ESC European Society of Cardiology

European Heart Journal (2018) **0**, 1–9
doi:10.1093/eurheartj/ehy153

CLINICAL RESEARCH
Valvular heart disease

Incidence and factors associated with infective endocarditis in patients undergoing left-sided heart valve replacement

Lauge Østergaard[1]*, Nana Valeur[2], Nikolaj Ihlemann[1], Morten Holdgaard Smerup[1], Henning Bundgaard[1], Gunnar Gislason[3,4], Christian Torp-Pedersen[5,6], Niels Eske Bruun[7,8,9], Lars Køber[1], and Emil Loldrup Fosbøl[1]

[1]Heart Centre, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark; [2]Department of Cardiology, Bispebjerg Hospital, Bispebjerg Bakke 23, 2400 Copenhagen NV, Denmark; [3]Department of Cardiology, Herlev-Gentofte Hospital, Denmark; [4]Department of Cardiovascular Epidemiology and Research, The Danish Heart Foundation, Copenhagen, Denmark; [5]Department of Health Science and Technology, Aalborg University, Aalborg, Denmark; [6]Unit of Epidemiology and Biostatistics, Aalborg University Hospital, Aalborg, Denmark; [7]Clinical Institute, Aalborg University, Sdr. Skovvej 15, 9000 Aalborg, Denmark; [8]Department of Cardiology, Roskilde University Hospital, Sygehusvej 10, 4000 Roskilde, Denmark; and [9]Clinical Institute, Copenhagen University, Nørre Allé 20, 2200 Copenhagen N, Denmark

Received 4 May 2017; revised 28 July 2017; editorial decision 22 February 2018; accepted 3 March 2018

Aims Patients with left-sided heart valve replacement are considered at high-risk of infective endocarditis (IE). However, data on the incidence and risk factors associated with IE are sparse.

Methods and results Through Danish administrative registries, we identified patients who underwent left-sided heart valve replacement from January 1996 to December 2015. Patients were categorized in mitral and aortic valve replacement (MVR and AVR) and followed until: 12 years after valve surgery, end of study, death, emigration, or hospitalization due to IE, whichever came first. Multivariable adjusted Cox proportional hazard analysis was used to investigate which baseline characteristics were associated with IE. A total of 18 041 patients were included. The cumulative IE risk at 10 years follow-up was 5.2% in both MVR and AVR patients. In patients with MVR, male sex [hazard ratio (HR) = 1.68, 95% confidence interval (95% CI) 1.06–2.68], bioprosthetic valve (HR = 1.91, 95% CI 1.08–3.37), and heart failure (HR = 1.69, 95% CI 1.06–2.68) were among factors associated with an increased risk of IE. In AVR patients, male sex (HR = 1.59, 95% CI 1.33–1.89), bioprosthetic valve (HR = 1.70, 95% CI 1.35–2.15), and cardiac implantable electronic device (CIED) (HR = 1.57, 95% CI 1.19–2.06) were among factors associated with an increased risk of IE.

Conclusion Infective endocarditis after left-sided heart valve replacement is not uncommon and occurs in about 1/20 over 10 years. Male, bioprosthetic valve, and heart failure were among factors associated with IE in MVR patients while male, bioprosthetic valve, and CIED were among factors associated with IE in AVR patients.

Keywords Infective endocarditis • Mitral valve replacement • Aortic valve replacement • Incidence • Risk factors

Introduction

Infective endocarditis (IE) is associated with high mortality and morbidity.[1] Patients with a prosthetic left-sided valve after left-sided valve replacement are considered at high-risk for developing IE (≈1% per year in single centre studies from tertiary centre [2]), but nationwide data describing this relationship are sparse.[3] Randomized clinical trials and observational studies have studied the mortality and risk of complications after valve surgery (such as reoperation) in patients with left-sided valve replacement, however few studies have addressed the subsequent risk of IE in this high-risk population.[4–9] Knowledge on the incidence of IE in this high-risk population can be used to inform practice patterns and monitoring of patients after left-sided valve replacement. Further, it is unknown which patient characteristics are associated with IE risk and identification of such may guide clinical decisions and monitoring. A meta-analysis of three randomized

* Corresponding author. Tel: +45 41132400, Fax: +45 35453545, Email: laugeoestergaard@gmail.com

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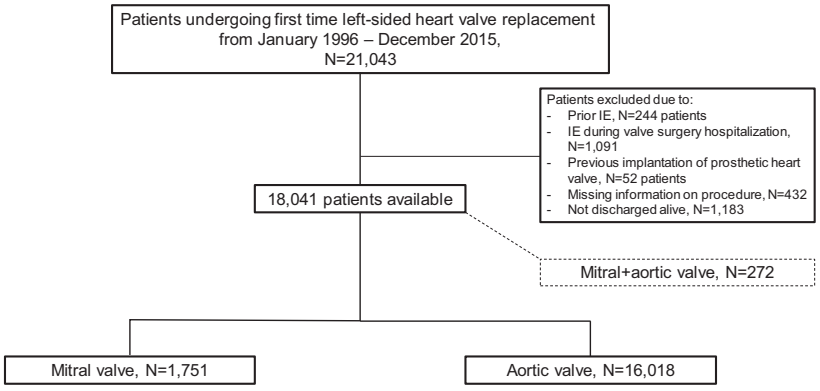

Figure 1 Patient selection. The figure shows a flow chart of the patient selection for the study population. FU, follow-up; IE, infective endocarditis.

trials have suggested that patients with mechanical prostheses compared with bioprothetic valves have a lower risk of IE on long-term follow-up.[10]

To address this, we investigated the incidence of IE and risk factors at baseline associated with IE in a nationwide cohort of patients after left-sided valve replacement identified from nationwide administrative registries in Denmark. Further, we examined the risk of IE according to type of valve prosthesis (mechanical vs. bioprosthetic).

Methods

Data sources

In Denmark, every citizen is provided with a unique personal number making it possible to identify every Danish citizen in national administrative registries. We used the National Patient Registry, the Danish Population Registry, the Danish Prescription Registry, and the Danish Cause of Death Registry. The National Patient Registry was established in the beginning of 1977 where all hospital admissions in Denmark are recorded by a physician.[11] Up until 1994, the International Classification of Diseases (ICD)-8 was used and afterwards the ICD-10. Further, the registry holds information on surgical procedures based on the Nordic Medico-Statistical Committee (NOMESCO) classification of surgical procedures. Surgical procedures were added from 1996 and specific codes on treatment and medical examinations (including pacemaker implantation) were added in 2000 to the National Patient Registry. Clinical information regarding echocardiography and microbiology is not available through the National Patient Registry. The Danish Population Registry holds information on birth date, sex, and migration while the Danish Cause of Death Registry holds information on date of death. The Danish Prescription Registry holds information on date and type of drug redeemed from Danish pharmacies since 1994 based on the Anatomic Therapeutic Chemical (ATC) Classification system. Claimed prescriptions for beta blockade medication, lipid lowering medication, vitamin K antagonists (VKA), renin–angiotensin system inhibitors, and glucose lowering medication six months prior to heart valve surgery were obtained to study baseline medication (for ATC-codes see Supplementary material online, *Table S1*). Glucose lowering medication was used as a proxy for diabetes mellitus.

The Danish registries are validated and described in further detail previously and are of high quality and complete.[11,12]

Study population

We identified all patients who underwent left-sided valve replacement [mitral valve replacement (MVR) or aortic valve replacement (AVR)] in the period from 1 January 1996 to 31 December 2015. See Supplementary material online, *Table S1* for specific procedure codes. Patients with prior IE, IE during valve replacement, patients who died during hospitalization for valve surgery, and those who had previously underwent surgery with implantation of a prosthetic heart valve were excluded (*Figure 1*).

Follow-up and outcome

Patients were followed from hospital discharge after valve surgery until one of following: 12 years after hospital discharge after valve surgery, end of study (31 December 2015), death, hospitalization due to IE, or emigration, whichever came first. The primary outcome of the study was rehospitalization due to IE identified by the ICD-10 code classification system (DI33, DI38, and DI39.8). The IE diagnoses in the National Patient Registry have been validated with a positive predictive value of 82%.[13] However, to improve the likelihood of the diagnosis, patients with a hospitalization length of stay <14 days were not counted as having IE. Patients who died in-hospital with an IE diagnosis and a hospitalization <14 days were counted as having IE. Since our data was based upon ICD-10 codes we were not able to differentiate between left-sided, right-sided, or prosthesis IE. Isolated cardiac implantable electronic device (CIED) infection was not included in the ICD-10 codes used to assess the primary outcome. The secondary outcome was all cause mortality. For purposes of sensitivity, analyses of incidence were carried out with an IE hospital duration of minimum 1 and 21 days if the patient was discharged alive.

Statistics

Patient characteristics were compared for patients with a MVR and an AVR. Categorical variables were presented as numbers and percentages while continuous variables were presented with a median and 25 and 75 percentiles, respectively. Crude IE incidences were calculated for the overall study population and by the two study groups per 10 000 person years. Cumulative incidence plots were drawn from time of valve surgery to IE by the two study groups with death as a competing risk. The Gray's test was performed for the analysis of difference between curves. Further, we plotted a Kaplan–Meier curve illustrating mortality rate by the two study groups and the log-rank test was used to test for differences between curves. Factors at

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Table 1 Baseline characteristics for patients undergoing mitral and aortic valve replacement

	Mitral valve	Aortic valve
Demographics and clinical characteristics		
Number	1751	16 018
Male (%)	51.1	65.3
Age (years), median (25 and 75 percentiles)	65.1 (55.4–72.7)	71.2 (63.4–77.0)
Mechanical valve at valve surgery (%)	66.0	68.5
Bioprosthetic valve surgery (%)	34.0	31.5
CABG at valve implantation (%)	23.6	34.1
Hospital duration at valve surgery, median (25 and 75 percentiles)	15.0 (10.0–25.0)	12.0 (9.0–19.0)
Cardiac implantable electronic device before or during valve surgery (%)	8.4	5.7
Valve disorder at surgery (%)		
Aortic stenosis	4.1	83.3
Aortic regurgitation	2.6	12.6
Other aortic valve disorder	0.9	7.6
Mitral regurgitation	73.5	3.6
Mitral prolapse	8.6	0.2
Mitral stenosis	11.3	0.2
Other mitral valve disorder	4.3	0.3
Comorbidity, medical history of (%)		
IHD	44.7	54.1
PVD	3.5	5.7
Heart failure	38.4	21.6
CVD	7.5	10.3
COPD	9.1	9.1
Cardiogenic shock	5.1	3.4
Renal dialysis	0.6	0.7
Renal disease	5.5	4.4
Atrial fibrillation	46.0	26.3
Rheumatic disease	5.1	7.0
Cancer	8.5	11.1
Diabetes	4.3	10.5
Prehospital medication (%)		
Beta blocker	34.6	39.2
VKA	30.0	11.7
Lipid lowering medication	22.8	46.3
RAS inhibition	43.8	38.7

CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; IHD, ischaemic heart disease; PVD, peripheral vascular disease; RAS, renin–angiotensin system; VKA, vitamin K antagonist.

baseline associated with IE were analysed using multivariable adjusted Cox proportional hazard analysis for patients with a mitral and an aortic valve prosthesis. Covariates included in the multivariable Cox proportional hazard analyses are presented in Supplementary material online, *Table S1*. The proportional hazard assumption was assessed through formal testing for relevant covariates (valve type, CIED, sex, glucose lowering medication, and renal disease). Age and sex were tested as effect modifiers for the relevant covariates. Continuous variables were tested for linearity. For differences between MVR and AVR, baseline characteristics were tested for effect modification on the primary outcome.

Results were presented as hazard ratios (HRs) with a 95% confidence interval (CI). A *P*-value <0.05 was considered statistical significant. All statistical analyses were performed using the SAS statistical software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Pre-planned analysis regarding type of valve prosthesis (mechanical vs. bioprosthetic)

European and American guidelines recommend a mechanical valve in patients <65 years and <60 years for MVR and AVR, respectively as long as there are no contraindications for anticoagulant treatment.[14–16] A bioprosthetic valve is recommended in patients >70 years and >65 years for MVR and AVR, respectively.[14–16] For patients in the age middle group (60–70 years) both valve prostheses are acceptable, and the choice of valve prosthesis depends on other patient factors than age.[14–16] Thus, we expected to find significant differences in patient characteristics between patients receiving a mechanical and bioprosthetic valve. These differences were expected to translate into differences in outcomes. If the multivariable adjusted Cox proportional hazard analysis confirmed this hypothesis, we planned to carry out

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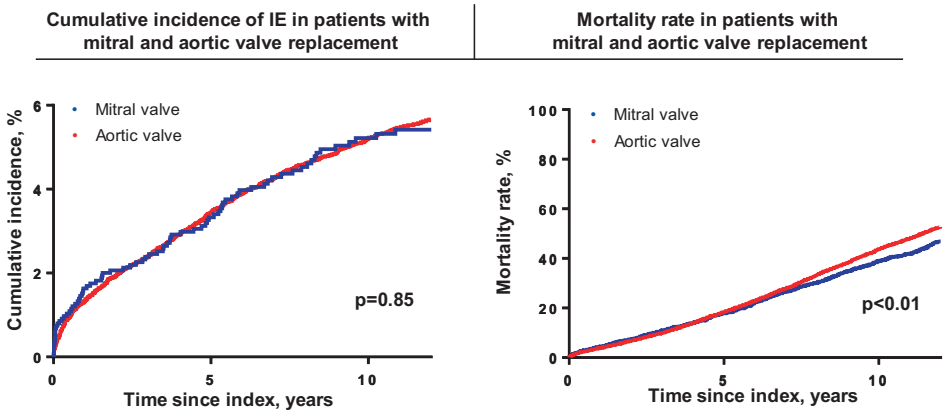

Figure 2 Cumulative incidence of infective endocarditis and mortality rate by valve type. The figure on the left shows the cumulative incidence of infective endocarditis by the two study groups. The figure on the right shows the mortality rate by the two study groups.

two matched analysis: (i) MVR patients and (ii) AVR patients for the comparison of mechanical and bioprosthetic valve in each study group. For comparison of patients by type of valve prosthesis, patients were matched on age, sex, ischaemic heart disease, coronary artery bypass grafting at valve surgery, chronic obstructive pulmonary disease, CIED, renal disease, and the propensity score of receiving a bioprosthetic valve using the greedy match macro algorithm.[17] The propensity scores were generated and included as a covariate in the greedy match macro to account for confounding by indication. The propensity scores were generated from the covariates presented in Supplementary material online, *Table S1*. A difference of maximum 0.01 in the propensity score was accepted when the study cohort was matched by propensity score, while a maximum of 2 years difference was accepted when matching on age. Standardized differences were calculated for the included covariates. Sub-analyses in the matched population for patients 60–70 years of age were carried out.

Results

A total of 18 041 patients underwent left-sided valve replacement in the period from January 1996 to December 2015 in Denmark; 1751 (9.7%) patients had a MVR, 16 018 (88.8%) patients had an AVR, and 272 (1.5%) patients had both MVR and AVR. Baseline characteristics by type of valve (MVR vs. AVR) are presented in *Table 1*. Patients undergoing AVR were more often male patients and had a higher median age compared with patients undergoing MVR. Of the MVR patients, 5.9% had a mitral annuloplasty before index date. Patients were followed for a median of 5.6 years, 25 and 75 percentiles: 2.6–9.3 years. During follow-up 60 patients emigrated (0.3%).

Incidence of infective endocarditis

The overall incidence of IE was 69.8/10 000 person years. We found an IE incidence of 64.9/10 000 person years, 70.1/10 000 person years, and 89.4/10 000 person years in patients with MVR, AVR, and MVR + AVR, respectively. Cumulative incidence plots for time to IE and mortality rate by type of valve (MVR vs. AVR) are shown in *Figure 2*. *Table 2* shows baseline characteristics for patients hospitalized due to IE and patients without IE in the follow-up period. The IE cumulative risk was 3.3% and 5.2% for MVR and 3.4% and 5.2% for AVR patients at 5 and 10 years follow-up, respectively. The mortality rate at 5 and 10 years follow-up were 17.9% and 39.0% in the MVR group and 18.3% and 43.6% in the AVR group, respectively.

Factors associated with infective endocarditis

Figure 3 presents the association between selected baseline factors and IE for patients undergoing MVR and AVR. For patients with MVR, male sex, a bioprosthetic valve, other mitral valve disorders, and heart failure were among factors that were statistical significant associated with an increased risk of IE.

For patients with AVR, CIED, male sex, a bioprosthetic valve, atrial fibrillation, cancer, and diabetes were associated with an increased risk of IE. In interaction analyses, we found no differences in the patient characteristics presented in *Figure 3* and type of valve (MVR vs. AVR).

In MVR patients, time modified the effect of CIED ($P = 0.035$ for interaction). Cardiac implantable electronic device was associated with an increased risk of IE with follow-up time >1 year, HR = 2.47 (95% CI 1.08–5.64) while we identified an associated risk of IE with follow-up time <1 year at HR = 0.93 (95% CI 0.19–4.63). Sex modified the effect of a bioprosthetic MVR ($P = 0.01$ for interaction), where male sex was associated with a HR = 3.64 (95% CI 1.75–7.55) and female a HR = 0.80 (95% CI 0.29–2.23). In AVR patients, age modified the effect of renal disease ($P < 0.01$ for interaction). In patients <60 years the associated risk of IE was HR = 3.45 (95% CI 1.29–9.24) and in patients >60 years the associated risk of IE was HR = 1.11 (95% CI 0.72–1.69). Age and sex did not modify the effect of other relevant covariates in MVR or AVR patients.

For purposes of sensitivity, analyses of incidence were carried out with an IE hospital duration of minimum 1 and 21 days if the patient was discharged alive. This did not change the overall results.

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Table 2 Baseline characteristics for patients with and without infective endocarditis

	Patients with IE	Patients without IE
Demographics		
Number	752	17 289
Male (%)	70.6	63.4
Age (years), median (25 and 75 percentiles)	71.0 (64.1–76.4)	70.6 (62.3–76.6)
Valve disorder at surgery (%)		
Aortic stenosis	75.8	75.0
Aortic regurgitation	9.3	12.0
Other aortic valve disorder	7.9	7.0
Mitral regurgitation	12.6	11.2
Mitral prolapse	1.1	1.1
Mitral stenosis	1.9	1.5
Other mitral valve disorder	0.9	0.8
In-hospital		
Mechanical valve at valve surgery (%)	30.6	35.4
Bioprosthetic valve at valve surgery (%)	69.4	64.6
CABG at valve implantation (%)	31.1	32.9
Hospital duration of valve surgery in days, median (25 and 75 percentiles)	13.0 (9.0–21.0)	12.0 (9.0–19.0)
Cardiac implantable electronic device before or during valve surgery (%)	9.4	5.9
Comorbidity, medical history of (%)		
IHD	52.4	53.1
PVD	6.8	5.4
Heart failure	28.5	23.3
CVD	10.6	10.0
COPD	12.4	9.0
Cardiogenic shock	4.3	3.6
Renal dialysis	0.8	0.7
Renal disease	5.5	4.5
Atrial fibrillation	34.8	28.2
Rheumatic disease	8.1	6.8
Cancer	12.1	10.8
Diabetes	12.5	9.7
Prehospital medication (%)		
Beta blocker	41.0	38.5
VKA	16.2	13.6
Lipid lowering medication	44.6	43.7
RAS inhibition	42.2	39.1

CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; IE, infective endocarditis; IHD, ischaemic heart disease; PVD, peripheral vascular disease; RAS, renin–angiotensin system; VKA, vitamin K antagonist.

Pre-planned analysis regarding type of valve prosthesis (mechanical vs. bioprosthetic)

Major differences were found in baseline characteristics between patients with mechanical and bioprosthetic valves where patients receiving a mechanical valve were the youngest (13 and 15 years difference in median age for MVR and AVR patients, respectively, see Supplementary material online, *Table S2*).

The incidence of IE was 51.7/10 000 person years and 105.0/10 000 person years in patients with a mechanical MVR and a bioprosthetic MVR, respectively while the incidence of IE was 44.3/10 000 person years and 88.4/10 000 person years in patients with a mechanical AVR and a bioprosthetic AVR, respectively. *Figure 4* presents cumulative incidences for MVR and AVR patients categorized by mechanical and bioprosthetic valves. We matched mechanical and bioprosthetic MVR patients ($n = 154$) and mechanical and bioprosthetic AVR patients ($n = 3354$) where Supplementary material online, *Table S3* shows baseline characteristics for the matched cohorts. In the matched analysis, no events occurred among patients with a mechanical MVR and a HR could not be calculated. Four patients had IE during follow-up among patients with a bioprosthetic MVR. We found a higher associated risk of IE in patients receiving a bioprosthetic AVR vs. a mechanical AVR, HR = 1.94 (95% CI 1.37–2.75). See *Figure 5* for the unadjusted cumulative incidence curves.

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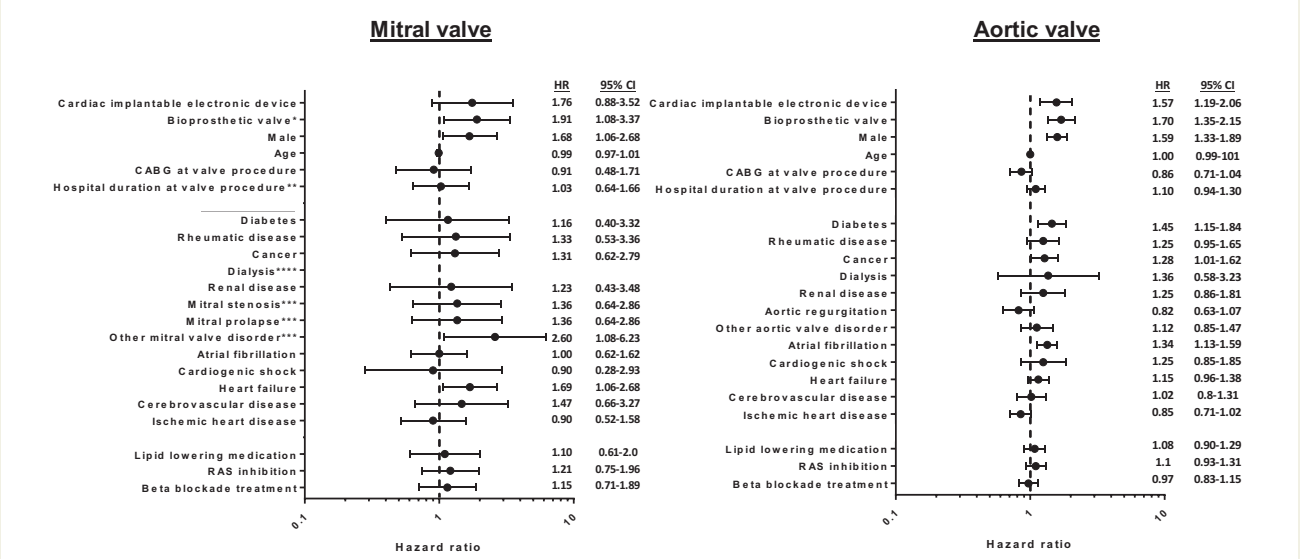

Figure 3 Factors associated with infective endocarditis in patients undergoing mitral and aortic valve replacement. The figures show the associated risk of infective endocarditis for relevant baseline patient characteristics for mitral valve replacement (left) and aortic valve replacement (right). Left figure: *compared with patients receiving a mechanical aortic valve. **Reference group: >median. ***Reference group: patients with mitral regurgitation. ****No events occurred in patients with renal dialysis. Right figure: *compared with patients receiving a mechanical aortic valve. **Reference group: >median. ***Reference group: aortic stenosis. ****We found an interaction between age and renal disease, see text. Age was analysed as a continuous variable. CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; RAS, renin–angiotensin system.

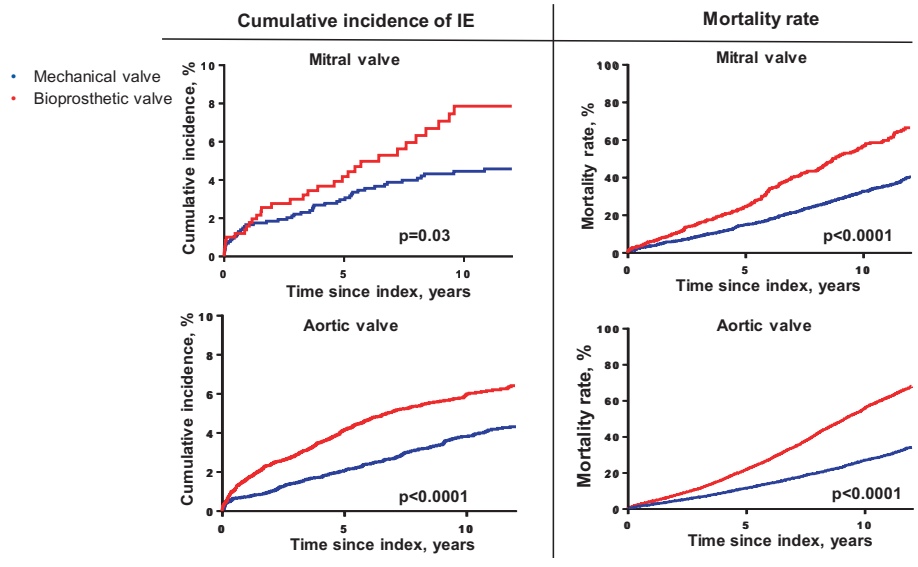

Figure 4 Cumulative incidence and mortality rate for mitral valve replacement and aortic valve replacement by type of valve prosthesis. The figure shows the cumulative incidence of infective endocarditis and mortality rate for mechanical and bioprosthetic valve in mitral valve replacement and aortic valve replacement patients.

For patients of 60–70 years of age, we identified no events in the mechanical MVR group and a HR could not be calculated. Bioprosthetic AVR was associated with a HR = 1.75 (95% CI 1.13–2.70) compared with a mechanical AVR in patients aged 60–70 years. See *Figure 5* for the unadjusted cumulative incidence curves.

Discussion

This study examined the incidence of IE and factors associated with IE in patients undergoing left-sided heart valve replacement. This study had three major findings. First, the cumulative risk of IE after MVR and

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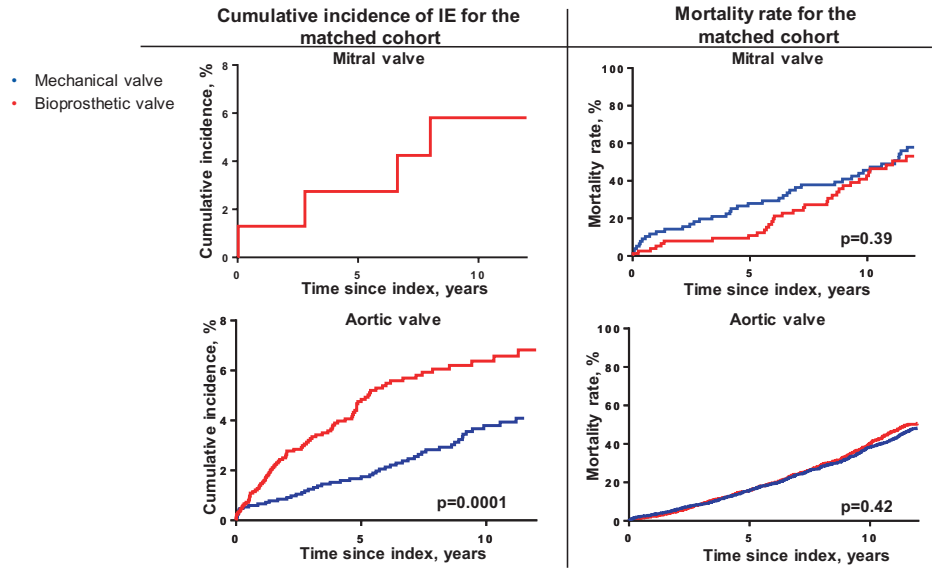

Figure 5 Cumulative incidence of infective endocarditis by valve type for the matched population. The figure shows the cumulative incidence of infective endocarditis and mortality rate for the mechanical and bioprosthetic valve in mitral valve replacement and aortic valve replacement patients for the matched cohort. No events occurred among the mechanical mitral valve replacement patients in the matched cohort.

AVR was 5.2% and 5.2% at 10 years follow-up, respectively. Second, in MVR patients, male sex and heart failure were factors at baseline associated with an increased risk of IE. In AVR patients, male sex, cardiac implantable electronic device, diabetes, atrial fibrillation, and cancer were factors associated with an increased risk of IE. Third, we found a higher incidence of IE in patients with a bioprosthetic valve for AVR patients; this association may be expected due to case mix.

The incidence of IE among patients undergoing left-sided heart valve replacement has been investigated in other observational studies. Khan *et al.*[18] found an incidence of IE at 0.3% per 100 patient years mechanical MVR and AVR and an incidence of 0.5% and 0.6% per 100 patient years in tissue MVR and AVR, respectively. Agnihotri *et al.*[19] carried out a cross-sectional study of patients who underwent AVR in the period from 1969–1992 ($n = 2443$). The authors found a 10 years of freedom from IE after AVR at 94.6%.[19] Our study found a higher incidence of IE compared with previous mentioned authors.[18,19] Reasons for these differences between may be due to differences in the populations examined.

Our study found an association between IE and male sex in MVR and AVR patients. Sex differences in cardiovascular disease remain a topic of much debate.[20] A meta-analysis have suggested that IE is relatively more common in men and that a relative increment among men have been seen since the 1970's.[21] In addition, mortality rates at 30 days and up to 10 years after IE are higher among women.[22,23] Understanding sex-based differences and patient factors associated with IE may help prevent future infections. Diabetes mellitus along with prior severe kidney disease have been associated to IE.[24] This is supported by the results of our study where it was found that diabetes was associated with an increased risk of IE.

The choice of valve type is reliant on patient age[14–16]; patients with age >65 years is recommended a bioprosthetic valve. A bioprosthetic valve has the advantage of no subsequent anticoagulant therapy, which is needed with a mechanical valve. However, bioprosthetic aortic valves have a higher rate of subsequent valve failure and reoperation.[25] A recent observational study has shown that patients receiving a bioprosthetic MVR or a bioprosthetic AVR are associated with a higher risk of death and reoperation compared with patients receiving a mechanical MVR or mechanical AVR, respectively (only for patients aged 40–69 years of age and 45–64 years age, respectively).[26] The risk of IE has been shown to be highest in male patients aged 75–79 years[27] why it is important to include age as a confounding factor. Our data analysis is carried out with multivariable adjustments including age.

Our results show that patients with a bioprosthetic MVR and AVR were associated with a higher risk of IE compared with patients with a mechanical MVR and AVR. Brennan *et al.*[28] studied patients with AVR and found the 12 year incidence of IE at 1.4% and 2.2% in the mechanical and bioprosthetic group, respectively. They found that patients with a bioprosthesic AVR were at increased risk of IE compared with patients with a mechanical valve, adjusted HR = 1.60 (95% CI 1.31–1.94). The choice of valve type in patients aged 50–69 years is debated, and a propensity matched cohort studied by Glaser *et al.*[29] showed an increased mortality in patients with a bioprosthetic AVR compared with a mechanical. However, these results and the results of our study must be interpreted with caution as the retrospective nature of these studies may confound the results, and therefore no causal link can be made between valve type (mechanical vs. bioprosthetic) and risk of IE. Even though propensity score matching have been carried out, the clinician's choice of prosthesis is made upon a patient identification that can be difficult to assess through registries, and our results may be due to case mix rather than valve specific differences.

Three randomized trials studying patients with mechanical vs. bioprosthetic heart valve found no difference in the occurrence of

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IE.[8,9,25] However, none of these studies had IE as a primary endpoint, and the power may be inadequate to detect any differences between valve types. Our study supplement earlier findings in a unique way with nationwide data, a large sample size, long-term follow-up with few patients lost-to-follow-up (0.3%), and patient inclusion and identification up to 2016 in a real-life setting.

Our study has several limitations. First, patients with IE were identified through national registries. This diagnosis has been well validated in a Danish and a Canadian setting.[13,30] The National Patient Registry, which our study is built upon, is based on ICD-10 codes. However, this coding system is not able to differentiate between left-sided, right-sided, or prosthesis IE. Further, no validation study has been conducted up until now on the positive predictive value of endocarditis in patients with a prosthetic valve. Second, no in-hospital characteristics of the patients were available, and therefore the microbiological aetiology of the IE or echocardiographic findings was not assessed. Third, to further improve the likelihood of the IE-diagnosis from the National Patient Registry, we applied the criteria that the hospital stay was >14 days if the patient was discharged alive. Finally, the retrospective nature of this study increases the risk of confounding even though confounders were assessed through multivariable models.

In conclusion, IE after left-sided heart valve replacement is not uncommon and occurs in about 1/20 over 10 years. Male sex, bioprosthetic valve, and heart failure were among factors associated with IE in MVR patients while male sex, bioprosthetic valve, cardiac implantable electronic device, cancer, atrial fibrillation, and diabetes were factors associated with IE in AVR patients.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: none declared.

References

1. Que Y-A, Moreillon P. Infective endocarditis. *Nat Rev Cardiol* 2011;**8**:322–336.
2. Piper C, Körfer R, Horstkotte D. VALVE DISEASE: prosthetic valve endocarditis. *Heart* 2001;**85**:590–593.
3. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta J-P, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, Miro JM, Mulder BJ, Plonska-Gosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P, Vilacosta I, Zamorano JL. 2015 ESC guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* 2015;**36**:3075–3128.
4. Schelbert EB, Vaughan-Sarrazin MS, Welke KF, Rosenthal GE. Valve type and long-term outcomes after aortic valve replacement in older patients. *Heart* 2008;**94**:1181–1188.
5. Peterseim DS, Cen YY, Cheruvu S, Landolfo K, Bashore TM, Lowe JE, Wolfe WG, Glower DD. Long-term outcome after biologic versus mechanical aortic valve replacement in 841 patients. *J Thorac Cardiovasc Surg* 1999;**117**:890–897.
6. Holper K, Wottke M, Lewe T, Baumer L, Meisner H, Paek SU, Sebening F. Bioprosthetic and mechanical valves in the elderly: benefits and risks. *Ann Thorac Surg* 1995;**60**:S443–S446.
7. Mykén PS, Caidahl K, Larsson P, Larsson S, Wallentin I, Berggren HE. Mechanical versus biological valve prosthesis: a ten-year comparison regarding function and quality of life. *Ann Thorac Surg* 1995;**60**:S447–S452.
8. Hammermeister KE, Sethi GK, Henderson WG, Oprian C, Kim T, Rahimtoola S. A comparison of outcomes in men 11 years after heart-valve replacement with a mechanical valve or bioprosthesis. Veterans Affairs Cooperative Study on Valvular Heart Disease. *N Engl J Med* 1993;**328**:1289–1296.
9. Bloomfield P, Wheatley DJ, Prescott RJ, Miller HC. Twelve-year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses. *N Engl J Med* 1991; **324**:573–579.
10. Kassaï B, Gueyffier F, Cucherat M, Boissel JP. Comparison of bioprosthesis and mechanical valves, a meta-analysis of randomised clinical trials. *Cardiovasc Surg Lond Engl* 2000;**8**:477–483.
11. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;**7**:449–490.
12. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011;**39**:38–41.
13. Sundbøll J, Adelborg K, Munch T, Frøslev T, Sørensen HT, Bøtker HE, Schmidt M. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open* 2016;**6**:e012832.
14. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Lung B, Lancellotti P, Pierard L, Price S, Schäfers H-J, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M; ESC Committee for Practice Guidelines (CPG), Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC), European Association for Cardio-Thoracic Surgery (EACTS). Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardio-Thorac Surg* 2012;**42**:S1–44.
15. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, O'gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, Thomas JD. 2014 AHA/ACC guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol* 2014;**63**:e57–e185.
16. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Muñoz DR, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL; Document Reviewers. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017; doi:10.1093/eurheartj/ehx391.
17. Locally Written SAS Macros—Division of Biomedical Statistics and Informatics—Mayo Clinic Research. http://www.mayo.edu/research/departments-divisions/department-health-sciences-research/division-biomedical-statistics-informatics/software/locally-written-sas-macros (12 March 2018).
18. Khan SS, Trento A, DeRobertis M, Kass RM, Sandhu M, Czer LSC, Blanche C, Raissi S, Fontana GP, Cheng W, Chaux A, Matloff JM. Twenty-year comparison of tissue and mechanical valve replacement. *J Thorac Cardiovasc Surg* 2001;**122**:257–269.
19. Agnihotri AK, McGiffin DC, Galbraith AJ, O'Brien MF. The prevalence of infective endocarditis after aortic valve replacement. *J Thorac Cardiovasc Surg* 1995;**110**:1708–1720. discussion 1720-1724.
20. Vaccarino V, Rathore SS, Wenger NK, Frederick PD, Abramson JL, Barron HV, Manhapra A, Mallik S, Krumholz HM; National Registry of Myocardial Infarction Investigators. Sex and racial differences in the management of acute myocardial infarction, 1994 through 2002. *N Engl J Med* 2005;**353**:671–682.
21. Slipczuk L, Codolosa JN, Davila CD, Romero-Corral A, Yun J, Pressman GS, Figueredo VM. Infective endocarditis epidemiology over five decades: a systematic review. *PLoS One* 2013;**8**:e82665.
22. Sambola A, Fernández-Hidalgo N, Almirante B, Roca I, González-Alujas T, Serra B, Pahissa A, García-Dorado D, Tornos P. Sex differences in native-valve infective endocarditis in a single tertiary-care hospital. *Am J Cardiol* 2010;**106**:92–98.
23. Dohmen PM, Binner C, Mende M, Daviewala P, Etz CD, Borger MA, Misfeld M, Eifert S, Mohr FW. Gender-based long-term surgical outcome in patients with active infective aortic valve endocarditis. *Med Sci Monit* 2016;**22**:2520–2527.
24. Strom BL, Abrutyn E, Berlin JA, Kinman JL, Feldman RS, Stolley PD, Levison ME, Korzeniowski OM, Kaye D. Risk factors for infective endocarditis: oral hygiene and nondental exposures. *Circulation* 2000;**102**:2842–2848.
25. Stassano P, Di Tommaso L, Monaco M, Iorio F, Pepino P, Spampinato N, Vosa C. Aortic valve replacement: a prospective randomized evaluation of mechanical versus biological valves in patients ages 55 to 70 years. *J Am Coll Cardiol* 2009;**54**:1862–1868.
26. Goldstone AB, Chiu P, Baiocchi M, Lingala B, Patrick WL, Fischbein MP, Woo YJ. Mechanical or biologic prostheses for aortic-valve and mitral-valve replacement. *N Engl J Med* 2017;**377**:1847–1857.
27. Selton-Suty C, Célard M, Le Moing V, Doco-Lecompte T, Chirouze C, Iung B, Strady C, Revest M, Vandenesch F, Bouvet A, Delahaye F, Alla F, Duval X, Hoen B; AEPEI Study Group. Preeminence of *Staphylococcus aureus* in infective endocarditis: a 1-year population-based survey. *Clin Infect Dis* 2012;**54**:1230–1239.

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28. Brennan JM, Edwards FH, Zhao Y, O'Brien S, Booth ME, Dokholyan RS, Douglas PS, Peterson ED; On behalf of the DEcIDE AVR (Developing Evidence to Inform Decisions about Effectiveness-Aortic Valve Replacement) Research Team. Long-term safety and effectiveness of mechanical versus biologic aortic valve prostheses in older patients: results from the Society of Thoracic Surgeons Adult Cardiac Surgery National Database. *Circulation* 2013;**127**:1647–1655.
29. Glaser N, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Aortic valve replacement with mechanical vs. biological prostheses in patients aged 50-69 years. *Eur Heart J* 2016;**37**:2658–2667.
30. Tan C, Hansen M, Cohen G, Boyle K, Daneman N, Adhikari NKJ. Accuracy of administrative data for identification of patients with infective endocarditis. *Int J Cardiol* 2016;**224**:162–164.

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