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Temporal trends in the incidence of infective endocarditis in patients with a prosthetic heart valve

Katra Hadji-Turdeghal ,[1] Andreas Dalsgaard Jensen,[1] Niels Eske Bruun,[2,3] Kasper Karmark Iversen,[4,5] Henning Bundgaard,[1,5] Morten Smerup,[6] Lars Kober,[1,5] Lauge Østergaard ,[1,7] Emil Loldrup Fosbøl[1]

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For numbered affiliations see end of article.

Correspondence to
Dr Katra Hadji-Turdeghal; katra.hadji-turdeghal@regionh.dk

ABSTRACT

Objective The incidence of infective endocarditis (IE) is increasing, as is the insertion of prosthetic heart valves. We aimed to examine nationwide temporal trends in the incidence of IE in patients with a prosthetic heart valve in Denmark from 1999 to 2018.

Methods Using the Danish nationwide registries, we identified patients who underwent heart valve implantation (for other reasons than IE) between 1999 and 2018. Crude incidence rates of IE per 1000 person-years (PY) were computed in 2-year intervals. IE incidences were compared using sex-adjusted and age-adjusted incidence rate ratios (IRR) using Poisson regression across calendar periods (1999–2003, 2004–2008, 2009–2013, and 2014–2018).

Results We identified 26 604 patients with first-time prosthetic valve implantation (median age 71.7 years (IQR 62.7–78.0), 63% males). The median follow-up time was 5.4 years (IQR 2.4–9.6). Patients in the time period 2014–2018 were older (median age of 73.9 years (66.2:80.3)), and with a higher burden of comorbidities compared with the time period 1999–2003 (median age of 67.9 years (58.3:74.5)) at the time of implantation. A total of 1442 (5.4%) patients developed IE. The lowest IE incidence rate was 5.4/1000 PY (95% CI 3.9 to 7.4) in 2001–2002, and the highest incidence rate was 10.0/1000 PY (95% CI 8.8 to 11.1) in 2017–2018 with an unadjusted increase during the study period (p=0.003). We found an adjusted IRR of 1.04 (95% CI 1.02 to 1.06) (p<0.0007) per two calendar-years increments. Age-adjusted IRR for men were 1.04 (95% CI 1.01 to 1.07) (p=0.002) per two calendar years increment, and for women 1.03 (95% CI 0.99 to 1.07) (p=0.12), with p=0.32 for interaction.

Conclusion In Denmark, the incidence of IE increased during the last 20 years in patients with prosthetic heart valves.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The incidence of infective endocarditis (IE) is increasing, as is the insertion of prosthetic heart valves. Data on the temporal changes in the incidence of IE in patients with prosthetic heart valves from unselected large cohorts are needed. It is unknown whether IE incidence is indeed increasing in this important subgroup.

WHAT THIS STUDY ADDS

⇒ We found a significantly increased incidence rate of IE following prosthetic valve implantation over a 20-year period.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We included 26 604 prosthetic heart valve implantation procedures and found 1442 (5.4%) IE cases in the population. Our results were obtained from an unselected, nationwide patient sample. The design of the study being population-based reduces the risk of referral and selection bias, and therefore, increases the validity of our study in contrast to some of the previous studies. In the daily clinical setting, we believe it is useful to know that the incidence of IE after prosthetic heart valve implantation has increased. Future studies are needed to try to explain this increase in the incidence of IE this high-risk group.

INTRODUCTION

Infective endocarditis (IE) is associated with significant morbidity and high mortality,[1 2] with long hospitalisation, rehabilitation, reduced quality of life and severe socioeconomic consequences for the individual and the society.[3] Hence, it is concerning that the incidence of IE has significantly increased in the adult population over the preceding decades.[4] Several reasons for this incline in the incidence have been suggested: an increasing elderly population, an increase in the prevalence of prosthetic heart valves and cardiac electronic devices, better diagnostics, and an increasing number of intravascular treatments.[4 5] We have previously estimated that the increased incidence was unrelated to some of these factors, but it was not examined in patients with prosthetic heart valves; the largest subgroup of high-risk patients.[6]

Prosthetic valve endocarditis (PVE) incidence is estimated to be 1%–2% per year,[7] it is an uncommon but severe complication

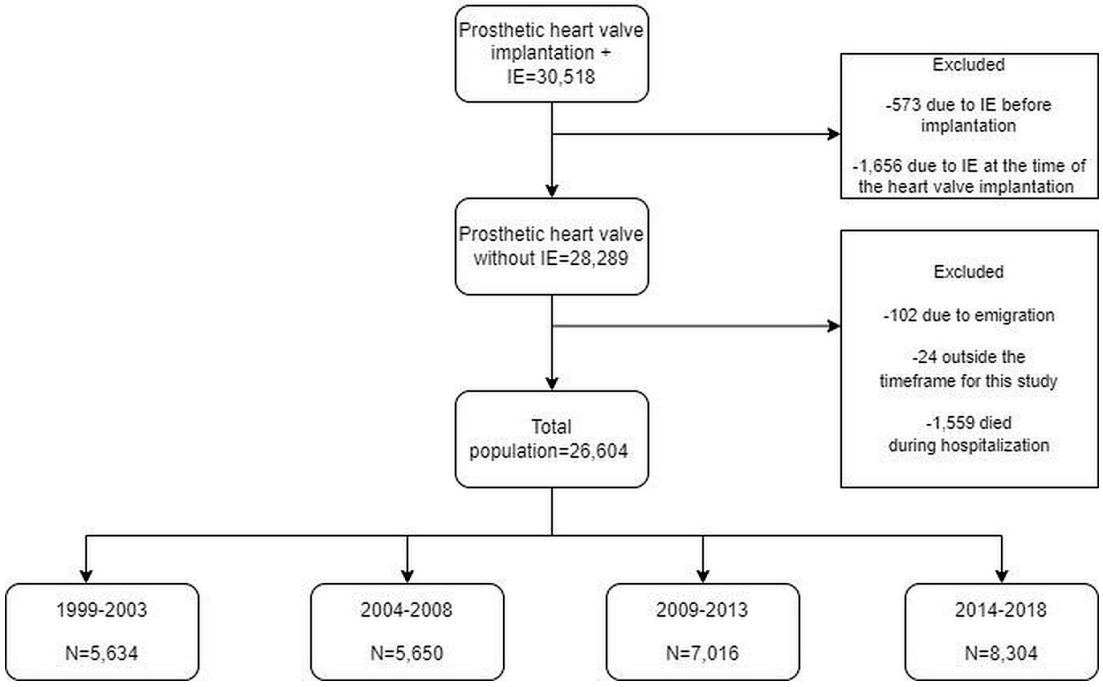

Figure 1 Flow chart. Flow chart of the patient selection. IE, infective endocarditis.

to surgical and transcatheter valve replacement. Early studies have estimated PVE to account for up to 5% of all IE cases,[8] however, in recent studies, PVE represents an increased proportion of overall IE cases –estimated to be 14%–20%.[9 10] The mortality rate in PVE patients is significantly higher than in patients with native valve endocarditis—in hospital mortality varies but is estimated from 22% to 40% for PVE,[9] and 1-year mortality for PVE varies broadly, and is estimated to 21%–80%.[8 11]

Data on temporal changes in the incidence of IE in patients with prosthetic heart valves from unselected large cohorts are needed. It is unknown whether IE incidence is indeed increasing in this important subgroup. Preventive measures could be affected by such data. The aim of this study was to examine the nationwide temporal trends in the incidence of IE following prosthetic valve replacement, and examine the clinical characteristics and the outcomes in Denmark from 1999 to 2018.

METHODS

Data sources

We conducted a retrospective nationwide population study from 1 January 1999 to 31 December 2018. Data on population characteristics were obtained from Statistics Denmark. It is possible to obtain information regarding each individual, as every person living in Denmark for more than 3 months is issued a unique Danish personal identification number (10 digits). This allows the linkage of information across registries at the individual level. The Danish National Patient Registry in Denmark has since 1978 registered all contacts with the hospital for all citizens. All discharged patients must have a primary discharge diagnosis (mandatory) and an optional secondary diagnosis according to The International Classification of Diseases (ICD). The 10th revision (ICD-10) has been used since 1994. Diagnoses prior to 1994 were coded according to the ICD-8 revision, and converted to equivalent ICD-10 codes.[12 13]

All information on surgical procedures is registered in the Danish National Patient Registry since 1996 according to the Nordic Medico-Statistical Committee coding system. In addition, The Danish National Patient Registry contains information on cardiac implantation electronic devices (CIED) and dialysis from 2000 and onward.

Data on baseline characteristics such as sex, date of birth, migration and comorbidities have been obtained from the Danish National Registry. Data on death have been obtained from the Danish Register of Causes of Death.[14]

The Danish National Prescription Registry is organised according to the Anatomical Therapeutic Chemical classification system (ATC codes), and contains information on all prescriptions redeemed from pharmacies since 1994.[15]

Study population

First, we identified all patients who underwent first-time prosthetic heart valve implantation (biological and mechanical aortic, mitral, tricuspid and pulmonary heart valves) from 1999 to 2018 from the Danish National Patient Registry (online supplemental table 1). We had available data on prosthetic heart valve implantation from 1996 and onward, and therefore, all patients alive and with a valve prosthesis at 1 January 1999 were included. Second, we identified all patients with first-time hospitalisation due to IE with ICD-10 primary and secondary diagnosis

Table 1 Baseline characteristics

	Overall	1999–2003*	2004–2008	2009–2013	2014–2018
	N (%)	N (%)	N (%)	N (%)	N (%)
First time PHV-implantation and first-IE-diagnosis	26 604 (100.0)	5634 (21.2)	5650 (21.2)	7016 (26.4)	8304 (31.2)
Age groups					
<70 years	5,327 (20)	1590 (28.2)	1286 (22.8)	1200 (17.1)	1251 (15.1)
≥70 years	21,277 (80)	4044 (71.8)	4364 (77.2)	5816 (82.9)	7053 (84.9)
Age (median, IQR)	71.7 (62.7–78.0)	67.9 (58.3–74.5)	70.6 (61.1–76.9)	72.9 (64.4–79.1)	73.9 (66.2–80.3)
Male	16 778 (63.1)	3433 (60.9)	3617 (64.0)	4418 (63.0)	5310 (63.9)
Comorbidities					
Cardiac implantable electronic device†	2378 (8.9)	177 (3.1)	379 (6.7)	724 (10.3)	1098 (13.2)
Dialysis†	349 (1.3)	39 (0.7)	92 (1.6)	100 (1.4)	118 (1.4)
Hypertension	17 344 (65.2)	3551 (63.0)	3778 (66.9)	4814 (68.6)	5201 (62.6)
Diabetes	3902 (14.7)	478 (8.5)	721 (12.8)	1240 (17.7)	1463 (17.6)
Acute myocardial infarction	3734 (14.0)	720 (12.8)	831 (14.7)	1053 (15.0)	1130 (13.6)
Renal disease	1753 (6.6)	197 (3.5)	304 (5.4)	551 (7.9)	701 (8.4)
Malignancy	3657 (13.7)	435 (7.7)	612 (10.8)	1035 (14.8)	1575 (19.0)
Chronic obstructive lung disease	2830 (10.6)	457 (8.1)	566 (10.0)	834 (11.9)	973 (11.7)
Atrial fibrillation/flutter	8172 (30.7)	1572 (27.9)	1687 (29.9)	2220 (31.6)	2693 (32.4)
Mitral regurgitation	3575 (13.4)	1276 (22.6)	762 (13.5)	715 (10.2)	822 (9.9)
Aortic stenosis	21 734 (81.7)	4042 (71.7)	4624 (81.8)	6031 (86.0)	7037 (84.7)
Heart failure	6911 (26.0)	1685 (29.9)	1422 (25.2)	1797 (25.6)	2007 (24.2)
Prehospital medication (within 6 months prior to admission)					
Beta blockers	14 474 (54.4)	2867 (50.9)	3265 (57.8)	4039 (57.6)	4303 (51.8)
Lipid lowering medication	13 152 (49.4)	1124 (20.0)	3076 (54.4)	4217 (60.1)	4735 (57.0)
Anticoagulant therapy‡	16 966 (63.8)	4591 (81.5)	4564 (80.8)	3949 (56.3)	3862 (46.5)
Glucose lowering medication—no insulin	2890 (10.9)	285 (5.1)	475 (8.4)	924 (13.2)	1206 (14.5)
Glucose lowering medication with insulin	1160 (4.4)	138 (2.4)	213 (3.8)	371 (5.3)	438 (5.3)
Corticosteroids	1652 (6.2)	289 (5.1)	307 (5.4)	477 (6.8)	579 (7.0)

*Patients were included from the year 1996, follow-up was initiated from 1 January 1999 if they have survived and have infective endocarditis.
†Data only available from 2000 and onward.
‡Vitamin K antagonist and novel oral anticoagulant.
PHV, prosthetic heart valve.

codes I33, I38 and I39.8 in the period from 1999 to 2018 from the Danish National Patient Registry. We included all patients with a primary or secondary diagnosis code of IE with a length of hospital stay over 14 days, and patients hospitalised with IE who died with a length of hospital stay under 14 days. We accounted for transfers between departments and hospitals during the course of IE by inserting criteria of at least 14 days of hospitalisation. Hospital admission for IE was identified as the combined hospitalisation in which a diagnosis of IE was given. The criteria of 14 days of hospitalisation have been validated for IE in the Danish National Patients Registry and have a positive predictive value (PPV) of 90%.[16] Patients who had IE prior to surgery or at the time of surgery, migrated outside Denmark or died during hospitalisation were excluded (figure 1).

Covariates

Information regarding comorbidities was obtained from the Danish Patient Registry with a primary or secondary diagnosis given at an inpatient or outpatient consultation. The following comorbidities were included: hypertension, acute myocardial infarction, congestive heart failure, diabetes, renal disease, malignancy, chronic obstructive lung disease, mitral regurgitation, aortic stenosis, and atrial fibrillation/flutter. Data on CIED and dialysis are available from the year 2000 and onward (online supplemental table 2). The diagnosis codes BFCA0 and BFCB0 were used to identify patients with CIED prior to heart valve implantation. The PPVs for these procedure codes in the Danish National Patient Registry have been validated with a PPV of 100% (95% CI 96% to 100%).[17]

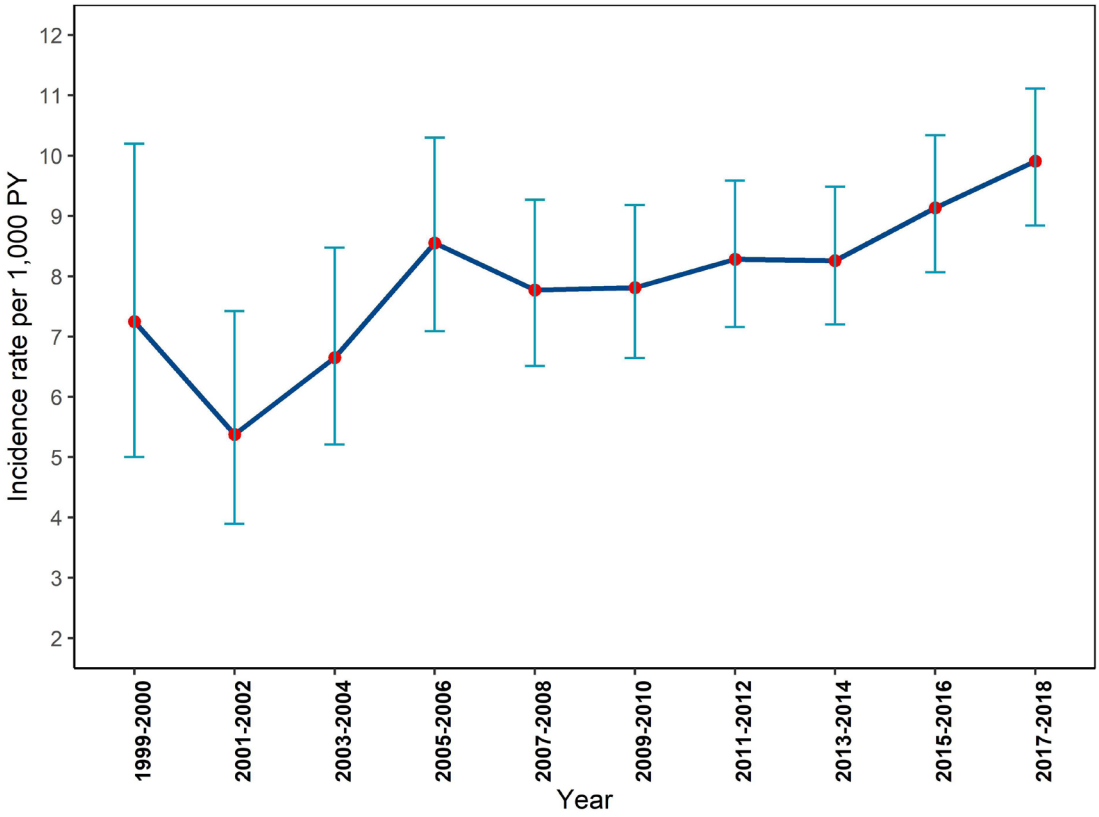

Figure 2 Incidence rate of IE. The figure shows the incidence rate of IE following heart valve implantation/1000 person-years (PY) by calendar year intervals of two for the overall population. Error bars indicate 95% CI. IE, infective endocarditi.

Prescriptions claimed within 6 months prior to prosthetic heart valve implantation admission were used to identify concomitant pharmacotherapy at baseline for patients with IE. All ICD codes used for comorbidities and ATC codes for pharmacotherapy are listed in online supplemental table 2.

Statistical analyses

Baseline characteristics are displayed for patients with IE in calendar periods (1) 1999–2003, (2) 2004–2008, (3) 2009–2013 and (4) 2014–2018. Categorical variables are shown as counts and percentages, and continuous variables with a median and 25 and 75 percentiles. The index date was defined as the date of discharge after heart valve implantation, and all enrolled patients were required to be alive at the index date. Patients were followed until admission for IE, death, emigration, or 31 December 2018. The incidence rates were calculated by 2-year intervals with the denominator being the sum of the person-years (PYs) for the study population and the numerator being the number of first time IE events. Trend for calendar year for incidence of IE was examined using a linear regression model.

Crude incidence rates per 1000 PY of IE were computed and presented in 2-year intervals (1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016, and 2017–2018) with PYs as the denominator and IE events as the numerator. Analyses were stratified by sex and age groups (<70 and ≥70 years). A linear regression model was plotted to examine crude differences per calendar year regarding sex and age groups. The years 1999–2000 were used as the reference years in the analysis. The incidence rate ratios (IRRs) were computed by dividing the incidence rate for each 2-year interval by the reference incidence rate. We used Poisson distribution to calculate sex-adjusted and age-adjusted IRR in a model where calendar year was computed as categorical, and in a model where calendar year was computed as numerical value. The incidence rate of IE per 2-year calendar periods was plotted and a linear regression model was used in order to compute differences in the temporal changes among males and females. Linear regression model was also used to calculate for the differences in the incidence rate of IE between the two age groups.

All statistical analyses were performed with the SAS statistical software, V.9.4. (SAS Institute).

It was not necessary to involve patients or the public in the design, conduct, reporting or dissemination plans of our research as it is an observational registry study.

RESULTS

Study population

We identified 26 604 patients with first time prosthetic valve implantation between 1 January 1999 and 31 December 2018. In this population, the median age was 71.7 (IQR 62.7–78.0) years at the time of implantation.

Sixty-three percent were men. The median follow-up time was 5.4 years (2.4:9.6). Baseline characteristics of the study population are shown in table 1.

Overall, patients in the time period 2014–2018 were older with a median age of 73.9 years (66.2:80.3), while the median age in the time period 1999–2003 was 67.9 years (58.3:74.5). The population was characterised by more men in all time periods accounting for an average of 63% (61;64). The burden of comorbidities increased throughout the time periods. We found an increase in concomitant CIED from 3.1% in 1999–2003 to 13.2% in 2014–2018. Likewise, we observed an almost twofold increase in the proportion of patients in need of dialysis from 0.7% in 1999–2003 to 1.4% in 2014–2018.

First time IE following heart valve implantation

We found 1442 (5.4%) cases of first time IE following heart valve implantation. In total, 17 389 (65.5%), had undergone biological aortic valve replacement (in this group 3951 patients (22.7%) underwent transcatheter aortic valve implantation), 6350 (23.8%) underwent mechanical aortic valve replacement, 938 (3.5%) underwent biological mitral valve replacement, 1365 (5.1%) underwent mechanical mitral valve replacement, and in the final group 562 (2.1%) underwent either mechanical pulmonary valve, mechanical tricuspid valve, biological pulmonary valve or biological tricuspid valve replacement before the diagnosis of IE.

Incidence of IE

The lowest crude incidence rate of IE was 5.4/1000 PY (95% CI 3.9 to 7.4) in the calendar period 2001–2002, and the highest incidence rate was 10.0/1000 PY (95% CI 8.8 to 11.1) in the calendar period 2017–2018 with an unadjusted increasing trend during the study period (p=0.003), (figure 2).

In further analyses, we calculated the adjusted IRRs of IE following prosthetic valve implantation per 2-year intervals (figure 3). We found an adjusted increase in IRR of 1.04 (95% CI 1.02 to 1.06) per 2-year interval for the overall population, (p=0.0007).

Incidence of IE stratified by sex and age

Analyses of crude incidence rates stratified by sex showed: in men the incidence rate was lowest in 2001–2002 (5.5/1000 PY, 95% CI 3.7 to 8.3) and highest in 2017–2018 (11.0/1000 PY, 95% CI 9.6 to 12.6). In women, the incidence rate was lowest in 2009–2010 (4.8/1000 PY, 95% CI 3.4 to 6.7) and highest in 2017–2018 (7.9/1000 PY, 95% CI 6.4 to 9.8). (figure 4). Across the study period, men had a higher crude incidence rate compared with women (online supplemental figure 1). We found an age-adjusted IRR of 1.04 (95% CI 1.01 to 1.07) (p=0.002) for men per 2-year calendar increments, and an IRR of 1.03

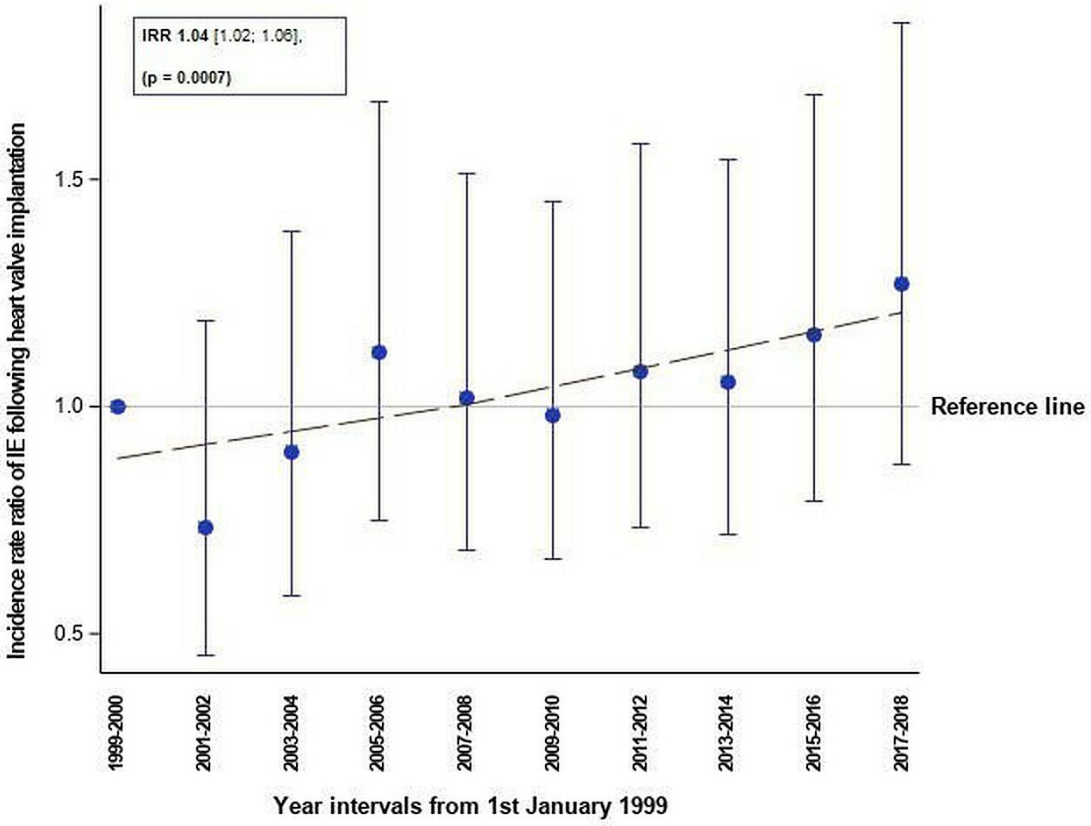

Figure 3 Incidence rate ratio of IE. The incidence rate ratio of IE following prosthetic valve implantation from 1999 to 2018 per 2-year intervals. IRR 1.04 (1.02; 1.06), (p=0.0007) per 2-year interval. Each year interval is in reference to the year interval: 1999–2000. IE, infective endocarditis; IRR, incidence rate ratio.

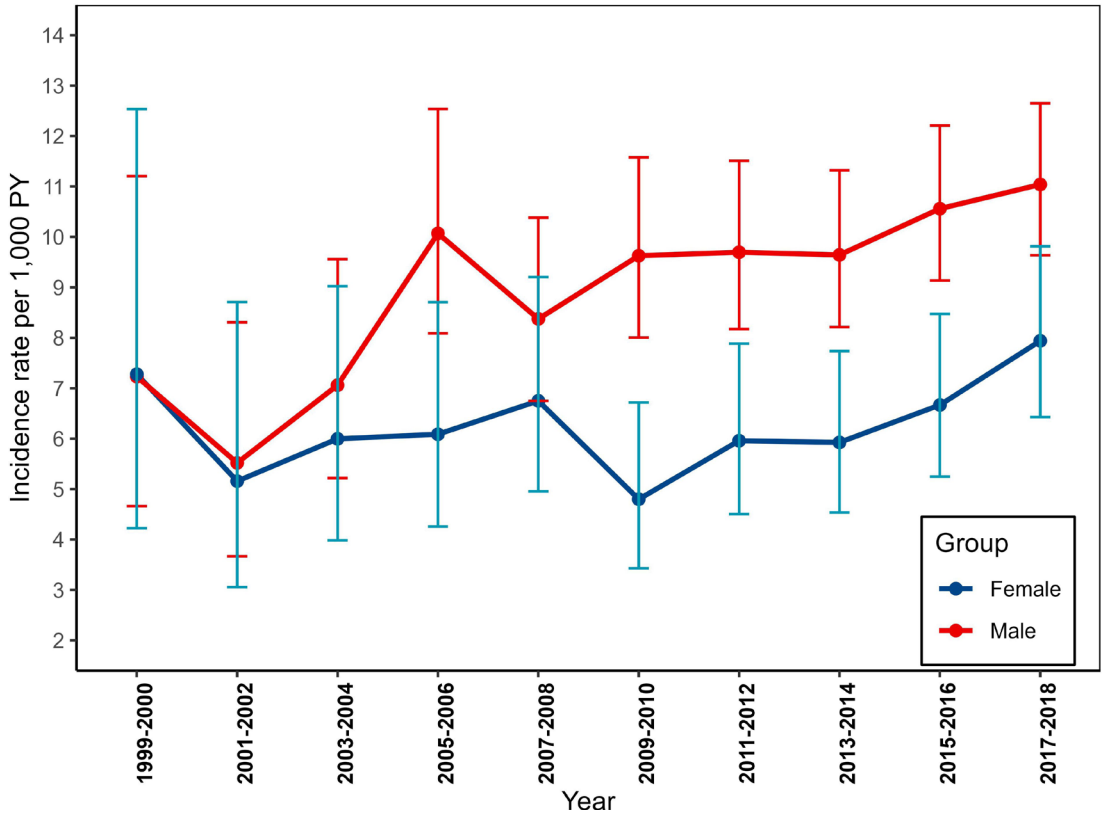

Figure 4 Incidence rate of IE stratified by sex. The figure shows the incidence rate of IE following heart valve implantation/1000 PY by calendar year intervals of two subdivided by sex. Error bars indicate 95% CIs. IE, infective endocarditis, PY, person-year.

(95% CI 0.99 to 1.07) (p=0.12) for women. The p value for the interaction was p=0.32.

Similar results were seen across age groups, with a trend of stepwise increase in the incidence rate of IE for patients below 70 years—the incidence rate was lowest in 2001–2002 (4.3/1000 PY, 95% CI 2.7 to 6.8) and highest in 2017–2018 (8.3/1000 PY, 95% CI 6.8 to 9.9). For patients over 70 years of age, the incidence rate was lowest in 2001–2002 (7.1/1000 PY, 95% CI 4.5 to 11.1) and highest in 2015–2016 (12.2/1000 PY, 95% CI 10.5 to 14.3) (figure 5). Across the study period, patients over 70 years of age had a higher crude incidence rate compared with patients below the age of 70 years. The p value for the interaction was p=0.62 (online supplemental figure 2).

Incidence of IE stratified by heart valve type

In the group with mechanical heart valves, the lowest incidence rate of IE was in 2001–2002 (4.2/1000 PY, 95 % CI 2.7 to 6.6) and the highest incidence rate in 2009–2010 (6.2/1000 PY, 95 % CI 4.7 to 8.1). In the group with biological heart valves, the lowest incidence rate of IE was in 2001–2002 (7.8/1000 PY, 95% CI 4.9 to 12.6), and the highest in 1999–2000 (12.4/1000 PY, 95% CI 7.5 to 20.6) (figure 6). Across the study period, patients with biological prosthetic heart valves had a higher crude incidence rate compared with patients with mechanical prosthetic heart valves. When adjusting for age, sex and calendar years, we found an IRR of 1.60 for biological heart valves compared with mechanical heart valves 95% CI (1.15 to 2.23) (p=0.006).

DISCUSSION

In this retrospective nationwide study, we examined the incidence of IE in patients at high risk represented by a prosthetic heart valve. Our study explored the temporal trends of IE following prosthetic valve implantation from 1999 to 2018 in a large comprehensive unselected nationwide patient cohort. We found a significant increasing incidence rate of IE following prosthetic valve implantation over a 20-year period with similar results across age and sex.

Patients in our population were older, and the burden of comorbidities increased throughout the time periods. We found an increase in concomitant CIED and an almost twofold increase in the proportion of patients in need of dialysis. This could explain some of the increase in the incidence, and it should be noted that data on dialysis in Danish registries are available from the year 2000 and onward.

Several meta-analyses and systematic reviews have found a lower incidence of PVE after prosthetic valve implantation than we found in our study,[18–24] however, some studies have found an even higher incidence than in our study.

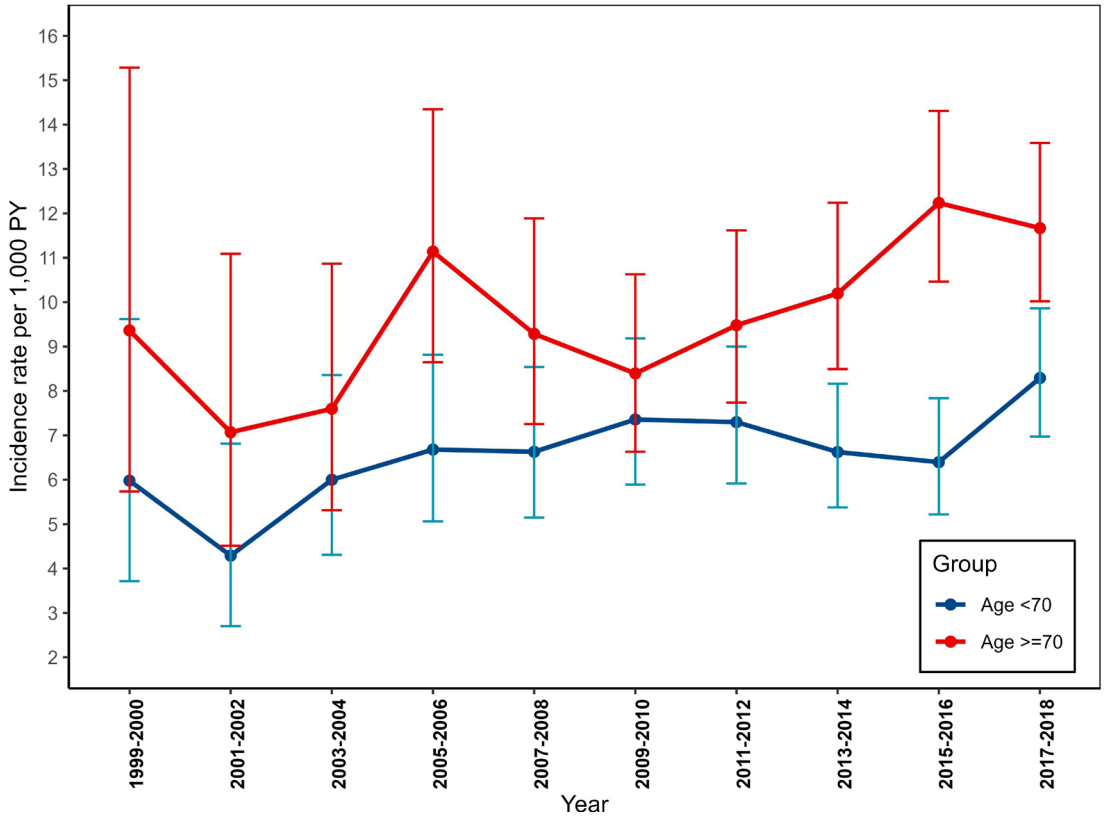

Figure 5 Incidence rate of IE stratified by age. The figure shows the incidence rate IE /1000 PY by calendar year intervals of two stratified by age group <70 and ≥70. Error bars indicate 95% CI. IE, infective endocarditis; PY, person-year.

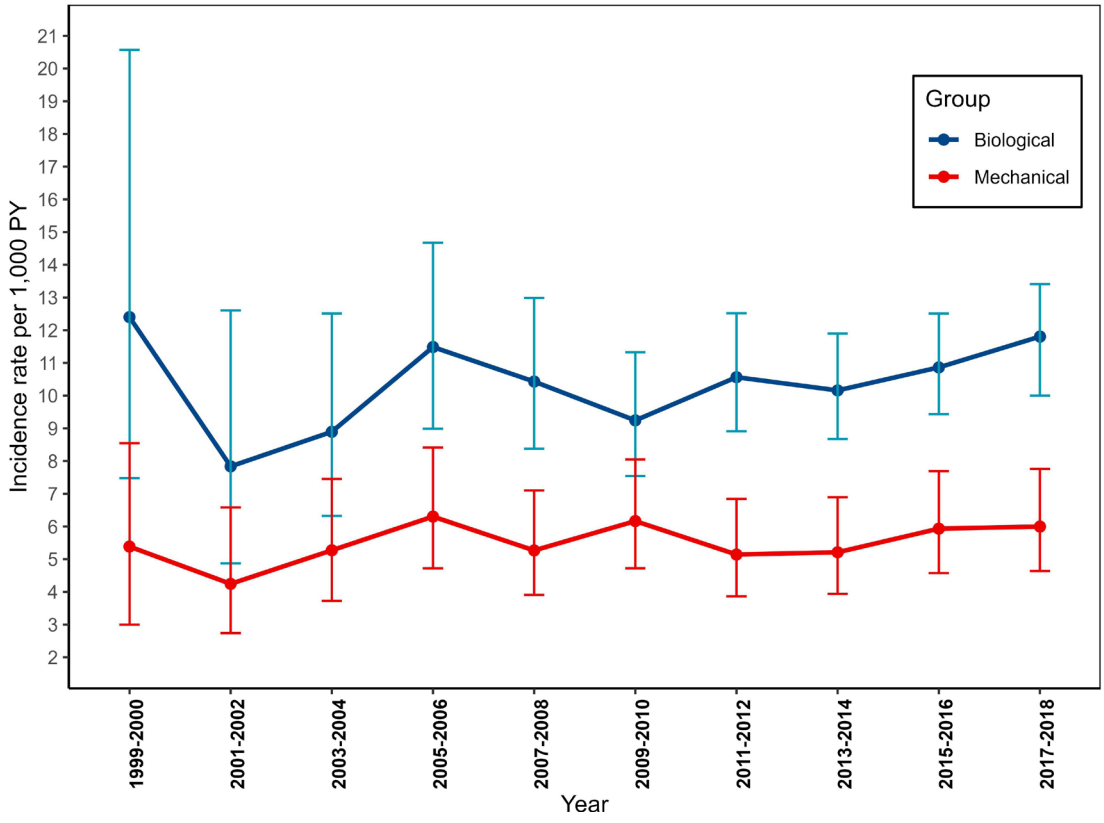

Figure 6 Incidence rate of IE stratified by heart valve type. The figure shows the incidence rate IE /1000 PY by calendar year intervals of two stratified by mechanical and biological heart valves. Error bars indicate 95% CI. IE, infective endocarditis, PY, person-year.

The incidence of IE has increased significantly in the last decades worldwide,[25] and the epidemiology has changed—patients have become older, a higher burden of patients with prosthetic heart valves are affected.[4 9 10 26] Previous studies have suggested reasons for this incline such as: (A) improvement in the diagnosis—better coding/registration, (B) increasing elderly population and thus degenerative heart disease and (C) increase in the prevalence of prosthetic heart valves and intracardiac electronic devices and increasing number of invasive procedures (such as non-cardiac invasive procedures and interventions such as haemodialysis and central venous catheter).[26–28] Current guidelines from the European Society of Cardiology (ESC) from 2015 [29] and American Heart Association (AHA) from 2007[30] regarding prevention of IE in high-risk patients recommend antibiotic prophylaxis use before dental procedures, personal hygiene, general precautions regarding body art (tattoos) and piercing, but no other specific preventive measurements are recommended.

In our study, we found an increase in the incidence rate of IE following prosthetic valve implantation over a period of 20 years. We speculate whether other preventive measures should be taken into account in addition to the general recommendations from the ESC and AHA guidelines in this risk population, for example, prophylactic antibiotic treatment for patients on dialysis. An ongoing randomised clinical trial has been initiated to examine the efficacy of safety of oral prophylactic antibiotics administered in relation to haemodialysis (ClinicalTrials.gov Identifier: NCT05248620). In addition, more focused follow-up for patients at high risk.

Strengths and limitations

The strength of this study is the size of the cohort, which is also unselected and nationwide ranging from 1999 to 2018. Thus, our study provides unique data insight from a large, unselected, nationwide patient sample. The Danish National Patient Registry is of high quality.[12] A study by Østergaard *et al* validated the IE diagnosis code in the Danish National Patients Registry with a PPV of 90%—and the criteria of hospitalisation of 14 days was applied to our study.[16] The design of the study being population-based reduces the risk of referral and selection bias.

However, there are several limitations to this study related to the use of administrative data sets, as they can be subject to inaccurate coding. Second, clinical data at the individual level and data on paraclinical findings to verify the diagnosis such as microbiological aetiology, echocardiography data such as vegetation size, the placement of the vegetation, and relation to a CIED—were not available. The PPV of the IE diagnosis codes and a 14-day admission criterion has been identified at 90% in the Danish National Patient Registry, but the validity of the PVE diagnosis in the Danish National Patient Registry has not yet been examined, which is also a limitation for our study.

CONCLUSION

In this nationwide study, we found an increasing incidence rate of IE following prosthetic heart valve implantation across the last 20 years in Denmark. This increase seems to be irrespective of age, gender and comorbidities. More studies are needed to try to explain this increase in IE—in this high-risk group as well as in the broader general population.

Author affiliations
[1]Department of Cardiology, University Hospital of Copenhagen, Rigshospitalet, Copenhagen, Denmark
[2]Department of Cardiology, Zealand University Hospital Roskilde, Roskilde, Denmark
[3]Clinical Institutes, Aalborg University and University of Copenhagen, Aalborg, Copenhagen, Denmark
[4]Department of Emergency Medicine, Copenhagen University Hospital Herlev and Gentofte, Herlev, Denmark
[5]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[6]Department of Cardiothoracic Surgery, University Hospital of Copenhagen, Rigshospitalet, Copenhagen, Denmark
[7]Department of Cardiology, Copenhagen University Hospital Bispebjerg and Frederiksberg, Copenhagen, Denmark

Contributors KH-T: data acquisition, data analysis, data interpretation, planning, conducting and reporting this manuscript, submission management, final approval of the version to be published. ADJ: aided with data acquisition, data interpretation and critical revision of the article. NEB: data interpretation and critical revision of the article. KKI: data interpretation and critical revision of the article. HB: data interpretation and critical revision of the article. MS: data interpretation and critical revision of the article. LK: data interpretation and critical revision of the article. LØ: data acquisition, data analysis, data interpretation and critical revision of the article. ELF: conception or design of the work, data analysis, data interpretation, critical revision of the article, general supervision throughout the process and final approval of the version to be published. KH-T and ELF are responsible for the overall content as the guarantors.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Register-based studies, which a conducted in relation to statistical and scientific research, do not require ethical approval or informed consent by law in Denmark. All personal identifiers were anonymised. The study is approved by the data responsible institute (Capital Region of Denmark—Approval number: P-2019-401) in accordance with the General Data Protection Regulation. The study follows all national ethical principles regarding register-based studies issued by the National Ethics Committee in Denmark.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement No data are available.

ORCID iDs
Katra Hadji-Turdeghal http://orcid.org/0000-0003-3763-6777

Lauge Østergaard http://orcid.org/0000-0003-3298-1467

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