ORIGINAL RESEARCH

Occurrence of Postpericardiotomy Syndrome: Association With Operation Type and Postoperative Mortality After Open-Heart Operations

Joonas Lehto, MD; Tuomas Kiviniemi, MD, PhD; Jarmo Gunn, MD, PhD; Juhani Airaksinen, MD, PhD; Päivi Rautava, MD, PhD; Ville Kytö, MD, PhD, MSocSc

***Background*—**Postpericardiotomy syndrome (PPS) is a common complication after cardiac surgery. However, large-scale epidemiological studies about the effect of procedure type on the occurrence of PPS and mortality of patients with PPS have not yet been performed.

***Methods and Results*—**We studied the association of PPS occurrence with operation type and postoperative mortality in a nationwide follow-up analysis of 28 761 consecutive patients entering coronary artery bypass grafting, aortic valve replacement, mitral valve replacement, or ascending aortic surgery. Only PPS episodes severe enough to result in hospital admission or to contribute as a cause of death were included. Data were collected from mandatory Finnish national registries between 2005 and 2014. Of all the patients included, 493 developed PPS during the study period. The occurrence of PPS was significantly higher after aortic valve replacement (hazard ratio, 1.97; 95% confidence interval, 1.58–2.46; $P<0.001$), mitral valve replacement (hazard ratio, 1.62; 95% confidence interval, 1.22–2.15; $P<0.001$), and aortic surgery (hazard ratio, 3.06; 95% confidence interval, 2.24–4.16; $P<0.001$), when compared with coronary artery bypass grafting in both univariable and multivariable analyses. The occurrence of PPS decreased significantly with aging ($P<0.001$). The occurrence of PPS was associated with an increased risk of mortality within the first year after the surgery (adjusted hazard ratio, 1.78; 95% confidence interval, 1.12–2.81; $P=0.014$).

***Conclusions*—**The occurrence of PPS was higher after aortic valve replacement, mitral valve replacement, and aortic surgery when compared with the coronary artery bypass grafting procedure. Aging decreased the risk of PPS. The development of PPS was associated with higher mortality within the first year after cardiac or ascending aortic surgery. **(*J Am Heart Assoc*. 2018;7: e010269. DOI: 10.1161/JAHA.118.010269.)**

Key Words: epidemiology • mortality • pericardium • postpericardiotomy syndrome • thoracic surgery

Postpericardiotomy syndrome (PPS) is a well-known complication after cardiac surgery. The syndrome has been assumed to be an immune-mediated process,[1] triggered by direct pericardial trauma, pericardial bleeding, and individual predisposition.[2] A wide variety of studies about the predictors of PPS have previously been published, but only a few have evaluated the effect of procedure type on the incidence of the syndrome; the results have been largely conflicting.[3–5] The syndrome is known to cause prolonged hospital treatment, readmissions, and invasive interventions, including pericardial and/or pleural drainage, but the prognosis of the syndrome has been considered to be benign. However, in the past few decades, this has been mainly based on clinical experience, and only a handful of recent studies have evaluated mortality after PPS.[4,6] Thus, there is an unmet clinical need for accurate epidemiological assessment of mortality in the presence of PPS.

In this multicenter nationwide study, we sought to evaluate the association of PPS occurrence with the operation type and postoperative mortality.

Methods

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the National Institute for Health and Welfare at http://www.thl.fi/en.

From the Heart Center (J.L., T.K., J.G., J.A., V.K.) and Clinical Research Center (P.R.), Turku University Hospital, Turku, Finland; University of Turku, Finland (J.L., T.K., J.G., J.A., V.K.); and Department of Public Health (P.R.) and Research Center of Applied and Preventive Cardiovascular Medicine (V.K.), University of Turku, Finland.

Correspondence to: Joonas Lehto, MD, Heart Center, Turku University Hospital, PO Box 52, FI-20521 Turku, Finland. E-mail: jojuleh@utu.fi

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Clinical Perspective

What Is New?

- The occurrence of postpericardiotomy syndrome is higher after aortic valve replacement, mitral valve replacement, and aortic surgery when compared with coronary artery bypass grafting, and the development of postpericardiotomy syndrome is associated with higher mortality.

What Are the Clinical Implications?

- Higher mortality supports the use of preventive measures for postpericardiotomy syndrome, especially in patients undergoing extensive/large-scale cardiac surgery.

Design

Patients aged ≥18 years who underwent open-heart cardiac or ascending aortic surgery during 9 consecutive years in Finland were studied in this population-based nationwide cohort study. The major outcomes of interest were as follows: (1) the association of operation type on the occurrence of PPS severe enough to require hospital admission or contributing to death and (2) the association of PPS with 1-year all-cause postoperative mortality. The inclusion and exclusion criteria and the study flow chart are outlined in Figure 1.

Data Collection

Patients who underwent open-heart coronary artery bypass grafting (CABG), aortic or mitral valve replacement, or operation of the ascending aorta in Finland between January 1, 2005, and December 31, 2013, were retrospectively identified from the Care Register for Healthcare in Finland, maintained by the Finnish National Institute for Health and Welfare. The data included cardiovascular admissions from 131 healthcare units in total. Each hospital admission is provided with basic baseline data (eg, age and sex), data on the length of stay, performed procedures, and *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnostic codes. Individual-level mortality data were obtained from the Cause of Death registry maintained by Statistics Finland. Both registries are nationwide, obligatory, and automatically collected. Postoperative admissions with PPS (*ICD-10* code I97.0) as the primary, secondary, or tertiary cause of admission, or as any cause of death were identified from Care Register for Healthcare in Finland and Cause of Death registry. The follow-up ended on December 31, 2014. The Charlson Comorbidity Index was calculated according to the previously used algorithm.[7]

The study was approved by the National Institute for Health and Welfare in Finland (permission Nos. THL/143/5.05.00/2015 and THL/1349/5.05.00/2015) and Statistics Finland (TK53-1410-15). The requirement for obtaining informed consent from the study participants was waived.

Statistical Analysis

Scale variables were presented as mean±SD or median (25th–75th percentile), as appropriate. Categorical variables were presented as counts or percentages with 95% confidence intervals (CIs), as appropriate. The data were tested for normal distribution using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Cox regression was used for studying the hazard of PPS and the association of PPS with mortality. The multivariable model was performed by including age, sex, Charlson Comorbidity Index, the urgency of the procedure, procedure type, and resternotomy. Associations of concomitant CABG in valve and aortic procedures, use of the left internal thoracic artery in CABG, and use of the mechanical valve in aortic valve replacement (AVR) with PPS occurrence were studied by subgroup analyses. $P<0.05$ was considered statistically significant. Statistical analyses were conducted with SAS system, version 9.4 (SAS Institute Inc, Cary, NC), and SPSS, version 24.0, statistical software (IBM SPSS Inc, Chicago, IL).

Results

Patient Cohort and Index Event

Figure 1 presents a flow chart of the patients forming the study population. The final patient cohort included 28 761 patients undergoing open-heart surgery. Of the cohort, 64.9% (N=18 679) underwent CABG, 19.7% (N=5674) underwent AVR, 10.3% (N=2964) underwent mitral valve replacement (MVR), and 5.0% (N=1444) underwent ascending aortic surgery, when combination procedures were excluded. Patient characteristics and procedure differences are detailed in Table 1.

The study period included 493 PPS episodes. Of these, 99.4% were admissions with PPS as the primary, secondary, or tertiary cause of admission and 0.6% were recognized postmortem. Median latency between operation and PPS was 22 (25th–75th percentile,12–49) days.

Predictors of PPS

The predictors for PPS are detailed in Table 2. In univariable analysis, a younger age was associated with a higher risk of PPS after operation. No significant differences were detected in Charlson Comorbidity Index and sex distribution in patients

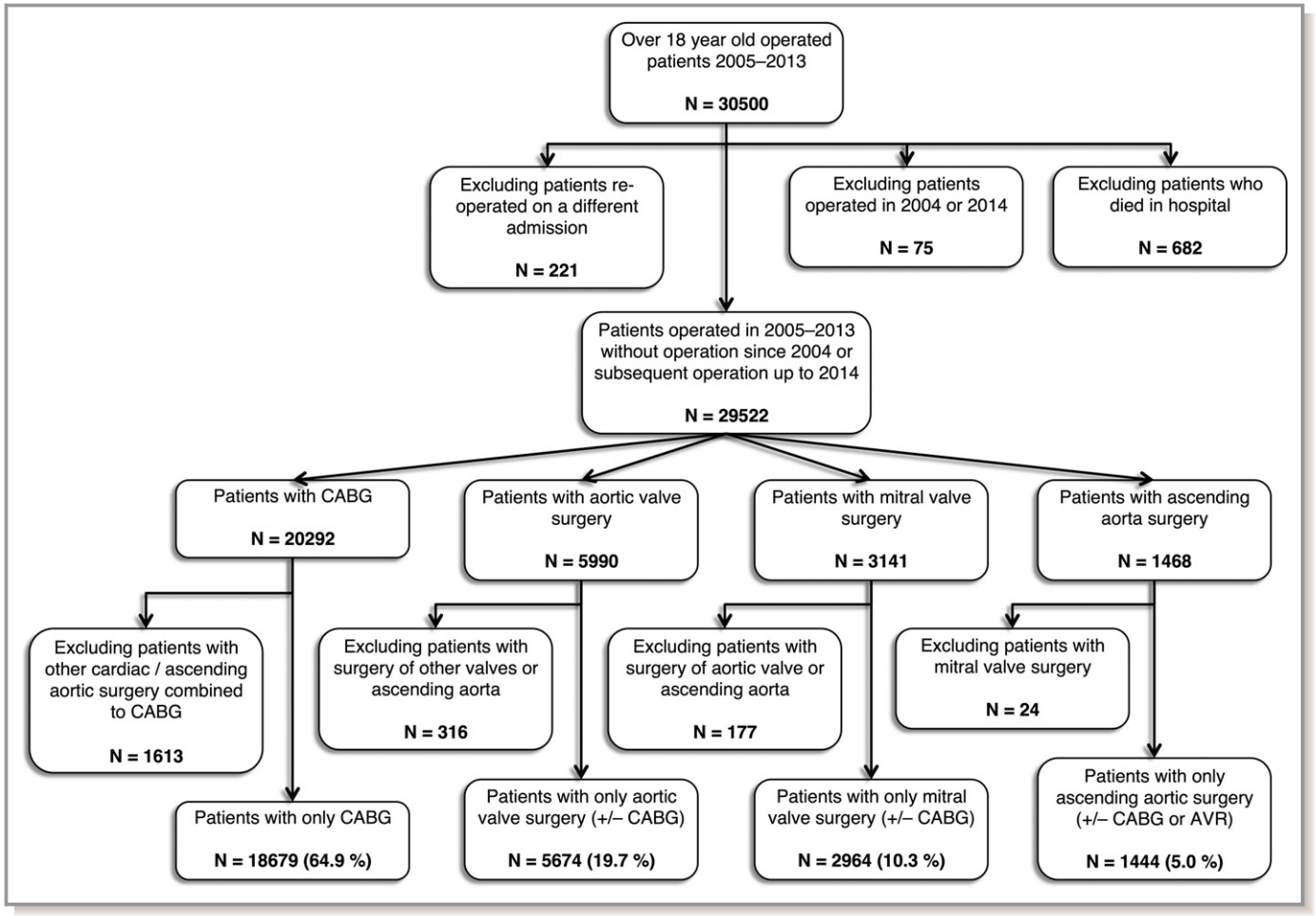

Figure 1. Study population flow chart. AVR indicates aortic valve replacement; CABG, coronary artery bypass grafting.

with and without PPS. The occurrence of PPS was significantly higher after AVR, MVR, and aortic surgery, when compared with CABG. A need to perform the operation urgently or in an emergency was associated with a higher risk of PPS. No significant differences in the rate of PPS were detected in patients with and without resternotomy.

The extent of the procedure remained an independent predictor of higher PPS risk on Cox proportional hazards regression after adjustment for covariables. Patients undergoing AVR, MVR, and aortic surgery had a higher risk of PPS when compared with those undergoing the CABG procedure. An advanced age at operation decreased the risk, and urgent or emergent procedure increased the risk, of PPS, after multivariable adjustment (Table 2).

The cumulative rate of PPS stratified by different risk factors is detailed in Figure 2. The occurrence was equally higher in those undergoing AVR and MVR procedures when compared with those undergoing CABG, but clearly the highest occurrence appeared after aortic surgery (Figure 2B).

Concomitant CABG in valve and aortic procedures (hazard ratio [HR], 1.27; 95% CI, 0.94–1.71; *P*=0.120), the use of the left internal thoracic artery in CABG (HR, 1.06; 95% CI, 0.67–1.68; *P*=0.795), and the use of a mechanical valve in AVR (HR, 1.26; 95% CI, 0.89–1.79; *P*=0.192) did not have an effect on the occurrence of PPS.

PPS and Mortality

A total of 907 patients (3.2%) died within the first year after the surgery. Patients who died within 30 days after the surgery (244 patients [0.8%]) were excluded from the mortality analyses to minimize the false-negative diagnoses of PPS. PPS was associated with a 72% increase in risk of mortality within the first year after the surgery on an unadjusted model (HR, 1.72; 95% CI, 1.09–2.71; *P*=0.021), and the results were also similar on the multivariable adjusted model (HR, 1.78; 95% CI, 1.12–2.81; *P*=0.014). Survival after cardiac and ascending aortic surgery on patients with and without PPS is detailed in Figure 3. Of those patients with PPS who died within the first year after surgery, 10.5% had the diagnosis included in the death certificate. The mean time between the diagnosis of PPS

Table 1. Patient Characteristics and Procedure Differences

Characteristics	Total (N=28 761)	CABG (N=18 679)	AVR (±CABG) (N=5674)	MVR (±CABG) (N=2964)	Aortic Surgery (±AVR or CABG) (N=1444)
Age, y	66.3 (66.2–66.5)	66.7 (66.5–66.8)	69.6 (69.3–69.9)	62.0 (61.5–62.4)	58.0 (57.3–58.7)
Female sex, %	26.1 (25.5–26.6)	21.7 (21.0–22.2)	40.8 (39.6–42.1)	27.3 (25.7–28.9)	22.9 (20.7–25.1)
CCI	0.82 (0.80–0.83)	0.90 (0.89–0.92)	0.63 (0.60–0.65)	0.49 (0.46–0.52)	1.13 (1.09–1.16)
Low risk (CCI, 0)	48.3 (47.7–48.9)	44.6 (43.9–45.3)	60.3 (59.1–61.6)	66.3 (64.6–68.0)	11.7 (10.0–13.4)
Mild risk (CCI, 1)	32.8 (32.3–33.4)	34.0 (33.3–34.7)	24.6 (23.5–25.7)	23.1 (21.6–24.6)	70.3 (67.9–72.6)
Moderate risk (CCI, 2)	12.0 (11.6–12.3)	13.2 (12.7–13.7)	10.0 (9.2–10.8)	7.3 (6.4–8.3)	13.3 (11.5–15.0)
High risk (CCI, ≥3)	6.9 (6.6–7.2)	8.2 (7.8–8.6)	5.1 (4.5–5.6)	3.2 (2.6–3.9)	4.7 (3.6–5.8)
Urgent or emergency procedure, %	7.4 (7.1–7.7)	7.3 (6.9–7.7)	4.2 (3.7–4.8)	6.3 (5.4–7.1)	24.4 (22.1–26.6)
CABG, %	69.1 (68.6–69.6)	···	15.2 (14.2–16.1)	8.1 (7.1–9.1)	5.9 (4.7–7.2)
Resternotomy, %	3.8 (3.6–4.1)	3.7 (3.4–3.9)	3.6 (3.1–4.0)	4.3 (3.6–5.0)	6.3 (5.0–7.6)

Continuous variables are reported as mean (95% confidence interval); categorical variables are reported as percentage (95% confidence interval). AVR indicates aortic valve replacement; CABG, coronary artery bypass grafting; CCI, Charlson Comorbidity Index; MVR, mitral valve replacement.

and death was 137±102 days in patients who died within the first year after surgery. Ischemic heart disease (*ICD-10* codes I20-I25) was the most common cause of death (36.8%) in patients with PPS who died within the first year after the surgery. Causes of death were similar between patients with and those without PPS.

Discussion

The main findings of this nationwide multicenter study are the following: (1) the occurrence of PPS severe enough to require hospital admission or to contribute to death is higher after more extensive procedures, such as AVR, MVR, and aortic surgery, when compared with CABG; (2) PPS is associated with a >1.7-fold increase in the risk of mortality within the first year after index surgery.

This study has several clinical implications. Epidemiological data on PPS are scarce. Neither the influence of procedure type nor the association with mortality has previously been reported in the general population. These should be better understood to provide effective targeting of possible preventive strategies and to determine the acceptable number of adverse events for the prophylactic methods used.

Patients with PPS had a >1.7-fold risk of mortality within the first year after the surgery when compared with patients without PPS. The syndrome is known to cause prolonged hospital stay, readmissions, and invasive interventions, including pericardial and/or pleural drainage, but the prognosis of the syndrome has been considered to be benign.[1] However, the data on the association of PPS and mortality are scarce. A recent single-center study including 822 patients undergoing valve surgery concluded that patients with PPS had an excellent 1-year prognosis.[4] The study included 119 patients with PPS overall and fewer patients with complete follow-up for death, of whom only 4 died within the first year after surgery (expected value, 5). Therefore, no clear conclusions can be drawn from these results. Moreover, few other studies have evaluated the mortality rates, but the numbers of patients have not been sufficient for making reliable conclusions.[6]

The reasons for higher mortality in patients with PPS remain to be elucidated. None of the causes of death was overrepresented in patients with PPS who died within the first year after surgery. Instead, patients with PPS had a higher overall mortality, with ischemic heart disease as the most common cause of death. Death occurred typically 2 to 6 months after the diagnosis of PPS, so a direct link to the hemodynamic problems caused by the syndrome is unlikely. According to previous clinical trials, the use of colchicine has no significant effect on the overall mortality.[8,9] The effect of short-term corticosteroids on mortality in the presence of heart disease is poorly documented. Although long-term use of high-dose corticosteroids is associated with an increased risk of cardiovascular disease and mortality,[10] the effect appears within several years rather than months[11] and in high cumulative exposure.[12,13] The use of nonsteroidal anti-inflammatory drugs is also associated with myocardial infarctions and higher mortality attributable to coronary heart disease,[14] but the effect is insignificant in therapies with a length of <1 month,[15] which is typical in the treatment of PPS. Therefore, the medical therapies for PPS are unlikely to be responsible for the higher mortality. Instead, we presume it to be related to the underlying immunological changes caused by or resulting in PPS. A more detailed mechanism cannot be

Table 2. Predictors for PPS

Variable	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age class		<0.001		0.006
18–40 y vs ≥71 y	2.51 (1.56–4.04)	<0.001	1.61 (0.98–2.64)	0.062
41-50 y vs ≥71 y	1.93 (1.38–2.69)	<0.001	1.77 (1.25–2.50)	0.001
51–70 y vs ≥71 y	1.22 (1.00–1.48)	0.050	1.27 (1.03–1.55)	0.024
Female sex	1.06 (0.87–1.29)	0.566	1.04 (0.84–1.27)	0.744
CCI		0.739		0.833
Mild risk (CCI, 1) vs low risk (CCI, 0)	1.00 (0.82–1.21)	0.965	0.93 (0.75–1.14)	0.698
Moderate risk (CCI, 2) vs low risk (CCI, 0)	0.86 (0.63–1.16)	0.308	0.89 (0.66–1.21)	0.618
High risk (CCI, ≥3) vs low risk (CCI, 0)	0.91 (0.63–1.32)	0.620	1.00 (0.68–1.46)	0.992
AVR (±CABG) vs CABG	1.91 (1.54–2.36)	<0.001	1.97 (1.58–2.46)	<0.001
MVR (±CABG) vs CABG	1.76 (1.33–2.32)	<0.001	1.62 (1.22–2.15)	<0.001
Aortic surgery (±AVR or CABG) vs CABG	3.49 (2.63–4.63)	<0.001	3.06 (2.24–4.16)	<0.001
Urgent or emergency procedure	1.54 (1.16–2.05)	0.003	1.36 (1.00–1.83)	0.047
Resternotomy	1.37 (0.92–2.05)	0.127	1.24 (0.82–1.88)	0.299

PPS severe enough to require hospital admission or to contribute to death. AVR indicates aortic valve replacement; CABG, coronary artery bypass grafting; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; MVR, mitral valve replacement; PPS, postpericardiotomy syndrome.

deduced until the pathophysiological characteristics of PPS are unraveled.

The association with an increased mortality supports the use of relatively aggressive prophylactic methods to prevent PPS. Therefore, for example, the increased risk of gastrointestinal adverse effects of colchicine should not necessarily be interpreted as an insuperable obstacle for the preventive use of the drug.[16] It should, however, also be taken into consideration that there is no evidence that preventive therapies would diminish the risk of mortality associated with PPS, as described in the current study.[8]

This study implicates that the incidence of PPS is markedly higher in those undergoing AVR, MVR, and aortic procedures when compared with those undergoing CABG. Thus, more traumatic procedures seem to cause a higher incidence of PPS. Only a few previous studies have evaluated the influence of procedure type on the incidence of PPS. In a study released in 1988, patients undergoing AVR were at a greater risk for PPS, and patients undergoing MVR appeared to have a reduced risk of PPS.[3] However, the diagnostic criteria were significantly different compared with the criteria currently in use. Moreover, in a recently published study containing 119 patients with PPS, MVR significantly increased the risk of PPS.[4] Also, combined heart surgery has been associated with a significantly higher incidence of PPS.[5] However, neither of the last 2 reached statistical significance in the multivariable analyses.

The cause of PPS has remained partially unclear. The syndrome has been assumed to be an immune-mediated process[1] triggered by direct pericardial trauma, pericardial bleeding, and individual predisposition.[2] AVR, MVR, and aortic procedures all present a more extensive pericardial trauma during the surgery, which supports the previously mentioned hypothesis and could explain the higher incidence of PPS in these procedures. Isolated valve procedures present lower postoperative bleeding within the first 12 hours after the operation compared with the CABG procedure.[17] Therefore, pericardial bleeding alone is presumably not responsible for the higher occurrence of PPS within valve procedures, although it may play a role in the pathophysiological characteristics of PPS. Besides a more extensive trauma, a more complex procedure usually means longer time in cardiopulmonary bypass[18] and, therefore, longer pericardial exposure to air and other unphysiological materials. Because the cause remains obscure, these hypothetical causative factors should be investigated in further research.

We found a younger age to be associated with a higher occurrence of PPS. This finding is in line with the results of a previously published population-based registry study.[19] Although the overall incidence of autoimmune diseases increases with age,[20] different autoimmune diseases can affect a specific age group predominantly,[21] which could explain the higher occurrence of PPS within younger patients. The increased risk may also be associated with aging-related changes in immune response, such as the reducing activity of T and B cells.[22]

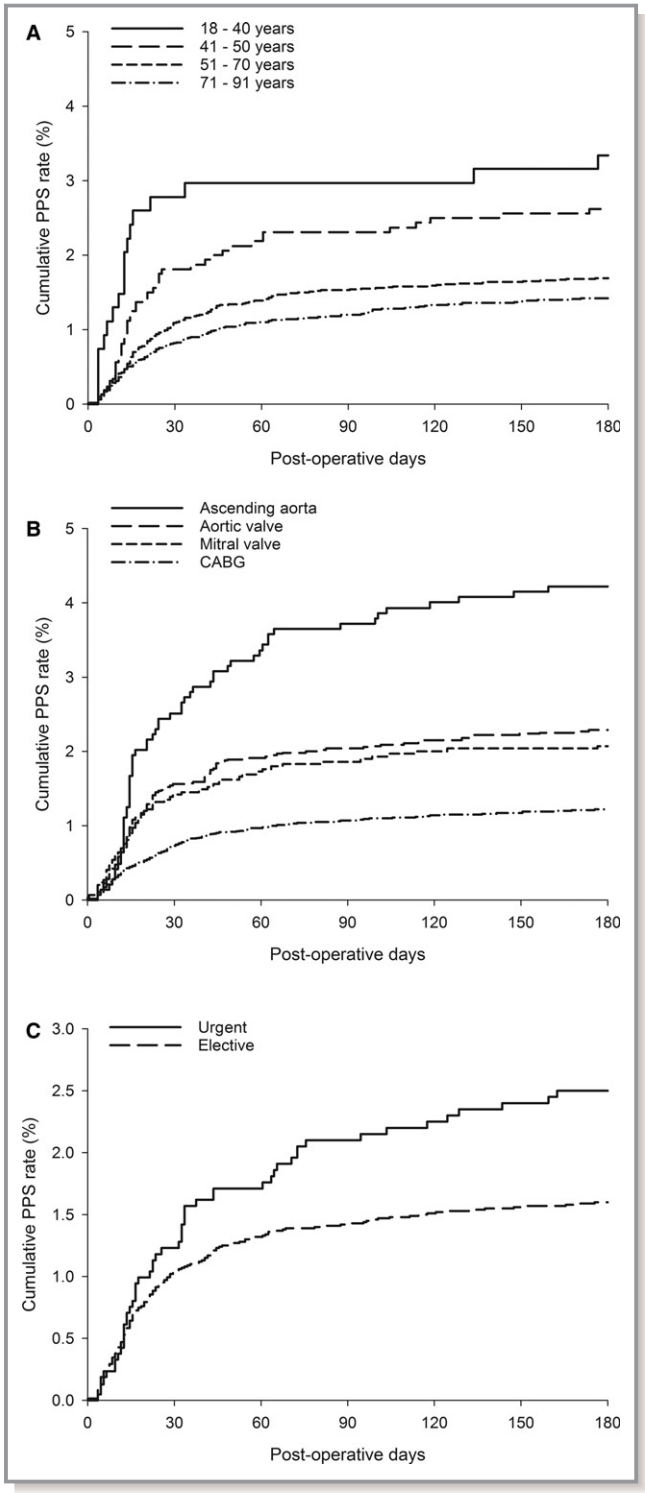

Figure 2. Cumulative postpericardiotomy syndrome (PPS) occurrence stratified by age (**A**), procedure type (**B**), and urgency of the procedure (**C**). CABG indicates coronary artery bypass grafting.

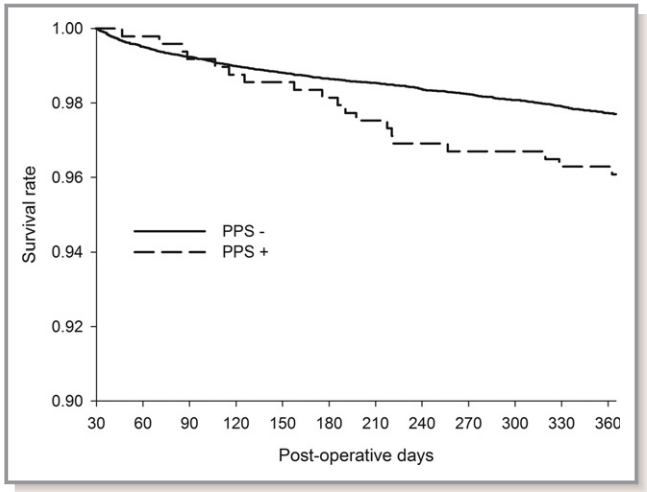

Figure 3. Survival after cardiac and ascending aortic surgery and occurrence of postpericardiotomy syndrome (PPS). Patients alive 30 days after the surgery are included.

The retrospective nature of this study is a limitation. Although we included all hospitals that perform cardiac operations in Finland, in addition to all central hospitals and the largest regional hospitals nationwide, it is possible that a few patients with PPS were treated in some of the smaller regional hospitals that were not included in data collection. Also, only patients admitted to a hospital were included in the present study. Because patients with mild symptoms can be treated at outpatient clinics, they were not included in our data. Besides, there is also a possibility of underdiagnosing in the presence of one or few mild PPS-related symptoms, when the physician treats the symptoms (eg, by anti-inflammatory medications), but the exact PPS diagnosis is not set. Therefore, the conclusions presented can be directly applied only to PPS cases severe enough to result in hospital admission, and, for instance, the effect on mortality would presumably be less substantial within patients with mild PPS. The medications patients are receiving may have a positive or negative influence on PPS occurrence. Although the specific medications used after different cardiac procedures should not affect the occurrence of PPS, this bias cannot be ruled out, because the medication data were unavailable. In the present study, treating physicians made the diagnoses. Ideally, this should mean better differential diagnostic procedures and more certain diagnoses in this real-world setting. However, the lack of nationwide criteria was unavoidable, because there were no standardized criteria for the syndrome until 2015.[16] It is also possible that the assignment of PPS diagnosis became disturbed in the presence of other more dominant conditions, such as stroke or death. This would, however, only further strengthen the conclusion of increased risk of postoperative mortality within patients with PPS. Besides, AVR, MVR, and aortic procedures all present generally more postoperative complications when compared with the CABG procedure and, therefore, this would also further strengthen the conclusion of higher PPS occurrence after AVR, MVR, and aortic procedures.[23–27]

In conclusion, these large nationwide data show that the occurrence of PPS is higher after AVR, MVR, and aortic surgeries when compared with the CABG procedure. Patients with PPS had higher mortality within the first year after the surgery, suggesting that effective preventive measures need to be identified.

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