fi/bitstream/handle/10024/130780/URN_ISBN_978-952-302-669-8.pdf?sequence=1&isAllowed=y; 2016.
[12] Prineas RJ, Crow RS, Blackburn HW. The Minnesota Code Manual of Electrocardiographic Findings. June, 1982. Littleton, MA: John Wright-PSG, Inc.; 1982.
[13] Recommendations for Measurement Standards in Quantitative Electrocardiography. The CSE working party. Eur Heart J 1985;6:815–25.
[14] Sund R. Quality of the Finnish hospital discharge register: a systematic review. Scand J Public Health 2012;40:505–15. https://doi.org/10.1177/1403494812456637.
[15] World Health Organization, International Diabetes Federation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation. Available from, http://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/; 2006.

[16] Aizawa Y, Sato T, Akazawa K. Prevalence, significance and reversal of abnormal P-wave indices in hypertension: a review and meta-analysis. J Electrocardiol 2019; 53:13–7. https://doi.org/10.1016/j.jelectrocard.2018.12.008.
[17] Heikkila J, Hugenholtz PG, Tabakin BS. Prediction of left heart filling pressure and its sequential change in acute myocardial infarction from the terminal force of the P wave. Heart 1973;35:142–51. https://doi.org/10.1136/hrt.35.2.142.
[18] Rasmussen MU, Fabricius-Bjerre A, Kumarathurai P, Larsen BS, Domínguez H, Kanters JK, et al. Common source of miscalculation and misclassification of P-wave negativity and P-wave terminal force in lead V1. J Electrocardiol 2019;53:85–8. https://doi.org/10.1016/j.jelectrocard.2019.01.088.
[19] Ariyarajah V, Apiyasawat S, Moorthi R, Spodick DH. Potential clinical correlates and risk factors for interatrial block. Cardiology 2006;105:213–8. https://doi.org/10.1159/000091642.
[20] Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial fibrillation: epidemiology, pathophysiology, and clinical outcomes. Circ Res 2017;120:1501–17. https://doi.org/10.1161/CIRCRESAHA.117.309732.
[21] Lavie CJ, Pandey A, Lau DH, Alpert MA, Sanders P. Obesity and atrial fibrillation prevalence, pathogenesis, and prognosis. J Am Coll Cardiol 2017;70:2022–35. https://doi.org/10.1016/j.jacc.2017.09.002.
[22] Chhabra L, Devadoss R, Chaubey VK, Spodick DH. Interatrial block in the modern era. Curr Cardiol Rev 2014;10:181–9. https://doi.org/10.2174/1573403X10666140514101748.
[23] Wachtell K, Okin PM, Olsen MH, Dahlöf B, Devereux RB, Ibsen H, et al. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive therapy and reduction in sudden cardiac death: the LIFE study. Circulation 2007; 116:700–5. https://doi.org/10.1161/CIRCULATIONAHA.106.666594.
[24] Weng L-C, Hall AW, Choi SH, Jurgens SJ, Haessler J, Bihlmeyer NA, et al. Genetic determinants of electrocardiographic P-wave duration and relation to atrial fibrillation. Circ Genomic Precis Med 2020;13:387–95. https://doi.org/10.1161/CIRCGEN.119.002874.
[25] Nicholls SJ, Lincoff AM, Garcia M, Bash D, Ballantyne CM, Barter PJ, et al. Effect of high-dose Omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. JAMA 2020;324:2268. https://doi.org/10.1001/jama.2020.22258.
[26] Pääkkö TJW, Perkiömäki JS, Silaste M-L, Bloigu R, Huikuri HV, Antero Kesäniemi Y, et al. Dietary sodium intake is associated with long-term risk of new-onset atrial fibrillation. Ann Med 2018;50:694–703. https://doi.org/10.1080/07853890.2018.1546054.
[27] O'Neal WT, Zhang Z-M, Loehr LR, Chen LY, Alonso A, Soliman EZ. Electrocardiographic advanced interatrial block and atrial fibrillation risk in the general population. Am J Cardiol 2016;117:1755–9. https://doi.org/10.1016/j.amjcard.2016.03.013.
[28] Baranchuk A, Alexander B, Cinier G, Martinez-Selles M, Tekkesin AI, Elousa R, et al. Bayés' syndrome: time to consider early anticoagulation? North Clin Istanb 2018;5:370–8. https://doi.org/10.14744/nci.2017.60251.
[29] Huang Z, Zheng Z, Wu B, Tang L, Xie X, Dong R, et al. Predictive value of P wave terminal force in lead V1 for atrial fibrillation: a meta-analysis. Ann Noninvasive Electrocardiol 2020;25. https://doi.org/10.1111/anec.12739.
[30] Müller-Edenborn B, Chen J, Allgeier J, Didenko M, Moreno-Weidmann Z, Neumann F-J, et al. Amplified sinus-P-wave reveals localization and extent of left atrial low-voltage substrate: implications for arrhythmia freedom following pulmonary vein isolation. EP Eur 2020;22:240–9. https://doi.org/10.1093/europace/euz297.
[31] Bayés de Luna A, Baranchuk A, Martínez-Sellés M, Platonov PG. Anticoagulation in patients at high risk of stroke without documented atrial fibrillation. Time for a paradigm shift? Ann Noninvasive Electrocardiol 2017;22:e12417. https://doi.org/10.1111/anec.12417.
[32] Chen LY, Ribeiro ALP, Platonov PG, Cygankiewicz I, Soliman EZ, Gorenek B, et al. P-wave parameters and indices: a critical appraisal of clinical utility, challenges, and future research—a consensus document endorsed by the International Society of Electrocardiology and the international society for Holter and noninvasive Electrocardiology. Circ Arrhythm Electrophysiol 2022;15:e010435. https://doi.org/10.1161/CIRCEP.121.010435.
[33] Maheshwari A, Norby FL, Soliman EZ, Koene R, Rooney M, O'Neal WT, et al. Refining prediction of atrial fibrillation risk in the general population with analysis of P-wave Axis (from the atherosclerosis risk in communities study). Am J Cardiol 2017;120:1980–4. https://doi.org/10.1016/j.amjcard.2017.08.015.
[34] Park J-K, Park J, Uhm J-S, Joung B, Lee M-H, Pak H-N. Low P-wave amplitude (<0.1 mV) in lead I is associated with displaced inter-atrial conduction and clinical recurrence of paroxysmal atrial fibrillation after radiofrequency catheter ablation. Europace 2016;18:384–91. https://doi.org/10.1093/europace/euv028.
[35] Dilaveris PE, Gialafos EJ, Sideris SK, Theopistou AM, Andrikopoulos GK, Kyriakidis M, et al. Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. Am Heart J 1998;135:733–8. https://doi.org/10.1016/S0002-8703(98)70030-4.

Appendix

Table 1. Lost to follow-up analysis, baseline characteristics year 2000. There were 6058 eligible participants year 2000, of whom 368 got atrial fibrillation between the study points and were thus excluded. From the remaining 5690 participants 2466 had no ECG available year 2011 because of death or the non-participation to the Health 2011 survey or ECG recording.

	Participants with 2 ECGs		Lost to follow-up		
	n/mean	%/(SD)	n/mean	%/(SD)	p value
N	3224	56.7	2466	43.3%	
Age	47.86	(11.12)	55.53	(16.4)	<0.001
Men	1411	(43.8)	1146	(46.5)	0.042
BMI (kg/m^2)	26.47	4.34	27.20	4.88	<0.001
Smoking	614	19.1	654	26.6	<0.001
Hypertension	1156	35.9	1337	54.3	<0.001
Diabetes	98	3.0	221	9.0	<0.001
CHD	105	3.3	261	10.6	<0.001
HDL (mmol/L)	1.36	(0.37)	1.31	(0.38)	<0.001
LDL (mmol/L)	3.78	(1.12)	3.81	(1.28)	0.337
ECG-LVH	560	17.4	556	22.5	<0.001
Wide QRS	70	2.2	81	3.3	0.010
IVCD	233	7.2	229	9.3	0.005
Beta blocker	269	17.0	419	8.3	<0.001
ACEI/ARB	170	5.3	234	9.5	<0.001

BMI=Body Mass Index, CHD=Coronary Heart Disease, HDL=High-density Lipoprotein, LDL=Low-density Lipoprotein, SD=Standard Deviation, N=Number, ECG-LVH=Left Ventricular Hypertrophy in ECG (Minnesota 3.1, 3, 4 and Cornell voltage criteria), IVCD=Intraventricular Conduction Delay, ACEI=Angiotensin-converting Enzyme Inhibitor, ARB=Angiotensin II Receptor Antagonist

Table 2. All included Health 2000 participants divided by the IAB group and outcome year 2011.

	2011											
	Normal		pIAB		aIAB		AF		Death		No ECG	
2000	n	%	n	%	n	%	n	%	n	%	n	%
Normal	2266	44.2	477	9.3	35	0.7	260	5.1	545	10.6	1549	30.2
pIAB	202	23.4	213	24.7	11	1.3	91	10.6	110	12.8	235	27.3
aIAB	8	12.5	7	10.9	5	7.8	17	26.6	15	23.4	12	18.8

pIAB=Partial Interatrial Block, aIAB=Advanced Interatrial Block, n=Number of Participants per Group, AF=Atrial Fibrillation.

Table 3. All included Health 2000 participants divided by the PTF status and outcome year 2011.

	2011									
	No PTF		PTF		AF		Death		No ECG	
2000	n	%	n	%	n	%	n	%	n	%
No PTF	3093	53.1	39	0.7	343	5.9	620	10.6	1732	29.7
PTF	73	31.6	19	8.2	25	10.8	50	21.6	64	27.7

PTF=P Terminal Force, n=Number of Participants per Group, AF=Atrial Fibrillation.