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ORIGINAL RESEARCH

Lifetime Burden of Morbidity in Patients With Isolated Congenital Ventricular Septal Defect

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BACKGROUND: The lifetime burden of morbidity in patients with isolated congenital ventricular septal defect (VSD) is not completely described.

METHODS AND RESULTS: In a population-based cohort study in Denmark using nationwide medical registries, we included 8006 patients diagnosed with a congenital VSD before 2018 along with 79 568 randomly selected controls from the general Danish population matched by birth year and sex. Concomitant congenital cardiac malformations and chromosomal abnormalities were excluded. Cox proportional hazard regression, Fine and Gray competing risk regression, and Kaplan-Meier survival function were used to estimate burden of morbidity, compared with matched controls. Median follow-up was 23 years (interquartile range, 11–37 years). The hazard ratio (HR) of heart failure was high in both patients with unrepaired and surgically closed VSD when compared with their corresponding matched controls (5.4 [95% CI, 4.6–6.3] and 30.5 [95% CI, 21.8–42.7], respectively). Truncated analyses with time from birth until 1 year after VSD diagnosis (unrepaired) or surgery (surgically closed) censored revealed reduced but persisting late hazard of heart failure. Similarly, the late hazard of arrhythmias and pulmonary arterial hypertension was high irrespective of defect closure. The HR of endocarditis was 28.0 (95% CI, 19.2–40.9) in patients with unrepaired defect and 82.7 (95% CI, 37.5–183.2) in patients with surgically closed defect. The increased HR diminished after VSD surgery. In general, the incidence of morbidity among patients with unrepaired VSD accelerated after the age of 40 years.

CONCLUSIONS: Patients with isolated congenital VSD carry a substantial burden of cardiovascular morbidity throughout life, irrespective of defect closure.

Key Words: congenital heart disease ■ long-term outcome ■ morbidity ■ nationwide ■ population based ■ ventricular septal defect

The most common congenital heart disease, the ventricular septal defect (VSD), is most often diagnosed, and treated when indicated, within the first years of life. VSD is often classified as a "simple" lesion and, for decades, the assumption has been that it is associated with few, if any, long-term risks if treated correctly in childhood. However, in recent years, new evidence suggests that this assumption may be flawed. Clinical follow-up studies on patients with VSD with either a surgically closed or an unrepaired defect have reported a nonnegligible incidence of ventricular dysfunction,[1–6] a greater than anticipated incidence of infective endocarditis,[1,3,5,7–9] pulmonary arterial hypertension,[10–12] and arrhythmias.[1,2,4–6] The latest guidelines for managing patients with congenital VSD have therefore changed, now recommending routine follow-up of both symptomatic and asymptomatic patients.[13,14] Most recently, we demonstrated reduced survival in patients with operated and unoperated VSD,[15] and this suggests there may also be a significant burden of morbidity. In this population-based cohort study, we aimed to investigate the burden of morbidity in patients

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CLINICAL PERSPECTIVE

What Is New?

- Patients with isolated congenital ventricular septal defect (VSD) revealed a hitherto uncontemplated burden of cardiovascular morbidity.
- The incidence of cardiovascular morbidity was substantially higher in patients with isolated congenital VSD, irrespective of defect closure, compared with the general Danish population, and accelerated after the fourth decade of life.
- Compared with the general Danish population, the hazard ratio of arrhythmia, heart failure, infectious endocarditis, and pulmonary arterial hypertension in patients with VSD, whether closed or not, was higher than anticipated and persisted even when time from birth until 1 year after VSD diagnosis or surgery was censored, except for infectious endocarditis, which diminished after surgery.

What Are the Clinical Implications?

- The longer-term outcome for patients with isolated congenital VSD is not without complications.
- Patients with unrepaired VSD need to be followed up regularly after their fourth decade of life, whereas those with surgically closed VSD probably benefit from regular follow-up in specialized adult congenital heart disease clinics throughout life.
- Understanding the increased burden of morbidity and potentially modifying the lifetime risk for patients with VSD requires both diligent longitudinal follow-up and focused research in the future.

Nonstandard Abbreviations and Acronyms

DNPR Danish National Patient Registry

with VSD, compared with the general Danish population, using nationwide medical registries.

METHODS

Ethical Approval

The study was approved by The Danish Data Protection Agency (no. 1-16-02-184-19). Informed consent from included patients and controls was not required as the delivered data were made anonymous by replacing the personal identification number with a randomly selected code by Denmark Statistics. The data underlying this article cannot be shared publicly in accordance with the directive from the central authority of Statistics Denmark.

Study Population and Design

This is an epidemiological study based on data from nationwide medical registries in Denmark. Denmark, with a population of ≈5.8 million, has government-funded universal health care that is free of charge and equally accessible for all citizens. This accounts for all categories of health care, including all medical care for patients with congenital heart disease. Up until 2016, surgical and transcatheter treatment of patients with congenital heart disease was performed in 2 of 5 public university hospitals with highly specialized cardiac teams, as no private hospitals are allowed to manage these patients. Since 2016, surgical and transcatheter treatments for congenital heart disease have been centralized to Copenhagen University Hospital. Data from hospital care are collected in nationwide medical registries linked to a unique personal identification number provided for all citizens since 1968. Every inpatient and outpatient hospital contact is registered with the personal identification number, generating individual-level linkage of extensive networks of longitudinal population-based registries covering the entire nation.

Data were obtained from the Danish Civil Registration System[16] and the Danish National Patient Registry (DNPR).[17] From the Danish Civil Registration System, we extracted data on date of birth, sex, and date of death.[16] From the DNPR, we extracted morbidity data using *International Classification of Diseases Eighth* and *Tenth Revision* (*ICD-8; ICD-10*) diagnoses, covering both inpatient and outpatient diagnoses, date of admission and discharge, as well as surgical procedures.[17] The Danish Civil Registration System was established in 1968, and the DNPR was established in 1977, with data updated every year as it is mandatory for all public and private hospitals to provide data to the register.[17] Patients (n=6) and controls (n=2) who died before 1968 were excluded as dates of death were missing. Data from the hospitals are reviewed by the DNPR for missing codes, wrong digits, and inaccuracies in personal identification numbers, and corrected if necessary.

The cohort of patients with VSD was identified using *ICD-8* (code 746.39) and *ICD-10* (code DQ21.0) in the DNPR (from 1977 to 2018). This cohort was supplemented by patients with VSD (n=593) identified before the introduction of the DNPR (before 1977) and described elsewhere.[18] Patients with coexisting congenital cardiac malformation or chromosomal abnormalities were excluded. All patients diagnosed with an acute myocardial infarction in *ICD-8* or *ICD-10* before their VSD diagnosis were excluded to prevent including misclassified individuals with post-infarction VSD. The cohort of patients with surgically closed defects was defined as patients with VSD

who at any given time had received defect closure by suture, patch, or transcatheter closure. *ICD* codes used to identify intervention are outlined in Table S1.

To compare risk of morbidity in the population with VSD with the general Danish population, the Danish Civil Registration System was used to identify 10 controls per patient, matched by year of birth and sex. The controls were included so they did not have congenital heart disease and were alive at the date of VSD diagnosis for each patient.

Morbidity

Morbidity data included diagnosis of arrhythmia, arterial hypertension, ischemic cerebrovascular disease, chronic pulmonary disease, diabetes, infectious endocarditis, heart failure, ischemic heart disease, and pulmonary arterial hypertension. For each morbidity, the first date of diagnosis was collected. Event-free survival was defined as survival free from any of following: arrhythmia, infectious endocarditis, heart failure, pulmonary arterial hypertension, or death. The complete list of codes used for each morbidity according to *ICD-8* and *ICD-10* is presented in Table S2. Table S3 provides information on register coverage and validity of diagnoses.

Statistical Analysis

Follow-up started at time of birth (the index date) and continued until event, death, or end of follow-up (December 31, 2018), whichever came first.

Continuous data were described by median with interquartile range (IQR). The incidence rates were reported as the number of events per 10 000 person-years, computed as the number of events divided by the total follow-up time of the population. Cox proportional hazard regression model was used to compute hazard ratios (HRs) for morbidity with risk beginning at time of birth, underlying timescale being age in years, and compared with corresponding matched controls. Estimates of HRs were stratified by defect treatment. For the cohort of patients with unrepaired and surgically closed VSD, supplemental analyses with truncation were performed for arrhythmias, heart failure, infectious endocarditis, and pulmonary arterial hypertension, with risk starting 1 year after VSD diagnosis (patients with unrepaired defect) or VSD surgery (patients with surgically closed defect), underlying timescale being years since diagnosis (patients with unrepaired defect) or closure (patients with surgically closed defect), and compared with respective cohorts of matched controls. Patients (and their matched controls) were censored from the truncated analyses if they had developed any of the 4 above-mentioned morbidities before the truncation date (in the period from birth until truncation date). Kaplan-Meier failure function was used to compute death rate. Event-free survival was computed using Kaplan-Meier survival analysis with risk starting at birth for overall estimates and risk starting at 1 year after VSD diagnosis or surgery for the truncated estimates. Fine and Gray competing risk regression analysis[19] was used to estimate cumulative incidence of morbidity among patients, with age as underlying timescale and death as competing risk. The assumption of proportionality for Cox proportional hazard regression model and Fine and Gray competing risk regression analysis was verified graphically by log-minus-log plots. $P<0.001$ was considered statistically significant.

Analyses were performed using STATA 16.1 (StataCorp LP, College Station, TX).

RESULTS

We identified 13 738 patients diagnosed with VSD in Denmark. Of the total cohort, 4967 (36%) patients were excluded because of coexisting cardiac malformation, as defined above, and 523 (6%) patients were subsequently excluded because of chromosomal abnormalities. Last, 242 (3%) patients were excluded as they met the criteria for postinfarction VSD. The final cohort consisted of 8006 patients with a congenital VSD and 79 956 controls.

Study Population

Median age at time of VSD diagnosis was 117 days (IQR, 11 days–6.0 years) for the total patient cohort, where the majority (58%) were diagnosed within first year of life. Demographics of the study population are presented in Table 1. Surgical closure was performed in 682 (8.5%) patients with VSD, of whom 8 patients (1.2%) were closed by percutaneous transcatheter device. Eisenmenger syndrome was identified in 20 patients, of whom 18 had an unrepaired defect during follow-up, with the majority (70%) receiving their VSD diagnosis before 1990. During follow-up, 518 (6.4%) patients (465 unrepaired and 53 surgically closed) and 2475 (3.1%) controls died.

Morbidity

Overall, patients with VSD had a higher HR of morbidity and a lower event-free survival compared with their matched controls.

The overall HR of heart failure in the total cohort of patients with VSD was 7.4 (95% CI, 6.5–8.5) compared with the total cohort of matched controls. Stratified by treatment, both patients with unrepaired VSD and patients with surgically closed VSD displayed higher HR for heart failure when compared with their corresponding matched controls, demonstrated in Table 2.

Table 1. Baseline Characteristics of Patients With Isolated Congenital VSD and Matched Controls From the General Population

Characteristic	VSD unrepaired (n=7324)	Controls (n=72765)	VSD closed (n=682)	Controls (n=6803)
Female sex, n (%)	3817 (52.1)	37905 (52.1)	306 (44.9)	3056 (44.9)
Follow-up, median (IQR), y	22.9 (11.7–37.2)	23.6 (12.3–38.0)	21.8 (9.4–37.7)	23.5 (11.3–38.9)
Age at time of VSD diagnosis, median (IQR), d	185 (8 d–6.3 y)	…	141 (48 d–2.1 y)	…
Age at time of VSD surgery, median (IQR), y	…	…	1.4 (169 d–5.7 y)	…

Data are presented as absolute numbers with percentage or as median with IQR.
IQR indicates interquartile range (25th percentile–75th percentile); and VSD, ventricular septal defect.

The HR did not normalize in either subgroup when estimates were truncated at 1 year after surgery or diagnosis; data are presented in Table 3. Adjusted for atrial fibrillation, the HR for heart failure in unrepaired patients was 4.3 (95% CI, 3.6–5.0), and it was 27.7 (95% CI, 19.6–40.0) in surgically closed patients. The HR of heart failure 1 year after surgery in patients in whom defect closure was performed through a right atriotomy (n=353) was 0.8 (95% CI, 0.1–5.9). Median age at surgical closure for this subpopulation was 237 days (IQR, 109 days–2.3 years), and median age at end of follow-up was 11.4 years (IQR, 5.2–18.8 years).

The HR of arrhythmias in the total cohort of patients with VSD was 3.6 (95% CI, 3.1–4.0) compared with the cohort of matched controls. The HRs stratified by VSD treatment are presented in Table 2. The HR of atrial fibrillation or atrial flutter was 3.7 (95% CI, 3.1–4.3) for patients with unrepaired VSD, and it was 7.2 (95% CI, 4.7–11.1) for patients with surgically closed VSD, compared with the matched controls.

The HR for infectious endocarditis was 35.4 (95% CI, 25.3–49.5) in the total cohort of patients with VSD. Both patients with unrepaired and patients with surgically closed VSD displayed high HR for the condition when compared with their corresponding matched controls (Table 2). Truncated analyses of the HR at 1 year after diagnosis or surgery showed the HR persisted in patients with unrepaired VSD, whereas it diminished in patients with surgically closed VSD.

The HR of pulmonary arterial hypertension in the total cohort of patients with VSD was 13.4 (95% CI, 9.5–19.0) compared with the matched controls. The HR of pulmonary arterial hypertension was high in both patients with unrepaired defects and patients with closed defects (Table 2). Truncated analyses 1 year after surgery or diagnosis revealed that also a late hazard of the condition exists (Table 3). Censoring time from birth until truncation date, 5 patients with surgically closed and 24 patients with unrepaired VSD developed pulmonary arterial hypertension. Median age at time of pulmonary arterial hypertension diagnosis for the latter group was 61 years (IQR, 45–76 years). These 24 patients had a median age at time of VSD diagnosis of 50 years (IQR, 24–64 years).

Patients with surgically closed VSD was not at increased risk in terms of HR of cerebrovascular events when compared with their matched controls, which, however, was the case for patients with unrepaired VSD. HRs and incidence rates for arterial hypertension, cerebrovascular disease, chronic pulmonary disease, diabetes, and ischemic heart disease are presented in Table 2. Cumulative incidence for each morbidity stratified by treatment is graphically illustrated in Figure 1, and the cumulative incidence of death stratified by treatment is illustrated in Figure 2.

The overall event-free survival for patients with unrepaired defects was 94% (95% CI, 94%–95%), 91% (95% CI, 90%–92%), 83% (95% CI, 82%–85%), 69% (95% CI, 66%–72%), and 48% (95% CI, 44%–52%) at 30, 40, 50, 60, and 70 years of age, respectively. Corresponding estimates for patients with surgically closed defect were 75% (95% CI, 71%–78%), 65% (95% CI, 60%–70%), 53% (95% CI, 46%–60%), 33% (95% CI, 23%–43%), and 19% (95% CI, 9.4%–30%). The cohorts of matched controls for the 2 patient groups had an event-free survival of 98% (95% CI, 98%–98%) and 97% (95% CI, 96%–98%) at 40 years of age and 90% (95% CI, 89%–91%) and 86% (95% CI, 84%–88%) at 60 years of age, respectively. Data are graphically illustrated in Figure 3A. Event-free survival truncated at 1 year after either VSD diagnosis (patients with unrepaired defect) or VSD closure (patients with surgically closed defect) is demonstrated in Figure 3B. Event-free survival truncated at 1 year after VSD diagnosis for patients with unrepaired defect was 97% (95% CI: 96-97) and 93% (95% CI: 91-94) at 20- and 40-years of follow-up, respectively. Corresponding estimates for patients with surgically closed VSD 1 year after defect closure was 95% (95% CI: 92-97) and 88% (95% CI: 82-92). The matched controls displayed an event-free survival of 96% (95% CI: 96-97) at 40-years of follow-up. Event-free survival stratified by morbidity (arrhythmia, heart failure, infectious endocarditis, and

Table 2. Incidence Rates and HRs for Morbidity From Birth to End of Follow-Up in Patients With Isolated Congenital VSD Compared With Matched Controls From the General Population

Morbidity	VSD unrepaired (n=7324)					VSD closed (n=682)				
	No. (%) of events		Incidence per 10 000 person-years			No. (%) of events		Incidence per 10 000 person-years		
	Patients	Controls	Patients	Controls	HR (95% CI)	Patients	Controls	Patients	Controls	HR (95% CI)
Arrhythmias	269 (3.7)	1043 (1.4)	14.2	5.3	3.4 (2.9–3.9)	47 (6.9)	116 (1.7)	28.5	6.4	5.8 (4.1–8.2)
Arterial hypertension	304 (4.2)	2170 (3.0)	16.1	11.1	1.7 (1.5–2.0)	32 (4.7)	199 (2.9)	19.0	11.1	2.0 (1.4–2.9)
Cerebrovascular disease	88 (1.2)	694 (1.0)	4.6	3.5	1.5 (1.2–1.9)	4 (0.6)	67 (1.0)	2.3	3.7	0.7 (0.2–1.9)
Chronic pulmonary disease	130 (1.8)	876 (1.2)	6.9	4.5	1.7 (1.4–2.0)	12 (1.8)	82 (1.2)	7.1	4.6	1.7 (0.9–3.0)
Diabetes	136 (1.9)	1083 (1.5)	7.2	5.5	1.4 (1.2–1.7)	14 (2.1)	109 (1.6)	8.2	6.1	1.4 (0.8–2.5)
Heart failure	226 (3.1)	569 (0.8)	11.9	2.9	5.4 (4.6–6.3)	119 (17.4)	50 (0.7)	76.6	32.8	30.5 (21.8–42.7)
Infectious endocarditis	93 (1.3)	38 (<0.1)	4.8	0.2	28.0 (19.2–40.9)	47 (6.9)	7 (0.1)	29.1	0.4	82.7 (37.3–183.2)
Ischemic heart disease	267 (3.6)	1344 (1.8)	14.1	6.9	2.5 (2.2–2.9)	29 (4.3)	120 (1.8)	17.3	6.7	3.0 (2.0–4.5)
Pulmonary hypertension	54 (0.7)	56 (<0.1)	2.8	0.3	11.5 (7.9–16.8)	16 (2.3)	5 (<0.1)	9.4	0.3	34.3 (12.6–93.7)

HR indicates hazard ratio; and VSD, ventricular septal defect.

pulmonary arterial hypertension, including death) is embedded in Figure S1.

DISCUSSION

This nationwide cohort study including 8006 patients with a congenital isolated VSD revealed a substantial lifetime burden of morbidity, whether surgically closed or not, compared with matched controls from the general Danish population. The most important findings were that the life-long risk of arrhythmia, heart failure, infectious endocarditis, and pulmonary arterial hypertension was significantly higher than in matched controls, and that the incidence accelerated after the fourth decade of life.

Morbidity

Infants with a large VSD can present with heart failure. Otherwise, heart failure in childhood is a rare condition in patients with isolated VSD. Nonetheless, abnormal left ventricle dimensions and systolic and diastolic left ventricle dysfunction have been demonstrated in surgically closed[4,20] and even restrictive unrepaired[3,5] VSDs in patients in their early 40s. Furthermore, almost 20% of patients with small unrepaired VSDs aged >40 years developed heart failure in a report of >700 patients in a French study reported in 1977,[21] and 28% patients with closed VSDs needed medication for heart failure 30 years after surgical repair in a recently reported study of congenital heart disease outcomes in Finish patients.[6] Our data revealed a considerable incidence of heart failure in both patients with unrepaired defect and in those with a surgically closed defect, accelerating after the fourth or fifth decade of life. Dissecting the data, it is obvious that patients with VSD carry a risk of heart failure not only around time of VSD diagnosis or surgery but also many years later. Several hypotheses have been postulated as to the underlying pathogenesis, including an inappropriate adaption to the hemodynamics with age,[3] a consequence of acquired cardiac morbidities, such as aortic or mitral valve regurgitation,[21] or a consequence of chronic pressure and volume overload, leading to disturbed systolic function.[22] Left ventricular disease as part of a diffuse cardiovascular disease unrelated to the actual defect or an associated cardiomyopathy has also been proposed,[3,5] which hypothetically could explain our findings of increased risk of arterial hypertension and ischemic heart disease. Our study clearly cannot address causation but provides ample evidence that this is an area of future investigation and of clear unmet need. Pulmonary arterial hypertension is not only a characteristic of left-sided heart failure but when the dominant lesion also predisposes to right-sided heart failure. The latter could be the case in a proportion

Table 3. Incidence Rates and HRs for Morbidity From 1 Year After VSD Diagnosis in Patients With Unrepaired Defect and 1 Year After VSD Closure in Patients With Surgically Closed Defect Compared With Corresponding Matched Controls From the General Population

Morbidity	VSD unrepaired					VSD closed				
	No. (%) of events		Incidence per 10 000 person-years			No. (%) of events		Incidence per 10 000 person-years		
	Patients	Controls	Patients	Controls	HR (95% CI)	Patients	Controls	Patients	Controls	HR (95% CI)
Arrhythmias	156 (2.2)	767 (1.1)	12.6	5.9	2.2 (1.8–2.6)	29 (4.4)	94 (1.4)	27.6	7.7	3.6 (2.3–5.4)
Infectious endocarditis	47 (0.6)	26 (<0.1)	3.8	0.2	19.3 (11.9–31.1)	1 (0.2)	5 (<0.1)	0.9	0.4	2.4 (0.3–20.6)
Pulmonary hypertension	24 (0.3)	44 (<0.1)	1.9	0.3	5.7 (3.5–9.4)	5 (0.7)	4 (<0.1)	4.4	0.3	13.7 (3.7–51.0)
Heart failure	107 (1.5)	392 (0.5)	8.6	3.0	2.9 (2.3–3.6)	21 (3.6)	34 (0.6)	20.8	3.0	7.0 (4.1–12.1)
					2.4 (1.9–2.9)*					3.8 (2.1–6.8)*

HR indicates hazard ratio; and VSD, ventricular septal defect.
*Adjusted for atrial fibrillation.

of patients in our data set as we found a cumulative incidence for developing pulmonary arterial hypertension of ≈17% among patients with unrepaired defect and ≈22% among patients with surgically closed defect at the age of 80 years. In addition, atrial fibrillation predisposes to heart failure; however, our data demonstrate that the hazard of heart failure is not driven by atrial fibrillation. Regardless of the pathophysiology, which probably is multifactorial, our data add invaluable knowledge about the burden of heart failure and pulmonary arterial hypertension in patients with isolated VSDs throughout their lives, beyond middle age in particular. Interestingly, the hazard for heart failure was not increased in surgically closed patients when right atriotomy was performed; however, that might be explained by limited time of follow-up.

Our data demonstrate a high incidence of pulmonary arterial hypertension in patients with both unrepaired defect and surgically closed defect, with the latter subgroup being the most concerning with regard to published data on survival.[10,11,23,24] Late diagnosis with respect to high shunt ratio and impact on pulmonary vascular resistance might be the explanation in patients with unrepaired defects, although the high incidence, even in those deemed too small to require surgery, suggests a different mechanism may be at play. This is particularly likely, given the continued hazard of pulmonary hypertension even after successful surgery. In this regard, development of pulmonary arterial hypertension after defect closure might suggest that even pressure and volume overload during short periods early in life results in morphological changes of the pulmonary vascular bed that have lifelong consequences. Delayed closure of the defect where pulmonary vascular disease had already developed or presence of residual shunt in earlier eras clearly may be implicated, and one would hope that the trend toward earlier closure in recent decades may obviate this, but our findings of a high lifetime burden of pulmonary hypertension, with and without surgery, is both sobering and emphasizes the need for continued mechanistic investigation in the future. Indeed, our findings strongly support regular follow-up of patients with persistent or surgically closed shunt, even if successful closure was performed in childhood.

Patients with VSD have always been considered at risk for infective endocarditis. However, the rates vary in published reports because of differences in the constitution of the study population, surgical procedures, coexisting valve pathology, and possibly referral bias. This is the largest systematic study including burden of infectious endocarditis in patients with congenital VSD, and it adds invaluable knowledge about the long-term risk of the condition in this patient group. We found a cumulative incidence of

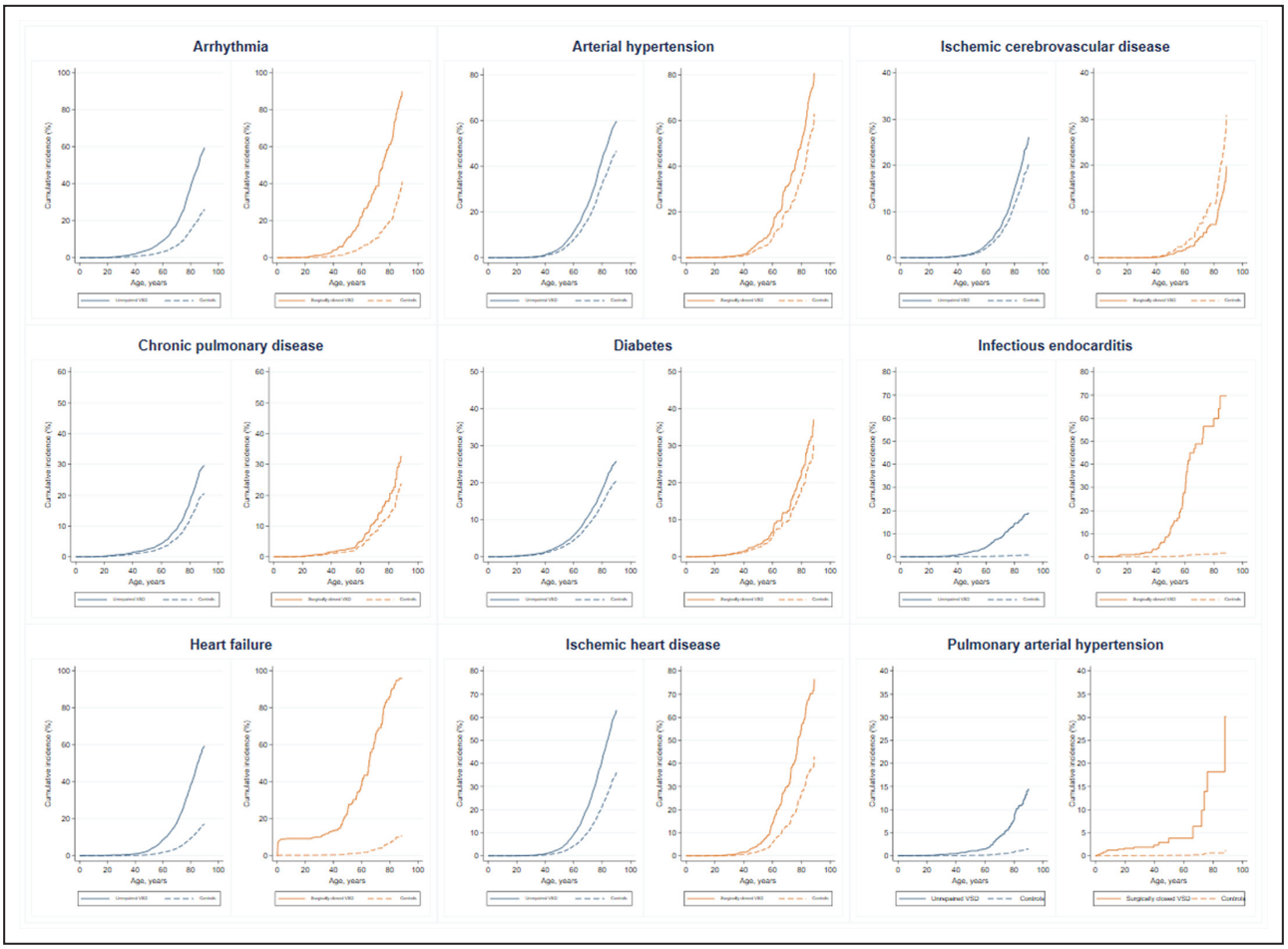

Figure 1. Cumulative incidence of morbidity.
Cumulative incidence of morbidity with death as competing risk in patients with unrepaired or surgically corrected ventricular septal defect compared with corresponding matched controls. VSD indicates ventricular septal defect.

infectious endocarditis of ≈19% in those with unrepaired defect and 50% in the group of patients with surgically closed defect (with congenital left-sided cardiac diseases excluded) at the age of 80 years. However, dissecting the data, patients with an unrepaired defect carried a substantial risk from birth throughout their lives, whereas the risk in patients with closed defect diminished after surgery. The latter finding might partly be explained by the elimination of turbulence through defect closure and partly by the fact that surgical closure was performed because of an episode of VSD-related infectious endocarditis. On the basis of our data, infectious endocarditis remains an important complication in patients with VSD, and closure of the defect seems to yield a lower risk, in line with current knowledge.[7,25,26]

The natural history of congenital VSD is not strongly associated with symptomatic arrhythmias, whereas it is not an uncommon complication after surgical VSD closure.[4,6] Arrhythmias have been sporadically reported in retrospective and observational studies of patients with unrepaired VSD,[2,5] but a comprehensive description of the burden of arrhythmia in the total population has been lacking. Both medically and surgically managed patients displayed a high incidence of symptomatic arrhythmias, in terms of atrial fibrillation or flutter throughout their lives, with a 4- and 7-fold increased late hazard, respectively, compared with the general population. We can only speculate, but we would suggest that in addition to the direct effects of surgical intervention (such as surgical scars and the effects of cardiopulmonary bypass), the aforementioned burden of heart failure and pulmonary hypertension leads to a secondarily increased burden of arrythmia, emphasizing the need for future studies to better understand, and potentially treat, this hitherto underrecognized consequence of VSD.

Limitation

There are clearly some limitations when interpreting our data. Our data originate from a registry where

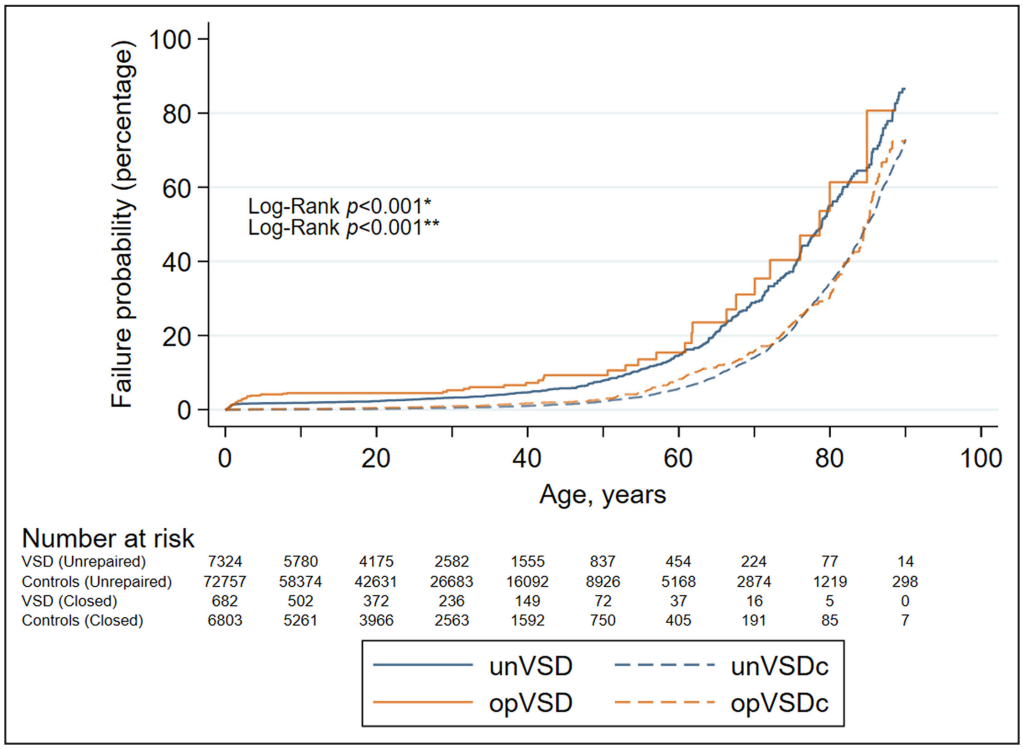

Figure 2. Cumulative incidence of death.
Cumulative incidence of death in patients with unrepaired and surgically corrected ventricular septal defect (VSD) compared with corresponding matched controls. *Comparison between patients with unrepaired VSD (unVSD) and their matched controls (unVSDc). **Comparison between patients with surgically closed VSD (opVSD) and their matched controls (opVSDc).

misclassification of diagnoses and of dates can occur. The validity of the comorbidity diagnoses included in this study has been reported previously, albeit with overall high positive predictive value[17] (Table S3). As expected, the validity has improved since 1977, with improved availability of diagnostics modalities, increased awareness of correct coding, and implementation of clear guidelines. We do not think ascertainment bias is a major factor for the increased reporting of morbidities in patients with VSD, as routine follow-up of patients with VSD has not been clinical practice, and Denmark's universal, free, health care neither deters nor biases treatment based on insurability or the effects of preexisting conditions for insurability that may be at play in other populations. On the other hand, we do not know whether general practitioners are more prone to admit patients with congenital heart disease with or without previous heart surgery to hospital. Consequently, the effect of such circumstances on risk estimates of morbidity is difficult to assess but might result in a slight overestimation of the risk when compared with the general population, and patients treated in other health care systems.

We lack morbidity data until the introduction of the DNPR in 1977 for both patients and controls. This limitation might potentially result in a delayed diagnosis of morbidity for a minority of the cohort and consequently an underestimation of the true HR. However, as the investigated morbidity most often debuts during adulthood, we consider that a long follow-up is paramount in this regard. The DNPR does not include clinical data, such as data from ECGs, echocardiography, and catheterizations. The lack of clinical data is not a limitation per se but hinders a more detailed and precise patient group stratification and limits any physiologic insights into possible causation. For example, as shunt data were unavailable, we were not able to define the unrepaired defects as small and restrictive but can only assume that the defect was unrepaired because it was considered so. Furthermore, patients with spontaneously closed VSD are also likely to have been included in the study, given our knowledge of the natural history of such defects diagnosed in early life. Consequently, the specific contribution of, and burden in, this subgroup of patients on the risk of morbidity is unknown. However, it further emphasizes that the late burden of morbidity is not only related to late hemodynamic burden of VSD but is also related to the "presence" of a VSD, whether persistent or spontaneously or surgically closed, and future studies

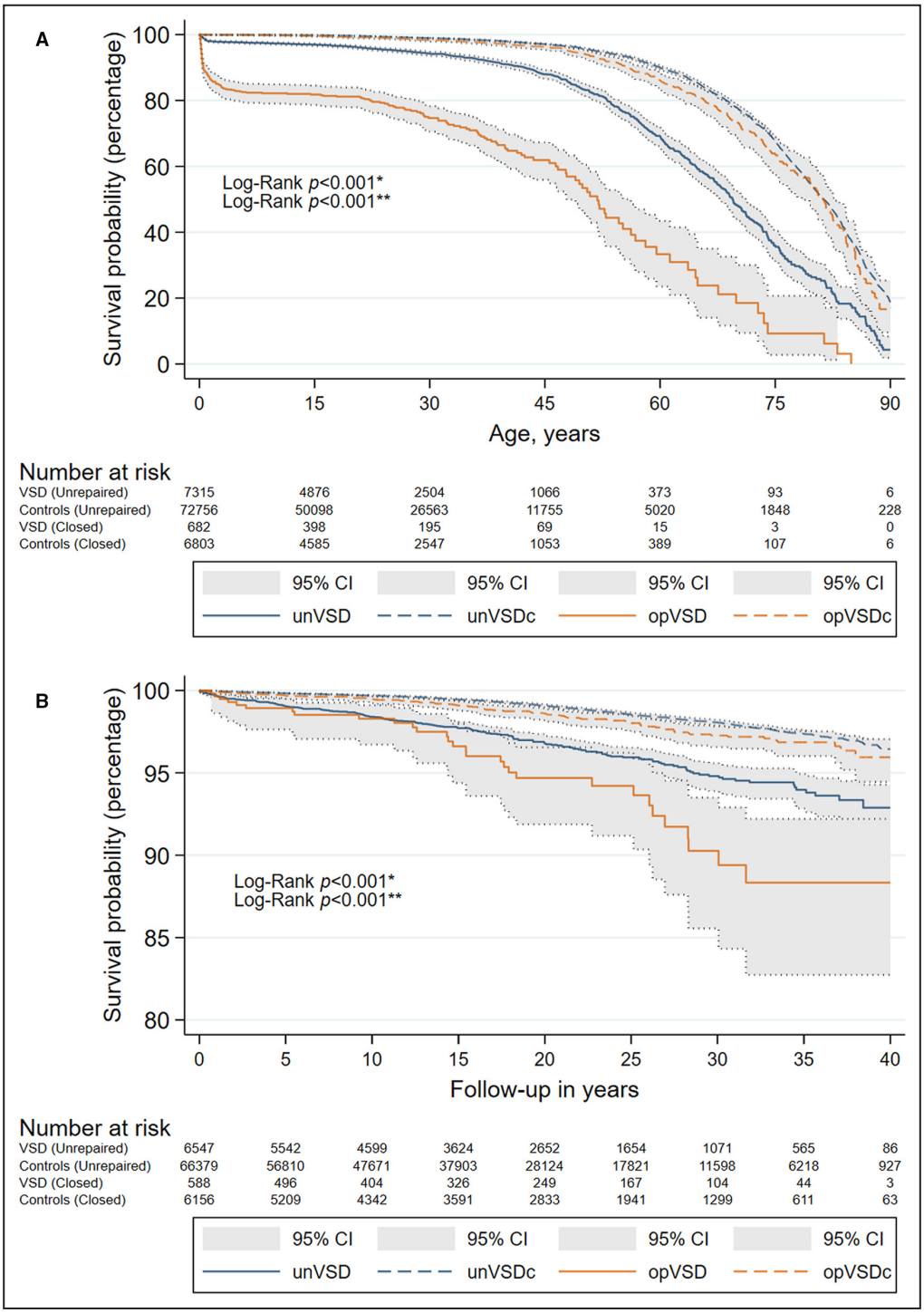

Figure 3. Event-free survival.
Event-free survival in patients with unrepaired and surgically corrected ventricular septal defect (VSD) compared with corresponding matched controls. Follow-up from birth (**A**) and from 1 year after VSD diagnosis (patients with unrepaired defect) or 1 year after surgery (patients with surgically closed defect) (**B**). *Comparison between patients with unrepaired VSD (unVSD) and their matched controls (unVSDc). **Comparison between patients with surgically closed VSD (opVSD) and their matched controls (opVSDc).

should examine the possibility that VSD is just one manifestation of a "cardiovascular phenotype" that is itself a target for mechanistic studies and possible treatment.

CONCLUSIONS

Patients with a congenital isolated VSD, either unrepaired or surgically closed, displayed a substantial

burden of arrhythmias, infectious endocarditis, heart failure, and pulmonary arterial hypertension. For patients with unrepaired defect, the incidence of morbidity was trivial before their fourth decade of life; however, it was amplified significantly hereafter. Patients with surgically closed defect present with significant morbidity earlier, after the second decade of life and, noticeably, a survival free from event clearly inferior compared with both unrepaired patients and controls from the general population. This difference persists even when morbidity from birth until the first year after surgery is censored. Our data support the latest recommendations on regular follow-up of patients with VSD[13,14] and highlight the potential development of significant cardiac morbidity after the fourth decade of life in patients with unrepaired VSD and third decade of life in patients with surgically closed VSD. Furthermore, the mechanisms underlying these significant burdens of mortality and morbidity are an area of unmet research need that may have a transformational impact for patients in the future.

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Disclosures

None.

Supplemental Material

Appendix S1Tables S1–S3Figure S1References[27–38]

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SUPPLEMENTAL MATERIAL

Table S1. **Codes according to International Classification of Disease 8th and 10th edition used to identify surgical or transcatheter closure of defect.**

	ICD-8	ICD-10
Surgery	30801*, 30809*, 30819*, 30899*, 31460†, 31540†	KFHB00, KFHB10, KFHB20, KFHB30, KFHB40, KFHB50, KFHB60, KFHB70, KFHB80, KFHB96, KFHC00, KFHC10, KFHC20, KFHC30, KFHC96
Percutaneous transcatheter	-	KFHB42

ICD, International Classification of Disease.

*Codes used during the period 1989-1995.

†Codes used during the period 1973-1988.

Table S2. **Codes according to International Classification of Diseases 8th and 10th edition used for identification of morbidity.**

	ICD-8	ICD-10
Arrhythmias	427.90, 427.91, 427.92, 427.93, 427.94	I47*, I48*
Arterial hypertension	401.99, 402.99, 403.99, 404.99	I10*, I11*, I12*, I13*, I15*
Ischemic cerebrovascular disease	433*, 434*, 435*, 436.01, 436.90	G45*, I63*
Chronic pulmonary disease	490*, 491*, 492*	J40*, J41*, J42*, J43*, J44*, J47*, J841C, J841X
Diabetes	249*, 250*	E10*, E11*
Eisenmenger syndrome[†]	746.39 *AND* 426.02 *AND* 426.00 *OR* 782.39 *OR* 783.19	Q218A, I278A
Heart failure	426.08, 426.09, 427.09, 427.10, 427.11, 427.19	I50*
Infectious endocarditis	421*	I38*, I39*
Ischemic heart disease	410*, 411*, 412*, 413*, 414*	I20*, I21*, I24*, I25*
Pulmonary arterial hypertension	426*	I27*

ICD, International Classification of Disease.

*Include all lower level of diagnose codes.

[†]Defined as pulmonary arterial hypertension in the presence of an intra-cardiac shunt (VSD), accompanied by cyanosis, hemoptysis, or cor pulmonale.

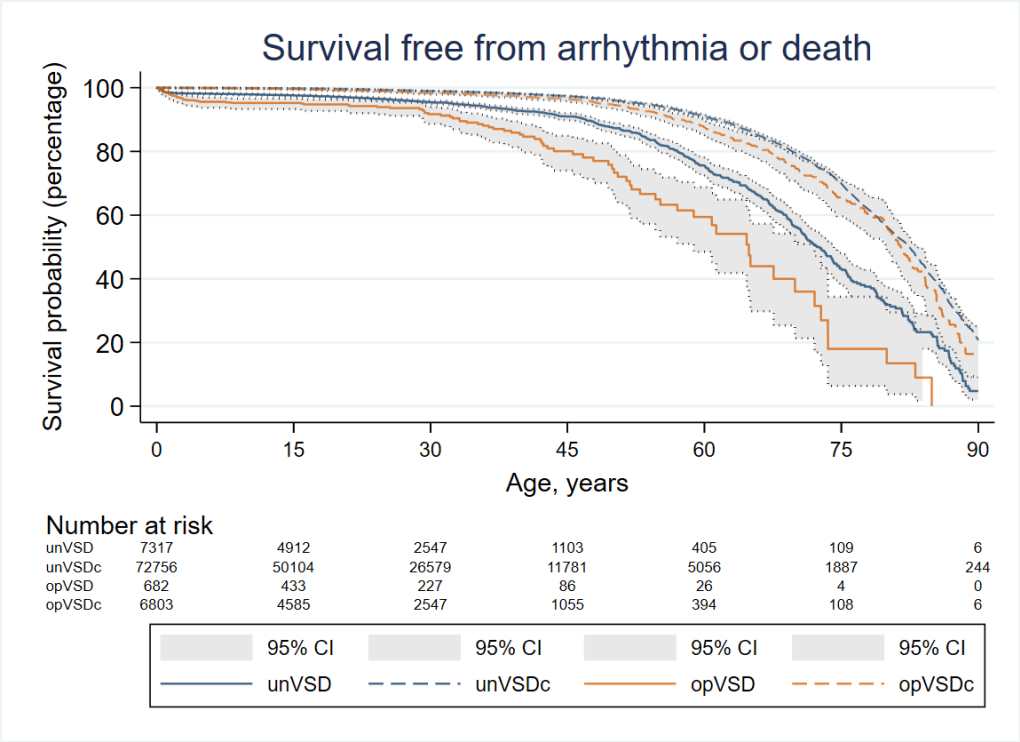
Table S3. **Validation studies for morbidities in the Danish National Patient Registry.**

	PPV % (95% CI)
Arrhythmias	95 (89-98)[27], 93 (89-95)[28]
Arterial hypertension	92 (85-96)[27], 88 (85-91)[29]
Ischemic cerebrovascular disease	97 (85-100)[30], 88 (80-93)[31]
Chronic pulmonary disease	100 (93-100)[32], 91 (86-94)[33]
Diabetes	96 (87-99)[32], 97 (90-99)[34], 96 (95-97)[35]
Heart failure	100 (93-100)[32], 76 (66-83)[27]
Infectious endocarditis	82 (73-89)[27]
Ischemic heart disease	94 (94-95)[36], 98 (90-100)[32], 100 (98-100)[37], 66 (63-68)[38]
Pulmonary arterial hypertension	87 (79-92)[27]

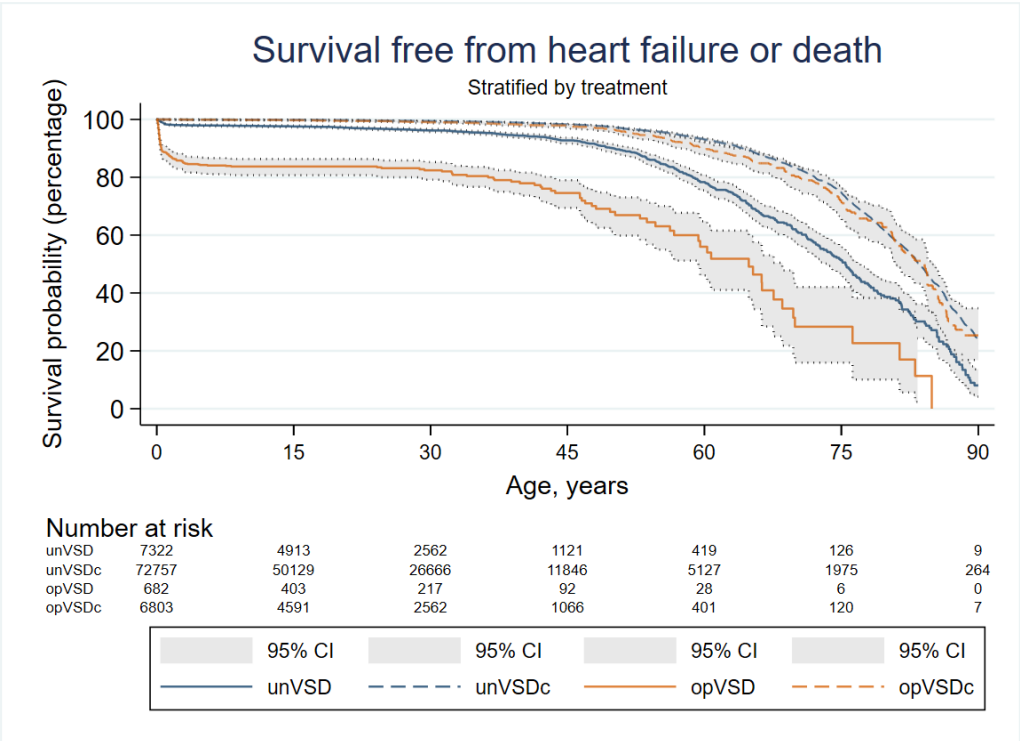
CI, confidence interval; PPV, positive predictive value.

Figure S1. Event-free survival stratified by morbidity in patients with unrepaired and surgically closed ventricular septal defect and their corresponding matched controls.

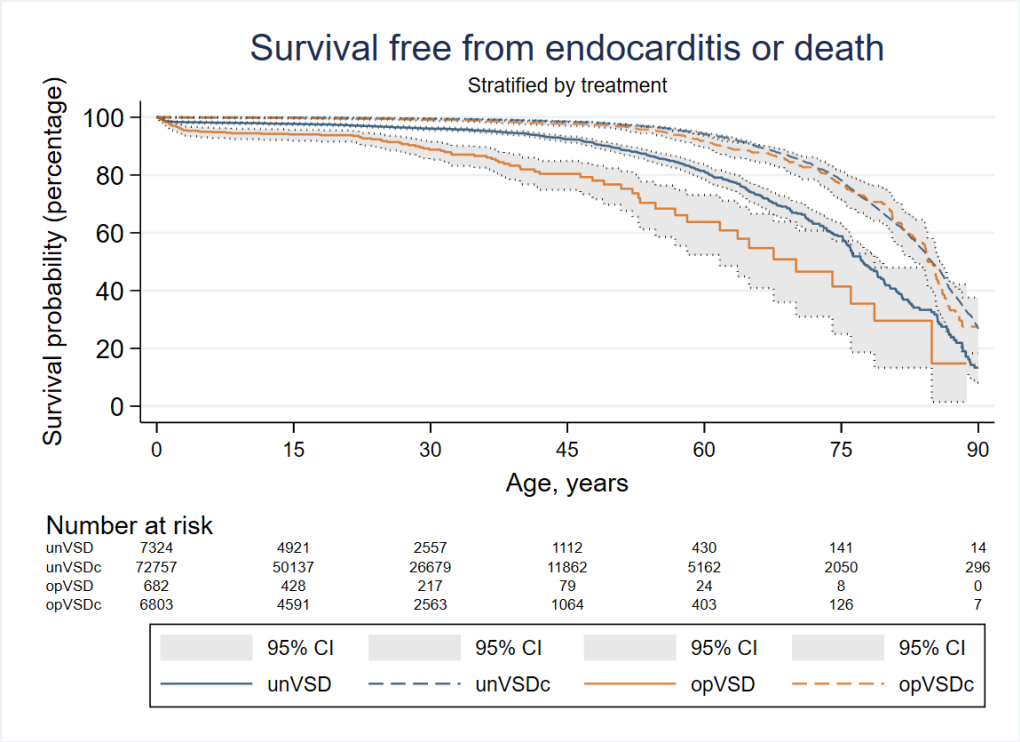
A. Survival free from arrhythmia or death



B. Survival free from heart failure or death



C. Survival free from infectious endocarditis or death



D. Survival free from pulmonary arterial hypertension or death