

Quantifying infective endocarditis risk in patients with predisposing cardiac conditions

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Aims

There are scant comparative data quantifying the risk of infective endocarditis (IE) and associated mortality in individuals with predisposing cardiac conditions.

Methods and results

English hospital admissions for conditions associated with increased IE risk were followed for 5 years to quantify subsequent IE admissions. The 5-year risk of IE or dying during an IE admission was calculated for each condition and compared with the entire English population as a control. Infective endocarditis incidence in the English population was 36.2/million/year. In comparison, patients with a previous history of IE had the highest risk of recurrence or dying during an IE admission [odds ratio (OR) 266 and 215, respectively]. These risks were also high in patients with prosthetic valves (OR 70 and 62) and previous valve repair (OR 77 and 60). Patients with congenital valve anomalies (currently considered 'moderate risk') had similar levels of risk (OR 66 and 57) and risks in other 'moderate-risk' conditions were not much lower. Congenital heart conditions (CHCs) repaired with prosthetic material (currently considered 'high risk' for 6 months following surgery) had lower risk than all 'moderate-risk' conditions—even in the first 6 months. Infective endocarditis risk was also significant in patients with cardiovascular implantable electronic devices.

Conclusion

These data confirm the high IE risk of patients with a history of previous IE, valve replacement, or repair. However, IE risk in some 'moderate-risk' patients was similar to that of several 'high-risk' conditions and higher than repaired CHC. Guidelines for the risk stratification of conditions predisposing to IE may require re-evaluation.

Keywords

Infective endocarditis • Incidence • Risk • Risk stratification • Risk quantification • Predisposing conditions • Guidelines • Antibiotic prophylaxis • Prevention

Introduction

Infective endocarditis (IE) is uncommon but has high morbidity and mortality. Prevention and early detection are therefore important.^{1,2}

International guideline committees have stratified individuals into those at high, moderate, or low risk of developing or suffering a poor outcome (see [Supplementary material online, Table S1](#)).^{3–5} Recent

estimates suggest there are >800 000 individuals at 'high risk' and 4.2–5.2 million with native valve disease at 'moderate risk' of developing IE in the USA alone.⁶ The study most widely used by guideline committees to stratify risk included little comparative data quantifying the risk of a poor outcome,⁷ and there are no data to quantify the relative risks of developing IE or dying during an IE admission associated with different predisposing cardiac conditions in a single large population-based cohort.

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The aim of this study was to identify individuals with different cardiac risk factors for IE and quantify the relative 5-year risk of developing IE or dying during an IE admission (as a marker of poor outcome) using data for all English hospital admissions between 2000 and 2013.

Methods

Data source

All patients admitted to English hospitals are assigned a unique National Health Service (NHS) number and coded in the Hospital Episode Statistics (HES) database according to age, gender, primary discharge diagnosis [ICD-10 <http://apps.who.int/classifications/apps/icd/icd10online> (1 November 2017)], or procedures performed [OPCS-4 <http://systems.digital.nhs.uk/data/clinicalcoding/codingstandards/opcs4> (1 November 2017)]. Patients who die during a hospital admission are recorded as discharged dead. All others are recorded as discharged alive.^{8,9} NHS Digital [<http://content.digital.nhs.uk> (1 November 2017)] provided an anonymized, uniquely numbered data extract for the period January 2000–March 2013 that allowed linkage of all hospital admission records for an individual but precluded access to identifiable patient data.

Risk cohorts

Within the data extract, ICD-10 and OPCS-4 codes were used to identify individuals admitted to hospital between January 2000 and March 2008 with diagnoses or cardiac procedures that might put them at risk of IE (see [Supplementary material online, Table S2](#)) and were divided into four groups:

- (A) 'High risk'—conditions that place individuals at high risk of IE [as defined by the current European Society for Cardiology (ESC)³ and American Heart Association (AHA)⁵ guidelines].
- (B) 'Moderate risk'—conditions that place individuals at moderate risk (as defined by the current ESC³ and AHA⁵ guidelines).
- (C) 'Unknown risk'—conditions where there is uncertainty, guideline disagreement, or lack of data regarding the risk of IE.
- (D) Reference—The English population in 2008.

Individuals were followed up within the HES database for a minimum of 5 years (up to March 2013) to identify subsequent hospital admissions with a primary discharge diagnosis of IE (ICD-10 code I33.0). A discharged 'dead' outcome was used as a measure of poor outcome. All IE hospital admissions in England and all IE admissions resulting in a discharged 'dead' outcome were recorded for the reference group.

Analysis

Patients with IE are often transferred between specialists in the same hospital or to another hospital for treatment. Previously described methodology was used to ensure single continuous episodes of IE were only counted once.¹⁰ Readmission for IE relapse was distinguished from admission with a new IE episode. Although molecular phenotyping of the causative pathogen is generally required to distinguish between relapse and a new infection,¹¹ episodes of IE occurring >6 months after a previous episode are generally regarded by researchers and clinicians as a new infection.^{12–17} A 'lockout period' of 6 months was therefore used to define any subsequent IE hospital admission as a new episode—any IE readmission within 6 months was excluded. Other lockout periods were also assessed (see [Supplementary material online, Figure S1](#)). Patients with one condition, e.g. cyanotic congenital heart disease (CHD), who subsequently had a procedure performed, e.g. repair using prosthetic material, were evaluated for up to 5 years as having cyanotic CHD. If the procedure was performed after 5 years, they were separately evaluated for up to 5 years as a patient with repaired CHD. If the repair happened during

the 5 years of cyanotic CHD follow-up, then they were analysed as having cyanotic CHD up to the point of the procedure. After that, until 5 years of evaluation as cyanotic CHD had elapsed, they were evaluated as if both conditions were running concurrently (and then as CHD repair only until 5 years had elapsed from the procedure).

The incidence data were expressed as (i) the number of individuals with that condition (or in the reference population) admitted to hospital with IE/million/year and (ii) the number of individuals admitted to hospital with IE who died during that admission/million/year.

Preliminary analysis showed that the effects of predictor variables upon IE-free survival were not additive or constant over time and therefore failed to satisfy the conditions for Cox's (proportional hazards) regression analysis (Cox proportional hazard assumption, $P < 0.0001$).¹⁸ One approach to address these problems is to include time as an interaction term. However, the large number of risk groups would make the model difficult to interpret. Therefore, logistic regression analysis was used to calculate the likelihood [expressed as odds ratio (OR)] of different groups developing IE or dying during an IE admission over the subsequent 5 years (compared with the reference group). This also allowed us to correct for the effect of age and gender. The reference data were the likelihood of anyone in the entire English population of 2008 ($n = 51\,815\,853$) developing IE or dying during an IE-admission over the subsequent 5 years. The Kaplan–Meier survival curves were derived for IE-free survival and survival free of death during an IE-admission to demonstrate time-related change in risk. Five-year number needed to harm figures were calculated¹⁹ and are shown in each Kaplan–Meier survival graph legend ([Figure 4](#)). Statistical analyses were performed using R statistical software [version 3.0, <https://www.r-project.org> (1 November 2017)].

As a robustness check to our logistic model, we estimated directly the standardized rates (using the English mid-year 2008 population, [Supplementary material online, Tables S3 and S4](#)) using two different bias correction methods (see [Supplementary material online Tables S5 and S6](#)). See [Supplementary material online](#) for more information.

Results

Epidemiology of infective endocarditis

The incidence of IE in the English population (reference group) was 36.2 cases/million/year with an IE admission-related mortality of 6.3/million/year (17.4%). More men developed IE (69%) and prevalence was highest in the 8th decade ([Figure 1](#)).

There were 96 021 individuals at 'high risk' of IE, of whom 2385 (2.5%) were admitted to hospital with an IE diagnosis within 5 years and 508 (21%) died during admission ([Table 1](#)). There were 265 436 'moderate-risk' individuals, of whom 3714 (1.4%) had an IE hospital admission within 5 years and 943 (25%) died during admission ([Table 1](#)). Although IE incidence was significantly lower in 'moderate-risk' individuals than those at 'high risk' ($P < 0.001$), the incidence of IE related death was significantly higher ($P = 0.002$). There were also marked differences in the age and gender distribution of individuals with different predisposing cardiac conditions (see [Supplementary material online, Figures S2–S4](#)).

Incidence of infective endocarditis and infective endocarditis-related death in individuals with different cardiac risk factors

The incidence of IE and death during an IE admission for patients with different predisposing cardiac conditions are shown in [Table 1](#).

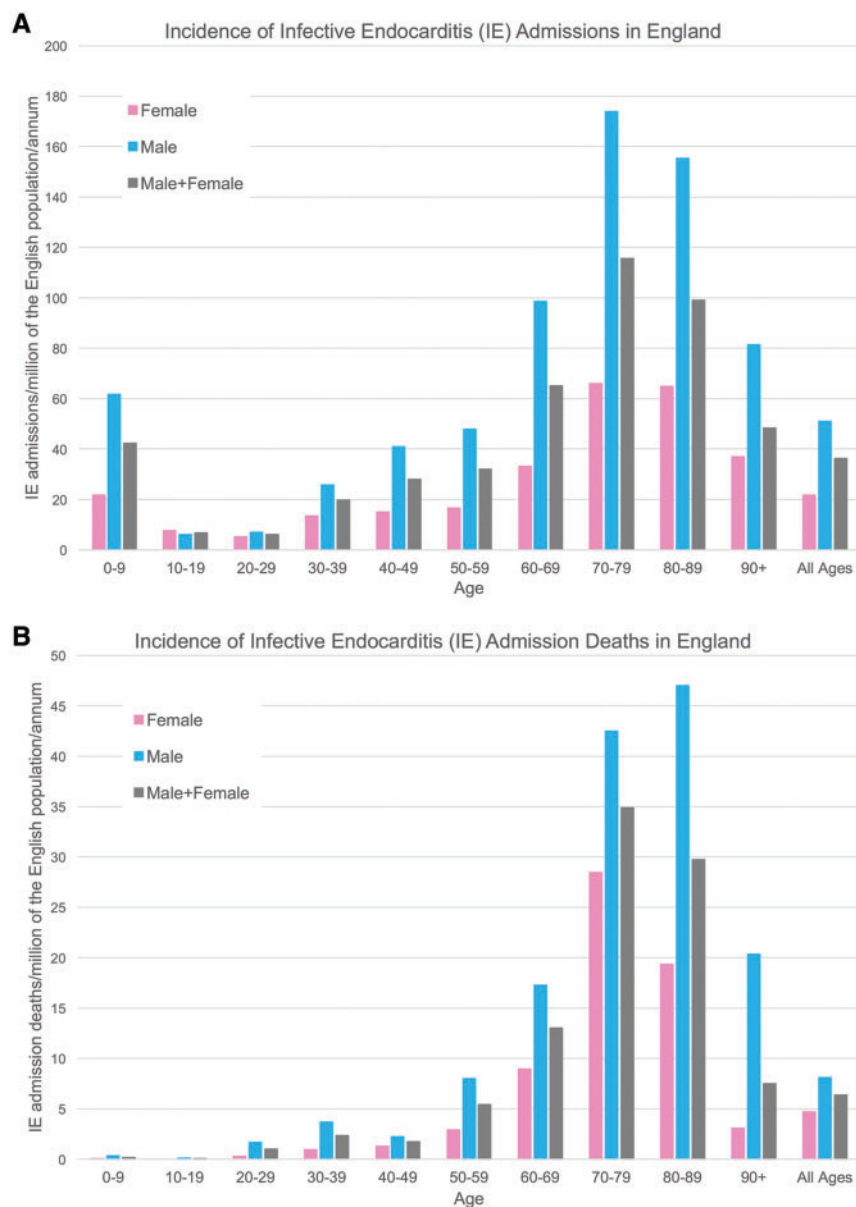


Figure 1 Incidence of infective endocarditis in England from January 2000 to March 2015. (A) Incidence of infective endocarditis admissions. (B) Incidence of infective endocarditis admissions where the patient dies during the admission.

Incidence was highest in those with a previous history of IE and in those with prosthetic or repaired valves. It was also high in those with congenital heart conditions (CHCs) with a shunt or conduit but lower in those with cyanotic CHC (and considerably lower in those with CHC repaired with prosthetic material). Indeed, incidence of IE and death during an IE admission were higher in those with a history of rheumatic fever or non-rheumatic valve disease (currently categorised 'moderate risk' by international guidelines)^{3,5} than in those with cyanotic CHC or CHC repaired with prosthetic material. Incidence of IE was higher in those with congenital valve anomalies than those with cyanotic congenital heart disease although mortality was lower.

Relative risk of developing infective endocarditis or infective endocarditis-related mortality

The 5-year risks of developing IE or dying during an IE admission with different cardiac conditions are compared with the reference group in Table 2 and Figure 2.

Previous IE conferred the highest risk of developing IE [OR 265.5, 95% confidence interval (CI) 244.2–288.2] or dying during an IE-related hospital admission (OR 214.9, 95% CI 179.2–255.6). These findings were independent of lockout period duration (see Supplementary material online, Figure S1). These risks were also high

Table 1 Incidence of IE or IE admission-related death in different predisposing risk conditions

Condition	Size of study population (n)	IE admissions in 5 years	Incidence of IE (cases/million/year)	IE admission deaths in 5 years (% of IE admissions)	Incidence of IE admission deaths (deaths/million/year)
High risk					
Previous IE	9388	674	14 359	138 (21%)	2940
Prosthetic valve replacement	52 746	1223	4637	288 (24%)	1092
Valve repair with prosthetic material	13 674	322	4710	62 (19%)	907
Unrepaired cyanotic CHC	12 028	114	1896	11 (10%)	183
CHC repaired with prosthetic material	6328	23	727	4 (17%)	126
CHC with palliative shunt or conduit	1857	29	3123	5 (17%)	539
Total—high risk	96 021	2385	4968	508 (21%)	1058
Moderate risk					
Rheumatic fever	66 004	1005	3045	305 (30%)	924
Non-rheumatic valve disease	190 451	2602	2732	630 (24%)	662
Congenital valve anomalies	8981	107	2383	8 (8%)	178
Total—moderate risk	265 436	3714	2798	943 (25%)	711
Unknown risk					
Heart transplant	993	1	201	0 (0%)	0
Prosthetic heart/VAD	69	2	5797	0 (0%)	0
Hypertrophic cardiomyopathy	4418	37	1675	1 (3%)	45
Implanted pacemaker/cardioverter	192 296	652	678	193 (30%)	201
Total—unknown risk	197 776	692	700	194 (28%)	196
Reference group					
The population of England (2008)	51 815 853	9386	36.2	1652 (18%)	6.4

CHC, congenital heart condition; IE, infective endocarditis; VAD, ventricular assist device.

in those with prosthetic or repaired valves, or palliative shunts/conduits. Along with cyanotic CHC, these are all categorized as 'high risk' by current guidelines.^{3,5}

For cyanotic CHC, the risk of IE (OR 55.4, 95% CI 45.6–66.6) was similar to that for those with a history of rheumatic fever (OR 51.4, 95% CI 47.9–55.0), currently categorized 'moderate risk'.^{3,5} However, the risk of poor outcome (defined by death during IE admission) was higher in cyanotic CHC (OR 133.6, 95% CI 68.8–231.7) than in those with a history of rheumatic fever (OR 54.5, 95% CI 48.0–61.7).

The risk of IE or dying during an IE admission in patients with congenital valve anomalies (currently categorized 'moderate risk') was similar to several 'high-risk' conditions (with overlapping CIs). Moreover, patients with CHC repaired with prosthetic material (currently considered 'high risk' for the first 6 months after surgery)^{3,5} had a lower risk of IE (OR 18.3, 95% CI 11.8–26.8) or death during an IE admission (OR 24.4, 95% CI 7.5–56.8) than all those currently considered at 'moderate risk' of IE.

In the 'unknown-risk' group, implanted pacemakers/cardioverters [cardiovascular implantable electronic devices (CIEDs)] conferred a small but significant risk of IE (OR 9.7, 95% CI 9.0–10.6) and IE-related death (OR 10.1, 95% CI 8.6–11.7), while the risk of IE (but not dying during an IE admission) was significant in patients with hypertrophic cardiomyopathy (OR 32.8, 95% CI 23.3–44.6 and OR 4.0, 95% CI 0.2–17.5). Prosthetic hearts/ventricular assist devices conferred a significant risk of IE, but the risk associated with a heart transplant was insignificant. In both conditions, the number of IE-related deaths was too small to calculate an OR.

The risk of IE or dying during an IE hospital admission was significantly higher in men (OR 2.15, 95% CI 2.08–2.23, $P < 0.0001$ and OR 1.65, 95% CI 1.53–1.77, $P < 0.001$) than women and in these aged 70–79 years (Table 2 and Figure 3).

Survival analysis for freedom from infective endocarditis and death during infective endocarditis admission

The 5-year Kaplan–Meier survival curves (Figure 4) show how risks changed with time and demonstrate that (i) the risk of developing IE or dying during IE admission in patients with shunts or conduits increased dramatically after 4 years compared with other conditions and (ii) these risks were consistently low in patients with CHC repaired with prosthetic material (including during the first 6 months after repair). Ten-year Kaplan–Meier curves are provided in Supplementary material online, Figures S5–S7.

Discussion

Summary of findings

Our study of the English population quantifies the risks of developing IE and dying during an IE admission (as a measure of poor outcome) with different predisposing cardiac conditions. It confirms that these risks are high in those with a history of previous IE or valve surgery but demonstrate that risks in other patient groups may be under- or

Table 2 Five-year risk of IE or dying during an admission with IE with different predisposing conditions, gender, and age

Predisposing condition	OR of developing IE in 5 years	95% CI	P-value	OR of dying during a hospital admission with IE	95% CI	P-value
High risk						
Previous IE	265.5	244.2–288.2	<0.0001	214.9	179.2–255.6	<0.0001
Prosthetic valve replacement	70.1	65.8–74.7	<0.0001	62.0	54.4–70.4	<0.0001
Valve repair with prosthetic material	76.7	68.3–85.8	<0.0001	59.5	45.6–76.1	<0.001
Cyanotic CHC	55.4	45.6–66.6	<0.0001	133.6	68.8–231.7	<0.001
CHC repaired with prosthetic material	18.3	11.8–26.8	<0.0001	24.4	7.5–56.8	<0.001
CHC with palliative shunt or conduit	86.1	58.1–122.1	<0.0001	314.5	111.6–688.0	<0.001
Moderate risk						
Rheumatic fever	51.4	47.9–55.0	<0.0001	54.5	48.0–61.7	<0.0001
Non-rheumatic valve disease	41.5	39.6–43.6	<0.0001	35.9	32.6–39.5	<0.0001
Congenital valve anomalies	66.4	55.4–80.1	<0.0001	56.7	25.8–106.0	<0.001
Unknown risk						
Heart transplant	5.5	0.3–24.2	0.089	NC	NC	NC
Prosthetic heart/VAD	124.2	20.3–398.9	<0.0001	NC	NC	NC
Hypertrophic cardiomyopathy	32.8	23.3–44.6	<0.0001	4.0	0.2–17.5	0.17
Implanted pacemaker/cardioverter	9.7	9.0–10.6	<0.0001	10.1	8.6–11.7	<0.001
Reference group						
The population of England (2008)	1.0			1.0		
Sex						
Female (reference group)	1.00			1.00		
Male	2.15	2.08–2.23	<0.0001	1.65	1.53–1.77	<0.001
Age						
0–9 years	0.93	0.87–1.0	0.047	0.04	0.02–0.07	<0.001
10–19 years	0.24	0.21–0.27	<0.0001	0.01	0.00–0.03	<0.001
20–29 years	0.30	0.27–0.33	<0.0001	0.26	0.2–0.33	<0.001
30–39 years	0.68	0.63–0.73	<0.0001	0.55	0.46–0.66	<0.001
40–49 years	0.84	0.79–0.90	<0.0001	0.39	0.32–0.47	<0.001
50–59 years (reference group)	1.00			1.00		
60–69 years	1.55	1.46–1.64	<0.0001	1.8	1.56–2.06	<0.001
70–79 years	1.96	1.85–2.07	<0.0001	3.28	2.90–3.72	<0.001
80–89 years	1.61	1.51–1.73	<0.0001	2.95	2.57–3.39	<0.001
90+ years	0.71	0.58–0.86	<0.001	0.94	0.62–1.37	0.76

P-values compare the odds ratio for each condition, gender, or age with the relevant reference group.

CHC, congenital heart condition; IE, infective endocarditis; VAD, ventricular assist device, NC, not calculable.

overestimated by current international guidelines. Some reclassification may be appropriate in light of this evidence. Specifically, the risks of developing IE or dying during IE-admission in those with congenital valve anomalies (currently considered 'moderate risk') were very similar (with overlapping CIs) to those for several 'high-risk' conditions (including patients with prosthetic heart valves, valves repaired with prosthetic material or cyanotic CHC). Risks were only slightly lower in other 'moderate-risk' conditions (history of rheumatic fever or non-rheumatic valve disease) and considerably higher than in patients with CHC repaired with prosthetic material.

Current guidelines only categorize individuals with CHC repaired with prosthetic material as 'high risk' for the first 6 months after surgery.^{3,5} However, our data showed that the 5-year risk of IE or death during IE admission in these individuals was persistently lower than

for all other 'high- or moderate-risk' conditions. In contrast, these risks (particularly dying during an IE admission) were markedly higher in CHC patients who underwent shunt or conduit implantation and increased further after 4 years. This suggests shunts and conduits carry innate risk or are used in patients with conditions that place them at particularly high risk.

The number of patients in the 'unknown-risk' group with heart transplants or ventricular assist devices was small, limiting the precise assessment of risk. However, although IE risk was significantly increased in patients with hypertrophic cardiomyopathy, the risk of a poor outcome was low. The risks of IE and dying during an IE admission were small but significant in patients with CIEDs.

The high proportion of individuals with a previous history of IE (21%), prosthetic (24%), or repaired heart valves (19%) who had a

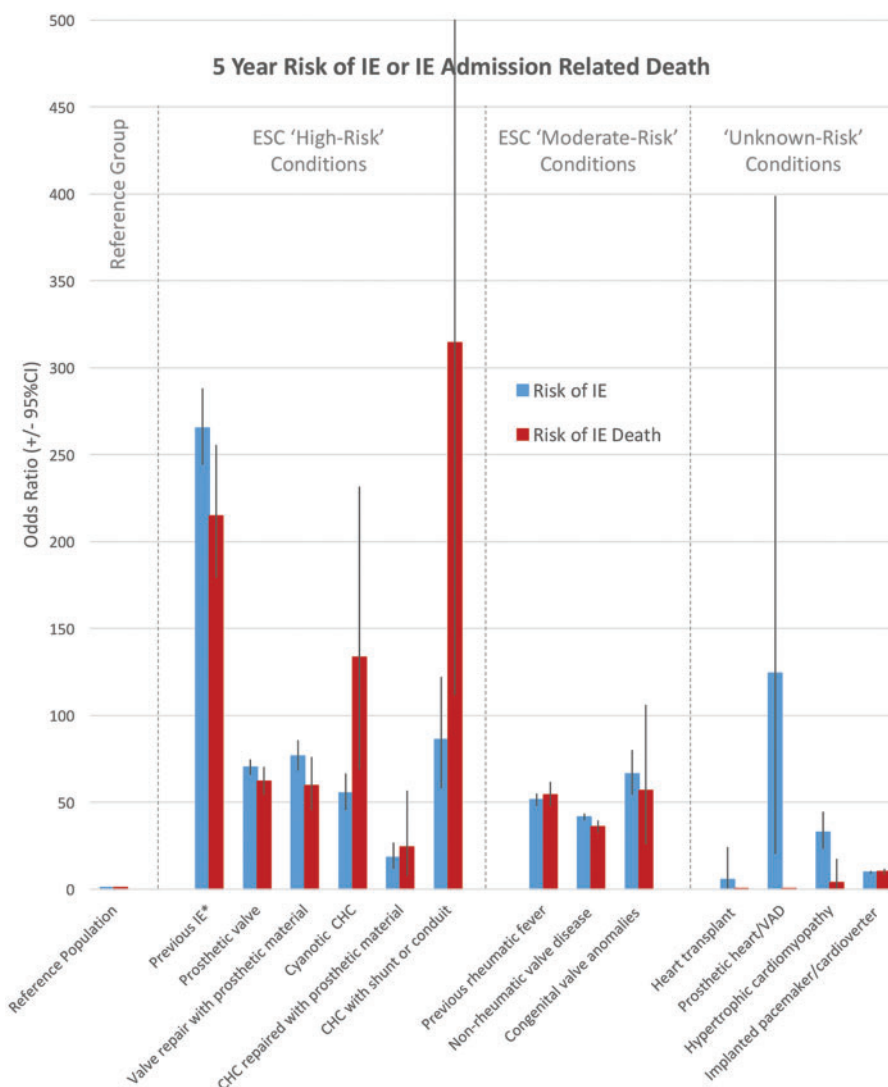


Figure 2 Five-year risk (odds) of developing infective endocarditis or dying during an infective endocarditis admission in different cardiac conditions. *Excluding recurrent infective endocarditis within 180 days of the original episode.

poor outcome and died during an IE admission is not surprising, and most guidelines recognize such individuals as 'high risk'. The significant number of individuals with CIEDs who develop IE and die (30%), however, has only recently been highlighted.^{20,21} Moreover, the high proportions with a previous history of rheumatic fever (30%) or non-rheumatic valve disease (24%) who have a poor outcome and die are unexpected and concerning. Several factors could explain this. Not being labelled 'high risk' could result in a lower index of suspicion for the early diagnosis of IE and an inappropriate sense that treatment need not be as intense as for those labelled 'high risk', leading to delayed diagnosis, less effective treatment, and worse outcomes. It is also possible that using hospital admission data to identify 'moderate-risk' individuals, we selected those with more severe disease or comorbidities that could increase their risk of IE (including health care-related IE).

Research in context

The incidence of IE (36.2 cases/million/year) in the English reference population agrees closely with the incidence of IE in the French population for the same year (33.8 cases/million/year)²² and a recent crude estimate (15–116 cases/million/year) based on data from 10 countries.²³ Moreover, we identified 361 457 individuals at increased risk of IE ['high risk' 96 021 (27%), 'moderate risk' 265 436 (73%)] in keeping with the US studies.⁶

Consistent with the current ESC and ACC/AHA guidelines,^{3,5} the 5-year risk of IE or a poor outcome (death during an IE admission) was high in patients with a previous history of IE, prosthetic or repaired heart valves, cyanotic CHC, or CHC repaired with a shunt or conduit. Although we found a very high incidence of IE in patients with a previous history of IE (14 359 cases/million/year or 1.44%), this was lower than some estimates from smaller, single-condition

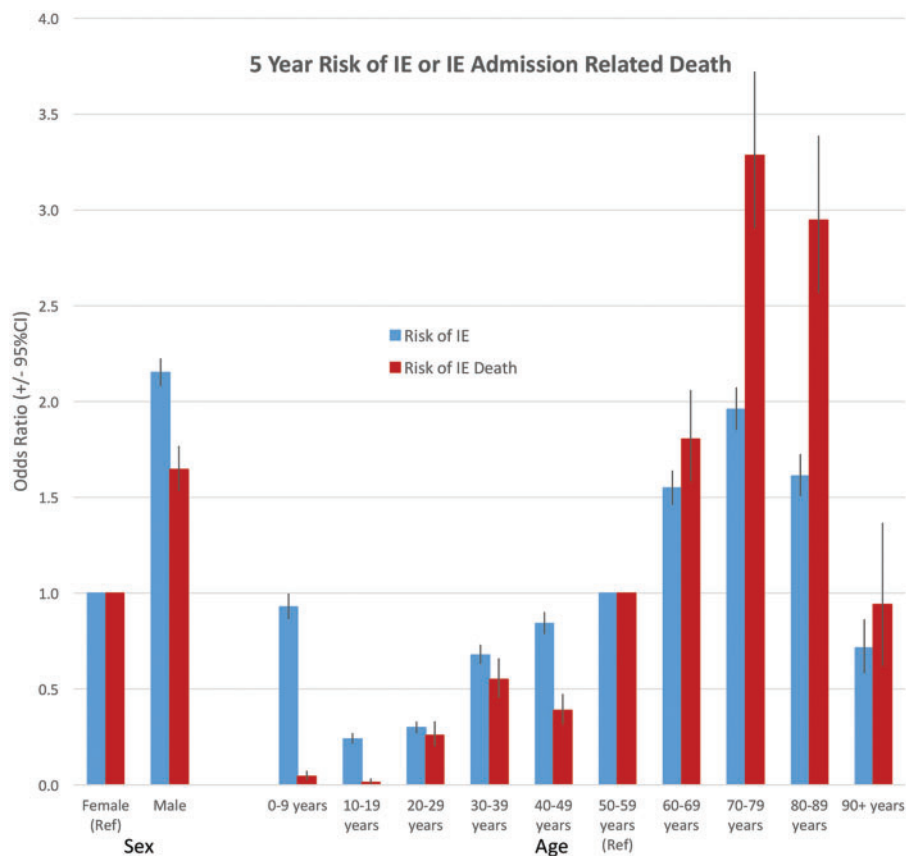


Figure 3 Five-year risk (odds) of developing infective endocarditis or dying during an infective endocarditis admission stratified by age and gender. Gender reference population = female, age reference population = 50–59 years.

studies, where the criteria that we used to exclude relapse were not always observed (2–22%).¹¹ Our incidence of prosthetic valve IE was also high (4637 cases/million/year or 0.46%) and close to that of several smaller studies (0.1–2.3%)²⁴ and our incidence of IE for unrepaired cyanotic CHC (1896 cases/million/year or 0.19%) closely matched a study of 1347 patients with ventricular septal defect (1450 cases/million/year [95% CI 990–2050 cases/million/year]).²⁵

We observed an elevated risk of IE (but low risk of death during IE admission) in patients with hypertrophic cardiomyopathy. These findings are consistent with previous data and suggest that patients with hypertrophic cardiomyopathy generally have better outcomes than with other conditions predisposing to IE.²⁶ The number of patients with CIEDs is increasing rapidly and our study supports recent data, suggesting a small but significant risk of IE in this group.²⁷ Indeed, our data indicate a risk of IE or dying during IE admission that is ~10 times greater than the general population.

Consistent with other studies,²⁴ the 5-year risk of men developing IE was more than twice that of women in this study, but there are few data concerning the risk of a poor outcome, which we found was 1.65 times higher in men. The increasing risks of IE with age (peaking in the 8th decade) are well recognized but an extra peak in risk of IE in children aged <10 years (principally due to CHC) was also noted. However, there was no associated increase in the risk of death during

IE-admission, suggesting that children generally have better outcomes from IE than older patients.

Strengths and weaknesses

Hospital Episode Statistics ICD-10 coding data, rather than individual patient medical records, were used to identify episodes of IE.²⁸ However, HES codes the discharge diagnosis of patients, which in the case of IE is based on Duke criteria in the UK, and therefore on the results of echocardiography and blood cultures (even though these data items were not directly collected). Despite this, National coding data does have limitations. Nonetheless, a recent study showed that Duke criteria positive IE cases were identified with 95% sensitivity (95% CI 86–99%) and 100% specificity (95% CI 100–100%) using similar methodology.²⁹ Our data were collected independently by trained and accredited coding personnel and should therefore be free of selection bias. Moreover, the size of the data set and the independence and consistency of the coding process minimize the likelihood of systematic errors.

A further limitation is that some of the categories used (such as non-rheumatic or congenital valve disease) were broad and could encompass conditions with widely differing risk of IE. Nonetheless, they reflect the categories currently used by international guideline committees.^{3,5}

Comorbidity data were not available, and we were unable to account for the effect of comorbidities, e.g. immunosuppression, diabetes or renal disease, on the risk of IE. Similarly, we were unable to evaluate the impact of different causal organisms on IE outcome. Using population data, a patient with one condition, e.g. cyanotic CHD, could undergo a procedure (e.g. repair with prosthetic material) that alters their risk status (in this case lowers it) for part of the 5-year follow-up period. In the context of the much larger number of individuals with no change, the number, duration, and effect of any change in status was very small. Nonetheless, such events could marginally inflate or deflate the true risk associated with any condition. In addition, the data set only recorded deaths during an IE hospital admission. Although this provides a simple and effective measure for quantifying poor outcome, it does not capture deaths following discharge from hospital and therefore underestimates the true mortality of IE.

Finally, there was a gradual increase in IE incidence during the study that accelerated in 2008.⁸ Although reference population data and use of ORs help to correct for changes in the relative risk of IE caused by background incidence changes, we cannot exclude the possibility that some risks might have changed during the study.

There were differences in the age and gender distribution of individuals with different conditions, e.g. those with CHC had a lower age profile than those with acquired conditions (see [Supplementary material online, Figures S2–S4](#)). Use of logistic regression to calculate the odds of developing IE or dying during IE admission allowed us to correct for the age and gender differences. As a result, the relative size of the OR does not always reflect the incidence data for the same condition. Generally, the OR was higher for CHC and lower for acquired conditions than the incidence figures might suggest.

Conclusions

Data on the risk of developing or dying from IE after different cardiovascular diagnoses and procedures is important for prognostication and patient risk–benefit advice. Risk stratification guidelines are also important in raising the diagnostic threshold of suspicion for IE in those at risk and guiding treatment and prevention strategies including advice on oral hygiene, dental care, avoidance of intravenous drug use, body piercings, and so on.

This study quantifies IE risk and its consequences from all causes and confirms the high-risk status of individuals with a previous history of IE or valve surgery. It also confirmed the high-risk status of most other conditions considered ‘high risk’ by international guideline committees. The risk of IE or dying during an IE admission for patients with congenital valve anomalies (currently categorized ‘moderate risk’) was, however, similar to several ‘high-risk’ conditions and the risk with other ‘moderate-risk’ conditions was only a little lower. In contrast, the risks associated with CHC repaired with prosthetic material (currently categorized ‘high risk’ for the first 6 months) were lower than for all ‘moderate-risk’ conditions. Our data also showed a highly significant ~10-fold increase in the risks of IE or death from IE in individuals with CIEDs. These findings suggest the need to consider re-evaluating IE risk stratification of cardiac conditions and provide valuable data for international guideline committees to take into

consideration in formulating recommendations for IE risk assessment, prevention, and management.

Supplementary material

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

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Conflict of interest: L.B. and P.L. are members of the American Heart Association (AHA) Committee on Rheumatic Fever, Endocarditis, Kawasaki Disease and were involved in producing the 2007 AHA guideline on Prevention of Infective Endocarditis. B.P. was a member of the Task Force on the Prevention, Diagnosis and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC) that produced the 2009 ESC guidelines. B.P. also acted as an external advisor to the committee that produced NICE clinical guideline 64 on Prophylaxis Against Infective Endocarditis in March 2008. M.D. was a non-voting, specialty advisor member of the committee that reviewed NICE clinical guideline 64 on Prophylaxis Against Infective Endocarditis in 2015. All other authors have no conflict of interest to declare.

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