

# openheart Occurrence and predictors of pericardial effusion requiring invasive treatment following heart valve surgery

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## ABSTRACT

**Objectives** To describe the occurrence of significant pericardial effusion, and to investigate characteristics associated with pericardial effusion within three months following heart valve surgery.

**Methods** A retrospective, observational cohort study including adult patients undergoing heart valve surgery at Odense University Hospital from August 2013 to November 2017. Data were gathered from The Western Denmark Heart Registry and electronic patient records.

Cox proportional hazard models were used to investigate the associations between characteristics associated with significant pericardial effusion during index admission and within 3 months. Results are presented as HR with 95% CI. **Results** In total, 1460 patients were included (70% men, median age 71 years (IQR 63–76)) and of those, n=230 patients (16%) developed significant pericardial effusion. EuroScore II was significantly associated with an increased risk of pericardial effusion during index admission and associated with a lower risk following discharge (index admission HR 1.05, 95% CI 1.02 to 1.08, after discharge HR 0.80, 95% CI 0.69 to 0.92). Increasing age (HR 0.97, 95% CI 0.95 to 0.98 per year) and concomitant coronary artery bypass grafting versus isolated valve surgery (HR 0.58, 95% CI 0.35 to 0.97) were significantly associated with a reduced risk of pericardial effusions in both periods. Being a man (HR 2.30, 95% CI 1.32 to 4.01) and aortic valve disease versus mitral valve disease (HR 2.16, 95% CI 1.20 to 3.90) were significantly associated with an increased risk after discharge.

**Conclusion** Significant pericardial effusions requiring drainage were present in 16% of cases following heart valve surgery, and different clinical characteristics were associated with the development of effusion.

## INTRODUCTION

Pericardial effusion is a well-known complication following cardiac surgery which may cause prolonged hospitalisations, rehospitalisations, and in the most severe cases, life-threatening cardiac tamponade.<sup>1–3</sup> Commonly, pericardial effusion develops within the first postoperative weeks and is usually diagnosed with echocardiography.<sup>3–4</sup> Incidences of pericardial effusions

## Key questions

### What is already known about this subject?

► Pericardial effusion is a well-known complication following cardiac surgery which may cause prolonged hospitalisations, rehospitalisations, and in the most severe cases, life-threatening cardiac tamponade.

### What does this study add?

► The study demonstrates how different factors detect patients at risk of pericardial effusion, including young male patients with aortic valve surgery.

### How might this impact on clinical practice?

► Identifying patients at risk of developing pericardial effusion may help improve postoperative management following heart valve surgery.

in available literature vary greatly from 1% to 64%, depending on definitions, study design, observation time and surgical population studied.<sup>1–4,9</sup> Opposed to other common complications following cardiac surgery such as atrial fibrillation, heart failure and infections, causes and characteristics of pericardial effusions have not been as thoroughly investigated.<sup>4</sup>

Most patients, with small pericardial effusion, remain asymptomatic and effusion requires no specific intervention.<sup>4</sup> When associated with symptoms or haemodynamic compromise, the effusion requires drainage either ultrasound-guided percutaneous or surgical depending on location or time from surgery.<sup>3</sup> There are no proven effective medical treatments of pericardial effusions without inflammation, but, when the pericardial effusion is associated with pericarditis, management should follow that of pericarditis.<sup>3</sup> Currently, there is a growing body of evidence of a beneficial effect of Colchicine in preventing recurrent pericardial effusion in pericarditis and postpericardiotomy syndrome,<sup>10–14</sup> whereas Colchicine is not



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recommended in the absence of inflammation.<sup>3</sup> Similarly, non-steroidal anti-inflammatory drugs are not indicated as a treatment and may be associated with an increased risk of side effects.<sup>3</sup> Thus, there is presently no medical treatment of pericardial effusions following surgery.<sup>13</sup>

In general, there is a scarcity of studies investigating factors associated with the development of pericardial effusion following heart valve surgery. A recent study of patients undergoing cardiac surgery has demonstrated how younger patients with lower surgical risk score (EuroScore), better cardiac function (measured by left ventricular ejection fraction, LVEF), less coronary artery disease and higher preoperative haemoglobin values undergoing heart valve surgery are at higher risk of developing late (>7 days) pericardial effusion.<sup>4</sup> In addition, preoperative or postoperative anticoagulation, surgery other than coronary artery bypass grafting (CABG), implantation of a mechanical valve prosthesis, and blood transfusions have been demonstrated to be associated with increased risk of cardiac tamponade.<sup>2,9</sup> Nevertheless, to prevent patients from developing significant pericardial effusions and to be aware of patients at increased risk, more knowledge about factors associated with pericardial effusions is needed.

Thus, the objectives of this study were to describe the occurrence of significant pericardial effusion defined as effusion requiring intervention and to investigate characteristics associated with pericardial effusion within 3 months following heart valve surgery.

## MATERIALS AND METHODS

### Study design

The study was designed as a retrospective observational cohort study.

### Participants and setting and recruitment

All consecutive patients undergoing open heart valve surgery (replacement or repair) at a tertiary Danish teaching facility, Odense University Hospital, Denmark, from August 2013 to November 2017 were included in the cohort study. Adult patients ( $\geq 18$  years) with aortic valve diseases, mitral valve diseases or tricuspid valve diseases were included based on their surgical procedure codes, Nordic/NOMESCO Classification of Surgical Procedures,<sup>15</sup> online supplemental table S1. Patients were grouped according to their primary valve disorder. Only patients with permanent residence in the Region of Southern Denmark were included.

### Data collection

#### Demographic and clinical data

Demographic and clinical data from the index admission were obtained from electronic medical records and the Western Denmark Heart Registry (WDHR).<sup>16</sup> Data on sex, age, smoking status (current or former smoker), alcohol consumption (above the national limit of  $\geq 7$  unit/week/women and  $\geq 14$  units/week/men), body mass index, length of hospital stay and medical treatment were

obtained from the electronic medical record. From the WDHR, information on the type of surgery, comorbidity, EuroScore II and blood transfusions were obtained.

Data on relevant medical treatment, including anti-coagulants, platelet aggregation inhibitors, direct oral anticoagulants and use of ibuprofen, were obtained from the medical records. Medications (prescription based) received during the 3 months follow-up were registered. Among patients developing pericardial effusion requiring drainage, medications prescribed before the drainage were registered and included, to ensure that only medication intake prior to drainage was included in the analyses.

### Outcomes

The primary study outcome was significant pericardial effusion defined as a pericardial effusion requiring drainage/pericardiocentesis (either percutaneous ultrasound-guided or surgical). Method/technique of drainage was decided by the treating cardiac surgeon and cardiologist, and if possible, percutaneous drainage was preferred. All significant pericardial effusions during both index admission and within the first 3 months after surgery were included. Data on significant pericardial effusions, including the type of drainage, date of drainage and whether it was performed before or after discharge were obtained from the patient electronic medical records. All pericardial effusions were registered, but only the first drainage was included in the overall analyses. Although patients could be transferred to or readmitted at local hospitals, the pericardial drainage was only performed at the tertiary centre, Odense University Hospital.

### Statistics

Baseline characteristics were presented as number and percentage for categorical data and median and 25th to 75th percentiles (IQR) for continuous data since the normality assumption was not met (tested with the Shapiro-Wilks test and visualised with QQ plot). To compare baseline characteristics, the  $\chi^2$ -test was used for categorical variables, and the Mann-Whitney U test was used to compare continuous data.

The proportion of patients with significant pericardial effusion, type of procedure and median time (days) from surgery to the procedure was calculated.

To investigate characteristics associated with significant pericardial effusion, first, univariable Cox proportional hazard models were performed in two different models. Model 1 investigated characteristics associated with the risk of developing significant pericardial effusion during the index admission and model 2 investigated characteristics associated with significant pericardial effusion drainage after discharge and up to 3 months post surgery. The underlying time scale was time to the first event measured in days. Second, multivariable Cox proportional hazard models were performed with outcomes similar to the above models. Variables included in the models

included covariates with a  $p$  value  $<0.20$  in the unadjusted analyses and characteristics assumed to be related to the significant pericardial effusion (age, EuroScore II, cardiac function, coronary artery disease and anticoagulants<sup>2,4,9</sup>). The underlying time scale in model 2 was time from discharge to the first event thereafter, measured in days. Analyses of potential interactions among variables were performed. In cases with collinearity, the variable that had the best performance in the model (tested with the likelihood ratio) was included, and in general, variables with only a few events were excluded. The proportional hazard was assessed graphically using hazard plots, and the assumptions were met. Results were presented as HRs with its 95% CIs.

A  $p$  value of  $<0.05$  was considered to be statistically significant. STATA IC V.16 (StataCorp) was used for the analyses.

## RESULTS

During the study period, 1460 patients underwent heart valve surgery and were included in the current study. Of those, 70% were men, the median age was 71 years (IQR 63–76), 62% were diagnosed with aortic valve stenosis, and median length of stay was 9 days (IQR 7–13). Demographic and clinical characteristics among the total population are summarised in [table 1](#). In total, 66 patients (4.5%) died during the first 3 months after surgery, the majority, 55 patients, during the index admission. In the period after surgery, 79% of the patients were treated with acetylsalicylic acid and 41% with warfarin ([table 2](#)).

### Occurrence of significant pericardial effusion

During the follow-up period of 3 months,  $n=230$  patients (16%) developed a significant pericardial effusion, 52% were drained as a subxiphoid (surgical) approach versus 48% as a parasternal/ultrasound-guided approach. In 125 patients (54%), the drainage was performed before discharge during the index admission, and in 105 patients (46%) after discharge ([figure 1](#) and online supplemental table S2). The median time to treatment of significant pericardial effusion was 10 days (IQR 6–17) for the entire population. Among patients who died, eight developed significant pericardial effusions before their death (all before discharge).

Patients developing significant pericardial effusion were more often men (76% vs 69%,  $p=0.035$ ), were more often in the younger age group from 18 to 65 years (50% vs 27%,  $p<0.001$ ), had a lower median EuroScore II (1.8 vs 2.2,  $p<0.001$ ) and fewer had coronary artery disease and were thus less likely to undergo concomitant CABG (13% vs 30%,  $p<0.001$ ) ([table 1](#)). Of the patients who developed significant pericardial effusion, 15 patients (7%) had drainage performed more than once. Colchicine was prescribed for  $n=5$  patients (0.3%) before the pericardiocentesis and for  $n=32$  patients (2%) after pericardiocentesis.

### Factors associated with significant pericardial effusion

Factors associated with significant pericardial effusion during index admission (univariable model 1) and after discharge (univariable model 2) are presented in [table 3](#). In the univariable models, EuroScore II was significantly associated with the risk of developing significant pericardial effusion during index admission and was associated with a reduced risk following discharge (EuroScore II, index admission HR 1.05, 95% CI 1.01 to 1.08, after discharge HR 0.63, 95% CI 0.52 to 0.75) ([table 3](#)).

In the adjusted analyses, EuroScore II (HR 1.05, 95% CI 1.02 to 1.08) was significantly associated with increased risk of significant pericardial effusion and increasing age (HR 0.97, 95% CI 0.95 to 0.98 per year) and concomitant CABG versus isolated valve surgery (HR 0.58, 95% CI 0.35 to 0.97) were associated with a reduced risk of significant pericardial effusion during index admission (model 1) ([figure 2](#)). After discharge, being a man (HR 2.30, 95% CI 1.32 to 4.01) and aortic valve disease versus mitral valve disease (HR 2.16, 95% CI 1.20 to 3.90) were associated with an increased risk of significant pericardial effusion. Conversely, increasing age (HR 0.95, 95% CI 0.93 to 0.97), EuroScore II (HR 0.80, 95% CI 0.69 to 0.92) and concomitant CABG versus isolated valve surgery (HR 0.42, 95% CI 0.21 to 0.82) were significantly associated with a reduced risk of significant pericardial effusion after discharge (model 2) ([figure 2](#)). When testing for interactions, the interaction between being a man and mechanical valve replacement were significantly associated with outcome ( $p$  value for interaction 0.028), no other significant interaction terms were found.

## DISCUSSION

In this retrospective cohort study, we investigated characteristics associated with significant pericardial effusion within the first 3 months following heart valve surgery. We found that 16% of patients developed pericardial effusion requiring drainage at any time during the first 3 months after surgery. Although the majority of effusions were managed during the first 2 weeks after surgery, some patients were treated more than 2 months after surgery. Several clinical and demographic characteristics were associated with significant pericardial effusion, although characteristics varied during index admission and after discharge. This knowledge might help clinicians assess and be aware of patients with a higher risk profile.

The incidence of significant pericardial effusion (16%) found in the current study is seemingly high when compared with previous studies.<sup>14–9</sup> This can be explained by several factors: several studies report incidences of significant pericardial effusions based on broad cardiac surgical populations, including patients undergoing isolated CABG. Previous studies have suggested CABG to be associated with a lower risk of postoperative pericardial effusion compared with valve procedures.<sup>2,4,8,17</sup> Thus, a direct comparison between these studies and the present study should be done with caution. The haemostasis

**Table 1** Baseline characteristics

	All	No significant pericardial effusion	With significant pericardial effusion*	P value†
N	1460	1230	230	
Characteristics				
Sex, male, n (%)	1019 (70)	845 (69)	174 (76)	<b>0.035</b>
Age, years, median (IQR)	71 (63–76)	72 (65–76)	65 (54–72)	<b>≤0.001</b>
Age-groups, n (%)				
18–65 years	453 (31)	337 (27)	116 (50)	<b>≤0.001</b>
>66 years	1007 (69)	893 (73)	114 (50)	
Preoperative information				
Reduced pulmonary function‡, n (%)	534 (37)	447 (36)	87 (39)	0.534
EuroScore II, median (IQR)	2.1 (1.2–3.7)	2.2 (1.3–3.8)	1.8 (0.9–2.9)	<b>≤0.001</b>
Estimated glomerular filtration rate§ mL/min<60, n (%)	318 (24)	280 (25)	38 (18)	<b>0.019</b>
Atrial fibrillation, n (%)	359 (25)	308 (25)	51 (22)	0.354
Anticoagulation, n (%)	233 (16)	209 (17)	35 (15)	0.332
Diabetes¶, n (%)	191 (13)	160 (13)	31 (13)	0.857
Ejection fraction ≤50, n (%)	453 (32)	379 (32)	74 (34)	0.540
Previous cardiac surgery, n (%)	144 (10)	132 (11)	12 (5)	<b>0.009</b>
Previous PCI, n (%)	134 (10)	114 (10)	20 (9)	0.757
NYHA class ≥3, n (%)	582 (40)	496 (41)	86 (39)	0.546
Body mass index, median (IQR)	26 (24–30)	26 (24–30)	27 (24–29)	0.624
Current or former smoker, n (%)	840 (58)	714 (58)	126 (55)	0.298
Alcohol intake above national high-risk limit, n (%)	152 (10)	132 (11)	20 (9)	0.353
Primary diagnosis, n (%)				
Aortic valve stenosis	902 (62)	777 (63)	125 (54)	<b>0.010</b>
Aortic valve regurgitation	246 (17)	186 (15)	60 (26)	<b>≤0.001</b>
Mitral valve stenosis or regurgitation	303 (21)	259 (21)	44 (19)	0.498
Surgical information, n (%)				
Type of valve procedure				
Aortic valve, biological	934 (64)	818 (67)	116 (50)	<b>≤0.001</b>
Aortic valve, mechanical	208 (14)	139 (11)	69 (30)	<b>≤0.001</b>
Aortic valve, repair	21 (1)	15 (1)	6 (3)	0.106
Mitral valve, replacement**	92 (6)	75 (6)	17 (7)	0.474
Mitral valve, repair	196 (13)	175 (14)	21 (9)	<b>0.036</b>
Concomitant CABG, n (%)	396 (27)	366 (30)	30 (13)	<b>≤0.001</b>
Postprocedure related				
ECC, min, median (IQR)	110 (90–141)	110 (90–139)	111 (91–150)	0.371
Re-operation, all, n (%)	132 (9)	105 (9)	27 (12)	0.120
Re-operation, bleeding, n (%)	27 (2)	21 (2)	6 (3)	0.352
Need for blood transfusions, n (%)	713 (49)	613 (50)	100 (44)	0.128
Postoperative atrial fibrillation, n (%)	876 (61)	726 (59)	150 (67)	<b>0.039</b>
New-onset postoperative atrial fibrillation, n (%)	609 (42)	503 (41)	106 (47)	0.095
Length of stay, days	9 (7–13)	9 (7–12)	11 (7.5–18)	<b>≤0.001</b>

IQR: 25th to 75th quartile.

\*A significant pericardial effusion was defined as a pericardial effusion requiring drainage/pericardiocentesis.

†A p value <0.05 was considered statistically significant (shown in bold).

‡Patients with forced expiratory volume, %≤80% of predicted value and/or a history of chronic obstructive pulmonary disease.

§Estimated glomerular filtration rate estimated by the Cockcroft–Gault equation.

¶Patients with diabetes; insulin, peroral and non-pharmacological treatment.

\*\*Both biological and mechanical mitral valve replacement.

CABG, coronary artery bypass grafting; ECC, extra corporal circulation; NYHA, New York Heart Association Class; PCI, percutaneous coronary intervention.

**Table 2** Relevant medical treatment following surgery and within the first 3 months among patients with significant pericardial effusions and without

	All	No significant pericardial effusion	With significant pericardial effusion	P value*
N	1460	1230	230	
<b>Anticoagulants</b>				
Dalteparin	623 (43)	522 (42)	65 (28)	<b>≤0.001</b>
Warfarin	595 (41)	457 (37)	111 (48)	<b>0.002</b>
Phenprocoumon	14 (1)	13 (1)	<5	0.374
<b>Platelet aggregation inhibitors</b>				
Acetylsalicyl acid	1160 (79)	1006 (82)	134 (58)	<b>≤0.001</b>
Ticagrelor	39 (3)	35 (3)	<5	0.080
Clopidogrel	188 (13)	152 (12)	27 (12)	0.793
Dipyridamol	34 (2)	29 (2)	5 (2)	0.865
<b>Direct oral anticoagulants, DOAC</b>				
Apixaban	83 (6)	73 (6)	6 (3)	<b>0.041</b>
Dabigatranetexilat	35 (2)	29 (2)	4 (2)	0.562
Rivaroxaban	97 (7)	87 (7)	10 (4)	<b>≤0.001</b>
<b>Combination of treatment</b>				
Monotherapy, anticoagulants	576 (39)	472 (39)	104 (45)	0.051
Dualtherapy, anticoagulants†	794 (54)	700 (57)	94 (41)	<b>≤0.001</b>
Single antiplatelet therapy (SAPT)	215 (15)	175 (14)	32 (14)	0.619
SAPT and anticoagulants	1392 (95)	1193 (97)	199 (87)	<b>≤0.001</b>
<b>Others</b>				
Non-steroidal anti-inflammatory drug (NSAID), ibuprofen	495 (34)	388 (31)	88 (38)	<b>0.046</b>

\*A p value <0.05 was considered statistically significant (shown in bold).

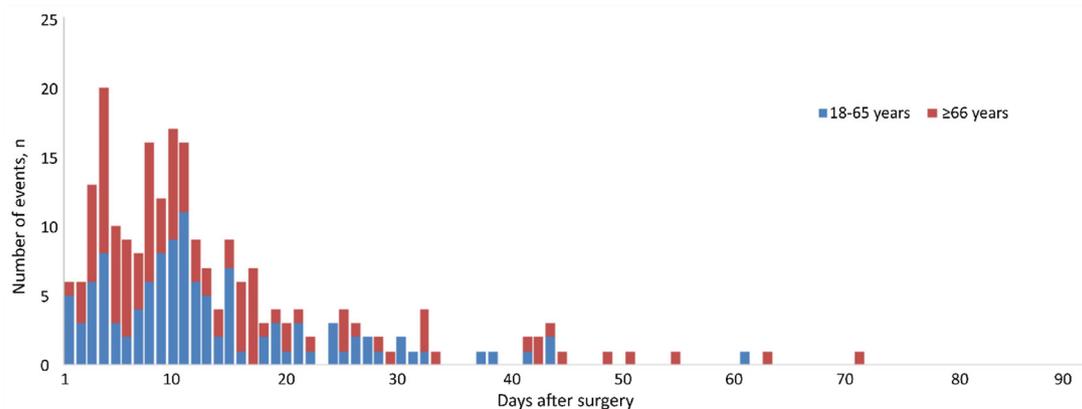
†Treatment with more than one type of anticoagulants.

DOAC, direct oral anticoagulants; NSAID, non-steroidal anti-inflammatory drug; SAPT, single antiplatelet therapy.

techniques in CABG in combination with a wide opening to the left pleura may facilitate drainage of pericardial fluid and prevent pericardial effusions.<sup>8</sup> Thus, it is expected that our study, only including patients undergoing valve surgery, will find a higher proportion of pericardial effusions. In addition, the definition of significant pericardial effusion versus cardiac tamponade varies

across studies<sup>14-918</sup> and in the current study, all significant pericardial effusions requiring drainage were included.

As significant pericardial effusions prolong hospitalisations, increase the risk of developing tamponade and are a significant burden for the patients,<sup>1-3</sup> gaining knowledge on how to identify patients at higher risk is important. This identification, for example, of higher

**Figure 1** Number of patients with significant pericardial effusions within 90 days after surgery.

**Table 3** Unadjusted characteristics associated with significant pericardial effusions within 90 days after surgery

Characteristics	Univariable model 1 Pericardial effusion, index admission (events, n=125)			Univariable model 2 Pericardial effusion, after discharge (events, n=105)		
	HR	95% CI	P value*	HR	95% CI	P value
<b>Characteristics</b>						
Sex, male vs female	0.89	0.61 to 1.30	0.556	<b>2.61</b>	<b>1.51 to 4.51</b>	<b>≤0.001</b>
18–65 years vs >65	<b>1.77</b>	<b>1.24 to 2.52</b>	<b>0.002</b>	<b>3.46</b>	<b>2.34 to 5.12</b>	<b>≤0.001</b>
Age (years)	<b>0.97</b>	<b>0.95 to 0.98</b>	<b>≤0.001</b>	<b>0.94</b>	<b>0.93 to 0.95</b>	<b>≤0.001</b>
<b>Preoperative information</b>						
Reduced pulmonary function†	<b>1.28</b>	<b>0.90 to 1.82</b>	<b>0.174</b>	0.93	0.61 to 1.40	0.722
EuroScore II	<b>1.05</b>	<b>1.01 to 1.08</b>	<b>0.006</b>	<b>0.63</b>	<b>0.52 to 0.75</b>	<b>≤0.001</b>
Estimated glomerular filtration rate‡ mL/min<60	1.06	0.70 to 1.61	0.782	<b>0.31</b>	<b>0.15 to 0.61</b>	<b>≤0.001</b>
Preoperative atrial fibrillation	<b>1.34</b>	<b>0.92 to 1.97</b>	<b>0.130</b>	<b>0.45</b>	<b>0.25 to 0.81</b>	<b>0.007</b>
Anticoagulation (before surgery)	1.29	0.73 to 2.27	0.382	0.45	0.18 to 1.11	0.083
Diabetes§	1.27	0.79 to 2.05	0.330	0.77	0.41 to 1.43	0.402
Ejection fraction, ≤50	<b>1.43</b>	<b>1.00 to 2.05</b>	<b>0.053</b>	0.79	0.50 to 1.25	0.139
Previous heart surgery	0.87	0.47 to 1.62	0.670	<b>0.11</b>	<b>0.02 to 0.82</b>	<b>0.031</b>
Previous PCI	0.83	0.44 to 1.59	0.584	1.05	0.55 to 2.02	0.881
NYHA class ≥3, n (%)	<b>1.37</b>	<b>0.96 to 1.94</b>	<b>0.082</b>	<b>0.57</b>	<b>0.37 to 0.89</b>	<b>0.013</b>
Body mass index	0.99	0.96 to 1.03	0.792	1.02	0.98 to 1.06	0.370
Current or former smoker	0.90	0.63 to 1.27	0.541	0.83	0.57 to 1.23	0.357
Alcohol intake above national recommendations	<b>0.50</b>	<b>0.23 to 1.08</b>	<b>0.076</b>	1.16	0.65 to 2.08	0.607
Aortic valve regurgitation vs stenosis	<b>1.60</b>	<b>1.03 to 2.49</b>	<b>0.036</b>	<b>2.37</b>	<b>1.55 to 3.64</b>	<b>≤0.001</b>
Aortic valve disease vs mitral valve disease	0.82	0.54 to 1.24	0.343	<b>1.70</b>	<b>0.97 to 2.99</b>	<b>0.064</b>
<b>Surgical information</b>						
Aortic valve, mechanical vs biological	<b>2.35</b>	<b>1.53 to 3.60</b>	<b>≤0.001</b>	<b>3.70</b>	<b>2.44 to 5.62</b>	<b>≤0.001</b>
Mitral valve, replacement vs repair	<b>2.48</b>	<b>1.17 to 5.28</b>	<b>0.018</b>	0.78	0.21 to 2.89	0.713
Concomitant CABG	<b>0.49</b>	<b>0.31 to 0.80</b>	<b>0.004</b>	<b>0.26</b>	<b>0.13 to 0.49</b>	<b>≤0.001</b>
<b>Postprocedure-related/complications</b>						
Re-operation due to bleeding	–	–	–	<b>3.46</b>	<b>1.41 to 8.50</b>	<b>0.007</b>
Postoperative atrial fibrillation	–	–	–	<b>0.65</b>	<b>0.44 to 0.97</b>	<b>0.033</b>
<b>Medical treatment prescribed after surgery</b>						
<b>Anticoagulants</b>						
Dalteparin	–	–	–	<b>0.66</b>	<b>0.44 to 0.99</b>	<b>0.043</b>
Warfarin	–	–	–	<b>1.73</b>	<b>1.18 to 2.53</b>	<b>0.005</b>
<b>Platelet aggregation inhibitors</b>						
Acetylsalicyl acid	–	–	–	<b>0.34</b>	<b>0.23 to 0.51</b>	<b>≤0.001</b>
Ticagrelor	–	–	–	0.33	0.05 to 2.37	0.271
Clopidogrel	–	–	–	0.82	0.44 to 1.53	0.535
Dipyridamol	–	–	–	0.75	0.18 to 3.03	0.685
<b>Direct oral anticoagulants, DOAC</b>						
Apixaban	–	–	–	<b>0.53</b>	<b>0.17 to 1.68</b>	<b>0.283</b>
Dabigatranetexilat	–	–	–	0.38	0.05 to 2.75	0.341
Rivaroxaban	–	–	–	–	–	–
<b>Combination of treatment</b>						

Continued

Table 3 Continued

	Univariable model 1 Pericardial effusion, index admission (events, n=125)			Univariable model 2 Pericardial effusion, after discharge (events, n=105)		
	HR	95% CI	P value*	HR	95% CI	P value
Dualtherapy, anticoagulants	–	–	–	1.22	0.83 to 1.79	0.312
SAPT and anticoagulants	–	–	–	<b>0.24</b>	<b>0.13 to 0.47</b>	<b>≤0.001</b>
Others						
Non-steroidal anti-inflammatory drug (NSAID), ibuprofen	–	–	–	<b>1.80</b>	<b>1.22 to 2.63</b>	<b>0.003</b>

IQR: 25th to 75th quartile.

\*A p value of <0.20 was considered statistically significant (shown in bold).

†Patients with forced expiratory volume, %≤80% of predicted value and/or a history of chronic obstructive pulmonary disease.

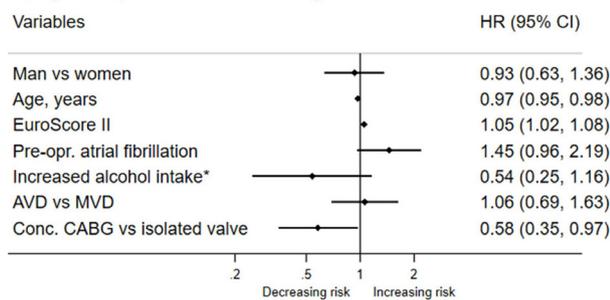
‡Estimated glomerular filtration rate estimated by the Cockcroft-Gault equation.

§Patients with diabetes; insulin, peroral and non-pharmacological treatment.

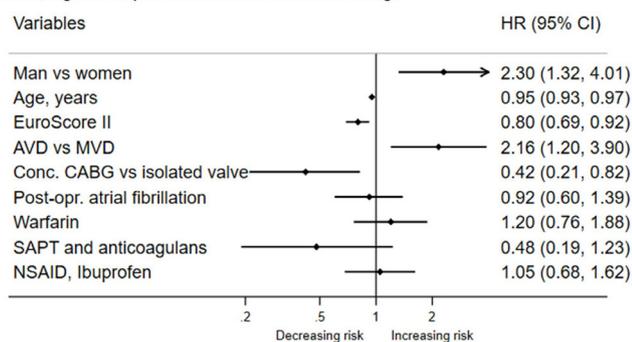
CABG, coronary artery bypass grafting; DOAC, direct oral anticoagulants; NSAID, non-steroidal anti-inflammatory drug; NYHA, New York Heart Association Class; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy.

risk among men with mechanical valve replacements, can increase awareness about the risk and support early echocardiography postoperatively and thus, manage pericardial effusions when developed. In the current study, a

Model 1, significant pericardial effusion during index admission



Model 2, significant pericardial effusion after discharge



**Figure 2** Characteristics associated with significant pericardial effusions at different time points. The figures illustrate characteristics associated with significant pericardial effusions during the index admission (model 1) and after discharge (model 2). The models included covariates with a p value <0.25 in the unadjusted analyses and/or characteristics assumed to be related to the significant pericardial effusion. AVD, aortic valve disease; CABG, coronary artery bypass grafting; Conc., concomitant; NSAID, non-steroidal anti-inflammatory drug; MVD, mitral valve disease; SAPT, single antiplatelet therapy.

significant finding was the association between younger age and the risk of developing significant pericardial effusions in both periods. Khan and colleagues have previously demonstrated a similar finding.<sup>4</sup> As younger patients most commonly present 'better'; have lower surgical risk (measured with EuroScore), fewer comorbidities and are less likely to suffer from ischaemic heart disease, many of the other significant variables in the current analyses might be explained by age. Whether the inflammatory response of the valve surgery is different in younger patients than more elderly has previously been speculated but never demonstrated.<sup>4 19</sup> Thus, whether the development of pericardial effusions following heart valve surgery is caused by the mechanical process of the surgery and/or an inflammatory process in the pericardium, is currently unknown.<sup>20</sup> Furthermore, as the pathogenesis of the pericardial fluid differs depending on the underlying pericardial disease, this might also be related to the development of pericardial effusions following surgery.<sup>20</sup> In general, findings of the current study suggest, that early development of significant pericardial effusions might be related to higher surgical risk, whereas the development longer after surgery (after discharge) might be related to other factors such as inflammatory response. Also, ibuprofen intake was not associated with pericardial effusion in the adjusted models which might be related to it being used as a treatment of postoperative pain, pro necessitate. Thus, whether ibuprofen influence the inflammatory response after discharge cannot be demonstrated in the current study. Future studies should incorporate markers of inflammation to better elucidate the importance of inflammation in the development of pericardial effusion.

The increased risk of pericardial effusions related to isolated valve surgery is in line with earlier studies and is commonly explained by the use of anticoagulant therapy.<sup>4 21</sup> In the univariable analyses, we demonstrated how the use of many anticoagulants appeared to be

associated with reduced risk of developing significant pericardial effusions, except for treatment with warfarin. In the adjusted analyses, these associations did not remain and as such, does not suggest that anticoagulation per se is associated with the development of significant pericardial effusion in the present study.

### Strengths and limitations

Our study has the strength of being performed on a complete set of data from electronic patient records and the WDHR.<sup>16</sup> Also, development of significant pericardial effusion was recorded from a thorough review of patient records and validated by two persons, and as this procedure is only performed in a single centre in the Region of Southern Denmark making it unlikely that procedures were missed. Moreover, the study included a consecutive cohort of all patients undergoing open heart valve surgery during the period. To ensure only medical treatment related to the outcome were included in the analyses, all medical treatment prescribed after the outcome had occurred was left out of the regression models.

The study also has limitations. The study was conducted as a single-centre study, where the outcome and results may reflect local patient selection and treatment protocols. This might restrict the generalizability of the results, and we acknowledge how a multicentre cohort study would have been a strength. Besides, the retrospective design has limitations. The retrospective design precludes any assumption of causality of identified associations. Yet, as data were based on prospectively captured register-data and real-life data from electronic patient records, we do not believe this influences the demonstrated associations.

The timing of the removal of pericardial drains might increase the risk of developing significant pericardial effusions, as described in earlier studies.<sup>4 17 22 23</sup> In current study removal drains were standardised and performed at the intensive care unit, but whether differences in reporting influence the current result is unknown. Finally, we acknowledge how the study is a descriptive, hypothesis-generating study and more knowledge on factors associated with outcomes based on prospective designs are needed before drawing a causal conclusion.

### CONCLUSION

In a consecutive cohort of patients undergoing heart valve surgery, significant pericardial effusions requiring invasive drainage were present in 16% of cases. Although the majority of effusions were managed during the first 2 weeks after surgery, some patients were treated more than 2 months after surgery. EuroScore II increased the risk of significant pericardial effusion during index admission and reduced the risk following discharge. Increasing age and concomitant CABG versus isolated valve surgery reduced the risk of significant pericardial effusions in both periods, whereas being a man and aortic valve disease versus mitral valve disease increased the risk after discharge.

The study highlights the need for further research investigating the potential inflammatory processes of pericardial effusions following open heart valve surgery.

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# Supplementary Materials

**Supplementary Table S1. Overview of procedure codes**

Type of valve	Procedure code
Aortic valve	KFCA00, KFCA50, KFCA60, KFCA70, KFMA20, KFMC00, KFMC20, KFMC96, KFMD, KFMD00, KFMD10, KFMD33, KFMD96
Mitral valve	KFKB, KFKB10, KFKC00, KFKC10, KFKC20, KFKC30, KFKC50, KFKC60, KFKC70, KFKC96, KFKD00, KFKD10, KFKD96, KDKW96
Tricuspid valve	KFGC10, KFGE10

**Supplementary Table S2. Characteristics of patients with significant pericardial effusion during index admission and after discharge**

	Pericardial effusion during index admission	Pericardial effusion after discharge
N	125	105
<b>Characteristics</b>		
Sex, male, n (%)	84 (67)	90 (86)
<i>Age-groups, n (%)</i>		
18-65 years	54 (43)	62 (59)
Age, years, median (IQR)	68 (58-73)	61 (52-71)
<b>Pre-operative information</b>		
Reduced pulmonary function <sup>a</sup> , n (%)	53 (42)	34 (34)
EuroScore II (logistic), median (IQR)	2.18 (1.21-3.80)	1.19 (0.68-2.28)
Estimated glomerular filtration rate <sup>b</sup> ml/min <60, n (%)	29 (24)	9 (10)
Atrial fibrillation, n (%)	38 (30)	13 (12)
Anticoagulations, n (%)	14 (11)	5 (5)
Diabetes <sup>c</sup> , n (%)	20 (16)	11 (10)
Ejection fraction <50, n (%)	49 (40)	25 (26)
Previous cardiac surgery, n (%)	11 (9)	<5
Previous PCI, n (%)	10 (8)	10 (10)
NYHA class ≥3, n (%)	60 (48)	26 (27)
Body Mass Index, median (IQR)	26.5 (23.4-29.6)	27.2 (24.0-29.2)
Current or former smoker, n (%)	69 (55)	57 (54)
Alcohol intake above national recommendations, n (%)	7 (6)	13 (12)
<i>Primary diagnosis, n (%)</i>		
Aortic valve stenosis	67 (54)	58 (55)
Aortic valve regurgitation	27 (22)	33 (31)
Mitral valve stenosis or regurgitation	30 (24)	14 (13)
<b>Surgical information, n (%)</b>		
<i>Type of valve procedure</i>		
Aortic valve, biological	63 (50)	53 (50)
Aortic valve, mechanical	31 (25)	38 (36)
Aortic valve, repair	<5	<5
Mitral valve, replacement <sup>d</sup>	14 (11)	<5
Mitral valve, repair	12 (10)	9 (9)
Concomitant CABG, n (%)	20 (16)	10 (10)
<b>Post-procedure related, n (%)</b>		
ECC, minutes, median (IQR)	118 (97-161)	103 (87-132)
Re-operation, all, n (%)	22 (18)	5 (2)
Re-operation, bleeding, n (%)	<5	5 (2)
Need for blood transfusions, n (%)	74 (59)	26 (26)

Post-operative atrial fibrillation, n (%)	102 (82)	48 (48)
New-onset postoperative atrial fibrillation, n (%)	68 (54)	38 (38)
Length of stay, days, median (IQR)	16 (13-23)	8 (6-10)

IQR, interquartile range, 25<sup>th</sup> to 75<sup>th</sup> quartile. PCI, Percutaneous Coronary Intervention, NYHA, New York Heart Association Class, CABG, Coronary Artery Bypass Grafting, EEC, Extra Corporal Circulation.

<sup>a</sup> Patients with forced expiratory volume, %  $\leq$ 80% of predicted value and/or a history of chronic obstructive pulmonary disease

<sup>b</sup> Estimated glomerular filtration rate estimated by the Cockcroft-Gault Equation

<sup>c</sup> Patients with diabetes; insulin, peroral and non-pharmacological treatment

<sup>d</sup> Both biological and mechanical mitral valve replacement

A significant pericardial effusion was defined as a pericardial effusion requiring drainage/pericardiocentesis