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BRIEF COMMUNICATION

Infective Endocarditis Hospitalizations and Outcomes in Patients With End-Stage Kidney Disease: A Nationwide Data-Linkage Study

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BACKGROUND: We investigated the clinical features, microbiology, and short- and long-term outcomes of incident infective endocarditis (IE) hospitalizations in patients with end-stage kidney disease (ESKD) requiring dialysis or with a kidney transplant over 25 years in Scotland.

METHODS AND RESULTS: In this retrospective, population-based cohort study linking national hospitalization and mortality data, we identified patients with a history of ESKD and hospitalized with IE in Scotland between January 1, 1990 and December 31, 2014. From January 1, 2008, individual IE hospitalizations were additionally linked to national microbiology data. Multivariable logistic regression, adjusting for patient demographics and comorbidities, evaluated the association between ESKD and all-cause death at 1 and 3 years. Of 7638 incident IE hospitalizations between 1990 and 2014, 2.8% (216/7638) occurred in 210 patients with ESKD and 97.2% (7422/7638) occurred in 7303 patients without ESKD. Positive findings from blood cultures were identified in 42% (950/2267) of incident IE hospitalizations from 2008. *Staphylococcus aureus* was isolated in 25.9% (21/81) and 12.8% (280/2186) of patients with and without ESKD, respectively (P=0.002). ESKD was associated with an increased odds of death at 1 (44.9% versus 31.4%; adjusted odds ratio [aOR], 2.47, 95% CI, 1.85–3.30;, P<0.001) and 3 years (63.9% versus 42.8%; aOR, 3.77; 95% CI, 2.79–5.12; P<0.001).

CONCLUSIONS: IE is associated with a poor prognosis in patients with ESKD, especially in the longer term. Compared with patients without ESKD, patients with ESKD were twice as likely to die within 1 year, and 3 times as likely to die within 3 years of IE hospitalization.

Key Words: end-stage renal disease ■ epidemiology ■ infective endocarditis

Infectious diseases are the second commonest cause of death after cardiovascular disease in patients with end-stage kidney disease (ESKD) requiring dialysis or with a kidney transplant.[1,2] The incidence of infective endocarditis (IE) is ≈50- to 70-fold higher in those with ESKD compared with the general population, partly attributable to the use of arterio-venous grafts and indwelling catheters in patients undergoing dialysis, and long-term immunosuppression in renal transplant recipients.[2–4] The limited data available—mostly from small or single-center studies with short follow-up—suggest that the prognosis of IE in patients with ESKD is poor.[2,3]

With the increasing global burden of ESKD,[5] contemporary population-based studies detailing the burden and outcomes of IE in patients with ESKD would be invaluable for planning healthcare provision for this at-risk group. The aim of this nationwide data linkage

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Nonstandard Abbreviations and Acronyms

ESKD	end-stage kidney disease
IE	infective endocarditis
SIMD	Scottish Index of Multiple Deprivation

study was to investigate the clinical features, microbiology and long-term outcomes of incident IE hospitalizations in patients with and without ESKD over the past 25 years in Scotland.

METHODS

Study Design

We conducted a retrospective, population-based cohort study linking national hospitalization, microbiology, and mortality data sets in Scotland (Data S1).[4]

Study Population

Using *International Classification of Diseases* (*ICD*) coding and a 5-year look-back period (Tables S1 and S2), incident IE hospitalizations were identified from national inpatient records in those aged ≥20 years admitted to any Scottish hospital between January 1, 1990 and December 31, 2014. To optimize specificity and sensitivity, we included only hospitalizations with a diagnostic code for IE appearing in the first 2 (of 6) positions of the national inpatient record. We extracted demographic data (age, sex, and deprivation status) and selected comorbidities (history of stroke, heart failure, myocardial infarction, cardiac device, and previous cardiac valvular surgery) (Data S1). Patients with ESKD were identified by searching linked inpatient records before incident IE hospitalization for relevant *ICD* codes (Table S1) appearing in any of the 6 available diagnostic positions. Additionally, between January 1, 2008 and December 31, 2014, incident IE hospitalizations were linked to blood culture data obtained from national microbiology records (Data S1).

Determination of Social Deprivation Status and Comorbidities

Social deprivation status was determined according to the Scottish Index of Multiple Deprivation (SIMD) (Data S1).[6] SIMD is a geographical-based measure of deprivation. It is measured in quintiles, where the first and fifth quintiles are the most and least deprived, respectively. Every patient was assigned an SIMD quintile based on their individual SIMD rank at the time of incident IE hospitalization—determined by social factors related to residential address (zip code). Comorbidities (history of myocardial infarction, stroke, heart failure hospitalization, implanted cardiac device, and prior valvular heart surgery) were defined by identifying relevant *ICD* codes attributed to inpatient records of hospitalizations and procedures during the 5 years preceding incident IE hospitalization (Data S1).[4]

Study Outcomes

Outcomes included stroke, heart failure, and subsequent valvular heart surgery at 1 and 3 years; and all-cause death at 30 days, 1 year, and 3 years.

Statistical Analysis

Clinical characteristics and outcomes were summarized according to ESKD status. Groupwise comparisons were performed using Chi-square tests, as appropriate. Multivariable logistic regression (adjusted for age, sex, social deprivation status; history of stroke, heart failure and myocardial infarction) evaluated the association between ESKD and all-cause death at 1 and 3 years in all patients hospitalized with IE. In a within-exposure analysis restricted to those with ESKD, multivariable logistic regression was used to determine factors associated with all-cause death at 1 and 3 years. Age, sex, and outcome data were complete for all IE hospitalizations. Data on social deprivation status were missing in 0.6% of all IE hospitalizations; these records were excluded from our analysis. Statistical analysis was performed in R, Version 3.5.1 (Vienna, Austria).

Ethical Considerations and Access to Study Data

The study was approved by the National Health Service Public Benefit and Privacy Panel (reference: 1516-0116). Patient consent was not sought as the analysis used fully anonymized data. Individual-level data are available via application to the National Health Service e-Data Research and Innovation Scotland team, which is part of Public Health Scotland. Access to original study data are restricted to approved members of the research team and will not be made publicly available. However, these individual-level data are available via application to the National Health Service e-Data Research and Innovation Scotland team, which is part of Public Health Scotland. Source analysis code will be made available upon request to the corresponding author.

RESULTS

Of 7638 incident IE hospitalizations between January 1, 1990 and December 31, 2014, 2.8% (216/7638) occurred in 210 patients with ESKD and 97.2%

Table. Clinical Characteristics and Outcomes of Patients With and Without ESKD Hospitalized With Incident Infective Endocarditis in Scotland Between 1990 and 2014

	ESKD	No ESKD
No. of hospitalizations, n (%)	216 (2.8)	7422 (97.2)
Mean age, y (SD)	58.9 (14.3)	65.2 (17.3)
Sex, n (%)		
Men	123 (56.9)	3595 (48.4)
Women	93 (43.1)	3827 (51.6)
SIMD quintile, n (%)*		
1 (most deprived)	49 (22.7)	1878 (25.3)
2	56 (25.9)	1687 (22.7)
3	51 (23.6)	1386 (18.7)
4	27 (12.5)	1273 (17.2)
5 (least deprived)	31 (14.4)	1156 (15.6)
Previous medical conditions, n (%)		
Myocardial infarction	14 (6.5)	339 (4.6)
Stroke	16 (7.4)	400 (5.4)
Heart failure	24 (11.1)	1141 (15.4)
Cardiac device	9 (4.2)	199 (2.7)
Prior cardiac valve surgery	18 (8.3)	679 (9.1)
All-cause death, n (%)		
30 d	40 (18.5)	1041 (14.0)
1 y	97 (44.9)	2329 (31.4)
3 y	138 (63.9)	3179 (42.8)
Other outcomes at 1 y, n (%)		
Stroke	13 (6.0)	310 (4.2)
Heart failure hospitalization	16 (7.4)	914 (12.3)
Subsequent cardiac valve surgery	30 (13.9)	783 (10.5)
Other outcomes at 3 y, n (%)		
Stroke	14 (6.5)	443 (6.0)
Heart failure hospitalization	21 (9.7)	1272 (17.1)
Subsequent cardiac valve surgery	34 (15.7)	942 (12.7)

ESKD indicates end-stage kidney disease; and SIMD, Scottish Index of Multiple Deprivation.

*SIMD quintile was available for 99.1% (214/216) and 99.4% (7,380/7,422) of patients with and without ESKD, respectively.

(7422/7638) occurred in 7303 patients without ESKD. Patients with ESKD were younger (58.9±14.3 versus 65.2±17.3 years) and more likely to be men (56.9% versus 48.4%) than patients without ESKD (Table). Between January 1, 2008 and December 31, 2014, there were a total of 950 (41.9%) positive blood cultures associated with 2267 incident IE hospitalizations (Table S3). During this period, the rate of positive blood cultures was higher in patients with ESKD than in patients without ESKD (58% [47/81] versus 41.3% [903/2186]) (P<0.004).

Staphylococcus spp. was the commonest genus identified in patients with (35.8%, 29/81) and without ESKD (17.1%, 374/2186) (P<0.001) (Table S3). *Staphylococcus aureus* was isolated in 25.9% (21/81) of patients with ESKD compared with 12.8% (280/2186) of patients without ESKD (P=0.002), whilst coagulase-negative *Staphylococcus* spp. were identified in 9.9% (8/81) of patients with ESKD versus 4.3% (94/2186) of patients without ESKD (P<0.03). In contrast, *Streptococcus* spp. was observed in 9.9% (8/81) of patients with ESKD and 15.1% (329/2186) of patients without (P=0.264).

Within 1 year of incident IE hospitalization, 13.9% (30/216) of patients with ESKD and 10.5% (783/7422) of patients without ESKD underwent valvular heart surgery (Table). At 3 years, these figures were 15.7% (34/216) and 12.7% (942/7422), respectively. All-cause mortality at 30 days was 18.5% (40/216) in patients with ESKD, compared with 14.0% (1041/7422) in patients without ESKD (Table). Within 1 year of incident IE hospitalization, 44.9% (97/216) of patients with ESKD and 31.4% (2329/7422) of patients without ESKD had died (adjusted odds ratio [aOR], 2.47; 95% CI, 1.85–3.30; P<0.001) (Figure [A]). At 3 years, these figures were 63.9% (138/216) and 42.8% (3179/7422), respectively (aOR, 3.77; 95% CI, 2.79–5.12; P<0.001) (Figure B).

In patients with ESKD, older age was associated with a significantly increased odds of death at both 1 (aOR, 1.34 per 10-year increase in age; 95% CI, 1.09–1.67; P<0.001) and 3 years (aOR, 1.44 per 10-year increase in age; 95% CI, 1.16–1.81; P=0.001) following incident IE hospitalization. However, lower levels of social deprivation were associated with a reduced odds of death at 3 years only (aOR, 0.34 for least versus most deprived SIMD quintile; 95% CI, 0.12–0.92; P=0.037) (Table S4).

DISCUSSION

To date, this is one of the largest nationwide data linkage studies to compare the clinical characteristics, microbiology, and long-term outcomes of IE in patients with and without ESKD. One fifth of patients with ESKD died within 30 days of their incident IE hospitalization, half died within 1 year, and two thirds within 3 years. Compared with those without ESKD, patients with ESKD were twice as likely to die within 1 year of IE hospitalization and >3 times as likely to die within 3 years. In patients with ESKD, older age was independently associated with a poorer prognosis at both 1 and 3 years, whilst the lowest level of deprivation was associated with better outcomes at 3 years only.

The few studies that have defined the microbiology of IE in patients with ESKD report *Staphylococcus aureus* infection rates of ≈50% to 80%[7,8]—substantially higher

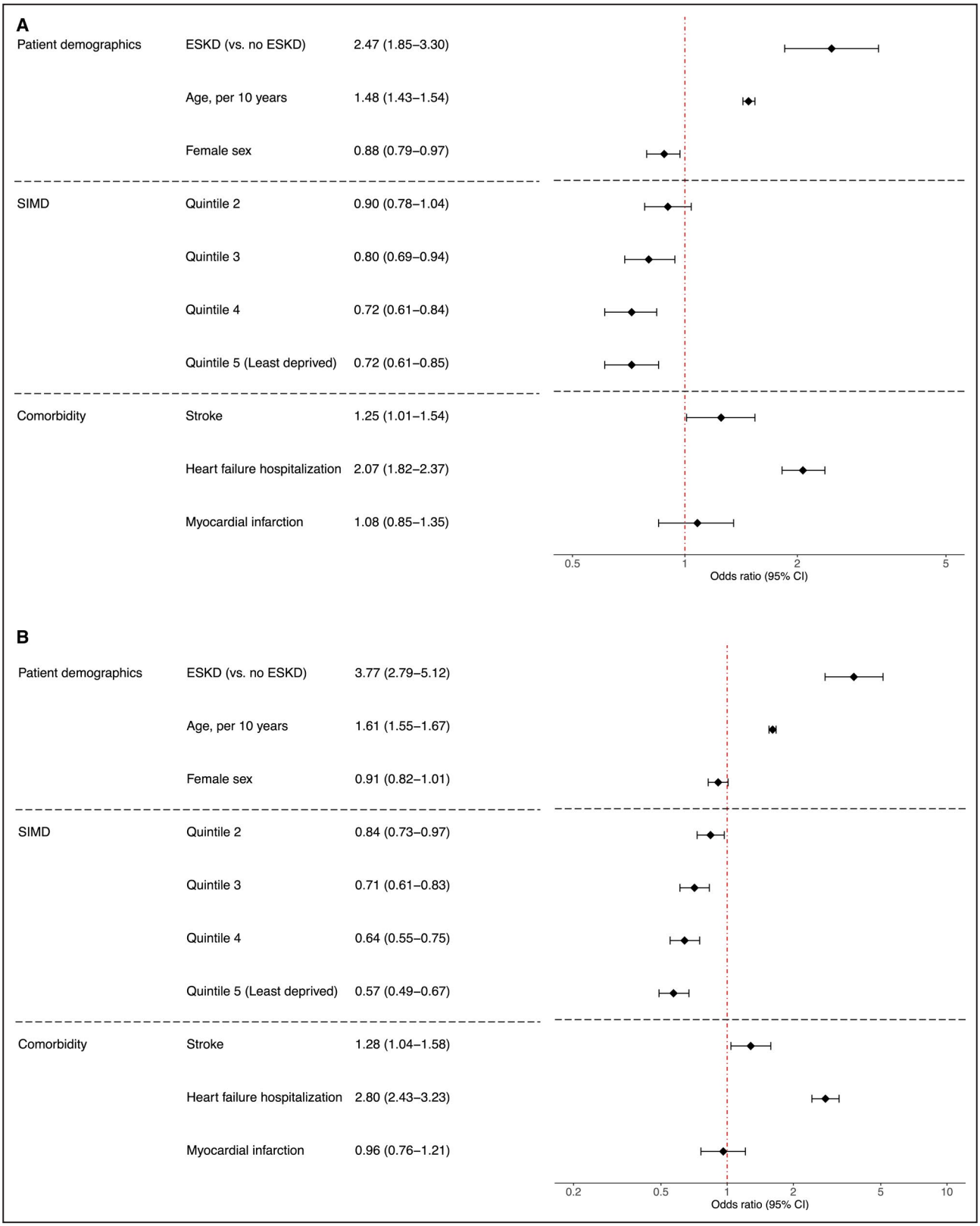

Figure. Forest plot showing adjusted odds ratios and 95% CIs from multivariable logistic regression models evaluating the association between end-stage kidney disease and all-cause death at 1 (A) and 3 years (B).
Number of observations (each model): 7594. Please note x-axes for (A and B) have different scales. ESKD indicates end-stage kidney disease; and SIMD, Scottish Index of Multiple Deprivation.

than in the current study. However, these types of cohort study often rely on cases of IE being identified by clinicians, increasing the risk of selection bias and thus, the proportion of patients with positive microbiology. In contrast, our study—which used individual patient-level blood culture data—was free from selection bias as all IE hospitalizations were identified from routine diagnostic coding, the accuracy of which was recently reported as ≈94% for cardiovascular diagnoses.[9]

Whilst short-term outcomes of IE are similar between those with and without ESKD, patients with ESKD do worse in the longer term. Our data are consistent with a contemporary Danish study[3] and compare favorably with an American study in patients with ESKD performed ≈20 years ago,[10] which described 1- and 3-year mortality rates of 61.6% and 81.7%, respectively. In addition, the in-hospital mortality described in a recently published single-center study from Taiwan was approximately double the figure we report at 30 days, despite similar *Staphylococcus aureus* infection rates.[11] Bhatia and colleagues[12] previously demonstrated a comparable increased risk of death in patients with and without ESKD. Although well-powered, their analysis was restricted to in-hospital death only. In this regard, the long-term outcomes we report are more relevant in the contemporary era, given ≈80% of patients with ESKD survive the initial IE hospitalization.

There are some limitations to consider. Our analysis was under-powered to stratify outcomes by renal replacement therapy (hemodialysis, peritoneal dialysis or renal transplant) or microbiological etiology, or to include these variables in the multivariable regression analyses. As we used routine administrative *ICD* codes to identify IE hospitalizations, our study was free from selection bias but subject to case ascertainment bias. To limit the impact of this, the study cohort was restricted to hospitalizations with a diagnostic code for IE in the first 2 (of 6) positions.

Overall, this comprehensive nationwide analysis over a 25-year period highlights the poor prognosis associated with IE in patients with ESKD compared with patients without ESKD, especially in the longer term. Our results underscore the importance of a multidisciplinary approach to the clinical management of this complex and vulnerable patient group.

ARTICLE INFORMATION

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Author contributions: Gallacher, Shah, and Dhaun conceived the study. All authors contributed to study design and data collection. Data analysis, interpretation, and drafting of the article were conducted by Gallacher, Shah, and Dhaun. All authors critically reviewed the article and approved the final version.

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Supplementary Material

Data S1
Tables S1–S4
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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Data sources

Scottish Morbidity Record 01 (SMR01)

The Scottish Morbidity Record 01 (SMR01) is an episode-based hospitalization record, indexed by community health index (CHI) number, relating to all inpatient and day case hospitalizations from non-obstetric and non-psychiatric specialties.[13] A record is generated when a patient completes an episode of inpatient or day case care. Up to six diagnoses are recorded using the International Classification of Diseases (ICD) classification, whilst interventions or procedures are recorded using the OPCS-4 classification. SMR01 data are considered amongst the best routinely-collected healthcare data worldwide in terms of granularity, population coverage and linkage capabilities. Across all SMR01 records, estimated completion and accuracy rates are 99% and 89%, respectively.[14] For SMR01 records relating to cardiovascular diagnoses, the accuracy rate is 94.2%.[9]

National Records of Scotland (NRS) Death Records

The NRS register is indexed by CHI number and records all deaths in Scotland, with ~55,000 deaths registered annually. Available data from individual patients include demographics, date of death, and primary and secondary causes of death.[15] These data were linked to patients identified as having a record of an incident IE hospitalization during the study period. Of note, it is a statutory requirement that any death occurring in Scotland, or out-with Scotland but within the United Kingdom, is registered on the NRS death register within 8 days of death. Although patients who emigrate to other countries will be lost to follow-up, the Scottish population is historically very stable, with a low rate (<0.5%) of overseas emigration each year.[16]

Electronic Communication of Surveillance in Scotland (ECOSS)

The Scottish microbiology surveillance registry or 'Electronic Communication of Surveillance in Scotland' (ECOSS), as it is termed by NHS National Services Scotland, was used to identify positive blood culture results from microbiology laboratories within NHS Scotland health boards pertaining to incident IE hospitalizations in SMR01 between 01/01/2008 and 12/31/2014. Causative organisms were defined as those identified ≤90 days on either side of the incident IE hospitalization date. Polymicrobial status was defined when >1 causative organism was identified on the same culture date. If >1 causative organism was identified on different dates ≤90 days on either side of the incident IE hospitalization date, then the organism identified closest to the incident IE hospitalization date was assigned as the causative organism.

Although data were first recorded in ECOSS from 2007, near-complete data are available from 2008 and so ECOSS records were linked to SMR01 in the present study from this year onwards.[17,18] ECOSS is maintained by NHS National Services Scotland on behalf of Health Protection Scotland. NHS National Services Scotland monitors the completeness and accuracy of ECOSS data through its 'Data Monitoring and Support Service'.[17] Further, NHS National Services Scotland routinely informs data users of any problems affecting the accuracy of these data. More information on ECOSS is available from https://www.hps.scot.nhs.uk/data/.

Identification of study participants

Incident hospitalizations with infective endocarditis (IE), end-stage kidney disease (ESKD) status and comorbidities were defined from SMR01 in patients aged ≥20 years admitted to any Scottish hospital between 01/01/1990 and 12/31/2014 using International Classification of Diseases (ICD) codes (**Table S1**). To optimize specificity and sensitivity, we included only hospitalizations with a diagnostic code for IE appearing in the first 2 (of 6) positions of the SMR01 record. We extracted demographic data (age, sex and deprivation status [see next section]) and selected comorbidities (history of stroke, heart failure, myocardial

infarction, cardiac device and previous cardiac valvular surgery) from SMR01 using records of hospitalizations and procedures during the 5 years preceding hospital admission (a 5-year 'look-back' period). Patients with ESKD were identified by searching linked inpatient records prior to hospitalization with IE for relevant ICD codes (**Table S1**) appearing in any of the 6 available diagnostic positions.

Definition of deprivation status: the Scottish Index of Multiple Deprivation (SIMD)

The Scottish Index of Multiple Deprivation (SIMD) is a geographical-based measure of deprivation. SIMD identifies small geographical regions (where each region is determined by zip code and corresponds to ~750 residents) of material deprivation based on information derived from seven domains (income; employment; health; education, skills and training; geographic access to services; crime; and housing).[6] Each domain is weighted according to its relative importance and provides a score which is then summed with the other domains. The total score for each geographical region enables the areas to be ranked. SIMD scores and ranks (quintiles/deciles) have been used extensively in published epidemiological research from Scotland.[6] In this study, all patients were assigned a SIMD quintile based on their individual SIMD rank at the time of incident IE hospitalization.

Description of look-back period

Table S2 illustrates the look-back period for the years 2000-2010 in three exemplar patients (patients A, B and C). The total incident count for each year is shown in the final column. Where a patient is hospitalized with an episode of IE, a '1' appears in the 'Admission' column. If no IE event has occurred in the 5-years prior (light grey shading), then the event is considered an incident event and a '1' will also appear in the 'Incident' column (dark grey shading).

Table S1. List of International Classification of Diseases codes employed in study to identify incident cases of infective endocarditis, patients with end-stage kidney disease and their comorbidities. Abbreviations: ICD – International Classification of Diseases.

	Relevant ICD codes
Infective endocarditis	
ICD-9	421.1, 424.91, 424.90, 424.99
ICD-10	I33, I38, I39
End-stage kidney disease	
ICD-9	V45.1, V45.11, V56.0 - V56.2, V56.8
ICD-10	Z49.0 - Z49.2, Z94.0, Z99.2
Myocardial infarction	
ICD-9	413
ICD-10	I21, I22
Stroke	
ICD-9	430 - 438
ICD-10	I60-I69
Heart failure	
ICD-9	428
ICD-10	I50
Cardiac valvular surgery	
OPCS-4	K04 - K12, K14, K17 - K34
Cardiac devices	
OPCS-4	K59 - K61

Table S2. Schematic of the five-year look-back period employed in this study in 3 fictional patients (A, B and C).

Year	Patient A		Patient B		Patient C		Total incident events
	Admission	Incident	Admission	Incident	Admission	Incident	
2000	0	0	0	0	0	0	**0**
2001	0	0	1	1	0	0	**1**
2002	0	0	0	0	0	0	**0**
2003	0	0	0	0	0	0	**0**
2004	0	0	0	0	0	0	**0**
2005	1	1	0	0	1	1	**2**
2006	1	0	0	0	0	0	**0**
2007	0	0	0	0	1	0	**0**
2008	0	0	1	1	0	0	**1**
2009	1	0	0	0	0	0	**0**
2010	0	0	0	0	0	0	**0**

Table S3. Clinical characteristics of patients with and without end-stage kidney disease hospitalized with infective endocarditis in Scotland between 2008 and 2014, and for whom microbiology data were available. *counts of ≤5 are redacted in line with regulatory approvals to protect patient confidentiality. Abbreviations: ESKD – end-stage kidney disease; SIMD – Scottish Index of Multiple Deprivation.

	ESKD	No ESKD
Number of hospitalizations, n (%)	**81 (3.6)**	**2,186 (96.4)**
Age, years (SD)	59.7 (13.1)	66.8 (17.8)
Sex, n (%)		
Men	52 (64.2)	1,138 (52.1)
Women	29 (35.8)	1,048 (47.9)
SIMD quintile, n (%)		
1 (most deprived)	20 (24.7)	507 (23.2)
2	23 (28.4)	497 (22.7)
3	22 (27.2)	435 (19.9)
4	7 (8.6)	379 (17.3)
5 (least deprived)	8 (9.9)	357 (16.3)
Previous medical conditions, n (%)		
Myocardial infarction	6 (7.4)	107 (4.9)
Stroke	7 (8.6)	105 (4.8)
Heart failure hospitalization	NA*	254 (11.6)
Cardiac device	NA*	53 (2.4)
Prior cardiac valve surgery	NA*	167 (7.6)
Microbiology, n (%)		
Staphylococcus aureus	21 (25.9)	280 (12.8)
Coagulase-negative *Staphylococcus* spp.	8 (9.9)	94 (4.3)
Streptococcus spp.	8 (9.9)	329 (15.1)
Other (polymicrobial/*Enterococcus* spp.)	10 (12.3)	200 (9.1)
Negative blood cultures/blood cultures not taken	34 (42.0)	1,283 (58.7)

Table S4. Odds ratios and 95% confidence intervals from logistic regression model for outcome of death at 1 and 3 years in patients with end-stage kidney disease (ESKD) only. The model adjusted for age, sex, deprivation status and history of stroke, heart failure hospitalization and myocardial infarction. Abbreviations: CI – confidence interval; SIMD – Scottish Index of Multiple Deprivation.

	Death at 1 year				Death at 3 years			
	Odds ratio	**Lower 95% CI**	**Upper 95% CI**	**p-value**	**Odds ratio**	**Lower 95% CI**	**Upper 95% CI**	**p-value**
Patient demographics								
Age, per 10 year increase	1.34	1.09	1.67	0.006	1.44	1.16	1.81	0.001
Female sex	0.77	0.43	1.38	0.379	1.03	0.56	1.90	0.928
SIMD quintile (*1 = most deprived; 5 = least deprived*)								
2 (*vs*. quintile 1)	0.79	0.35	1.76	0.565	1.07	0.45	2.55	0.880
3 (*vs*. quintile 1)	0.65	0.28	1.48	0.308	0.51	0.21	1.19	0.124
4 (*vs*. quintile 1)	1.51	0.56	4.18	0.418	1.52	0.50	5.01	0.470
5 (*vs*. quintile 1)	0.38	0.13	1.01	0.059	0.34	0.12	0.92	0.037
Comorbidities								
Stroke	0.71	0.21	2.13	0.552	0.75	0.24	2.38	0.612
Heart failure hospitalisation	0.77	0.29	1.96	0.593	2.01	0.71	6.68	0.213
Myocardial infarction	1.06	0.31	3.41	0.920	1.46	0.42	5.90	0.563