

1 **Title page**

2 **Early postoperative statin administration does not affect the rate of atrial fibrillation after cardiac**
3 **surgery**

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18 **Sentences for the visual abstract**

19

20 **Key question**

21 Do statins impact on the occurrence of atrial fibrillation after cardiac surgery?

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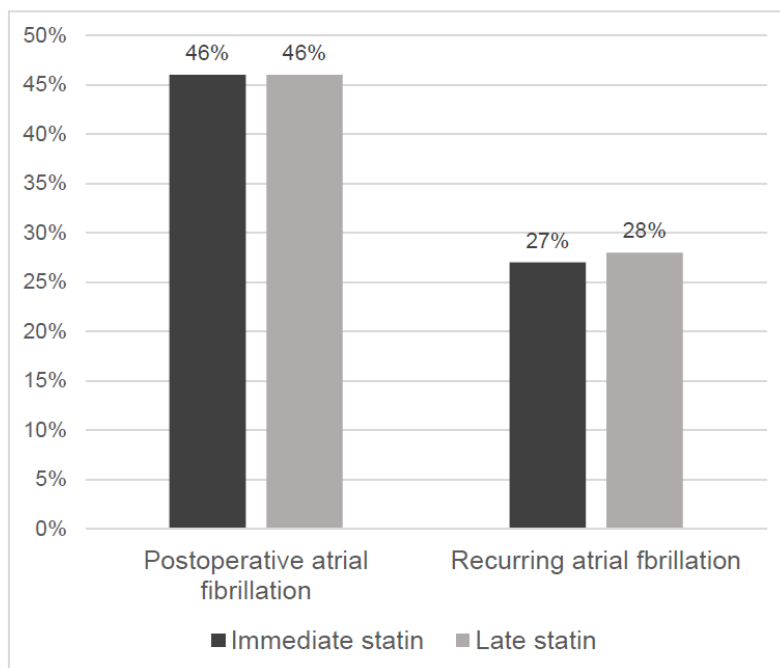
23 **Key findings**

24 Early postoperative statin administration did not decrease atrial arrhythmias in this randomized study.

25

26 **Take-home message**

27 Statin use immediately after cardiac surgery does not appear to be beneficial in preventing atrial fibrillation.



28

29 Abstract

30

31 **Objectives:** Postoperative atrial fibrillation is the most frequent complication after cardiac surgery, and the
32 use of statins in preventing them is being extensively studied. The aim of this study was to investigate
33 whether a pause in the administration of statins affects the occurrence of atrial fibrillation after cardiac
34 surgery in a prospective randomized and controlled setting.

35 **Methods:** A total of 301 patients without chronic atrial fibrillation with prior statin medication scheduled for
36 elective or urgent cardiac surgery involving the coronary arteries and/or heart valves were prospectively
37 recruited and randomized for statin re-initiation on either the first (immediate statin group) or the fifth (late
38 statin group) postoperative day, using the original medication and dosage. The immediate statin group
39 comprised 146 and the late statin group 155 patients. Except for a somewhat higher rate of males (85% vs.
40 73%, $p=0.016$) in the immediate statin group, the baseline characteristics and the distribution of procedures
41 performed within the groups were comparable. The occurrence of postoperative atrial fibrillation and the
42 clinical course of the patients were compared between the groups.

43 **Results:** The incidence of atrial fibrillation was 46% and the median delay after surgery before the onset of
44 atrial fibrillation three days in both groups ($p=NS$). There were no differences observable in the frequency of
45 the arrhythmia in any subgroup analyses or in other major complications or clinical parameters. No adverse
46 effects related to early statin administration were detected.

47 **Conclusions:** Early re-initiation of statins does not appear to affect the occurrence of postoperative atrial
48 fibrillation.

49

50 **Key words:** Atrial fibrillation; Cardiac surgery; Statins

51 **Clinical trial registration:** European Union Drug Regulating Authorities Clinical Trials Database
52 (EudraCT) - 2016-001655-44

53 **Introduction**

54

55 Postoperative atrial fibrillation is the most frequent complication after cardiac surgery, with an occurrence of
56 approximately 20%–50% [1–3]. The causes and mechanisms of atrial fibrillation remain incompletely
57 understood but are thought to include surgical trauma, inflammation, adrenergic activation, and oxidative
58 stress [4–7]. Statins are believed to have anti-inflammatory and anti-oxidative properties, and in recent years
59 a plethora of literature has emerged investigating the possible effect of statins on the development of
60 postoperative atrial fibrillation, with initially promising but subsequently contradictory and inconclusive
61 evidence [8–18].

62

63 The authors hypothesize that statin withdrawal after cardiac surgery might increase the risk for postoperative
64 atrial fibrillation. The aim of the present study was to investigate whether, in patients with prior statin
65 medication, a pause in the administration of statins impacts the occurrence of atrial fibrillation following
66 cardiac surgery in a randomized and controlled setting.

67 **Materials and Methods**

68

69 **Ethical statement**

70 The approval of the local Ethics Committee was obtained (approval date 13 June 2016), the Finnish
71 Medicines Agency was consulted, and the study was registered in the European Union Drug Regulating
72 Authorities Clinical Trials Database (EudraCT, 2016-001655-44) before initiation and patient enrollment.
73 The ethical principles laid out in the 1975 Helsinki Declaration were followed. The enrolled patients gave an
74 informed consent and did not partake in other interventional trials.

75

76 **Study design and patients**

77 The study was performed in the Heart Hospital, Tampere University Hospital, Tampere, Finland, a tertiary
78 referral center, between August 2016 and September 2019. Patients with prior statin medication undergoing
79 elective or urgent coronary and/or valve surgery were prospectively recruited. The patients with chronic
80 atrial fibrillation, endocarditis, pacemakers, and/or chronic renal insufficiency requiring dialysis were
81 excluded, as were those undergoing emergency or complication-related surgery and/or redo-procedures.
82 Patients on statins that had been initiated during the same hospitalization at least five days before surgery
83 were included. All recruited patients were randomized into two groups with a 1:1 ratio using a computer-
84 based random number generator. The recruitment of patients as well as their randomization were performed
85 by the investigators. In the immediate statin group, the statin medication was re-initiated on the first
86 postoperative day and in the late statin group on the fifth postoperative day. In both groups, the statin that
87 had been prescribed prior to surgery was used with the original dosage. The study was not blinded. Patients
88 who were unable to comply with the planned study protocols – for example, because of pharmacological
89 interactions restricting statin use – were excluded from the trial.

90

91 **Peri- and postoperative treatment**

The operations and postoperative care of the patients were otherwise performed according to the clinic standards. Following surgery, all patients were on continuous and recording electrocardiogram monitoring throughout the hospitalization. The nursing staff was well-trained in the prompt detection of atrial fibrillation, and an experienced cardiologist was available on a daily basis for rhythm-related consultations. Echocardiography was performed at least once on all patients, usually on the third postoperative day. Other medications, including diuretics, β -blockers, painkillers, antithrombotic agents, and anticoagulants, were at the attending clinician's discretion, as were postoperative imaging studies and laboratory examinations. The clinic's routine for treating postoperative atrial fibrillation entailed the intravenous administration of metoprolol (2.5–5 mg), followed by an infusion of amiodarone (300 mg during the first hour and then 900 mg over the next 23 hours), after which electric cardioversion was performed if the arrhythmia persisted. The routine prophylaxis for thromboembolic complications at the clinic consisted of subcutaneous injections of enoxaparin 40 mg daily. If atrial fibrillation persisted for more than 24 hours and no severe bleeding issues were present, the dosage of enoxaparin was increased, and oral anticoagulants, if not already in use, were considered by the attending surgeon and/or cardiologist.

Study outcomes and definitions

The primary study outcome was the occurrence of postoperative atrial fibrillation during the in-hospital period until referral for secondary care or hospital discharge. The patient demographics and medical history, the type and indication of surgery, as well as clinical parameters, such as perioperative details, the results of important laboratory parameters, the occurrence of complications, and the length of the hospitalization prior to hospital discharge or referral for secondary care, were recorded for each patient. The criterion for postoperative atrial fibrillation was a duration of at least five minutes in the continuous rhythm monitoring. Perioperative myocardial infarction was defined as the presence of two out of three of the following criteria: electrocardiographic evidence of myocardial damage, a significant elevation of serum cardiac biomarkers, and/or the detection of new regional cardiac wall motion abnormalities or loss of viable myocardium in the echocardiography within 48 hours after surgery. Until and including the 16th of May 2018, the institutional criterion for a significant rise in cardiac biomarkers was the elevation of creatine kinase isoenzyme MB

119 activity to over 75 U/L (≥ 3 times the upper limit of the reference range), and, thereafter, the elevation of
 120 creatine kinase isoenzyme MB mass to over 50 $\mu\text{g/L}$ (≥ 10 times the upper limit of the reference range).
 121 Stroke was documented when suggestive neurological symptoms were observed and a corresponding new
 122 lesion in computed tomography was discovered. If a patient required an extended stay in or was readmitted
 123 to the intensive care unit due to severe agitation, confusion, and/or hallucinations, the patient was classified
 124 as having postoperative delirium. The occurrence of postoperative infections, including surgical site
 125 infections, pneumonias, and cannula- and catheter-related infections, was recorded.

126

127 **Statistical analyses**

128 The occurrence of postoperative atrial fibrillation was compared between patients in the immediate-statin
 129 and late-statin groups using statistical methods with IBM SPSS version 24 statistical software. The Chi
 130 square and Fisher's exact test were used to compare categorical data, the Student's t-test was employed to
 131 compare the means of normally distributed variables, and the Mann-Whitney U-test was applied to compare
 132 the medians of nonparametric scale variables. Statistical significance was set at $p < 0.05$.

133

134 **Power analysis**

135 To observe a decrease from 45% to 35% in the occurrence of postoperative atrial fibrillation with $\alpha = 0.05$ and
 136 80% power would require 312 patients in both groups according to the power calculation [19]. An interim
 137 analysis was planned when 300 patients had been recruited to consider the continuation of the study and
 138 further patient recruitment at that time. In the interim analysis with 150 patients in both groups and otherwise
 139 corresponding parameters, the study would have 50% power to detect a similar decrease in the rate of
 140 postoperative atrial fibrillation.

141 **Results**

142

143 The present results represent those of the interim analysis based on which the recruitment of more patients
 144 was discontinued. A total of 303 patients were recruited, two of whom were excluded from the analysis, one
 145 due to accidental recruitment into two interventional studies and the other because of medical interactions
 146 limiting the planned statin use. The demographic information and medical history of the final study
 147 population are shown in Table 1. The groups were otherwise comparable, but there was a somewhat higher
 148 proportion of males in the immediate statin group. The statin medications prescribed for the patients are
 149 summarized in Table 2. For a total of 22% of the patients, the medication was initiated during the
 150 hospitalization when the surgery was performed, with no statistically significant differences between the
 151 study groups. The types of surgery performed as well as the perioperative details and major outcomes of the
 152 study patients are depicted in Table 3.

153

154 A total of 46% (95% CI 40-52%) of the patients had a postoperative episode of atrial fibrillation and 28%
 155 (95% CI 23%–33%) more than one episode. Figure 1 illustrates the main results of the study, showing no
 156 significant differences in the main study outcome – the occurrence of postoperative atrial fibrillation –
 157 between the groups. Most of the procedures were performed for coronary disease, followed by single-valve
 158 surgeries, which were mostly for aortic valves, and combination procedures. There were no statistically
 159 significant differences in the occurrence or the recurrence rate of postoperative atrial fibrillation between the
 160 study groups, nor was there an observable trend towards a lower incidence in the immediate statin group.
 161 Moreover, no significant differences were seen between different statins. Of the patients previously
 162 diagnosed with paroxysmal atrial fibrillation, 73% also had an episode postoperatively, in comparison to the
 163 corresponding 43% among other patients, $p=0.005$, but there were no statistically significant differences in
 164 the said proportions between the study groups. In patients for whom statins had been initiated during the
 165 same hospitalization, the rates of postoperative atrial fibrillation and recurring atrial fibrillation were 48%
 166 and 29%, respectively, with no statistically significant differences between the study groups. The median

167 delay between surgery and the development of postoperative atrial fibrillation was three days in both groups,
168 $p=0.26$. The occurrence of other major adverse outcomes was also similar between the groups. The mean
169 peak C-reactive protein concentration was slightly lower in the immediate statin group when compared to the
170 late statin group. The prevalence of sinus rhythm at referral for secondary care or hospital discharge was
171 97%, with no differences between the groups.

172 Discussion

173

174 Postoperative atrial fibrillation remains a challenge in the care of cardiac surgical patients, and its
175 significance may even be increasing as contemporary surgical programs face older, more morbid patients,
176 with higher rates of extensive as well as urgent and emergency procedures performed. Though frequently
177 considered a minor complication, atrial fibrillation is also associated with an inferior prognosis and an
178 increased risk of stroke in long-term follow-up, even if its prevention may not mitigate these risks as clearly
179 [20–22]. Statins have demonstrated clear beneficial effects in several patient subgroups with cardiovascular
180 diseases and are also currently being studied in the prevention of atrial arrhythmias following cardiac
181 surgery. The postulated mechanisms of action are the pleiotropic effects of statins, which are still
182 incompletely understood [23]. The present study was initiated to ascertain whether statin withdrawal affects
183 the occurrence of atrial fibrillation after cardiac surgery but based on the results of the interim analysis in
184 which no apparent effect or trend was observable, the study was discontinued. Furthermore, no adverse
185 effects related to early statin reinstitution, nor changes in the creatine kinase levels, were detected in this
186 study.

187

188 The rationale for the present study was the relatively high occurrence of postoperative atrial fibrillation at the
189 study center, which was also observable in the present study [1]. Earlier, the institutional protocol for
190 patients on prescribed statins prior to surgery was to reinstitute them on the fifth postoperative day, and the
191 discourse regarding the impact that statins might have on the development of atrial arrhythmias after major
192 procedures such as surgery led to the present hypothesis. Other possible explanations for the high incidence
193 include changes in the patient material that is being referred for surgery – and in the respective prevalence of
194 consequential comorbidities – and/or a better detection rate with the adoption of continuous rhythm
195 monitoring, when compared to preceding studies performed in the 1990s and 2000s. Despite the high
196 occurrence of atrial fibrillation episodes in the present material, virtually all patients were in sinus rhythm at
197 the end of the treatment period, implying efficient measures in treating the episodes.

198

199 While the prevention of postoperative atrial fibrillation is relevant for virtually all patients undergoing
200 cardiac surgery as well as other major procedures, the authors recognize that some preventive methods might
201 apply to some but not all patient subgroups. For example, the study included patients both with and without
202 paroxysmal atrial fibrillation. Previous atrial fibrillation is an established risk factor for postoperative atrial
203 arrhythmia episodes, and these patients may represent a cohort in which preventive measures have a different
204 magnitude of effect. In the subgroup analyses performed, however, there was no observable trend for a
205 benefit in any patient subgroup. The only statistically significant difference between the groups was seen in
206 the C-reactive protein concentration, but in the absence of an association with clinical events, its significance
207 remains unclear and the result may have been coincidental. The authors speculate that, even if statins would
208 be theoretically beneficial in the early postoperative phase, their absorption from the gastrointestinal tract
209 might be significantly impaired at this stage, thus diminishing their possible effect. A similar finding has
210 been reported regarding β -blockers, for example [24]. Furthermore, while the plasma half-life of statins
211 ranges from a few hours to approximately one day, the duration of their pleiotropic effects is not known [25].
212 Should they last for several days, they could diminish the effects of a short statin pause and contribute to the
213 negative results of the present study. As to whether statins might prevent postoperative atrial fibrillation
214 remains uncertain, and caution is warranted in postulating possible mechanisms of action.

215

216 Though procedures involving the atrioventricular valves or the thoracic aorta as well as combination
217 procedures are associated with a clear risk of atrial fibrillation, the study did not include many such patients,
218 for two reasons. Firstly, these procedures, with the exception of those concerning the mitral valve, are not as
219 frequent as others, such as coronary bypass surgery. Secondly, it became apparent that many of these patients
220 were either young and otherwise healthy and therefore not receiving statins, or they had already developed
221 chronic atrial fibrillation, thus excluding them from the study. It would have also been interesting to compare
222 the rates of postoperative atrial fibrillation to an otherwise similar group of patients with no concurrent statin
223 treatment. However, virtually every patient who was referred for surgery with an indication for statins was

224 already on prescribed statins, making it impossible to recruit such patients in sufficient numbers. All in all,
225 these results are more representative of patients in need of coronary or aortic valve procedures.

226

227 The decision to recontinue the statins that were already in use with the original dose may be criticized
228 because it allowed for heterogeneity in the study intervention, and it would have been clearer if a single class
229 and dosage of statins had been adopted. However, it is the opinion of the authors that, as most patients are
230 already on statins when referred for surgery, it may not be prudent to overlook the decisions of the primary
231 care physicians and the experiences of the patients, since it is not uncommon for patients to tolerate some but
232 not all statins [26]. The approach used here would have been well-suited for implementation in most
233 programs in the developed countries, but others might be more feasible in scenarios in which statin-naïve
234 patients are treated.

235

236 **Study limitations**

237 The main weaknesses of the present study include its single-center setting and the heterogeneity of the study
238 material and intervention. The decision to include patients with paroxysmal atrial fibrillation may be faulted,
239 but the authors argue that these patients are increasingly numerous and also represent those who are at a high
240 risk of postoperative arrhythmias and in whom the benefits of prophylaxis, i.e. decreased morbidity and
241 reduced need for therapeutic measures, may be relevant. The institutional criteria for perioperative
242 myocardial infarction differed from what has been suggested in clinical guidelines, and the rates may thus
243 not be directly compared to other studies. The study may not have sufficient statistical power to completely
244 refute the study hypothesis, but should there be an effect, it would appear extremely unlikely, minimal, and
245 not demonstrable even if the present study would have been completed. It is important to remember, that
246 while this study does not disprove a possible preventive role of statins in postoperative atrial fibrillation, it
247 would appear that whether or not they are administered postoperatively does not clearly affect the occurrence
248 of the arrhythmia. It is also possible that the effect of statins is more pronounced initially, as the reduction in

249 postoperative atrial fibrillation has been mostly observed in statin-naïve patients with a short duration of
250 statin therapy prior to surgery.

251 **Conclusion**

252

253 The authors report that, in patients receiving statins prior to cardiac surgery, whether or not statins were
254 given immediately after surgery had no apparent effect on the occurrence of postoperative atrial fibrillation
255 in this randomized controlled study.

256

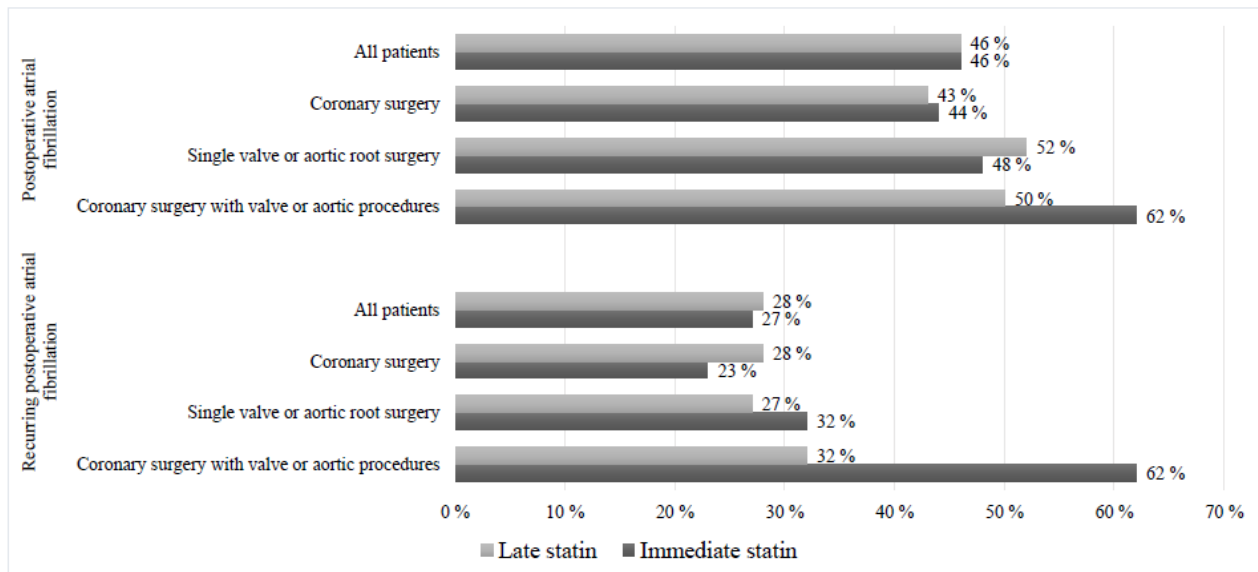
257 **Funding Statement:** this work was not supported by commercial or non-commercial funding.

258

259 **Conflict of interest:** none declared.

Figure legends

Figure 1. The occurrence and recurrence of postoperative atrial fibrillation in patients treated with immediate and late statin protocols. There were no statistically significant differences between the groups or within subgroups according to the statin treatment protocol



267 **Table 1.** The baseline characteristics of included patients.

	Immediate statin	Late statin	p
Number of patients	146	155	
Male (%)	85%	73%	0.016
Mean age (years)	69 (8.5)	67 (7.9)	0.08
Mean body mass index (kg/m ²)	28 (4.4)	29 (4.7)	0.24
Diabetes	36%	28%	0.17
Coronary disease	79%	86%	0.13
Hypertension	75%	74%	0.90
Active smoking	8.9%	12%	0.46
Former smoking	27%	27%	0.90
Chronic pulmonary disease	10%	9.7%	0.86
Peripheral artery disease	11%	5.8%	0.14
Paroxysmal atrial fibrillation	9.6%	10%	0.60
Family history of heart diseases	40%	37%	0.54
Preoperative glomerular filtration rate (ml/min)	82 (20)	84 (23)	0.46
Preoperative hemoglobin (g/L)	139 (14)	139 (16)	0.99
Urgent surgery	29%	25%	0.52
NYHA 3–4 (%)	51%	52%	0.82
Mean Euroscore-II	2.2%	1.9%	0.62
Mean preoperative LVEF	60%	56%	0.21
Mean left atrial size (mm)	40 (7.5)	40 (6.2)	0.68

268 Results are presented as means and standard deviations for numeric variables and percentages for categorical
 269 variables.

270 **Table 2.** The distribution of the classes of statins as well as the proportions of applied dosages within each
 271 class that were in use among the recruited patients. There were no statistically significant differences
 272 between the groups.

Statin class and dosage	Immediate statin (n=146)	Late statin (n=155)
Atorvastatin	47%	52%
10 mg	19%	6.2%
20 mg	29%	38%
40 mg	48%	50%
80 mg	4.3%	6.2%
Simvastatin	32%	26%
10 mg	6.5%	7.5%
20 mg	22%	35%
40 mg	67%	58%
60 mg	0%	2.2%
80 mg	0%	2.2%
Rosuvastatin	17%	16%
5 mg	20%	13%
10 mg	44%	50%
20 mg	32%	33%
40 mg	4.0%	4.2%
Pravastatin	2.1%	3.9%
20 mg	100%	50%
40 mg	0%	50%
Fluvastatin	2.1%	2.6%
20 mg	33%	25%
80 mg	67%	75%

Lovastatin	0%	0.6%
40 mg	0%	100%

274 **Table 3.** The types of procedures performed, perioperative details, and the major outcomes in study patients.

	Immediate statin (n=146)	Late statin (n=155)	p
Coronary surgery	70%	65%	0.33
Single-valve or aortic root surgery ¹	21%	21%	0.99
Coronary surgery with valve or aortic procedures ²	8.9%	14%	0.21
Mean X-clamp time (min)	107 (41)	104 (41)	0.52
Mean on-pump time (min)	132 (49)	129 (52)	0.60
Mean weight gain ³ (kg)	6.4 (3.0)	6.4 (2.9)	0.90
Median peak creatine kinase (U/L) ³	511 (382)	484 (415)	0.44
Mean peak C-reactive protein concentration (mg/L) ³	160 (60)	175 (77)	0.049
Mean maximal hemoglobin decrease (g/L) ³	41 (19)	41 (15)	0.79
Perioperative myocardial infarction ⁴	4.3%	4.1%	0.99
Reoperation for bleeding	6.2%	3.9%	0.43
Postoperative infections	4.1%	3.2%	0.77
Stroke	2.7%	0.6%	0.20
Delirium ⁵	6.2%	3.2%	0.28
Median length of hospital stay (days)	5 (2)	5 (3)	0.11
In-hospital mortality	0%	1.4%	0.23

275 Results are presented as means and standard deviations or medians and interquartile ranges for numeric

276 variables and as percentages for categorical variables.

277 ¹Includes 52 procedures involving the aortic valve, eight involving the aortic valve and root, one involving
278 the aortic valve and ascending aorta, two involving the mitral valve, and one involving the tricuspid valve.

279 ²Includes 26 procedures involving the aortic valve, five involving the aortic valve and root, one involving the
280 mitral valve, one involving the tricuspid valve, and two involving the ascending aorta in addition to coronary
281 bypasses.

282 ³Within seven days after surgery.

283 ⁴Diagnostic criteria include two out of three of the following: electrocardiographic changes indicative of
284 ischemia, a significant elevation in cardiac biomarkers (creatine kinase MB activity exceeding 75 U/L [≥ 3 x
285 the upper limit of the reference range] until and including the 16th of May 2018, or creatine kinase isoenzyme
286 MB mass over 50 μ g/L [≥ 10 x the upper limit of the reference range] thereafter), and/or the presence of
287 cardiac wall motion abnormalities or loss of viable myocardium in echocardiography within 48 hours after
288 surgery.

289 ⁵Requiring extended stay in or readmittance to the intensive care unit.

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291

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