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Long-Term Mortality in Different Age Groups of Patients with Infective Endocarditis Who Undergo Aortic Root Replacement: A Nationwide Study

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ABSTRACT

Background: Infective endocarditis (IE) with involvement of the aortic root is associated with high short-term mortality and morbidity. Long-term data are sparse, and the existing studies with long-term data are restricted by a low number of patients and do not report mortality risks of different age groups.

Objective: This study examined the all-cause mortality risk postoperatively of patients with first-time IE who underwent aortic root replacement (ARR), according to age at the time of surgery, with one and 10 years follow-up.

Methods: Patients with first-time IE who underwent ARR surgery from 2000-2016 were identified in Danish nationwide administrative registries and divided into age groups: ≤60, 61-74, and ≥75 years. We compared one- and 10-year mortality risk using multivariable Cox regression across the three age groups.

Results: We identified 258 patients who underwent ARR (26.0% female, 42.6% with prosthetic valves, median age 64 years (IQR 55-73), of whom 98, 112, and 48 patients were ≤60 years, 61-74 years, and >75 years, respectively. The corresponding in-hospital mortality risk was 10.2%, 22.3%, and 29.2% (P = .01), respectively. The one-year postoperative mortality risk was 17.3%, 28.6%, and 33.3% (P = 0.05), while at 10 years after surgery, it was 31.8%, 62.9%, and 77.1% (P < 0.01), respectively. The adjusted 10-year hazard ratio was higher in the 61-74 and >75-year age groups (HR 1.94 [1.18-3.16] and 2.46 [1.35-4.49]) compared with the ≤60.

Conclusion: Aortic root replacement in patients with first-time IE was associated with a high in-hospital and one- and 10-year mortality with worse outcomes with age.

INTRODUCTION

Infective endocarditis (IE) with involvement of the aortic root (root abscess or aortic prosthetic valve endocarditis) is associated with high short-term mortality and morbidity [Jassar 2012; Musci 2010; Olmos 2017]. A root abscess can be defined as an infection that has penetrated the valvular annulus, without communication with the cardiovascular lumen, and caused a necrotic area containing purulent material. Studies have indicated that the incidence of periannular abscesses is 28-40% in patients with IE [Arnett 1976, Graupner 2002; Olmos 2017; Ramos 2019] with the aortic valve having a higher predisposition than the mitral valve [Graupner 2002; Ramos 2019]. Patients with prosthetic valve endocarditis also have a higher incidence of abscesses than patients with native valve IE [Anguera 2006; Graupner 2002; Musci 2010; Ramos 2019]. Guidelines on the management of IE recommend surgery in patients with aortic root involvement (class B recommendation) [Pettersson 2017], but the surgical technique is challenging, and the perioperative risk is high [Jassar 2012; Musci 2010]. Contraindications for surgery are relative and an individual evaluation of the patient

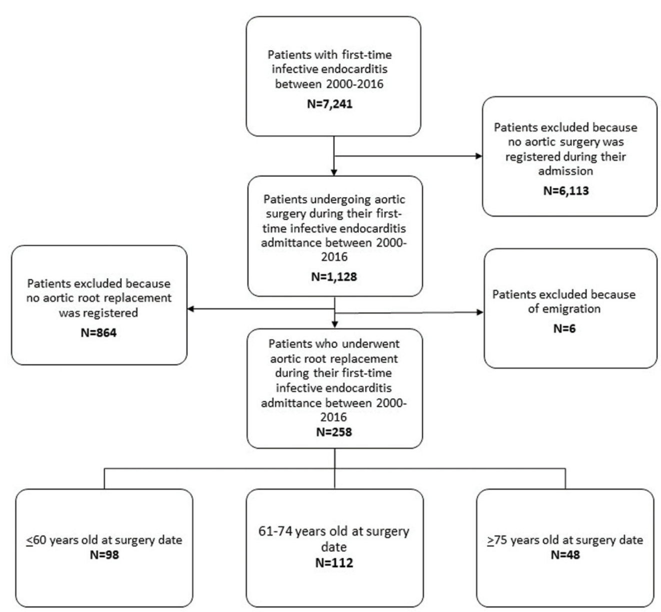

Figure 1. Patient selection and the different age groups.

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Table 1. The selected baseline characteristics of the full cohort divided by age groups (<60 years, 61-74 years, and ≥ 75 years)

	All, N (%)	<60 years, N (%)	61-74 years, N (%)	≥75 years, N (%)	*P*-value
All	258 (100.0)	98 (100.0)	112 (100.0)	48 (100.0)	
Median age (IQR) (years)	64 (55-73)	50 (39-57)	67 (64-71)	79 (76-80)	
Female	67 (26.0)	18 (18.4)	31 (27.7)	18 (37.5)	.040
History					
Aortic stenosis	126 (48.8)	29 (29.6)	59 (52.7)	38 (79.2)	<.001
Prosthetic aortic valve	110 (42.6)	26 (26.5)	50 (44.6)	34 (70.8)	<.001
CIED*	15 (5.8)	4 (4.1)	7 (6.3)	4 (8.3)	.568
Atrial fibrillation	49 (19.0)	7 (7.1)	29 (25.9)	13 (27.1)	.001
Diabetes	28 (10.9)	5 (5.1)	15 (13.4)	8 (16.7)	.056
Hypertension	112 (43.4)	29 (29.6)	58 (51.8)	25 (52.1)	.002
IHD*	73 (28.3)	17 (17.3)	37 (33.0)	19 (39.6)	.007
CHF*	44 (17.1)	14 (14.3)	19 (17.0)	11 (22.9)	.428
AMI*	22 (8.5)	8 (8.2)	9 (8.0)	5 (10.4)	.873
Stroke	18 (7.0)	6 (6.1)	7 (6.3)	5 (10.4)	.584
Chronic renal failure	19 (7.4)	7 (7.1)	11 (9.8)	<4 (<8.3)	.228
Cancer	28 (10.9)	5 (5.1)	19 (17.0)	4 (8.3)	.018
COLD*	20 (7.8)	6 (6.1)	8 (7.1)	6 (12.5)	.380
Concomitant medical treatment					
Lipid-lowering medication	87 (33.7)	20 (20.4)	46 (41.1)	21 (43.8)	.002
Beta blockers	80 (31.0)	20 (20.4)	42 (37.5)	18 (37.5)	.016
ACE inhibitors	59 (22.9)	21 (21.4)	27 (24.1)	14 (29.2)	.589
Antithrombotic	150 (58.1)	41 (41.8)	73 (65.2)	36 (75.0)	<.001

*CIED, cardiac implantable electronic device; IHD, ischemic heart disease; CHF, congestive heart failure; AMI, acute myocardial infarct; COLD, chronic obstructive lung disease

in question is important, why no age limit is present in recent guidelines [Pettersson 2017]. Age consistently has been associated with an increased risk of early and late death in studies of cardiac surgery in general, and of aortic valve surgery in patients with IE specifically [Fayad 2011; Lund 1999; Martínez-Sellés 2014; McGiffin 1992; Nashef 2012; Olmos 2017]. However, long-term data are sparse, and the existing studies with long-term data are restricted by a low number of patients and do not report mortality risk of different age groups [Jassar 2012; Knosalla 2000; Müller 2003; Nguyen 2010]. Jassar et al. found that the overall perioperative mortality was 22% and the 5-year mortality was 41% among 134 patients with a mean age of 58.3 years who underwent aortic root replacement (ARR) for complex active endocarditis. Hence, better long-term data on mortality according to age after ARR are needed to optimize selection for surgery.

In order to better inform the selection of patients for surgery, we examined the one- and 10-year risks of mortality, overall and according to age, in patients with first-time IE, treated with ARR.

METHODS

Data sources

The unique and permanent civil registration number of all Danish residents was used to link data from the following registries on an individual level. We used Danish nationwide administrative registries to identify the patients in our study. In the Danish National Patient Registry, all admittances to Danish hospitals since 1978 are registered with diagnoses coded according to the International Classification of Diseases (ICD) 8 until the end of 1993 and ICD-10 from thereafter [Schmidt 2015]. All prescriptions dispensed in Danish pharmacies since 1995 are coded according to the Anatomical Therapeutic Chemical Classification System and recorded in the National Prescription Registry along with the date of purchase and the amount of drug dispensed [Wallach 2011]. All registries previously have been described in detail [Ostergaard 2018; Rasmussen 2016; Wallach 2011].

We obtained information on sex, date of birth, and date of emigration for every patient in The Civil Registry. The date of death was obtained through the Registry of Causes

Supplementary Table 1. The Eastern Danish cohort divided by age groups (<60 years, 61-74 years, and ≥ 75 years)

	All, N (%)	<60 years, N (%)	61-74 years, N (%)	≥75 years, N (%)	*P*-value
All	156 (100.0)	61 (100.0)	70 (100.0)	25 (100.0)	
Female	34 (21.8)	10 (16.4)	17 (24.3)	7 (28.0)	.39
Two valves*	44 (28.2)	17 (27.9)	24 (34.3)	<4 (<16.0)	.10
CABG*	23 (14.7)	7 (11.5)	10 (14.3)	6 (24.0)	.33
Reoperation due to bleeding	14 (9.4)	5 (8.2)	6 (8.6)	<4 (<16.0)	.88
POAF*	27 (17.3)	7 (11.5)	12 (17.1)	8 (32.0)	.08
Stentless xenograft*	91 (59.5)	33 (54.1)	42 (60.0)	16 (64.0)	.65
Homograft	32 (20.9)	15 (24.6)	13 (18.6)	4 (16.0)	.49
Acute operation*	55 (35.5)	19 (31.1)	31 (44.3)	5 (20.0)	.06
Median time of aortic clamp (IQR) (min)	127.5 (99.0-162.5)	123.0 (96.0-167.0)	132.0 (99.5-157.5)	118.0 (107.0-168.0)	.39

*Two valves were inserted during surgery; CABG, coronary artery bypass grafting; POAF, postoperative atrial fibrillation; Stentless xenograft, the grafts registered as such, were all FreestyleTM bioprostheses; Acute operation, <24 hours from admission until surgery.

of Death. Since 1970, any death among Danish citizens dying in Denmark has been registered in this database [Helweg-Larsen 2011].

The East Denmark Heart Registry is a prospectively collected database where all cardiac surgery performed at the Copenhagen University Hospital, Rigshospitalet is registered and contains detailed clinical and procedural data, including e.g. type of procedure(s), type of prosthetic valve(s), length of extracorporeal circulation, and common complications to heart surgery at the time of surgery and post-surgery [Özcan 2016]. It is mandatory that the above-mentioned information on cardiac surgery is registered and done so by a clinician. The surgery type is classified, according to Nordic Medico-Statistical Committee Classification of Surgical Procedures. The database was instated in 2000, and the catchment population is approximately half of Denmark corresponding to about 2.3 million people.

The detailed information on cardiac surgery was not available for Western Denmark, why detailed surgery data only is described for the 156 patients in our cohort who underwent surgery at the Copenhagen University Hospital, Rigshospitalet.

Study population

In this study, we included cases of first-time IE (2000-2016), who underwent ARR within the timespan of the admittance. Patients with a diagnosis of IE (ICD-10: I33, I38, I398, or ICD-8: 421) and a minimum of 14 days of admittance or patients with a diagnosis of IE who died within the first 14 days were included. This method of inclusion has been validated with a positive predictive value of 90% [Ostergaard 2018]. If the patient was discharged from a hospital and admitted to another within 24 hours, it was registered as being one coherent hospitalization.

The study population was divided, according to age into three groups (≤60, 61-74, ≥75 years), as previously done [Østergaard 2020]. Figure 1 describes the selection and exclusion of patients.

Covariates

By cross-linking Danish nationwide registries, comorbidities, shown in Table 1, were linked to the patients through their civil registration number if the ICD-10 or -8 code was registered as a primary or secondary diagnosis and was registered before dating of admission. Patients, who had a prosthetic aortic valve implantation surgery registered in the Danish National Patient Registry prior to the time of admittance, were listed as having a prosthetic aortic valve. The surgical procedure codes used for this purpose is listed in Table 3 supplementary.

Prescriptions redeemed within six months up to the date of the surgery were assigned to each patient using the National Prescription Registry. Patient characteristics were identified by cross-linking the above-mentioned databases.

Of the 258 patients, 156 of the patients underwent surgery at hospitals in Eastern Denmark. These patients have been included in the Eastern Danish Heart registry and more detailed data were available. Table 1 supplementary shows characteristics of the Eastern Danish Heart Registry.

Follow-up and outcome: The patients were followed from the date of surgery until December 31, 2018, until death, emigration, or 10 years after surgery, whichever came first. The outcome of this study was all-cause mortality, which was obtained from the Registry of Causes of Death. There was no loss to follow up.

Statistics

Differences in baseline and procedural characteristics between the three age groups were tested by applying the chi-squared test for categorical variables and the Kruskal-Wallis test for continuous variables. In-hospital mortality risk was estimated using a one-sample t-test,

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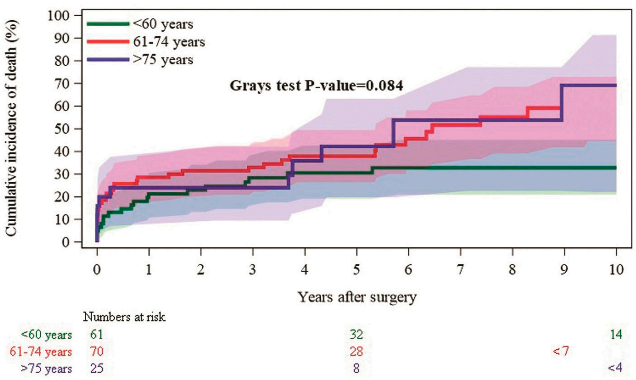

Figure 1 supplementary. Ten-year mortality of the Eastern Danish cohort divided by age groups (<60 years, 61-74 years, and ≥ 75 years). The confidence limit is set at 95%.

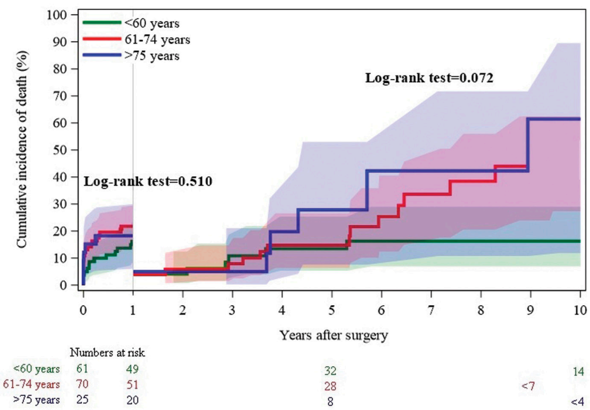

Figure 2 supplementary. The landmark analysis for the Eastern Danish cohort divided by age groups (<60 years, 61-74 years, and ≥ 75 years).

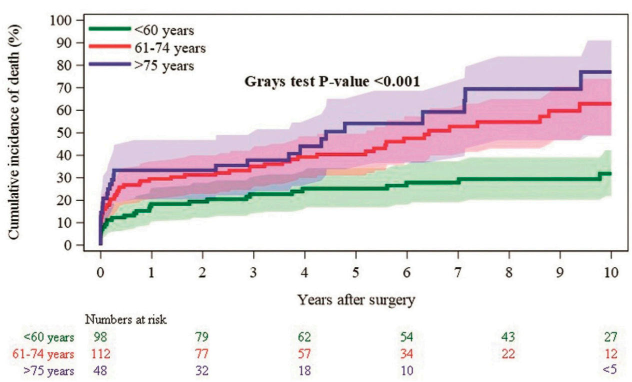

Figure 2. Ten-year cumulative mortality of the total cohort divided by age groups (≤60 years, 61-74 years, and ≥75 years). The confidence limit is set at 95%.

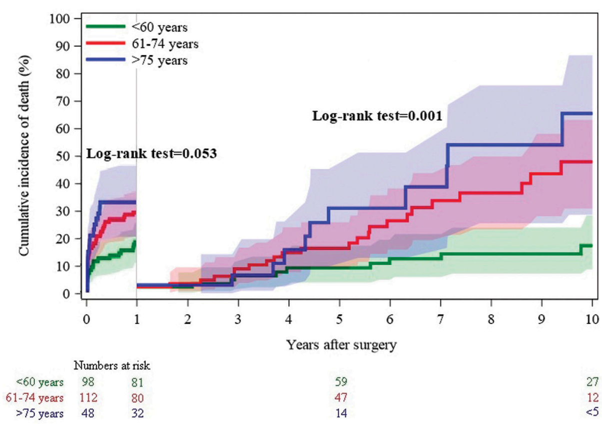

Figure 3. The landmark analysis for the total cohort divided by age groups (≤60 years, 61-74 years, and ≥ 75 years).

while differences between the groups were estimated using a chi-squared test. The absolute one- and 10-year risks of mortality were estimated using the Kaplan-Meier method, and log-rank tests were used to estimate the difference between the three age groups. To differentiate the mortality at one year from the mortality the following 9 years, landmark analyses were completed with the landmark time set at one-year post-surgery. Multivariable Cox regression analyses were used to estimate one- and 10-year hazard ratios for all-cause mortality as well as for the landmark analysis divided into age groups, with the ≤60 years-group as reference and hazard ratios for all-cause mortality for patients with a previously implanted aortic valve prosthesis at the time of admittance compared to patients with a native aortic valve as reference. A two-sided $P < .05$ was considered statistically significant. All analyses were performed with SAS statistical software version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

A total of 258 patients were included in the study. A flowchart of patient selection is shown in Figure 1.

Short-term mortality: In-hospital mortality risk was significantly higher with age. The in-hospital mortality risk was 10.2% (95% CI 5.0-18.0%), 22.3% (15.0-31.2%) and 29.2% (17.0-44.1%) (P = .01) for the three age groups, from youngest to oldest. The adjusted HRs of all-cause in-hospital mortality were 2.21 (1.02-4.8) and 2.88 (1.20-6.95) for the two older groups compared with the ≤60 years.

The mortality risks at one year postoperatively were 17.3% (95% CI 10.6-25.5%) for the patients ≤60 years, 28.6% (20.5-37.1%) for the 61-74 year-old patients, and 33.3% (20.4-46.8%) for the patient >75 years. The adjusted and unadjusted HRs of all-cause mortality, presented in Table 2, show a non-significant trend of higher mortality risks with age at one year after surgery. Only the unadjusted HR for the oldest patients compared with the youngest group was significantly above 1.

Table 2. Hazard ratios of all-cause mortality for the total cohort at 1 year and 10 years post-surgery as well as the hazard ratios estimated using the landmark analysis. The <60 years age group is used as the reference (hazard ratio = 1.0).

	No. (%)	Unadjusted (95% CI)	Adjusted* (95% CI)	Adjusted† (95% CI)
1 year post-surgery				
≤60 years	17 (17.35)	Ref	Ref	Ref
61-74 years	32 (28.57)	1.78 (0.99-3.22)	1.79 (0.98-3.28)	1.67 (0.89-3.14)
≥75 years	16 (33.33)	2.16 (1.09-4.29)	2.10 (0.98-4.46)	2.09 (0.99-4.42)
10 years post-surgery				
≤60 years	28 (28.57)	Ref	Ref	Ref
61-74 years	56 (50.00)	2.24 (1.42-3.54)	2.07 (1.29-3.32)	1.94 (1.18-3.16)
≥75 years	27 (56.25)	2.82 (1.65-4.80)	2.41 (1.32-4.37)	2.46 (1.35-4.49)
Landmark analysis				
1-10 years post-surgery				
≤60 years	11 (13.58)	Ref	Ref	Ref
61-74 years	24 (30.00)	3.02 (1.47-6.20)	2.48 (1.17-5.26)	2.44 (1.10-5.41)
≥75 years	11 (34.38)	4.07 (1.75-9.47)	3.02 (1.13-8.05)	3.29 (1.21-8.96)

*Adjusted for sex, PVE, aortic stenosis and diabetes. †Adjusted for sex, PVE, aortic stenosis, diabetes, ischemic heart disease, stroke, atrial fibrillation, chronic obstructive lung disease and cancer

Long-term mortality: As presented in Figure 2, the cumulative incidence of death was significantly higher with age ($P < .001$). At 10 years postoperatively, the mortality was 31.8% (21.8-42.2%), 62.9% (49.0-73.9%), and 77.1% (48.5-91.0%), respectively. Compared with patients ≤60 years, both patients aged 61-74 years and ≥75 years had significantly higher 10-year mortality risks (HR 2.24 (95% CI 1.42-3.54) and 2.82 (1.65-4.80), respectively).

The crude mortality risk of the landmark analysis (from year 1 to 10) is shown in Figure 3. The short-term risk up until the first year showed a non-significant trend of higher mortality risk with age. Among the patients who survived to one year, the mortality risk was significantly higher with age ($P < .001$).

Subgroups: The mortality was higher in the group of patients with a previously implanted aortic valve prosthesis at both one and 10 years post-surgery compared with patients with a native valve, with the mortality being 28.2% against 23.0% at one year and 45.5% versus 41.2% at 10 years post-surgery. Adjusted HR of all-cause mortality was calculated at both one and 10 years post-surgery for patients with a previously implanted aortic valve prosthesis with patients having a native aortic valve as reference. The HR showed no significant difference between the two patient groups at one or 10 years after surgery, with the adjusted HR being 0.62 (95% CI 0.37-1.02) and 0.76 (0.40-1.45), respectively.

The supplementary Table 1 shows more detailed characteristics and procedures for the Eastern Danish cohort.

The median time of extracorporeal circulation was 127.5 minutes and 28.2% had multiple valves replaced during surgery. There were no significant differences between the three age groups, though there were non-significant trends showing the oldest age group having the lowest frequency of acute surgeries and surgeries where multiple valves were replaced while having the highest percentage of patients developing postoperative atrial fibrillation. The majority (59.5%) had a stentless xenograft implanted, while homografts were used in 20.9% of the patients.

The supplementary Table 2 shows HRs of all-cause mortality for the Eastern Danish cohort per age group.

All HRs of all-cause mortality was higher at all time points, but no adjusted HRs were significantly higher than the reference.

There was a non-significant trend of higher mortality for the two older age groups compared with the youngest at 10 years after surgery, Figure 1 supplementary, and among the patients surviving the first year after surgery, Figure 2 supplementary.

No difference in risk of mortality at one year after surgery was found in the Eastern Danish cohort. This is shown in Figure 2 supplementary.

DISCUSSION

In this nationwide cohort study, we examined patients with first-time IE who underwent aortic root and valve replacement and compared characteristics and mortality by age. Our study yielded three main findings. First, we found that one-year post-surgery mortality risks were for the three age groups from youngest to oldest 17.3%, 28.6%, and 33.3%, respectively. Second, there was no statistically significant difference in one-year mortality risk, according to

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Supplementary Table 2. Hazard ratios of all-cause mortality for the Eastern Danish cohort at 1 year and 10 years post-surgery, as well as the hazard ratios estimated using the landmark analysis. The <60 years age group is used as the reference (hazard ratio = 1.0).

	No. (%)	Unadjusted (95% CI)	Adjusted* (95% CI)	Adjusted† (95% CI)
1 year post-surgery				
≤60 years	12 (19.7)	Ref	Ref	Ref
61-74 years	19 (27.1)	1.50 (0.73-3.08)	1.56 (0.74-3.28)	1.47 (0.66-3.28)
≥75 years	5 (20)	1.07 (0.38-3.04)	1.20 (0.38-3.80)	1.69 (0.51-5.66)
10 years post-surgery				
≤60 years	19 (31.2)	Ref	Ref	Ref
61-74 years	34 (48.6)	1.86 (1.06-3.28)	1.80 (1.00-3.24)	1.68 (0.90-3.13)
≥75 years	11 (44.0)	1.68 (0.80-3.54)	1.81 (0.76-4.29)	1.99 (0.82-4.87)
Landmark analysis				
1-10 years post-surgery				
≤60 years	7 (14.3)	Ref	Ref	Ref
61-74 years	15 (29.4)	2.54 (1.03-6.27)	2.10 (0.79-5.54)	2.34 (0.85-6.42)
≥75 years	6 (30.0)	2.92 (0.97-8.79)	3.43 (0.85-13.91)	3.44 (0.76-15.58)

*Adjusted for sex, PVE, aortic stenosis and diabetes. †Adjusted for sex, PVE, aortic stenosis, diabetes, ischemic heart disease, stroke, atrial fibrillation, chronic obstructive lung disease and cancer

the age when adjusted for comorbidities. Third, the mortality risk, as well as the adjusted HRs, at 10 years post-surgery was significantly higher with age, with the ≥75 years group having a 10-year survival of 22.9%, the lowest of the groups.

It has been concluded in several studies that age is an independent risk factor for mortality in IE patients undergoing valve surgery [Fayad 2011; Lund 1999; Martínez-Sellés 2014; McGiffin 1992; Olmos 2017; Toumpoulis 2005]. Our population had a median age of 64 years at the time of surgery, which is higher than that of most studies on surgery on IE patients [Jassar 2012; Knosalla 2000; Müller 2003; Musci 2010; Nguyen 2010], but similar to that of Olmos et al. [Olmos 2017]. In the Danish guidelines for surgery in cases of patients with IE, age above 80 is considered especially high risk [Moser 2020], though there is no specific age limit.

Nashef et al found age to be a significant predictor of mortality for patients >60 years of age [Nashef 2012]. We found that higher age was associated with a higher HR of all-cause mortality at 10 years and a non-significant trend at 1-year post-surgery. The reason for the lack of significant difference in HR between the age groups at 1-year post-surgery in our cohort could be a strict selection of patients eligible for surgery, which could result in a high number of comorbid older patients being rejected.

Toumpoulis et al found that patients over 75 years of age, who underwent heart valve surgery and were discharged alive, had a survival rate of less than 25% at 2 years post-discharge. The survival rate was more than 55% for patients aged 58 to 68 and more than 75% for patients aged 58 or younger, 2 years post-discharge [Toumpoulis 2005]. The ≥75 years group in our cohort has a substantially higher survival rate compared with the same age group in the study by Toumpoulis et al, despite that their cohort of 1105 patients contained only 3.9% IE-patients.

Chen et al performed a meta-analysis on the outcome of surgical intervention for aortic root abscess, including seven retrospective observational studies with a total of 781 episodes of IE complicated by an aortic root abscess. The mean age ranged from 37±13 to 62±15 years, which is lower than our median age. The analysis estimated a one- and 10-year mortality risk of 28% and 36% [Chen 2018], respectively. These mortality risks were higher than in our youngest group both at one and 10 years, but lower compared with our 61-74 group at 10 years and similar at one year after surgery. Thus, results must be considered similar, especially since Chen et al suggest that missing data could have led to an underestimation of the long-term mortality rates [Chen 2018].

In the present study, patients with a previously implanted prosthetic aortic valve constituted 42.6% of the patients of the entire cohort, while this was the case for 70.8% of the patients in the oldest age group. We found no significant difference in HR for all-cause mortality between the patients with a previously implanted prosthetic aortic valve compared to patients with native valves at any time points after surgery. PVE has been associated with worse outcomes than NVE in prior studies [David 2007; Musci 2010]. The cohort of 221 IE patients, who underwent ARR with a homograft in Musci et al, had a 1-, 5- and 10-year mortality rate that was significantly higher in the PVE-group compared to the NVE-group (P = .03) [Musci 2010]. Having PVE also means that an ARR would be at least a second surgery, which will increase perioperative and postoperative risk of complications and unfavorable outcomes [Di Marco

Supplementary Table 3. How the comorbidities have been defined

Category	Type	Codes
Study population		
IE	ICD-10	I33.x, I38.x or I39.8
	ICD-8	421
Surgery		
Aortic root replacement	NOMESCO	KFMD20, KFMD30, KFMD33, KFMD40, KFCA60, KFCA70
Previously implanted aortic valve	NOMESCO	KFMD00, KFMD10, KFMD20, KFMD30, KFMD33, KFMD40, KFMD96, KFCA60, KFCA70
CIED1	Danish procedure codes for medical examinations	BFCA0, BFCB0
Comorbidities		
Aortic stenosis	ICD-10	I350
	ICD-8	395, 396
Atrial fibrillation	ICD-10	I48
	ICD-8	42793, 42794
Diabetes	ICD-10	E10.x to E14.x
	ICD-8	250
	ICD-8	425, 428
Hypertension2	ATC	C02A, C02B, C02C, C02DA, C02DB, C02DD, C02DG, C02L, C03A-B, C03D-E, C03X, C07A-D, C07F, C08 C08G, C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52
IHD3	ICD-10	I20-I25
	ICD-8	410-414
CHF4	ICD-10	I11.0, I13.0, I13.2, I42.x, I50.x
	J81.9	
	ICD-8	425, 428
AMI5	ICD-10	I21.x, I22.x
	ICD-8	410
Stroke	ICD-10	I63, I64
	ICD-8	430-434, 436
Chronic renal failure	ICD-10	N02-N08, N11, N12, N14, N18, N19, N26, N158-N160, N162-N164, N168, Q612, Q613, Q615, Q619, E102, E112, E132, E142, T120, M300, M313, M319, M321B, T858, T859, Z992
	ICD-8	403, 404, 581-584, 25002, 40039, 59009, 59320, 75310, 75311, 75319
Malignancy	ICD-10	C00 to C97
	ICD-8	140 to 209
Chronic obstructive lung disease	ICD-10	J42, J43, J44
	ICD-8	490, 491, 492
Medicine		
Lipid lowering medication	ATC	C10
Beta blockers	ATC	C07
ACE inhibitors6	ATC	C09A
Antithrombotics	ATC	B01

ICD-, procedure and ATC-codes. 1CIED, cardiac implantable electronic device; 2Hypertension, if the patient had >2 antihypertensive medicinal products prescribed the patient was registered to have hypertension; 3IHD, ischemic heart disease; 4CHF, congestive heart failure; 5AMI, acute myocardial infarction; 6ACE inhibitors, angiotensin-converting enzyme inhibitor. IE, infective endocarditis, ATC, anatomical therapeutic chemical classification system; ICD, international classification of diseases; NOMESCO, The Nordic Medico-Statistical Committee

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2016]. However, the preoperative component probably does not entirely cover the increased risk seen in PVE patients compared to NVE patients. For example, patients with PVE more often had abscess formation with severe aortic root destruction, leading to a higher rate of aortic-ventricular dehiscence than the patients with NVE, 69.7% versus 35.4%, respectively [Musci 2010]. Our cohort is selected by the surgery and not by the extent of the infection, which could mean that NVE patients in our cohort have more extensive endocarditis than the PVE patients. PVE often results in an ARR because the sewing ring is involved, while ARR only is selected for NVE in the case of invasive disease and destruction of the annulus [Pettersson 2017]. This could be a pivotal factor in the comparison of NVE patients and patients with a previously implanted prosthetic valve in our cohort, possibly explaining the lack of a difference in the outcome. If abscess formation is more insidious in the PVE patient, David TE et al could not statistically confirm the difference; they found the 5- and 10-year mortality to be 26% and 38% for NVE and 32% and 48% for PVE, respectively, after surgery for a paravalvular abscess (P = .41) [David 2007].

Study strengths and limitations: The main strength of the study is the nationwide, complete data. The Danish health care system is funded by taxes and all residents do in theory have equal access to the services provided. The registration of patients with IE has been validated in the Danish registries with a positive predictive value of 90% [Ostergaard 2018]. However, our study has several limitations that need to be acknowledged. The main limitation is that we do not have detailed knowledge of what the indication was for choosing surgery for each patient, which means the individual severity of IE is not described for the patients. We did not have any data on those patients with an aortic root abscess and IE who did not undergo surgery. Our results are dependent on the quality of notification and coding done by the physicians at the hospital, which may vary in quality. The universal health care system and the socioeconomic status in Denmark may limit the generalizability of the study.

CONCLUSION

Of patients with first time IE who underwent aortic root replacement during the IE disease course, about one-tenth of patients <60 years, one-fifth of 61-74 years, and one-third of patients > 75 years died in hospital while at 10 years postoperatively one-third, three-fifths, and three-quarters had died, respectively.

As expected, higher age was associated with higher mortality rates, both early and late. This study presents the mortality rates for the three defined age groups at three postoperative time points, which could be used as a prognostic tool for first-time IE patients undergoing ARR.

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