

Clinical characteristics, treatment strategies, and outcomes of patients with aortic valve infective endocarditis with and without aortic root abscess: insights from the NIDUS registry

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Abstract

Background and Aims

Aortic root abscess is a severe and diagnostically challenging complication of infective endocarditis (IE). This study aimed to examine differences between IE patients with and without aortic root abscesses in patient characteristics, treatment strategies, and clinical outcomes.

Methods

We conducted nationwide, unselected, registry-based cohort study using National Danish Endocarditis Studies registry. All patients with aortic valve endocarditis in Denmark from 2016 to 2021 were included. Clinical and microbiological characteristics, treatment, and mortality were compared according to status of aortic root abscess. Mortality was adjusted for clinically relevant covariates.

Results

The study population included 1902 patients with aortic endocarditis, of whom 316 (17%) had an aortic root abscess. Patients with an abscess versus those without were significantly younger (median 71.5 vs 75.1 years, P -value $\leq .001$), more often male (76.3% vs. 69.7%, P -value = .02), prosthetic valve (50.0% vs. 30.4%, P -value $\leq .001$), AV-block (10% vs 1.7%, P -value $\leq .001$), coagulase-negative staphylococci and streptococci in their blood cultures, and were surgically treated (59.5% vs 16.1%). In multivariable Cox regression, patients with abscesses had significantly higher 1-year mortality rate compared with those without (HR 1.41, 95% CI: 1.13–1.76). When stratifying for surgery,

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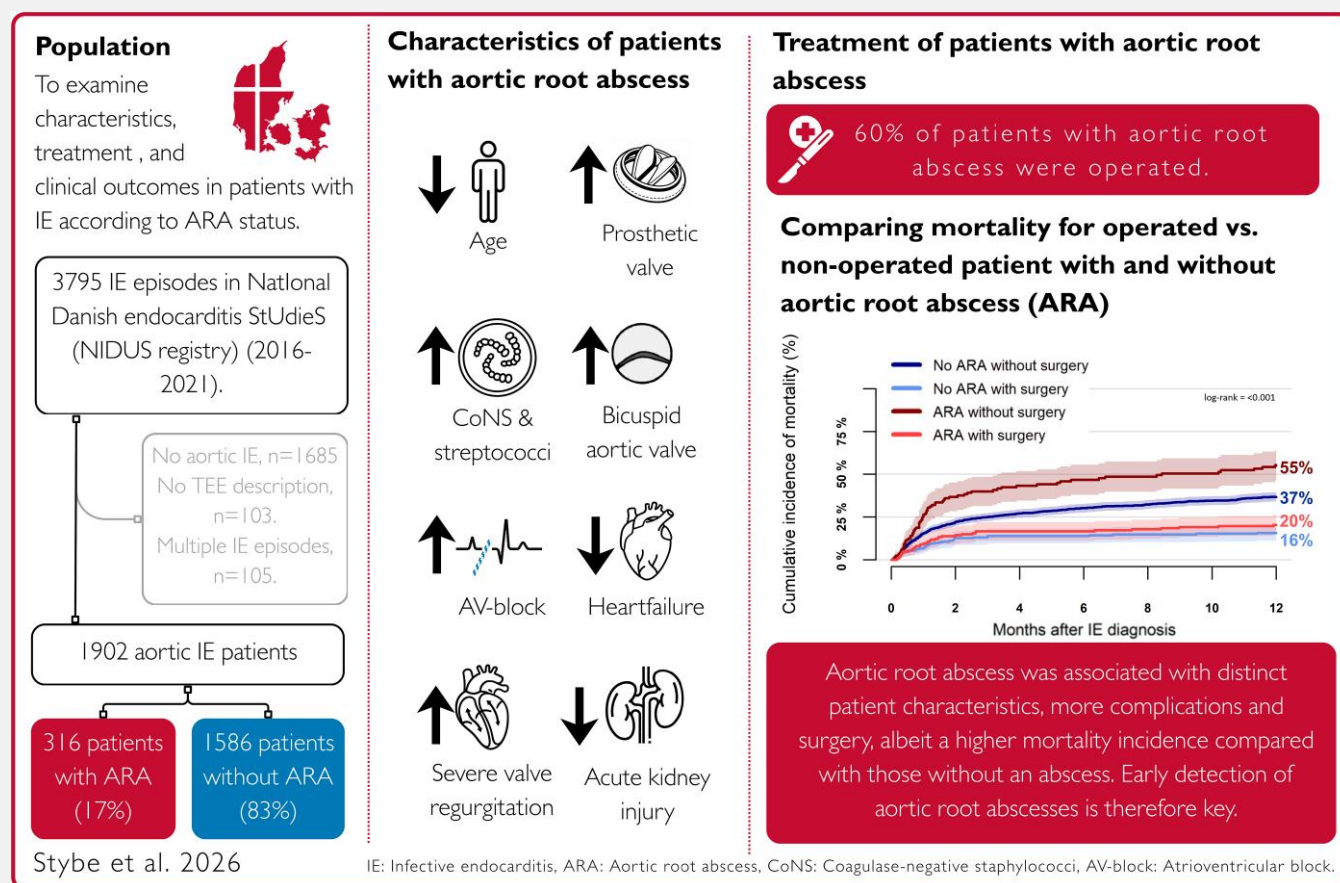
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non-operated patients with an abscess had the highest 1-year mortality 55.4%, alongside a high pre-operative risk (median age 79, 38% not self-reliant, more comorbidities including 12% active cancer).

Conclusions

Aortic root abscess was present in 17% of patients with aortic valve endocarditis and was associated with distinct clinical and microbiological characteristics, a higher frequency of complications, greater prevalence of surgery albeit a higher mortality rate compared with those without an abscess.

Graphical Abstract



Keywords

Infective endocarditis • Aortic root abscess • Aortic valve disease • Clinical outcomes • Paravalvular complications • Cardiac surgery

Introduction

Infective endocarditis (IE) is a severe disease with an in-hospital mortality rate of 11%–24%.¹ Aortic root abscess (ARA) is a lethal complication to IE and can be diagnostically challenging. Aortic root abscess is associated with high risk of in-hospital mortality^{2–4} and a poor prognosis.⁵ A multicentre prospective cohort of 2781 patients (38% with aortic valve endocarditis) found that 14% had intracardiac abscesses, making it the most common paravalvular complication to IE.^{3,5}

Given that ARA is a Class I indication for surgery,^{2,5} diagnostic uncertainty poses a major challenge, since clinicians must consider urgent surgery even when imaging often does not provide a definitive diagnosis. Studies have found that patients with paravalvular complication and

intracardiac abscess had a significantly higher mortality than IE patients without.^{3,4} Despite its clinical significance, limited data exist on the characteristics and outcomes of these patients in a nationwide, unselected cohort.³ Data on ARA are primarily derived from tertiary referral centres,⁵ limiting generalizability. Although several cohorts have evaluated outcomes in patients undergoing surgery for ARA, these are typically from single institutions or selected surgical populations. Nationwide data capturing both surgically and non-surgically managed patients are scarce.⁶

Aortic root abscesses particularly difficult to diagnose, which is why identifying key clinical characteristics of such patients could help refine clinical diagnostic strategies. Therefore, this study aimed to examine patients with aortic valve endocarditis with and without ARA using data

from the National Danish Endocarditis Studies (NIDUS) registry.⁷ The primary objective of this registry-based study was to examine differences between IE patients with and without ARA in patient characteristics, treatment strategies, and clinical outcomes.

Methods

The NIDUS registry⁷ included all patients hospitalized with IE in Denmark during 2016–21 (definite or possible IE) according to modified diagnostic criteria of ESC 2015 and modified Duke Criteria.^{8,9} The design and rationale of the registry have been described in detail previously.^{7,10}

Study population

From the 3795 IE episodes recorded in the NIDUS registry, we selected unique patients hospitalized with aortic valve endocarditis. Patients with incomplete or insufficient echocardiographic descriptions regarding the presence of an ARA were excluded. Patients with aortic IE and ARA were compared with patients with aortic IE without ARA. Patients with ARA were defined as those with either definite or possible ARAs identified on transoesophageal echocardiography (TEE) at the time of diagnosis by the treating cardiologist documented in medical records.

Baseline characteristics and covariates

Specific factors of interest included clinical characteristics and comorbidities, echocardiographic findings upon admission, and microbiological findings, treatment strategies, and complications. In addition, sensitivity analyses were performed for specific subgroups based on treatment strategy.

Outcomes and follow-up

The primary outcome was all-cause mortality. Patients were followed from the date of IE diagnosis (index date) until either clinical follow-up data, death, 31 December 2021, or 1 year post-diagnosis. Additional outcomes, including surgical complications, recurrent IE (defined as relapse, re-bacteraemia, or new-onset IE) and unplanned surgery intervention at discharge during follow-up, were assessed separately.

Statistical analysis

Categorical variables were reported as frequencies with percentages, and differences between groups were assessed using the χ^2 test or Fisher's exact test, where appropriate. Continuous variables were reported as medians with interquartile range (IQR), and Wilcoxon rank-sum test was used to assess differences between groups. Cumulative incidences with corresponding 95% confidence intervals were calculated for time-to-event outcomes.

We calculated cumulative incidences of all-cause mortality within 6- and 12-month post-diagnosis. The Kaplan–Meier method was used for all-cause mortality, and the log-rank test was used to assess differences between groups and further stratified by whether valve surgery was performed or not.

We performed multivariable Cox regression analyses for all-cause mortality within 6 and 12 months after diagnosis and estimated hazard ratios (HRs) with 95% confidence intervals (CIs) for ARA versus no ARA. The model was adjusted for the following covariates: age, sex, prosthetic valve endocarditis (PVE), microbiology in blood cultures, known prior renal disease, chronic obstructive pulmonary disease (COPD), stroke, and self-reliant in daily activities of living prior to admission. Due to the very low proportion of missing data (<1%), analyses were performed using complete case analysis. A *P*-value (*P*) calculated to be less than .05 was considered statistically significant.

The percentage of missing data is shown for each variable in the tables. Proportions (%) shown were calculated using the total number of patients (column totals) as the denominator.

Data from the NIDUS database were analysed using SAS Enterprise (Statistical Analysis Software SAS/STAT, SAS Institute, Inc., Cary, NC, USA) and RStudio software version 4 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics

The study adheres to national ethical guidelines for registry-based research by the Danish National Committee on Health Research Ethics. Informed consent was waived, and data collection was approved by the Danish Data Protection Agency (P-2020-92).

Consent

Informed consent from patients was not required, since this study used pseudo-anonymized registry-based data.

Results

Baseline characteristics and clinical characteristics at admission

The study population comprised 1902 patients with aortic valve endocarditis (Figure 1), of whom 316 (16.6%) had ARA. Among these, 131 patients had definite (41%) and 185 patients had possible ARA (59%) (Table 1).

Patients with ARA compared to patients without ARA were significantly younger (median age 71.5 [IQR: 60.7–78.6] vs. 75.1 years [IQR: 67.2–81.6], *P* < .001), more often male (76% vs. 70%, *P* = .02), had more prosthetic valves and PVE (50% vs. 30%, *P* < .001) except for TAVI, and congenital heart disease (13% vs. 5%, *P* < .001), particularly bicuspid aortic valve malformations (Table 1). Patients with ARA were more often self-reliant in daily activities and employed. Comorbidity profiles and risk factors were otherwise comparable in both groups (Table 1).

Patients with ARA were more often diagnosed with IE by PET–CT (13% vs. 8%, *P* = .02).

Symptoms at admission including peripheral stigmata of endocarditis did not differ between groups (Table 2). On the diagnostic echocardiography, left ventricular function was similar in both groups. Patients with ARA presented with larger vegetations on their aortic valve and more complications upon admission, including embolism (14% vs. 10%, *P* = .04, severe or worsening of valve regurgitation (15% vs. 6%, *P* < .001), and atrioventricular block (AV-block) (10.1% vs. 1.7%, *P* < .001). Other complications upon admission such as heart failure and sepsis were similar.

Microbiological aetiology

The microbiological aetiology differed significantly between patients with and without ARA (Figure 2). The most common microorganism was *Staphylococcus aureus* in both groups, but its prevalence was significantly lower in those with ARA (24% vs. 30%). Patients with ARA had higher proportions of *Streptococcus* spp. (34% vs. 30%), coagulase-negative staphylococci (CoNS) (9% vs. 7%), rare genera (8% vs. 5%), and blood culture–negative IE (11% vs. 8%) compared to those without ARA. However, patients with ARA had lower proportions of *Enterococcus* spp. (16% vs. 19%) compared to those without ARA. These differences were statistically significant (*P* = .01) (Figure 2). For streptococci (strep.), strep. Mitis was more common in patients with ARA (14% vs. 9%) and strep. Sangius (4% vs. 2%), while other streptococci were similar including strep. anginosus, strep. bovis, strep. Group B and C/G, strep. mutans, strep. oralis, strep. pneumoniae, strep. salvarium, and strep. pyogenes.

IE-related complications during admission and mortality

During hospitalization, patients with ARA more frequently developed clinical complications than those without ARA (Supplementary Table S1). AV-block of any type during admission (21.5% vs. 8.0%,

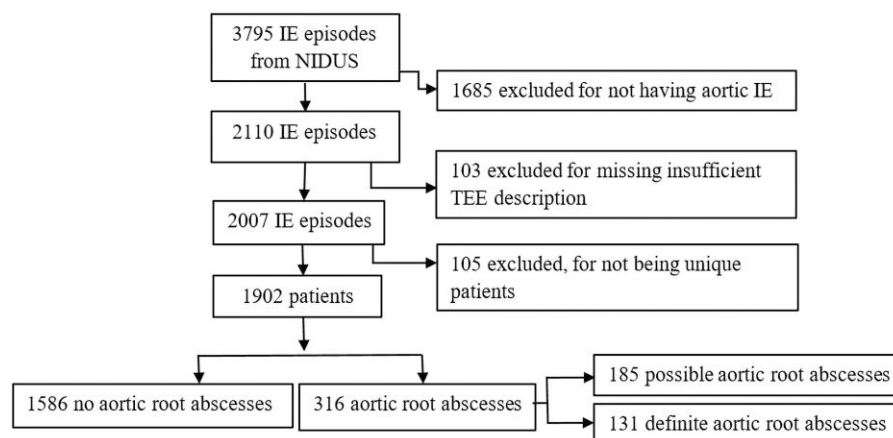


Figure 1 Flow chart of the study population selection. Possible and definite aorta root abscess was registered as findings on the diagnostic transoesophageal echocardiography. Included patients had infective endocarditis of the aortic valve but was not limited to singular valve affliction. IE, infective endocarditis; NIDUS, the National Danish endocarditis studies; TEE, transoesophageal echocardiography.

$P < .001$), heart failure (11% vs. 7%, $P = .004$), severe valve regurgitation (13% vs. 8%, $P = .002$), and acute kidney injury (25% vs. 17%, $P < .001$) occurred more often in patients with ARA.

In-hospital mortality was 21% among patients with ARA (67/316) and 18% among those without ARA (280/1586) ($P = .15$).

Within 1 year after diagnosis, the cumulative incidence of mortality was 34.5% (95% CI: 29.2%–39.9%) in patients with ARA and 33.8% (95% CI: 31.4%–36.2%) in patients without ARA (Figure 3 and Supplementary Figure S1). After adjusting for age, sex, PVE, microbiology in blood cultures, known prior renal disease, chronic obstructive lung disease, stroke and self-reliance in daily living, ARA was associated with a significantly higher rate of mortality compared with no ARA within 1-year of diagnosis (HR 1.41, 95% CI: 1.13–1.76).

Secondary outcomes within six months post discharge

The incidence of secondary outcomes, including reinfection and unplanned reintervention, was low in both groups. The composite endpoint of reinfections occurred with an incidence 4.8% (95% CI 2.6–8.0) among patients with ARA and 4.6% (95% CI 3.6–5.8) among patients without ARA. Unplanned surgical intervention within 6 months after discharge was rare; three events occurred among patients with ARA 1.2% (95% CI 0.34–3.3), while the incidence among patients without ARA was 2.0% (95% CI 1.3–2.9).

Surgical treatment and mortality

Surgical intervention was performed significantly more often in patients with ARA (60% vs. 16%, $P < .001$) (Supplementary Table S1). Overall, 95% of operated patients with ARA had an aortic valve replacement surgery compared with 93% of patients without ARA ($P = .43$). Among these procedures, the most common valve replacement types were bioprosthetic valves (37% vs. 61%), root-sparing surgery/Freestyle (43% vs. 14%), and mechanical valves (9% vs. 17%) ($P < .001$). Peri-operative complications were also more frequent in patients with ARA, including dialysis, prolonged intubation, delirium, reoperation due to bleeding, tracheostomies, tamponade, other complications, and peri-operative death and higher had pre-operative ASA scores (American Society of Anaesthesiologist physical status classification system) (Supplementary Table S1).

Significantly more patients with ARA had a coronary artery bypass graft surgery performed (25% vs. 13%, $P < .001$) or a fistular or ventricular septal defect repaired (16% vs. 2%, $P < .001$) than patients without ARA as part of their treatment during admission.

The highest mortality within 1 year of diagnosis was observed in non-operated patients with ARA (55.4% [95% CI 45.9%, 63.9%]), followed by non-operated patients without ARA (37.2% [95% CI 34.6%, 39.9%]) (log-rank $\leq .001$). Among non-operated patients with ARA, who survived to discharge, 27.3% received lifelong antibiotic prescriptions. In contrast, mortality was lowest among surgically treated patients, with no significant difference between those with ARA (20.4% [95% CI 14.8%, 26.6%]) and without ARA [15.7% (95% CI 11.5%, 20.5%)] (Figure 3).

When stratified by possible, definite and no ARA, definite ARA without surgery had the worst outcomes, followed by possible ARA without surgery ($P < .001$). Surgically treated groups had lower and overlapping mortality estimates.

Sub-analysis of surgically treated and non-surgically treated patients

In a sub-analysis (Table 3), non-surgically treated patients with ARA were more often classified as possible rather than definite ARA (75% vs. 25%, $P < .001$) and were significantly older, with 40% aged ≥ 80 years compared with 4% of surgically treated patients with ARA ($P < .001$). Compared with surgically treated patients with ARA, non-surgically treated patients with ARA also had a higher prevalence of kidney disease, congenital heart disease (especially bicuspid aortic valve), prior cardiac implanted electronic device, active cancer, prior heart failure, lower functional independence, and prior stroke (all $P < .05$). No differences were observed in PVE, diabetes, COPD, liver disease, or prior cancer (Table 3).

The majority of patients with an ARA were operated. Of the non-operated patients with ARA, 54 had no known contraindication for surgical treatment, and all of these patients had a possible and not a definite ARA. Known reasons for no surgical treatment for patients with ARA and indication of valve surgery included poor functional status or prognosis (74%), stroke (7%), intracranial haemorrhage (3%), heart failure (6%), haemodynamic instability (4%), inconsistency with goals of care (16%), patient refusal (11%), pre-operative death (4%), and other reasons (19%).

Variable (%)	Level	ARA (n = 316)	No ARA (n = 1586)	Total (n = 1902)	P-value	Missing
Sex	Male	241 (76.3)	1105 (69.7)	1346 (70.8)	.02 ^a	—
Age (years)	Median [IQR]	71.5 [60.7, 78.6]	75.1 [67.2, 81.6]	74.4 [66.0, 81.2]	<.001 ^a	—
	<70 years	144 (45.6)	504 (31.8)	648 (34.1)	<.001 ^a	—
	70–80 years	113 (35.8)	598 (37.7)	711 (37.4)		
	>80 years	59 (18.7)	484 (30.5)	543 (28.5)		
Primary vegetation location	Prosthetic valve	158 (50.0)	486 (30.6)	644 (33.9)	<.001 ^a	—
	Native valve	158 (50.0)	1100 (69.4)	1258 (66.1)		
DUKE criteria	Definite endocarditis	291 (92.1)	1208 (76.2)	1499 (78.8)	<.001 ^a	—
	Possible endocarditis	25 (7.9)	378 (23.8)	403 (21.2)		
Prior endocarditis		20 (6.3)	71 (4.5)	91 (4.8)	.16	<2%
Known native valve heart disease		50 (16.0)	214 (13.5)	264 (13.9)	.28	<1%
Prior heart valve surgery	In total	159 (50.3)	499 (31.5)	658 (34.6)	<.001 ^a	—
	Prior aorta valve surgery ^b	159 (100.0)	482 (96.6)	641 (97.4)	.02 ^a	—
Type of aorta surgery	Mechanical aortic valve	46 (14.6)	81 (5.1)	127 (6.7)	<.001 ^a	—
	Biological prosthetic valve	82 (25.9)	265 (16.7)	347 (18.2)	<.001 ^a	
	TAVI	21 (6.6)	136 (8.6)	157 (8.3)	.26	
	Freestyle aortic valve	10 (3.2)	7 (0.4)	17 (0.9)	<.001 ^a	
Congenital heart disease		41 (13.0)	82 (5.2)	123 (6.5)	<.001 ^a	—
Bicuspid aortic valve		32 (10.1)	64 (4.0)	96 (5.0)	<.001 ^a	—
Comorbidities						
	Prior cancer	40 (12.7)	249 (15.7)	289 (15.2)	.17	—
	Active cancer	20 (6.3)	169 (10.7)	189 (9.9)	.02 ^a	—
	Prior stroke	43 (13.6)	257 (16.2)	300 (15.8)	.25	—
	Prior known heart failure	46 (14.6)	284 (17.9)	330 (17.4)	.15	—
	Diabetes	75 (23.7)	378 (23.8)	453 (23.8)	.97	—
	Liver disease	12 (3.8)	82 (5.2)	94 (4.9)	.30	—
	Renal disease	43 (13.6)	267 (16.8)	310 (16.3)	.16	—
Chronic obstructive lung disease		34 (10.8)	260 (16.4)	294 (15.5)	.01 ^a	—
Cardiac implantable electrical device		39 (12.3)	241 (15.2)	280 (14.7)	.19	—
Prior CABG		40 (12.7)	145 (9.2)	185 (9.7)	.055	<1%
Not self-reliant in daily activities of living		64 (20.3)	487 (30.7)	551 (29.0)	<.001 ^a	<1%
Retired		221 (69.9)	1282 (80.8)	1503 (79.0)	<.001 ^a	<1%
Dental procedures 3 months prior to admission		16 (5.1)	69 (4.4)	85 (4.5)	.52	<5%

QQR, interquartile range; DUKE, DUKE criteria for diagnosing infective endocarditis; TAVI, transcatheter aortic valve implantation; LVEF, left ventricular ejection fraction. Heart failure, LVEF <45%; missing: per cent missing out of the total amount of patients <3; microdata: less than three observations.

In a supplementary analysis (Supplementary Table S3), we found no substantial difference in comorbidities between non-operated patients with and without ARA, with the exception that patients

Discussion

In this study of patients with aortic valve endocarditis with and without ARA, we had three major findings. First, patients with ARA were

Table 2 Clinical presentation, echocardiographic findings, and complications upon admission according to status of aortic root abscess

Variable (%)	Level	ARA (n = 316)	No ARA (n = 1586)	Total (n = 1902)	P-value	Missing
Symptoms at admission	Fever	192 (60.8)	912 (57.5)	1104 (58.0)	.08	<5%
	Myalgia	80 (25.3)	411 (25.9)	491 (25.8)	.79	<5%
	Dyspnoea	109 (34.5)	510 (32.2)	619 (32.5)	.20	<5%
	Osler's nodes	3 (0.9)	7 (0.4)	10 (0.5)	.25	—
	Petechiae	12 (3.8)	33 (2.1)	45 (2.4)	.067	—
	Janeway lesions	7 (2.2)	13 (.8)	20 (1.1)	.03 ^a	—
	Splinters	20 (6.3)	70 (4.4)	90 (4.7)	.14	—
Blood culture	Negative	36 (11.4)	133 (8.4)	169 (8.9)	.086	—
	Positive	280 (88.6)	1453 (91.6)	1733 (91.1)		
Complications at admission						
Embolism at admission		44 (13.9)	159 (10.0)	203 (10.7)	.04 ^a	<1%
Heart failure		15 (4.7)	46 (2.9)	61 (3.2)	.089	0%
Severe or worsening of valve regurgitation		46 (14.6)	88 (5.5)	134 (7.0)	<.001 ^a	0%
Sepsis		67 (21.2)	367 (23.1)	434 (22.8)	.45	0%
Conduction abnormalities		38 (12.0)	56 (3.3)	94 (4.9)	<.001	<1%
Bundle branch block		5 (1.6)	23 (1.5)	28 (1.5)		
AV-block		32 (10.1)	27 (1.7)	59 (3.1)	<.001	<1%
Type	AV-block 1st degree	13 (4.1)	14 (0.9)	27 (1.4)	<.001 ^a	
	AV-block 2nd degree	6 (1.9)	4 (0.3)	10 (.5)	<.001 ^a	—
	AV-block 3rd degree	17 (5.4)	17 (1.1)	34 (1.8)	<.001 ^a	
Diagnostic echocardiography						
LVEF ^b	Normal (55%–60%)	187 (59.2)	862 (54.4)	1049 (55.2)	.42	<15%
	Mild reduction (45%–55%)	53 (16.8)	264 (16.6)	317 (16.7)		
	Moderate reduction (30%–45%)	32 (10.1)	162 (10.2)	194 (10.2)		
	Severe reduction (<30%)	7 (2.2)	62 (3.9)	69 (3.6)		
AV vegetation size	median [IQR]	10 [8, 15]	8 [5, 12]	8 [5, 12]	<.001 ^a	<20%
AV vegetation size ^b	Large (>25 mm)	24 (7.6)	51 (3.2)	75 (3.9)	<.001 ^a	
	Medium (10–25 mm)	84 (26.6)	225 (14.2)	309 (16.2)		<20%
	Small (<10 mm)	144 (45.6)	1069 (67.4)	1213 (63.8)		
Severe aortic stenosis		33 (10.5)	111 (7.0)	144 (7.6)	.045 ^a	<2%
Severe aortic regurgitation		54 (19.1)	156 (9.8)	210 (11.6)	<.001 ^a	<5%
IE diagnosis made by PET–CT		42 (13.3)	133 (8.4)	175 (9.2)	.02 ^a	<1%

^aSignificant result.^bPercent is calculated from the total amount of patients including missing values.CoNS, coagulase-negative staphylococci; AV-block, atrioventricular block; HACEK, *Haemophilus* spp., *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*; IQR, interquartile range; IE, infective endocarditis; PET–CT, positron emission tomography–computed tomography scan; LVEF, left ventricular ejection fraction; heart failure, LVEF <45%; AV, aortic valve; missing: per cent missing out of the total amount of patients; NS, not significant.

younger, more often male, and had more predisposing cardiac conditions (prosthetic valves or BAV) than patients without ARA. Second, they also presented with more complications at admission, during admission, and in relation to surgery, indicating a higher disease burden. After multivariable adjustment, ARA was associated with a higher mortality, suggesting a more aggressive disease course and worse short-term prognosis than aortic endocarditis without ARA. Third, although

surgery was performed far more often in patients with ARA than in those without, non-surgically managed ARA patients were too ill to be surgically treated; they were significantly older, had substantial comorbidities, and were more frail. The nationwide and unselected design of this study extends previous findings by providing real-world estimates of prevalence, incidence, management, and outcomes of ARA across the entire Danish population.

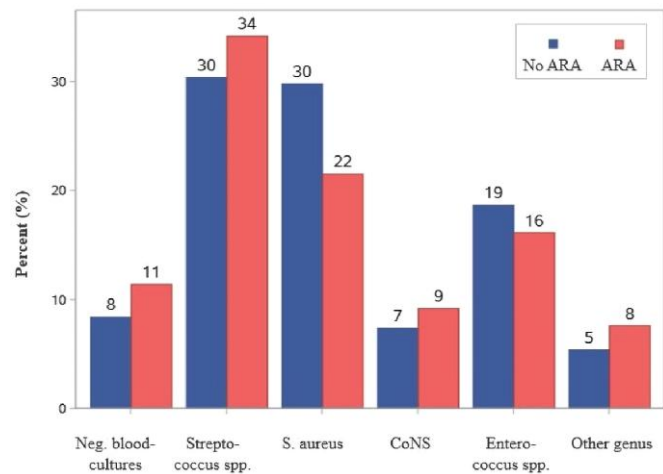


Figure 2 Histogram of microorganisms in blood cultures. Primary infective genus from blood cultures. P -value = .01. Blue, no aortic root abscess (no ARA); red, aortic root abscess (ARA). Neg. blood cultures, blood culture–negative patients; CoNS, coagulase-negative staphylococci. Other genus includes HACEK and fungi (*Candida albicans*, *Candida parapsilosis*, *Chlamydia pneumoniae*, *Enterobacter cloacae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae*, *Pseudomonas aeruginosa*, other)

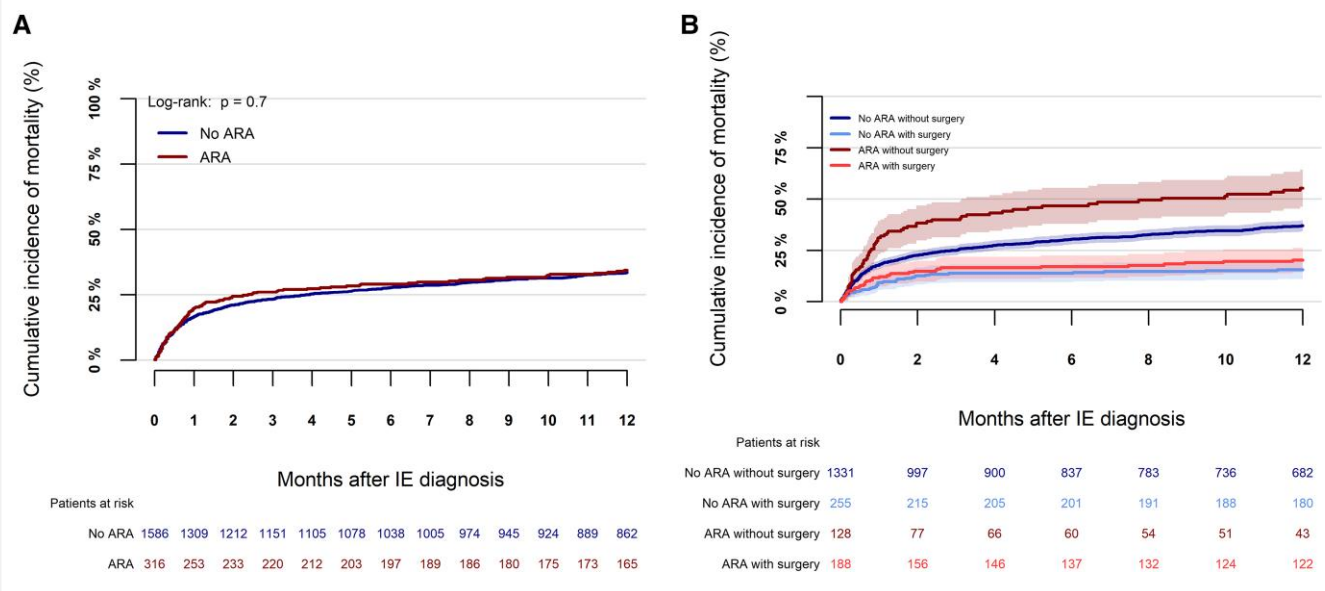


Figure 3 Kaplan–Meier curve for mortality within 1 year of diagnosis. (A) The Kaplan–Meier curve for mortality within 1 year of diagnosis. The x-axis shows months from diagnosis. The y-axis shows the cumulative incidence of mortality (%). Red, aortic root abscess; blue, no aortic root abscess. Log-rank = .67. The Kaplan–Meier curve for 1-year mortality for patients with aortic root abscess, with and without surgery, and patients without aortic root abscess, with and without surgery (B). Light red, aorta root abscess patients with surgery; dark red, aorta root abscess without surgery; light blue, no aorta root abscess with surgery; dark blue, no aorta root abscess without surgery. The x-axis shows 12 months from diagnosis. Log-rank <.001. ARA, aortic root abscess

Characteristics and differences in patients with and without aortic root abscess

This study highlights key differences in patients with aortic valve endocarditis complicated by ARA, including younger age, male sex, and presence of BAV. Prosthetic valve is a known risk factor for endocarditis^{5,11} and was in

this study found to be significantly more common in patients with ARA, consistent with previous studies.^{12,13} Patients with ARA were also younger, which aligns with other findings from our study, showing that these patients were more often self-reliant in activities of daily living and less often retired. Common pathogens in IE include staphylococci, streptococci, and enterococci, with *S. aureus* being the most common overall cause.¹

Table 3 Sub-analysis: characteristics of patients with aortic root abscess, with and without surgery

Variable (%)	Level	ARA and surgery (n = 188)	ARA and no surgery (n = 128)	Total (n = 316)	P-value	Missing
Aorta root abscess	Possible	89 (47.3)	96 (75.0)	185 (58.5)		
	Definite	99 (52.7)	32 (25.0)	131 (41.5)	<.001 ^a	—
Sex	Male	152 (80.9)	89 (69.5)	241 (76.3)	.02 ^a	—
Age (years)	median [25th,75th percentile]	66.8 [55.4, 73.4]	78.5 [71.4, 83.0]	71.5 [60.7, 78.6]	<.001 ^a	—
	<70 years	115 (61.2)	29 (22.6)	144 (45.6)	<.001 ^a	—
	70–80 years	65 (34.6)	48 (37.5)	113 (35.8)		
	>80 years	8 (4.3)	51 (39.8)	59 (18.7)		
Primary vegetation location	Prosthetic valve	92 (48.9)	66 (51.6)	158 (50.0)	.65	—
	Native valve	96 (51.1)	62 (48.4)	158 (50)		
DUKE criteria	Definite endocarditis	174 (92.6)	117 (91.4)	29 (92.1)	.71	—
	Possible endocarditis	14 (7.5)	11 (8.6)	25 (7.9)		
Prior endocarditis		14 (7.4)	6 (4.7)	20 (6.3)	.31	<1%
Known native valve heart disease		28 (14.9)	22 (17.2)	50 (15.8)	.60	<1%
Prior heart valve surgery	In total	93 (49.5)	66 (51.6)	159 (50.3)	.71	—
	Prior AV surgery ^b	93 (100.0)	66 (100.0)	159 (100.0)	1	—
Type of aorta surgery	Mechanical AV	32 (17.0)	14 (10.9)	46 (14.6)	.13	—
	Biological prosthetic valve	50 (26.6)	32 (25.0)	82 (26.0)	.75	
	TAVI	4 (2.1)	17 (13.3)	21 (6.7)	<.001 ^a	
	Freestyle AV	5 (2.7)	5 (3.9)	10 (3.2)	.53	
Congenital heart disease		31 (16.5)	3 (2.3)	34 (10.8)	<.001 ^a	—
Bicuspid aortic valve		31 (16.5)	<3		^a	—
Comorbidities						
Prior cancer		19 (10.1)	21 (16.4)	40 (12.7)	.098	—
Active cancer		5 (2.7)	15 (11.7)	20 (6.3)	.001 ^a	—
Prior stroke		16 (8.5)	27 (21.1)	43 (13.6)	.001 ^a	—
Prior known heart failure		17 (9.0)	29 (22.7)	46 (14.6)	<.001 ^a	—
Diabetes		46 (24.5)	29 (22.7)	75 (23.7)	.71	—
Liver disease		6 (3.2)	6 (4.7)	12 (3.8)	.49	—
Renal disease		18 (9.6)	25 (19.5)	43 (13.6)	.01 ^a	—
Chronic obstructive lung disease		15 (8.0)	19 (14.8)	34 (10.8)	.053	—
Cardiac implantable electrical devices		17 (9.0)	22 (17.2)	39 (12.3)	.03 ^a	—
Not self-reliant in daily activities of living		16 (8.5)	48 (37.5)	64 (20.5)	<.001	<2%
Retired		107 (56.9)	114 (89.1)	221 (69.9)	<.001	<2%
Dental procedures 3 months prior to admission		12 (6.4)	4 (3.1)	16 (5.1)	.16	<10%

^aSignificant result.^bOut of those with prior valve surgery.

ARA, aortic root abscess; AV, aortic valve; COPD, chronic obstructive lung disease; heart failure: LVEF <45%; LVEF, left ventricular ejection fraction; TAVI, transcatheter aortic valve implantation.

Staphylococcus aureus was also the most frequent single pathogen in patients with ARA in this study, but it was significantly more common in patients without ARA. Patients with ARA were more likely to present with *Streptococcus* spp., particularly *Streptococcus mitis*, which is a

common bacteria causing IE.¹⁴ Similar bacterial causes were found by Yang et al.¹² in a study of 336 patients, of whom 179 had root abscesses.

Upon admission, patients with ARA were significantly more likely to present with complications such as an embolism or AV-block of any

type, and they had worse findings on the diagnostic TEE, including larger vegetations and more severe aortic stenosis or regurgitation. Increased regurgitation could possibly be due to other paravalvular complications, such as leaflet perforation or erosion. In a study of 285 patients with definite ARA or no ARA, Mahmoud *et al.* did not find an increased risk of major complication, including mortality. However, they similarly reported that patients with ARA more often had bicuspid aortic valves, larger aortic vegetations, and paravalvular leakage.¹⁵ Although mortality was not adjusted for relevant risk factors, Yang *et al.*¹² also found more peri-operative complications in patients with ARA, particularly prolonged ventilation, transfusions, and intensive care stays.

Surgical treatment strategy

The 2023 ESC Guidelines point out that periannular complications are strong predictors of poor outcome in patients with IE.⁵ We found that ARA was associated with a higher mortality rate. This finding is consistent with broader literature on IE, surgical treatment, and studies specifically examining ARA, which report that having periannular complications confer increased risk of death.^{3,13,16} Similarly, Yang *et al.* found ARA to be a significant risk factor for all-cause mortality but found no difference in the cumulative incidence of long-term mortality between ARA and aortic IE patients.

The ESC Guidelines support this interpretation by emphasizing that complications such as abscesses warrant early surgical consideration—provided that the patient is a surgical candidate.⁵ Several prior studies have found that patients with IE who receive surgery during their admission have lower mortality compared with those managed medically,^{3,17} largely due to non-operated ARA patients being especially high risk. Our cumulative incidence curves show that surgically managed patients with ARA have a higher mortality than surgically managed patients without an ARA, but with considerable overlap in confidence intervals. This is also supported by ARA patients having more surgical complications and higher pre-operative ASA scores. Non-surgically managed patients have a high mortality, with patients with ARA having a higher mortality than those without ARA.

Early and clear diagnosis of ARA is therefore vital, as the recommended treatment for patients with ARA is surgery.⁵ In accordance with this, we found that significantly more patients with ARA underwent surgery compared with those without ARA (60% vs. 16%, P -value < .001). To investigate why 40% of patients with ARA did not undergo surgery, we performed a sub-analysis (Table 3). As expected, significantly higher proportions of non-surgically managed patients were classified as possible rather than definite ARA (76% vs. 48%, P -value < .001). Non-surgically managed patients with ARA were significantly older, had more comorbidities, and were more frail. Non-surgically managed patients with ARA were considered ineligible for surgery due to stroke or intracranial haemorrhage, heart failure, haemodynamic instability, patient refusal of surgery, or death before surgery. The most common contraindication to surgery was a poor pre-operative prognosis due to severely reduced functional status (74%). Thus, patient selection was strongly driven by pre-operative surgical risk, which largely explains the very high mortality among inoperable patients with ARA. In our sub-analysis of non-operated patients with and without ARA (Supplementary Table S3), we found minimal differences in age and comorbidity burden, although patients with ARA had more PVE.

In conclusion, the most vulnerable subgroup was non-surgically managed patients, especially those with ARA. Surgery was associated with lower mortality, but even with surgical treatment, mortality remained substantial in patients with ARA. However, it is important to consider that our sub-analysis suggests that when patients with ARA are not operated, it may also be because they often are inoperable due to poor prognosis, poor functional status, and a larger prior disease burden

(Table 3). Thus, our data support current ESC recommendations advocating for surgical consideration in treating operable patients with ARA.

Strengths and limitations

The nearly complete inclusion of all IE cases in the study period in Denmark, with minimal missing data, is a strength of this study. However, some limitations must be acknowledged. Records lacked information regarding loss-to-follow up beyond previously stated dates, new pacemaker implantation as part of treatment, coronary artery assessments and status, peri-operative risk scores and clinical frailty, long-term outcomes¹⁸, lifestyle factors, laboratory findings, findings during surgery, detailed findings on other imaging modalities, and systematic registration of other paravalvular complications. As with all observational studies, findings are vulnerable to selection bias and confounding by indication. Although multivariable Cox regression analysis was used to adjust for measured covariates, residual confounding may remain. The retrospective design limits causality inferences; we have instead identified associations and generated hypotheses.⁷ Long-term consequences of ARA remain insufficiently explored.

Conclusion

In this nationwide cohort of patients with aortic valve endocarditis, ARA identified a distinct, high-risk subgroup characterized by younger age, prosthetic or congenital valve disease, and more severe clinical presentation. Aortic root abscess was independently associated with higher mortality. Patients with ARA who underwent surgery were substantially younger and had a significantly lower comorbidity burden and lower mortality, which suggests a clinically relevant selection of patients. Early detection of ARAs is therefore key.

Supplementary data

Supplementary data are available at [European Heart Journal – Valvular and Structural Heart Disease](https://www.heart-journal.com/valvular-and-structural-heart-disease) online.

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Author Contributions

Thea Stybe (Data curation, Formal analysis, Methodology, Visualization, Writing—original draft, Writing—review & editing [lead]), Amna Alhakak (Data curation, Formal analysis, Methodology [supporting], Writing—review & editing [equal]), Peter Laursen Graversen (Methodology, Writing—review & editing [supporting], Validation [equal]), Katra Hadji-Turdeghal (Validation [equal], Writing—review & editing [supporting]), Niels Eske Bruun (Writing—review & editing [supporting]), Jacob Eifer Møller (Writing—review & editing [supporting]), Jeppe K. Petersen (Writing—review & editing [supporting]), Andreas Dalsgaard Jensen (Validation, Writing—review & editing [supporting]), Jonas A. Povlsen (Writing—review & editing [supporting]), Claus Ernst Moser (Writing—review & editing [supporting]), Morten Smerup (Writing—review & editing [supporting]), Hanne Sortsøe Jensen (Writing—review & editing [supporting]), Peter Godsk Jørgensen (Writing—review & editing [supporting]), Lauge Østergaard (Writing—review & editing [supporting]), Henning Bundgaard (Writing—review & editing [supporting]), Kasper Iversen (Writing—review & editing [supporting]), Lars Køber (Writing—review & editing [supporting]), Jesper James Linde (Conceptualization [supporting], Writing—review & editing [equal]), and Emil L. Fosbøl (Conceptualization, Project administration, Supervision [lead], Writing—review & editing [equal]).

Declarations

Disclosure of Interest

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Data Availability

The data underlying this article are accessible through using the National Danish Endocarditis Studies (NIDUS) registry but cannot be shared publicly due to restrictions imposed by the Danish data protection legislation.

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Ethical Approval

The study adheres to national ethical guidelines for registry-based research by the Danish National Committee on Health Research Ethics. Informed consent was waived, and data collection was approved by the Danish Data Protection Agency (P-2020-92).

Pre-registered Clinical Trial Number

None supplied.

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