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ORIGINAL SCIENTIFIC PAPER

Intraventricular conduction delays as a predictor of mortality in acute coronary syndromes

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Aims

Initial proof suggests that a non-specific intraventricular conduction delay (NIVCD) is a risk factor for mortality. We explored the prognosis of intraventricular conduction delays (IVCD)—right bundle branch block (RBBB), left bundle branch block (LBBB), and the lesser-known NIVCD—in patients with acute coronary syndrome (ACS).

Methods and results

This is a retrospective registry analysis of 9749 consecutive ACS patients undergoing coronary angiography and with an electrocardiographic (ECG) recording available for analysis (2007–18). The primary outcome was cardiac mortality. Mortality and cause of death data (in ICD-10 format) were received from the Finnish national register with no losses to follow-up (until 31 December 2020). The risk associated with IVCDs was analysed by calculating subdistribution hazard estimates (SDH; deaths due to other causes being considered competing events). The mean age of the population was 68.3 years [standard deviation (SD) 11.8]. The median follow-up time was 6.1 years [interquartile range (IQR) 3.3–9.4], during which 3156 patients died. Cardiac mortality was overrepresented among IVCD patients: 76.9% for NIVCD ($n = 113/147$), 67.6% for LBBB ($n = 96/142$), 55.7% for RBBB ($n = 146/262$), and 50.1% for patients with no IVCD ($n = 1275/2545$). In an analysis adjusted for age and cardiac comorbidities, the risk of cardiac mortality was significantly higher in all IVCD groups than among patients with no IVCD: SDH 1.37 (1.15–1.64, $P < 0.0001$) for RBBB, SDH 1.63 (1.31–2.03 $P < 0.0001$) for LBBB, and SDH 2.68 (2.19–3.27) for NIVCD. After adjusting the analysis with left ventricular ejection fraction, RBBB and NIVCD remained significant risk factors for cardiac mortality.

Conclusion

RBBB, LBBB, and NIVCD were associated with higher cardiac mortality in ACS patients.

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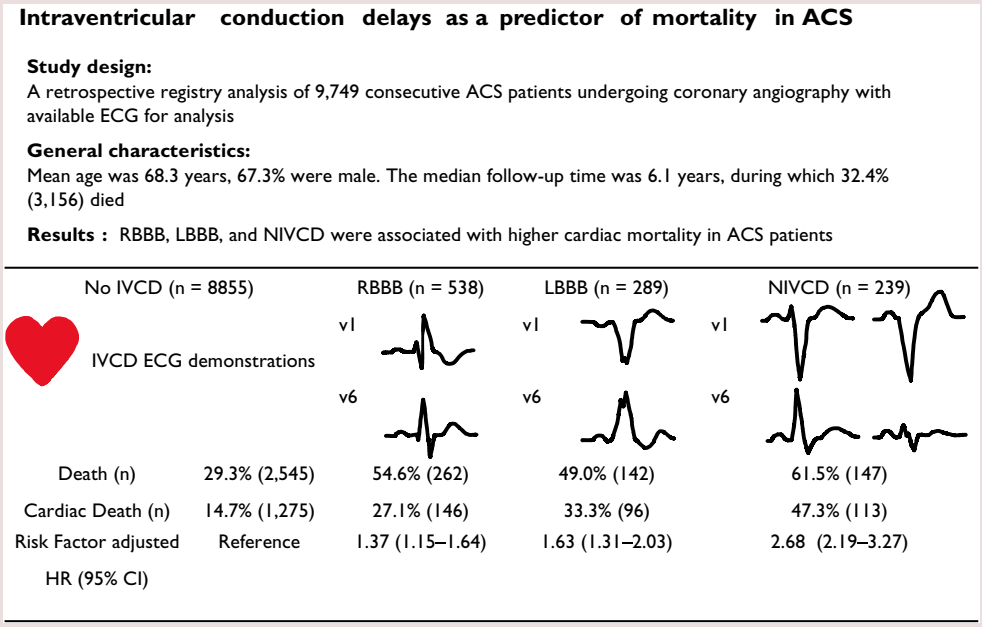
Graphical Abstract



Keywords Intraventricular conduction delay • Left bundle branch block • Right bundle branch block • Acute coronary syndrome • Acute myocardial infarction • Unstable angina pectoris • Non–ST-elevation myocardial infarction • ST-elevation myocardial infarction

Introduction

The treatment of acute coronary syndromes (ACS) changed dramatically when percutaneous coronary intervention (PCI) replaced thrombolysis as the preferred reperfusion therapy, and the mortality rates related to ACS have continued to decrease during the past two decades.[1] Extending electrocardiographic (ECG) interpretation beyond the analysis of ST-T changes has an important role in the recognition of patients with a higher risk of mortality,[2] and those with bundle branch blocks, with right (RBBB) and left bundle branch block (LBBB) in particular, are at the highest risk from all ECG presentations of ACS.[3,4] However, the prognostic value of bundle branch blocks complicating ACS has been mostly derived from either the thrombolytic[3,5,6] or the early PCI era with no routine invasive evaluation.[7–9]

Extensive ischaemic damage beyond the main branches of the cardiac conduction system results in a block that is typical of neither LBBB nor RBBB and is referred to as a non-specific intraventricular conduction delay (NIVCD) or a peri-infarction block.[8,10] Although preliminary data from the revascularization era suggested that this type of block carried the highest risk of cardiac death in ACS,[10] its prognostic value has been neglected in subsequent major studies exploring bundle branch blocks in the revascularization era.[4,11,12]

To date, the largest study exposing the mortality of NIVCD patients with chronic coronary syndromes was the Multicenter Unsustained Tachycardia Trial,[13] which only included patients with a left ventricular ejection fraction (LVEF) of < 40% enrolled over three decades ago. The more recent studies with ACS patients either were modest-sized,[10,14] only included patients with an ST-elevation myocardial infarction (STEMI),[15,16] or did not entail an invasive evaluation of most patients.[8]

Thus, we composed a study to investigate the long-term prognostic value of NIVCD and compare the prognosis to those presenting with LBBB and RBBB in a large cohort of consecutive post-infarction patients, all of whom underwent invasive evaluation for ACS, in the modern revascularization era.

Methods

Study population

This study is based on the retrospective data of consecutive patients undergoing invasive evaluation for ACS at Tays Heart Hospital between 1 January 2007 and 31 December 2018. Tays Heart Hospital is the sole provider of acute invasive cardiologic care for patients suffering from ACS in the Tampere Region with a population of ~0.5 million. The follow-up for mortality lasted from the first hospitalization (beginning from 1 January 2007) until 31 December 2020. Only the first ACS for each patient was recorded as a baseline event, even if multiple ACS incidents were recorded during the observation period. During the study period (2007–18), a total of 11 352 angiographies were performed for ACS on 10 314 patients. After excluding patients with no recorded ECG within the predefined time frame ($n = 455$) or with a ventricular-paced ECG ($n = 112$) and accepting only the first ACS as the index event for each patient, 9749 patients were followed up for cardiac mortality. Patients not diagnosed invasively by means of coronary angiography were not included in the study (less than 10% of all ACS patients in the study centre).[17] This exclusion was done because the diagnosis of ACS in patients who have not undergone an invasive evaluation is not accurate due to possible confounding issues caused by type II myocardial infarctions and because the reason for adopting a non-invasive strategy for these

patients was usually based on a poor overall prognosis.[17,18] This study is part of the retrospective Mass Data in Detection and Prevention of Serious Adverse Events in Cardiovascular Disease (MADDEC) study, which aims to utilize mass data for the prediction and prevention of serious cardiovascular adverse events.[19]

Baseline phenotype data collection

The baseline data were extracted from the MADDEC database, which retrospectively combines data collected from the 1990s onwards from different electronic databases used in specialized health care to create a comprehensive study registry focusing on patients treated at Tays Heart Hospital. This database combines electronic health record (EHR) data with the prospectively collected and actively maintained KARDIO database data (data collection performed by physicians and nurses during the treatment of patients) and with data gathered retrospectively by physicians using a full-disclosure review of written healthcare records. Acute coronary syndrome and its subtypes were defined by the European Society of Cardiology (ESC) and American College of Cardiology (ACC) criteria.[2,20,21] The data collection has been described previously in more detail.[19] Patients and the public were not involved.

Main exposure variables

The priori selected main exposure variables in this study were LBBB, RBBB (with or without left anterior/posterior fascicular block), and NIVCD. A cut-off point of QRS > 119 ms for NIVCD was used so that the IVCD groups would be as comparable as possible with each other, since the same QRS duration criteria are used for LBBB and RBBB. The presence of these features was extracted by using the automatic Marquette detection algorithm, which applies the Minnesota classification for intraventricular conduction disorders. Furthermore, all patients with borderline QRS duration (QRS > 117 ms) classified as NIVCD by the algorithm were manually checked for the presence of QRS > 119 ms by two independent physicians (R.L. and J.R.). Of 277 evaluated borderline EGCs, 66 ECGs were reclassified as NIVCD (> 119 ms).

Electrocardiographic recordings were included if they were taken at least 7 days prior to or a maximum of 2 months after the angiography, using the most recent ECG recording. The majority ($n = 9353$, 96.0%) of the recordings was taken on the same day as or within 1 week after the angiography (same day, $n = 1123$, 11.6%; 1–7 days after the angiography, $n = 8230$, 84.4%). Only 12 (0.1%) ECGs were taken before the angiography.

Follow-up and endpoint definitions

The follow-up for each patient lasted from the index event to death or until the end of the year 2020 (31 December 2020). Causes of death data were retrieved from Statistics Finland in International Classification of Diseases, Tenth Revision format. The causes of death registry by Statistics Finland provides 100% coverage of all deaths of citizens and permanent residents of Finland. The cause of death is reported to the registry according to the ICD code of the primary or immediate cause of death, which is extremely precise in Finland. Consequently, there were no losses to follow-up. Patients whose cause of death was coded as I20–I52 were classified as having died of a cardiac cause.

Statistical analysis

Comparisons between the patient groups were performed with normal χ^2 testing for categorical variables, with Student's *t*-test or ANOVA for normally distributed continuous variables, and with the Kruskal–Wallis or Mann–Whitney *U* test for non-normally distributed continuous variables. The cumulative incidence of cardiac mortality and the prognostic value of IVCDs during the entire follow-up were modelled using unadjusted and adjusted (continuous variables entered to the models without categorization) subdistribution hazard models, which account for competing risk due to other causes of death. The analyses were performed with SPSS (version 27, IBM) and R software (version 4.1.3; packages survival and cmprisk).

Results

General characteristics of the study population

The mean age of the entire population at baseline was 68.3 (11.8) years, and 67.3% ($n = 6633$) of the patients were men. The median follow-up time was 6.1 years [interquartile range (IQR) 3.3–9.4], during which 3156 patients died. Approximately half (52.9%, $n = 1668$) of the patients died of cardiac causes.

Most of the patients (89.9%, $n = 8681$) did not have an observable RBBB, LBBB, or NIVCD in their ECG. In contrast, 5.5% ($n = 539$) had an RBBB, 3.0% ($n = 288$) had an LBBB, and 2.5% ($n = 239$) had an NIVCD in their ECG.

In general, patients with RBBB, LBBB, or NIVCD were older and had a higher prevalence of comorbidities at baseline, when compared with patients with no observable conduction disorders (*Table 1*). Interestingly, patients with LBBB and NIVCD were less frequently admitted for STEMI (17.1% for LBBB and 23.0% for NIVCD) than were patients with RBBB (35.1%) or those with no conduction disorders (37.0%), but they made up for the difference mostly by the higher percentage of non–ST-elevation myocardial infarctions (NSTEMI) (56.9% for LBBB and 60.4% for NICVD vs. 45.2% for no conduction disorders and 46.4% for RBBB).

Association between intraventricular conduction delays and cardiac mortality

We observed that cardiac causes among patients with IVCDs were significantly overrepresented as a cause of death: a cardiac cause of death was recorded for 76.9% of the patients with an NIVCD ($n = 113/147$), 67.6% of patients with an LBBB ($n = 96/142$), 55.7% of those with an RBBB ($n = 146/262$), and 50.1% of patients with no IVCD ($n = 1275/2545$). The cumulative incidences of deaths due to other causes and of those due to cardiac causes are presented in *Figure 1*. In brief, the cumulative incidence of cardiac mortality during the first 12 years of follow-up was 19.6% among patients with no IVCD, differing dramatically from the cumulative incidence among patients with an IVCD of 33.2% for RBBB, 46.2% for LBBB, and 57.0% for NIVCD ($P < 0.001$ for comparison). The numbers of deaths due to cardiac and other causes, as well as their relative numbers, are presented in *Table 2*. The cumulative incidences of other deaths at 12 years were 21.9% (no IVCD), 29.1% (RBBB), 22.6% (LBBB), and 19.7% (NIVCD).

In non-adjusted analysis, the risk of cardiac death was over two-fold elevated among patients with RBBB and LBBB and four-fold elevated among patients with NIVCD (*Table 2*). The cardiac mortality risk related to these IVCDs became less evident but remained highly significant when adjusted for age and sex or for all significant traditional risk factors of cardiac mortality (*Table 2*). Interestingly, LBBB was no longer a significant predictor of cardiac mortality when LVEF measured during hospitalization was added to the analysis [hazard ratio (HR) 1.15, 95% confidence interval (CI) 0.92–1.44, $P = 0.225$]. Even then, NIVCD was associated with an almost two-fold increase in cardiac mortality (HR 1.96, 95% CI 1.59–2.43, $P < 0.001$) and RBBB with a more modest but statistically significant increase in cardiac mortality (1.30, 95% CI 1.08–1.56, $P = 0.005$).

Unlike LBBB and NIVCD, RBBB was associated with a higher risk of death due to non-cardiac causes (adjusted HR 1.23 with 95% CI 1.01–1.49, $P = 0.043$; analysis adjusted with age, prevalent valvular heart disease, prevalent diabetes, previous coronary artery bypass grafting, serum creatinine value, ACS type, prevalent peripheral artery disease, a history of atrial fibrillation, and a history of stroke).

Cardiac risk associated with IVCDs classified by subtype of ACS [unstable angina pectoris (UAP), NSTEMI, and STEMI)] is presented in *Table 3*. When adjusting with age and sex, RBBB remained as a

Table 1 General characteristics of patients undergoing coronary angiography for acute coronary syndrome between 2007 and 2018 at Tays Heart Hospital

	No IVCD $n = 8681$ (89.1%)	RBBB $n = 539$ (5.5%)	LBBB $n = 288$ (3.0%)	NIVCD $n = 239$ (2.5%)	*P* value
Age (years)	67.5 (11.8)	73.7 (9.9)	74.8 (9.6)	73.1 (10.3)	<0.001
Sex (female)	33.6% (2972)	22.5% (121)	34.6 (100)	18.6% (33)	<0.001
BMI (kg/m^2)	28.1 (5.1)	28.5 (5.8)	28.3 (4.9)	29.4 (5.4)	0.016
Diabetes	24.1% (2078)	32.7% (174)	36.1% (104)	41.8% (100)	<0.001
Hypertension	59.4% (5118)	66.9% (357)	68.3% (196)	71.0% (169)	<0.001
Dyslipidaemia	57.3% (4119)	54.8% (292)	67.2% (193)	67.5% (160)	<0.001
CKD	5.7% (491)	7.2% (39)	12.2% (35)	10.9% (26)	<0.001
VHD	6.3% (551)	9.1% (49)	12.8% (37)	17.6% (42)	<0.001
AF[a]	18.6% (1545)	25.0% (129)	30.8% (85)	32.9% (75)	<0.001
PAD	6.8% (585)	10.8% (58)	12.6% (36)	16.8% (40)	<0.001
Cancer	7.9% (650)	11.5% (59)	9.9% (27)	12.4% (28)	0.002
Smoking (active)	26.5% (2172)	16.9% (85)	12.0% (32)	19.6% (44)	0.001
Previous stroke	7.6% (660)	11.3% (61)	13.5% (39)	11.3% (27)	<0.001
Previous MI	15.2% (1315)	23.2% (125)	34.3% (99)	34.7% (83)	<0.001
Previous PCI	10.8% (871)	13.9% (75)	18.1% (52)	14.2% (34)	<0.001
Previous CABG	6.6% (575)	14.5% (78)	21.2% (61)	23.0% (55)	<0.001
Dementia (any)	2.3% (202)	4.1% (22)	2.1% (6)	3.4% (8)	0.055
Beta-blocker use[b]	86.7% (7498)	83.5% (446)	85.4% (246)	84.8% (201)	0.159
Amiodarone use[b]	1.2% (101)	0.4% (2)	1.4% (4)	3.4% (8)	0.009
Previous ICD	0.1% (13)	0.2% (1)	1.4% (4)	1.3% (3)	<0.001
ACS type					<0.001
UAP	17.8% (1545)	18.6% (100)	25.3% (73)	16.7% (40)	
NSTEMI	45.2% (3924)	46.4% (250)	56.9% (164)	60.4% (144)	
STEMI	37.0% (3212)	35.1% (189)	17.1% (51)	23.0% (55)	
Peak troponin T[c] (ng/L)	577 (114–2189)	648 (130–2925)	330 (65–1557)	630 (146–2054)	<0.001
LVEF, mean (SD)	51.9 (11.5)	50.7 (12.5)	42.7 (12.3)	42.6 (13.8)	<0.001
LVEF ≤ 35%	10.4% (832)	14.3% (71)	32.7% (89)	35.6% (80)	<0.001
eGFR(mL/min/1.73 m^2)	80 (21)	72 (21)	70 (20)	70 (22)	<0.001

CKD, chronic kidney disease (previous diagnosis of chronic kidney disease or estimated glomerular filtration rate <60 mL/min); VHD, valvular heart disease; AF, atrial fibrillation/flutter; PAD, peripheral artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ICD, implantable cardioverter-defibrillator; ACS, acute coronary syndrome; UAP, unstable angina pectoris; NSTEMI, non–ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; LVEF, left ventricular ejection fraction; and eGFR, estimated glomerular filtration rate. Dementia was defined as previously diagnosed neurodegenerative disease with documented memory loss or MMSE <25 even in the absence of accurate diagnosis.

[a]Previous history of atrial fibrillation (17.2%), atrial fibrillation (9.0%), or atrial flutter (0.9%) in ECG during hospital admission.

[b]At discharge or at hospital before death.

[c]Median (interquartile range), *P* value tested with the Kruskal–Wallis test

significant risk factor in NSTEMI and STEMI. Left bundle branch block remained significant in UAP and NSTEMI. Non-specific intraventricular conduction delay was a significant risk factor in all ACS subtypes, and the prognosis was worst in NSTEMI (HR 3.26, 95% CI 2.48–4.29) and STEMI (HR 4.19 95% CI 2.94–5.94). When additionally adjusting STEMI with TIMI flow pre-procedure, TIMI flow post procedure, and time from ECG to first balloon expansion, RBBB (HR 1.55 95% CI 1.03–2.34) and NIVCD (HR 3.86 95% CI 2.15–6.94) remained as sign of poor prognosis.

Discussion

We described in a large cohort of 9749 patients, all undergoing invasive evaluation for ACS, that RBBB, LBBB, and NIVCD predicted high cardiac mortality. Patients with NIVCD had a particularly high risk of cardiac death, especially in NSTEMI and STEMI, and even after adjustment for left ventricular function, both RBBB and NIVCD remained significant risk factors for mortality.

The observation that NIVCD was associated with strikingly high rates of cardiac mortality was one of the main findings of the present study. To the best of our knowledge, this is the largest study to date with consecutive ACS patients with NIVCD undergoing modern invasive evaluation. In the thrombolytic era, a prolonged QRS but not RBBB was associated with an impaired prognosis in a large cohort of ACS patients.[22] The association with increased mortality was also seen in two smaller previous studies dealing with STEMI patients, but without available echocardiographic data.[15,16] In a meta-analysis of 1311 ACS patients, QRS prolongation was associated with impaired perfusion.[23]

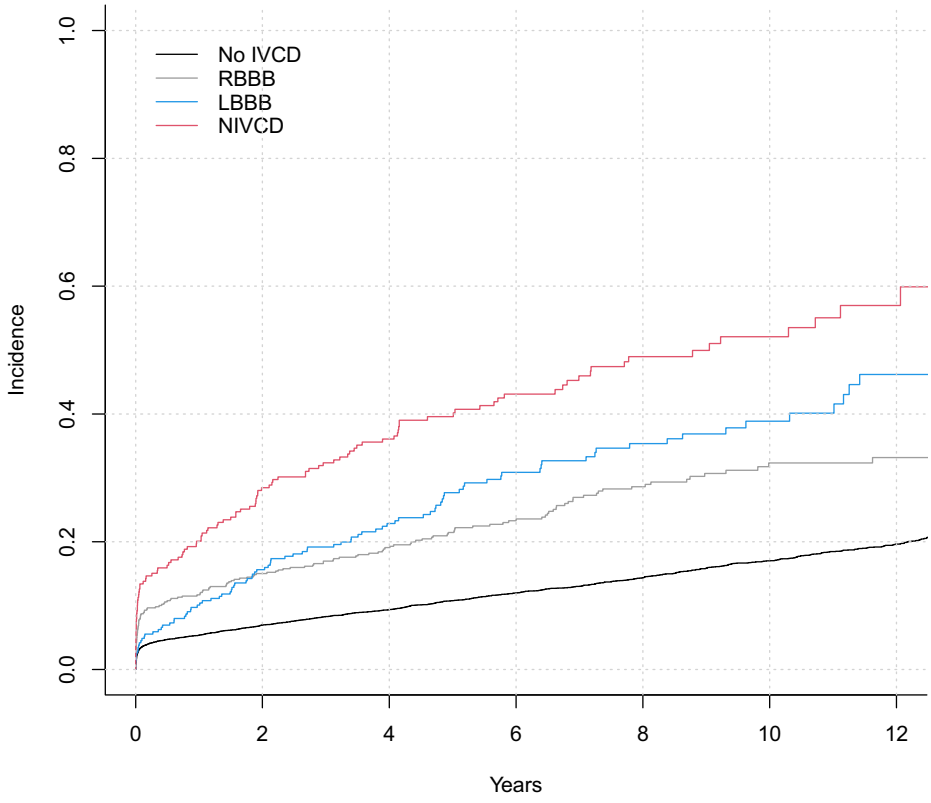


Figure 1 Cumulative incidence of cardiac mortality among patients undergoing coronary angiography for acute coronary syndrome ($P < 0.001$ for the comparison).

In contrast, in a cohort of ACS patients from two decades ago, NIVCD was not associated with all-cause mortality, but coronary angiography was performed on only 34.7% of these patients.[8] In the current study, the mortality risk associated with NIVCD was independent of several clinical risk factors, including the subtype of ACS, although the prognosis was worse in NSTEMI and STEMI.

Proposed mechanisms that link NIVCD to increased mortality include arrhythmia and heart failure. However, an impaired prognosis after an ACS event may be related to not only the mechanical pump function, as NIVCD remained an independent predictor of cardiac mortality even after adjustment for in-hospital LVEF in our study. Previously, NIVCD has been associated with a high rate of cardiac arrests during treatment in STEMI patients,[16] and the subgroup analysis of Multicenter Automatic Defibrillator Implantation Trial II showed that patients with a prolonged QRS benefited more from a prophylactic implantable cardioverter-defibrillator (ICD) than those with a normal QRS,[24]favoring the arrhythmic risk hypothesis. In our study, the use of beta-blocker was similar in all IVCD groups, but the use of amiodarone was slightly more frequent in NIVCD patients (3.4%, $n = 8$). This could indicate that NIVCD patients are more prone to ventricular irritability, but due to the low use of amiodarone, there is no significant effect on the overall results. Similarly, the amount of previous ICDs was low in all groups and no conclusions can be made. Moreover, the NIVCD population had a higher prevalence of previous myocardial infarctions and had more frequently undergone coronary revascularization than those with RBBB or with no conduction block in our study, further supporting the occurrence of more severe coronary artery disease. Finally, NIVCD had especially bad prognosis in NSTEMI and STEMI. Although the old ECGs should be checked to conclude weather the NIVCD was new or old, we suspect that NIVCD after NSTEMI and STEMI more often reflects greater infarction and severe disease than an old conduction disorder. Therefore, we suggest that NIVCD is a powerful predictor of an adverse outcome in post-ACS patients, correlating with the severity of the underlying cardiopathy.

In our study, LBBB was associated with increased cardiac mortality after adjustment for clinical risk factors—however, in contrast to NIVCD patients, this association was lost after including LVEF in the analysis. Our finding supports the concept of decreased LVEF due to mechanical dyssynchrony as one of the most important negative prognostic factors in LBBB. This is further supported by the fact that biventricular pacing, which corrects dyssynchrony, is associated with a reversal of left ventricular mechanical decline, as well as with better outcomes in patients with heart failure and LBBB.[25,26] Unfortunately, our study lacks data on biventricular pacing, which has a beneficial prognostic effect. Nevertheless, while other studies from the revascularization era may not have taken in-hospital LVEF into account in mortality prediction as was done in the current study,[4,11,12,27] patients with a new permanent LBBB following ACS represent a high-risk population.

In our study, RBBB proved to yield an increased risk of long-term mortality, independently of LVEF and the type of ACS. In a previous study, the 1-year mortality rate was 19.9% among ACS patients who had an RBBB at admission, but only 33.4% of the RBBB patients received thrombolysis or coronary angioplasty.[6] In the other study, 86% of patients with an RBBB were treated with coronary angioplasty, and the 1-year mortality rate was 15%.[7] Most recently, Widimsky et al. described in their retrospective study that in-hospital mortality was 14.3% among RBBB patients.[4] In our study, in which all patients were invasively evaluated for ACS, the 1-year mortality for RBBB was 12%.

Table 2 The association between different intraventricular conduction delays and cardiac mortality

	No IVCD $n = 8855$	RBBB $n = 538$	LBBB $n = 289$	NIVCD $n = 239$
Cardiac deaths	14.7% (1275)	27.1% (146)	33.3% (96)	47.3% (113)
Other deaths	14.6% (1270)	21.5% (116)	16.0% (46)	14.2% (34)
	Hazard ratio for cardiac death			
Unadjusted	1 (reference)	2.19 (1.85–2.60)	2.75 (2.24–3.49)	4.44 (3.66–5.39)
Age and sex adjusted	1	1.49 (1.25–1.77)	1.75 (1.42–2.16	3.32 (2.75–4.06)
Risk factor adjusted[a]	1	1.37 (1.15–1.64)	1.63 (1.31–2.03)	2.68 (2.19–3.27)
Risk factor + LVEF adjusted	1	1.30 (1.08–1.56)[b]	1.15 (0.92–1.44)[c]	1.96 (1.59–2.43)

[a]Model adjusted with age, prevalent valvular heart disease, prevalent diabetes, previous coronary artery bypass grafting, serum creatinine value, acute coronary syndrome type, prevalent peripheral artery disease, history of atrial fibrillation, and history of stroke.
All statistical comparisons $P < 0.001$ except for those marked with [b]($P = 0.005$) or [c]($P = 0.225$).

Table 3 The association between different intraventricular conduction delays and cardiac mortality classified by subtype of ACS

	No IVCD	RBBB	LBBB	NIVCD
		Hazard ratio for cardiac death		
UAP	1 (reference)	1.69 (1.05–2.72)	2.62 (1.69–4.13)	2.73 (1.44–5.17)
NSTEMI	1	2.00 (1.55–2.58)	2.94 (2.26–3.82)	4.34 (3.39–5.55)
STEMI	1	2.27 (1.74–2.98)	2.41 (1.47–3.95)	5.22 (3.60–7.56)
UAP[a] ($n = 1758$)	1	1.11 (0.68–1.81)	1.83 (1.16–2.87)	2.26 (1.16–4.40)
NSTEMI[a] ($n = 4482$)	1	1.48 (1.14–1.92)	1.89 (1.44–2.47)	3.26 (2.48–4.29)
STEMI[a] ($n = 3507$)	1	1.53 (1.15–2.03)	1.64 (0.98–2.74)	4.19 (2.94–5.94)
STEMI[b] ($n = 2001$)	1	1.55 (1.03–2.34)	1.65 (0.74–3.68)	3.86 (2.15–6.94)

[a]Adjusted with age and sex.
[b]Adjusted with age ($P < 0.001$), sex ($P = 0.38$), TIMI flow pre-procedure ($P = 0.004$), TIMI flow post procedure ($P < 0.001$), and time from ECG to first balloon ($P = 0.004$).

Thus, it appears that, despite modern revascularization and medical treatment for ACS, the mortality rates of these high-risk patients have not improved substantially.

Our study provides an update on the prognosis of bundle branch blocks and, most importantly, solidifies the significance of NIVCD as a mortality predictor. The present study population comprises all consecutive patients treated in a limited geographical area during a 12-year period. Consequently, this population can be considered to be an unselected and unbiased representation of patients diagnosed invasively for ACS. Furthermore, given the large overall sample size, the study has sufficient power to detect significant associations despite the small relative size of the patient groups with IVCDs. While our study was retrospective, the definition of ECG features in our study was conducted by an automatic algorithm in most cases and by investigators blinded to the outcome. This means that *post hoc* exposure variable adjudication is unlikely to have confounded the results.

As for limitations, the fact that non-invasively diagnosed patients were not included in this study means that the prognosis of these patients cannot be assessed. However, this exclusion was done because the diagnosis of ACS in patients not undergoing invasive evaluation is not accurate due to possible confounding issues caused by type II myocardial infarctions and because, with these patients, the reason for adopting a non-invasive strategy was usually based on a poor overall prognosis. Additionally, because IVCD patients were older, their mortality could be affected by factors such as frailty, poor functional capacity, and undiagnosed memory disorders, although the prevalence of clinically diagnosed dementia was not significantly different in controls or in patients with IVCD. Furthermore, due to the observational nature of our results, we cannot comment on the possible causal relationships of IVCDs or weather the IVCDs were new or old, but based on the strong associations, it is likely that patients with these conduction disorders should be treated as high-risk patients when considering possible medical interventions. Moreover, in relation to previous studies where RBBB and LBBB were classified by treating physicians in all-comers with ACS, the bundle branch block incidences were similar to our results.[28,29] Despite this, since the exposure variable adjudication in most of the cases was based on the GE Marquette algorithm (all cases with QRS > 119 ms and identified as LBBB, RBBB, or NIVCD by the algorithm), it is possible that some NIVCD cases were diagnosed incorrectly by the algorithm. It is unlikely that this would have contributed substantially to the results. Finally, more specific information on the cause of death and other acute endpoints such as incident heart failure requiring hospitalization or cardiogenic shock could help to refine the preventive treatment patients with IVCD. These issues should be addressed in future research.

In conclusion, in a large study of consecutive ACS patients, all of whom were undergoing invasive evaluation for ACS, those with NIVCD (new or old) presented a high-risk subgroup in comparison

with other patients. In contrast to LBBB, the risk associated with NIVCD was not related to LVEF. Our results support the ESC guidelines describing LBBB in patients as a high-risk feature, but a matter of debate remains in whether RBBB should be considered as a high-risk factor not only in STEMI but also in ACS patients. Furthermore, we find that guidelines should acknowledge NIVCD as a powerful predictor of mortality.

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Conflict of interest: None declared.

Data availability

Data available in anonymized form for research purpose pending the approval of the study steering comittee. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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