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Valvular disease burden in the modern era of percutaneous and surgical interventions: the UK Biobank

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ABSTRACT

Background The burden of valvular heart disease (VHD) has increased significantly among ageing populations, yet remains poorly understood in the present-day context of percutaneous and surgical interventions.

Objective To define the incidence, clinical correlates and associated mortality of VHD in the UK Biobank cohort.

Methods We interrogated data collected in the UK Biobank between 1 January 2000 and 30 June 2020. VHD incidence was determined using International Classification of Disease-10 codes for aortic stenosis (AS), aortic regurgitation (AR), mitral stenosis, mitral regurgitation (MR) and mitral valve prolapse. We calculated HRs for incident VHD and all-cause mortality. Clinical correlates of VHD included demographics, coronary artery disease, heart failure and atrial fibrillation. Surgical and percutaneous interventions for mitral and aortic VHD were considered time-dependent variables.

Results Among 486 187 participants, the incidence of any VHD was 16 per 10 000 person-years, with highest rates for MR (8.2), AS (7.2) and AR (5.0). Age, heart failure, coronary artery disease and atrial fibrillation were significantly associated with all types of VHD. In our adjusted model, aortic and mitral VHD had an increased risk of all-cause death compared with no VHD (HR 1.62, 95% CI 1.44 to 1.82, p<0.001 and HR 1.25, 95% CI 1.09 to 1.44, p=0.002 for aortic and mitral VHD, respectively).

Conclusion VHD continues to constitute a significant public health burden, with MR and AS being the most common. Age and cardiac comorbidities remain strong risk factors for VHD. In the modern era of percutaneous and surgical interventions, mortality associated with VHD remains high.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Valvular heart disease prevalence is rising in Europe and the USA with ageing populations. In the past decade, several percutaneous interventions have been approved for use in high-risk patients, and surgical techniques have dramatically improved.

WHAT THIS STUDY ADDS

⇒ The most common types of incident valve disease in this large, contemporary cohort from the UK are mitral regurgitation (8.2 per 10 000), aortic stenosis (7.2 per 10 000) and aortic regurgitation (5.0 per 10 000). Risk is increased by age and the presence of cardiac conditions. Despite the existence of surgical and percutaneous interventions for severe disease, mortality in patients with valve disease remains high.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Examination of real-world clinical practice patterns and guideline adherence for valvular interventions are warranted to investigate the causes of excess mortality among patients with valve disease.

INTRODUCTION

With the declining burden of rheumatic heart disease in non-endemic countries, valvular heart disease (VHD) has increasingly become a disease of ageing.[1 2] Multiple cohort-based studies show the sharp rise of incident VHD with age, particularly for mitral regurgitation (MR) and aortic stenosis (AS). The shift in VHD epidemiology from rheumatic disease in younger patients to degenerative valve disease in older adults with comorbidities has translated into widespread use of percutaneous interventions.[3] At the same time, improvement in postsurgical care has led to reduction of morbidity for surgical valve replacement[4] and repair.[5]

Prior studies have investigated the overall prevalence, clinical determinants, and outcomes of VHD in both USA and European cohorts.[1 2 6–8] Such investigations, some dating to the late 1990s and early 2000s, have highlighted the presence of modifiable risk factors such as hypertension and obesity,[7 9] for the development and progression of VHD. These studies have also underlined the high mortality associated with VHD.[1 8] However, they have not taken into account the more contemporary influence of percutaneous procedures and improved surgical techniques on VHD burden and outcomes.

By leveraging the UK Biobank, a large, contemporary prospective population-based study, we aimed to investigate (1) the incidence and clinical correlates of VHD taking

into consideration current burden of known cardiovascular risk factors for VHD and (2) the all-cause and cardiovascular mortality associated with VHD in the modern era of percutaneous and surgical interventions.

METHODS

Data sources

The UK Biobank is a large biomedical cohort of adults age 40–69 who were recruited between 2006 and 2010 across 22 assessment centres in the UK, with follow-up assessment until 2020. Participant data include baseline interview of self-reported conditions, physical measurements and linkage to International Classification of Disease-10 (ICD-10) codes used by National Health Services for primary care visits, hospital admissions and death records.[10] The UK Biobank includes a 'first occurrence' field for new diagnoses that appear in these data sources. Participant-level data provided to researchers are anonymised to protect identity. The study protocol was approved by the UK Biobank (Project 26751).

Patient and public involvement

The UK Biobank disseminates research generated from the database, including this study, for participants and the general public to view through their website and twitter feed (https://www.ukbiobank.ac.uk/). Given that the UK Biobank is a deidentified database, participants were not contacted or involved in the design and conduct of this retrospective study.

Study cohort

VHD was defined using ICD-10 codes and self-report codes for MR, mitral stenosis (MS), mitral valve prolapse (MVP), tricuspid regurgitation (TR), aortic regurgitation (AR) and AS (online supplemental table 1). Prior validation analyses using ICD-10 codes have found a high positive predictive value for all VHDs studied, with moderate or severe disease severity in the majority of cases, particularly for AS.[11] Due to the rare occurrence of congenital pulmonic valve disease and tricuspid stenosis among adults, these valvular conditions were not included in our investigation, which was based on an adult cohort.

MVP was defined by specific ICD-10 codes (online supplemental table 1). For the purpose of our study, we placed participants with codes for both MVP and MR in the general MR category.

Clinical correlates

We chose cardiovascular covariates that are considered contributors or comorbid conditions to VHD. Systolic blood pressure (SBP) and body mass index (BMI) were measured at participant enrolment. Obesity was defined as BMI>30 kg/m^2. ICD-10 codes (online supplemental table 2) were used to identify the presence of smoking disorder, dyslipidaemia, diabetes, coronary artery disease (CAD), congestive heart failure (CHF), rheumatic fever, atrial fibrillation/flutter (AF), infective endocarditis and pulmonary hypertension.

Valvular interventions

The Office of Population Census and Surveys version 4 procedural coding system was used to identify mitral and aortic valve surgery (repair and replacement), and percutaneous interventions including annuloplasties and repairs. Mitral valve interventions included diagnostic codes for MR or MS with a corresponding procedural K code. Percutaneous interventions also included a Y code defining the approach.[12] Aortic valve interventions included a procedural K code, with transcutaneous aortic valve replacement (TAVR) defined using addition of Y code. Tricuspid valve interventions were defined in a similar fashion (online supplemental table 3).

Outcomes

Incident VHD was defined as 'first occurrence' VHD between January 2000 and June 2020, after excluding prevalent cases diagnosed in December 1999 or earlier. Mortality outcomes included all-cause mortality and cardiovascular mortality due to myocardial infarction, stroke, cardiac arrest or CHF (see online supplemental table 4).

Statistical analysis

Continuous variables were expressed as median and interquartile ranges or mean and SDs if normally distributed. Categorical data were expressed as number and percentage of total subjects in each group. Incident rates were calculated per 10 000 person years. The assessment period of participants with and without VHD ended at the date of death or June 2020.We used Cox proportional hazard cause-specific models to calculate HRs and 95% CIs. Demographics (age, male sex), risk factors (SBP, obesity, smoking, dyslipidaemia, diabetes, CAD, CHF and AF) and valve interventions were treated as time-dependent covariates when calculating HR for incident VHD. We calculated HR for any VHD as well as valve disease subtypes: TR, MR, MS, AR, AS. As MVP is considered a genetic condition,[13] and its development unrelated to typical cardiovascular risk factors, we did not run multivariate Cox models for this valvulopathy.

Next, we assessed any VHD, mitral valve disease (inclusive of MR, MS and MVP) and aortic valve disease (inclusive of AR and AS) as predictors of all-cause and cardiovascular mortality using Cox proportional hazards models. These models were adjusted for age, sex, SBP, obesity, smoking, dyslipidaemia, diabetes, CAD and CHF as well as valvular interventions. We included only those interventions that were relevant to the affected valve (eg, for our aortic valve model we only included aortic valve interventions). Assessments of Kaplan-Meier versus predicted survival plots and log-minus-log survival plots demonstrated that proportional hazards assumptions were met for each outcome.

Statistical analysis was performed using Stata V.14 (StataCorp) and SAS V.9.4 (SAS Institute). All reported p values are two sided, and statistical significance is reported for α=0.05.

Table 1 Valvular heart disease incidence rate and age of diagnosis

Population	N	Age of diagnosis, years	IQR	IR (per 10 000 person-years)	95% CI
Any valve disease	13 615	66	60–72	16.3	16.0 to 16.5
MR	6900	64	59–71	8.2	8.0 to 8.4
MS	2095	61	55–67	2.5	2.4 to 2.6
MVP	1119	63	57–70	1.3	1.2 to 1.4
AS	6020	66	60–72	7.2	7.0 to 7.3
AR	4238	63	58–70	5.0	4.9 to 5.2
TR	1664	68	64–74	2.0	1.9 to 2.1

AR, aortic regurgitation; AS, aortic stenosis; IR, incidence rate; MR, mitral regurgitation; MS, mitral stenosis; MVP, mitral valve prolapse; TR, tricuspid regurgitation.

RESULTS

Population characteristics

A total of 486 187 subjects were included in the analysis. There were 13 615 cases of new VHD, including 6900 with MR, 6020 with AS, 4238 with AR, 2095 with MS, 1664 with TR and 1119 with MVP. Incidence rate per 10 000 person-years was 16.3 (95% CI 16.0 to 16.5) for all VHD, with the highest for MR at 8.2 (95% CI 8.0 to 8.4), followed by AS at 7.2 (95% CI 7.0 to 7.3) and AR at 5.0 (95% CI 4.9 to 5.2) (table 1). Demographic characteristics and comorbidities are summarised in table 2. Compared with those without VHD, those with any VHD tended to be older and were more commonly men (56% vs 45%). Rheumatic fever was rare, but a significant contributor to MS (present in 44% of cases) and MR (present in 12% of cases). Male sex was slightly more prevalent (66% males) among those with MVP (table 2). AF was common in all valve disease subtypes, but rare in the non-valvular population. There were 78 mitral valve (8 percutaneous), 238 aortic valve (36 percutaneous) and 25 tricuspid valve (5 percutaneous) interventions. Demographic characteristics and comorbidities of patients with VHD who did and did not receive interventions are summarised in online supplemental table 5. Patients with VHD treated with surgical or percutaneous interventions were predominantly male, and more likely to have CAD or AF. Patients who did not undergo valvular procedures had more CHF.

Comorbidity profiles of incident VHD

Fully adjusted Cox proportional hazard models of incident valve disease are shown in figure 1. All covariates studied were significantly associated with increased risk of incident VHD. Age significantly increased risk of all incident VHD types. Male sex was associated with incident AS, and AR, but not MS, MR or TR.

The greatest HRs for development of any VHD were the following cardiac conditions: AF (HR 9.45, 95% CI 9.08 to 9.93), CAD (HR 5.41, 95% CI 5.12 to 5.71) and CHF (HR 5.2, 95% CI 4.91 to 5.51). Strong positive associations for AF and CHF were observed across all VHD subgroups (figure 1). CAD was associated with increased hazard for all VHD subtypes except MS. Obesity, SBP, smoking, diabetes and dyslipidaemia were associated with increased risk of AS. Obesity and SBP were associated

Table 2 Demographics and comorbidities of incident valve disease

	No valve disease (N=472 328)	Any valve disease (N=13 615)	Mitral valve prolapse (N=1119)	Mitral regurgitation (N=6900)	Mitral stenosis (N=2095)	Aortic regurgitation (N=4238)	Aortic stenosis (N=6020)	Tricuspid regurgitation (N=1664)
Female, n (%)	259 071 (55)	5980 (44)	497 (44)	3242 (47)	1107 (3)	1829 (43)	2443 (41)	822 (49)
BMI >30 kg/m^2, n (%)	114 072 (24)	4418 (33)	144 (13)	1969 (27)	557 (27)	1320 (31)	2228 (37)	561 (34)
SBP (mmHg)	140±20	145±21	141±20	144±21	143±21	145±21	147±21	144±21
Smoking (%)	6722 (1)	513 (4)	26 (2)	207 (3)	15 (1)	94 (2)	205 (3)	86 (5)
Dyslipidaemia, n(%)	9958 (2)	1855 (14)	105 (9)	794 (11.5)	47 (2.2)	360 (8.5)	776 (12.9)	222 (13.3)
Diabetes, n (%)	9564 (2.0)	1527 (11.2)	37 (3.3)	590 (8.6)	40 (1.9)	225 (5.3)	735 (12.2)	229 (13.8)
CAD, n (%)	4491 (1.0)	2069 (15.2)	119 (10.6)	911 (13.2)	51 (2.4)	417 (9.8)	883 (14.7)	202 (12.1)
CHF, n (%)	1545 (0.3)	1801 (13.2)	68 (6.1)	1098 (15.9)	99 (4.7)	254 (6.0)	430 (7.1)	395 (23.7)
Rheumatic fever, n(%)	30 (0.0)	891 (6.5)	32 (2.9)	836 (12.1)	927 (44.3)	146 (3.5)	130 (2.2)	214 (12.9)
Infective endocarditis, n (%)	105 (0.0)	974 (7.2)	52 (4.7)	902 (13.1)	932 (44.5)	155 (3.7)	125 (2.1)	225 (13.5)
Atrial fibrillation and flutter, n (%)	3965 (0.8)	3840 (28.2)	271 (24.2)	2867 (41.6)	1022 (48.8)	1694 (40.0)	2002 (33.3)	540 (32.5)
Pulmonary hypertension, n(%)	54 (0.0)	320 (2.4)	38 (3.4)	147 (2.1)	35 (1.7)	34 (0.8)	48 (0.8)	185 (11.1)

Values are expressed as mean±SD or n (%).
BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; SBP, systolic blood pressure.

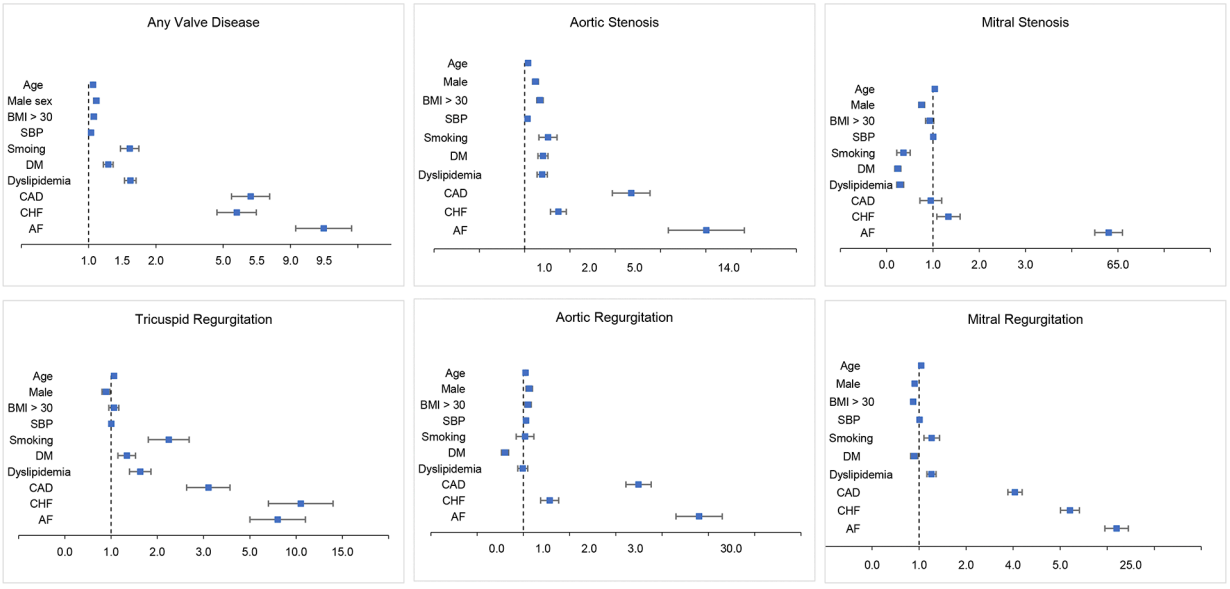

Figure 1 Clinical correlates of incident valvular heart disease (VHD). Forest plots of multivariate Cox regression of incident VHD, VHD subtypes and clinical correlates. AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; SBP, systolic blood pressure.

with increased risk of AR but smoking, diabetes and dyslipidaemia were not. Smoking and dyslipidaemia were associated with increased risk of MR but obesity, SBP and diabetes were not. None of these comorbidities (obesity, SBP, smoking, diabetes, dyslipidaemia) were associated with risk of incident MS.

Mortality and VHD

During 8 465 586 person-years of follow-up, there were 598 deaths among patients with incident valve disease, including 312 with aortic valve disease (0.37 deaths per 10 000 person-years), 213 with mitral valve disease (0.25 deaths per 10 000 person-years) and 43 with tricuspid valve disease (0.51 deaths per 10 000 person-years). Of the total deaths, 193 (79 with aortic valve disease and 83 with mitral valve disease) were from cardiovascular causes, all driven by cardiac arrest.

After adjusting for covariates, and despite a progressive increase in number of valve interventions over the years (figure 2), all-cause and cardiovascular mortality remained higher for patients with any VHD (HR 1.65, 95% CI 1.52 to 1.81 and HR 1.72, 95% CI 1.47 to 1.97, respectively) compared with those without VHD (figure 3). When considered separately, aortic VHD (HR 1.62, 95% CI 1.44 to 1.82; HR 1.39, 95% CI 1.09 to 1.69), mitral VHD (HR 1.25, 95% CI 1.09 to 1.44; HR 1.46, 95% CI 1.16 to 1.76) and TR (HR 2.74, 95% CI 2.24 to 3.37; HR 3.00, 95% CI 2.12 to 4.16) exhibited higher all-cause and cardiovascular mortality when compared with no VHD (figure 3). There was a trend towards higher mortality among patients who did not receive interventions compared with those who did, although not statistically significant (online supplemental figure 1).

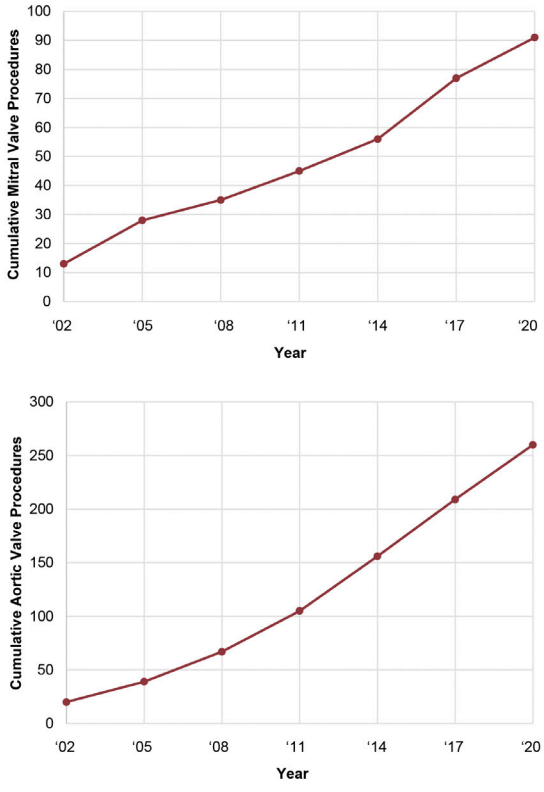

Figure 2 Cumulative number of mitral and aortic interventions. Number of valvular interventions during the study period includes both surgical and percutaneous procedures.

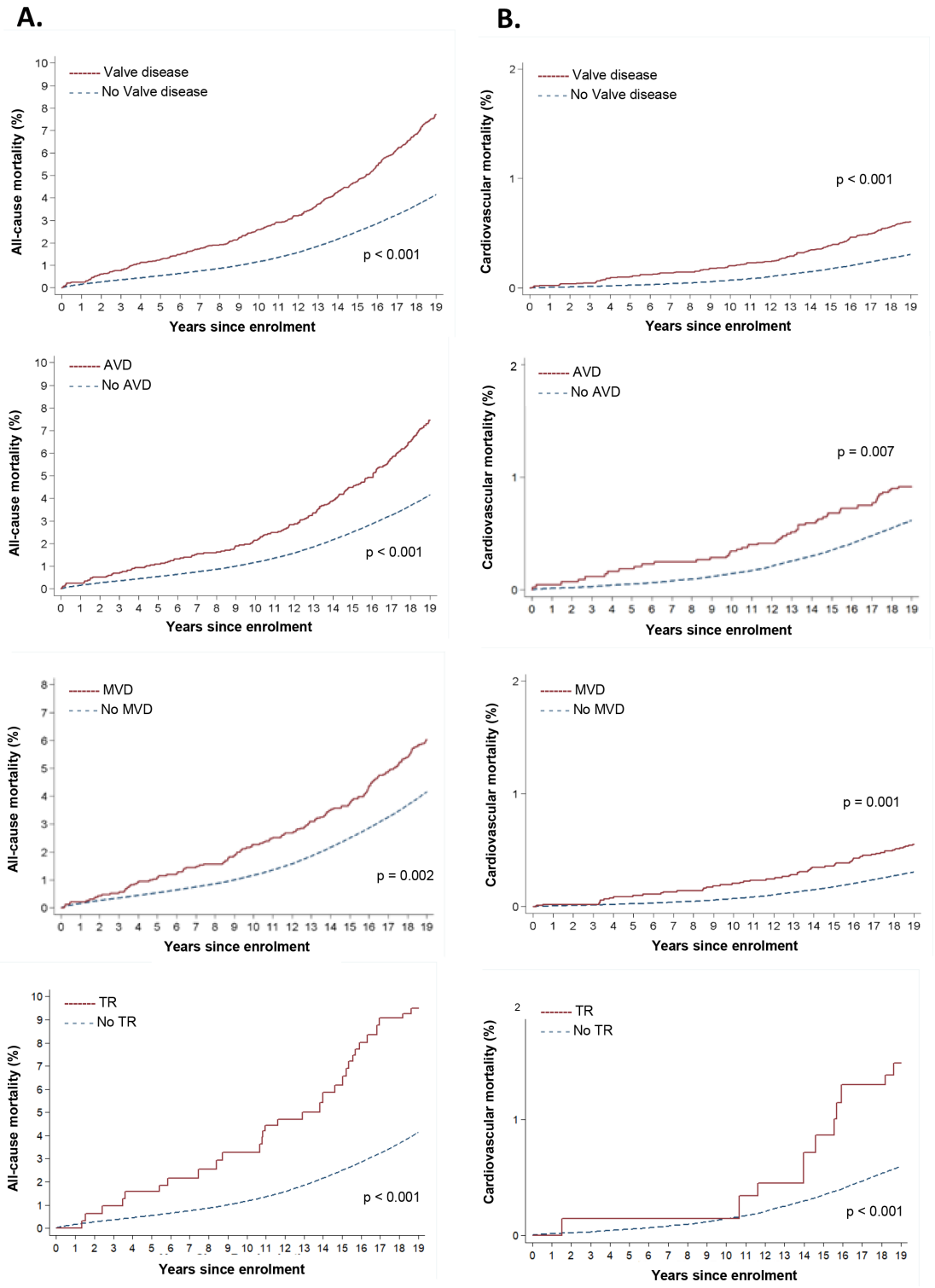

Figure 3 Cumulative mortality of valvular heart disease (VHD). Kaplan-Meier survival curves for all cause (A) and cardiovascular (B) mortality associated with all VHD, and (separately) aortic, mitral, and tricuspid VHD. Models were adjusted for age, sex, systolic blood pressure, obesity, smoking, dyslipidaemia, diabetes, coronary artery disease, congestive heart failure and valvular interventions. AVD, aortic valve disease; MVD, mitral valve disease; TR, tricuspid regurgitation.

DISCUSSION

We leveraged the UK Biobank, a large, contemporary, prospective population-based study, to demonstrate the following: (1) VHD is common and continues to constitute a significant public health burden, (2) Age and cardiac comorbidities like AF, CHF and CAD remain strong risk factors for VHD, (3) In the modern era of percutaneous and advanced surgical interventions, mortality associated with VHD remains high. The strengths of this study are the large size of the

cohort, with inclusion of participants recruited from multiple community-based centres across the UK, and comprehensive record of diagnoses through linkage to both outpatient and inpatient visits across the entire National Health Service.

VHD burden

In our study, the incidence rate of any VHD was 16.3 per 10 000 person-years, and the most common valve lesions were MR, AS and AR. Although the incidence rate of VHD in the UK Biobank was high, it was lower compared with other contemporary cohorts. A study of the entire Swedish population from 2003 to 2010 determined an incidence rate of VHD of 6.4 per 10 000 person-years.[6] Valve prevalence studies using transthoracic echocardiography to detect severe disease including the OxValve cohort in the UK[14] and USA studies[1] are in agreement with our findings that MR is the most common type of VHD, followed by AS and AR. TR incidence rate has not been previously defined in large cohorts, however, a community-based cohort identified a prevalence of 0.55% for moderate or greater TR by TTE, compared with a VA-based cohort where the prevalence was 15.6%.[15 16]

Risk factors for incident disease

Age and sex

Compared with other population-based studies where risk of VHD was assessed cross-sectionally, and only adjusting for age and sex,[1 6] we assessed incident VHD over 20 years, and analysed the contribution of multiple risk factors in a multivariate model. After adjustment for confounders and potential mediators, we demonstrate that ageing remained an important risk for incident VHD of any aetiology, confirming the importance of age-related degenerative valvular changes.

In our study, men were at higher risk of developing VHD overall, and more so aortic valve disorders. The latter finding may be explained by hormonal differences[17] or by a higher burden of other known risk factors such as aortopathies, endocarditis or bicuspid valves.[6]

The finding that MVP was slightly more common in men differs from other cohort-based and pedigree studies that have highlighted either a similar MVP burden in both sexes or a female predominance.[18 19] This may be related to a different genetic background[13 20] or different diagnostic definition (ICD codes in the UK Biobank, echocardiography in US studies).

Valvular comorbidities

Our finding that CAD and CAD risk factors (smoking, hypertension, obesity, hyperlipidaemia, diabetes) are significantly associated with incident AS supports the established paradigm that AS and its predecessor aortic sclerosis exist along the spectrum of atherosclerotic degeneration.[21]

Low BMI has previously been associated with both MR and TR.[7] MVP typically is found in individuals with a thin body habitus,[18] suggesting the coexistence of mild collagenopathies is some cases. We found that among cardiac conditions studied, AF was a strong predictor of all incident VHD subtypes. The interplay of left atrial dilation and AF has been well described and can explain this finding in the case of MR, where mitral annular dilation leads to failure of leaflets to coapt.[22] Similarly, functional TR occurs in the setting of AF even in the absence of left sided heart disease.[23] The heightened risk of AS among participants with AF was an unexpected finding and, to our knowledge, has not previously been described. This may reflect shared risk factors that lead to adverse remodelling of both the aortic valve and the atria. It is intriguing to consider the possibility that AF itself, such as due to a resultant unfavourable neurohormonal signalling, may lead to progression of AS.

There was a strong association between CHF and CAD with all incident VHD subtypes, which is consistent with other cohorts.[6] CAD and myocardial ischaemia can cause MR and TR, while shared underlying mechanisms may underlie atherosclerosis and predisposing lesions to MS (mitral annular calcification) and AS (aortic sclerosis). Similarly, the association with CHF may be explained by the presence of functional MR and TR in this cohort. All VHD subtypes increase risk of CHF, so there is likely reverse causation or collinearity given presence of shared risk factors. Further, since most patients with CHF and CAD undergo echocardiography, VHD is more likely to be detected.

Valve disease and mortality

The presence of any VHD independently increased the risk of all-cause mortality by 65% and increased the risk of cardiovascular mortality by 72%, even after adjusting for percutaneous and modern-age surgical interventions. In comparison, a multivariate model from a Belgian cohort including age, left ventricular hypertrophy, left ventricular ejection fraction <50%, dyspnoea, Cumulative Illness Rating Scale (CIRS), found a 42% increase risk of all-cause mortality and a twofold increased risk of cardiovascular mortality, with moderate-to-severe valve disease.[24] Adjustment for CIRS and echocardiographic abnormalities may explain the difference in mortality risk.

Only 316 patients in the UK Biobank cohort received aortic or mitral valve interventions. Even if we assume that only 10% of reported AS in this sample was severe, this would imply less than half received an aortic valve intervention, which is similar to a recent finding using the US-based Cardiovascular Health Study.[25] A French population-based cohort found similar low uptake of valvular interventions despite high associated societal burden in mortality, readmissions and healthcare costs.[26] Others have highlighted the under-referral of patients with severe MR for surgical repair[27] or transcatheter edge-to-edge repair,[28] and of patients with severe AS for TAVR or SAVR.[29] The low absolute number of valvular interventions identified in our study may be a consequence of incorrect or insufficient coding efforts leading to underestimation of the true number of surgical or

percutaneous procedures. However, the persistent excess mortality related to VHD, and across different types of VHD (figures 2 and 3), despite a cumulative increase in interventions over the past 20 years (figure 2), raises the possibility of low adherence to guideline-directed therapy, including referral to valve centres and access to interventions, similar to what observed in other European and US cohorts. In addition, similar all-cause and cardiovascular mortality in untreated compared with treated VHD suggests that valvular interventions have yet to be incorporated into current practice in a way that offers survival benefit at the population level.

Study limitations

Our study has several limitations. First, UK Biobank participants have lower rates of self-reported chronic diseases and are on average less socioeconomically deprived and more white, compared with UK census data.[30] Second, available ICD-10 codes did not allow grading of VHD severity, though prior studies in Sweden and the USA have shown presence of VHD codes predict moderate or severe disease.[6 11] Further studies using echocardiography to quantify valvular disease severity are needed to confirm appropriateness of interventions and low-adherence to valvular guidelines in the UK. Third, participants did not undergo universal transthoracic echocardiography screening, and participants with known cardiac conditions like CAD, CHF and AF are more likely to get screened with echocardiography. Hence, VHD may be detected at higher rates among these individuals.

In the UK Biobank, VHD continues to constitute a significant public health burden, with MR and AS being the most common. Age and cardiac comorbidities, namely CHF, CAD and AF remain strong risk factors for VHD. In the modern era of percutaneous and advanced surgical interventions, mortality associated with VHD remains high. The link between excess mortality in VHD and low-adherence to guideline-directed therapies warrants further investigation.

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Contributors MT and FND contributed to conception and design of the study, including analytical methods and wrote the paper. GN and JT accessed the UK biobank data and performed all statistical analyses. GM advised on study design, data interpretation and paper writing. All authors checked and approved the final manuscript. MT and FND are guarantors.

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Patient consent for publication Not applicable.

Ethics approval UK Biobank received ethical approval from the North West - Haydock Research Ethics Committee (reference 21/NW/0157). Participants of the UK Biobank gave written informed consent prior to enrollment in the database in accordance with the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data can be obtained by researchers through approved projects (ukbiobank.ac.uk/register-apply).

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Supplement

Supplemental Table 1. Valve disease (ICD-10 and UK Biobank Self-report)

Mitral valve prolapse	
I34.1	Mitral (valve) prolapse
1488*	Mitral valve prolapse
Mitral valve insufficiency	
I34.0	Nonrheumatic mitral (valve) insufficiency
I05.1	Rheumatic mitral insufficiency
I05.2	Rheumatic mitral stenosis with insufficiency
1585*	Mitral valve insufficiency
Mitral valve stenosis	
I34.2	Nonrheumatic mitral (valve) stenosis
I05.0	Rheumatic mitral stenosis
I05.2	Rheumatic mitral stenosis with insufficiency
1489*	Mitral valve stenosis
Aortic valve stenosis	
I35.0	Nonrheumatic aortic (valve) stenosis
I35.2	Nonrheumatic aortic (valve) stenosis with insufficiency
I06.0	Rheumatic aortic stenosis
I06.2	Rheumatic aortic stenosis with insufficiency
1490*	Aortic valve stenosis
Aortic valve insufficiency	
I35.1	Nonrheumatic aortic (valve) insufficiency
I35.2	Nonrheumatic aortic (valve) stenosis with insufficiency
I06.1	Rheumatic aortic insufficiency

I06.2	Rheumatic aortic stenosis with insufficiency
1587*	Aortic valve insufficiency

Tricuspid valve insufficiency

I36.1	Nonrheumatic tricuspid (valve) insufficiency
I36.2	Nonrheumatic tricuspid (valve) stenosis with insufficiency
I07.1	Rheumatic tricuspid insufficiency
I07.2	Rheumatic tricuspid stenosis with insufficiency

*UK biobank self-report codes

Supplemental Table 2. ICD-10 codes used for Comorbid conditions

Smoking

F17 (F17.0-17.9)	Mental and behavioral disorders due to use of tobacco
T65.2	Toxic effect: tobacco and nicotine
Z72.0	Tobacco use not otherwise specified
Z87.89	Personal history of nicotine dependence (excludes current nicotine dependence)

Coronary artery disease

I25.0	Atherosclerotic cardiovascular disease, so described
I25.1	Atherosclerotic heart disease
I25.2	Old myocardial infarction

Dyslipidemia

E78 (E78.0-E78.5)	Disorders of lipoprotein metabolism and other lipidaemias

Diabetes

E10 (E10.0-E10.9)	Type 1 diabetes mellitus
E11 (E11.0-E11.9)	Type 2 diabetes mellitus

E12 (E12.0-E12.9)	Malnutrition related diabetes mellitus
E13 (E13.0-E13.9)	Other specified diabetes mellitus
E14 (E14.0-E14.9)	Unspecified diabetes mellitus
N08.3	Glomerular disorders in diabetes mellitus
O24 (O24.0-O24.3)	Diabetes mellitus in pregnancy

Heart failure

I11.0	Hypertensive heart disease with (congestive) heart failure
I13.0	Hypertensive heart and renal disease with (congestive) heart failure
I13.2	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
I50 (I50.0-I50.9)	Heart failure

Rheumatic Fever

I00 (I00X)	Rheumatic fever without mention of heart involvement
I01 (I01.0-I01.9)	Rheumatic fever with heart involvement
I02 (I02.0-I02.9)	Rheumatic chorea
I09 (I09.0-I09.9)	Other rheumatic heart diseases

Pulmonary hypertension

I27.0	Primary pulmonary hypertension
I27.2	Other secondary pulmonary hypertension

Atrial fibrillation and atrial flutter

I48 (I48.0-I48.9)	Atrial fibrillation and flutter

Endocarditis

I33 (I33.0-I33.9)	Acute and subacute endocarditis
I38 (I38X)	Endocarditis, valve unspecified
I39 (I39.0-I39.8)	Endocarditis and heart valve disorders in diseases classified elsewhere

Supplemental Table 3. Valve Interventions denoted by Office of Population Census and Surveys version 4 (OPCS-4)

Aortic valve interventions	
K26 (K26.1-K26.9)	Plastic repair of aortic valve *K26 code is included in codes that are used for TAVR
Mitral valve interventions	
K25 (K25.1-K25.9)	Plastic repair of mitral valve (including both replacement and repair)
K30.1	Revision of plastic repair of mitral valve
K30.8	Other specified revision of plastic repair of valve of heart
K30.9	Unspecified revision of plastic repair of valve of heart
K34.1	Annuloplasty of mitral valve
K35.1	Percutaneous transluminal mitral valvotomy
K35.5	Percutaneous transluminal valvuloplasty
K35.8	Other unspecified therapeutic transluminal operations on valve of heart
K35.9	Unspecified therapeutic transluminal operations on valve of heart
Tricuspid valve interventions	
K27 (K27.1-K27.9)	Plastic repair of tricuspid valve
K34.2	Annuloplasty of tricuspid valve
Percutaneous interventions	
Y79	Approach to an organ through an artery
Y53	Approach to an organ under radiologic control
Y07.2	Clipping of organ NOC

Supplemental Table 4. Causes of Death included in Cardiovascular Mortality (ICD-10)

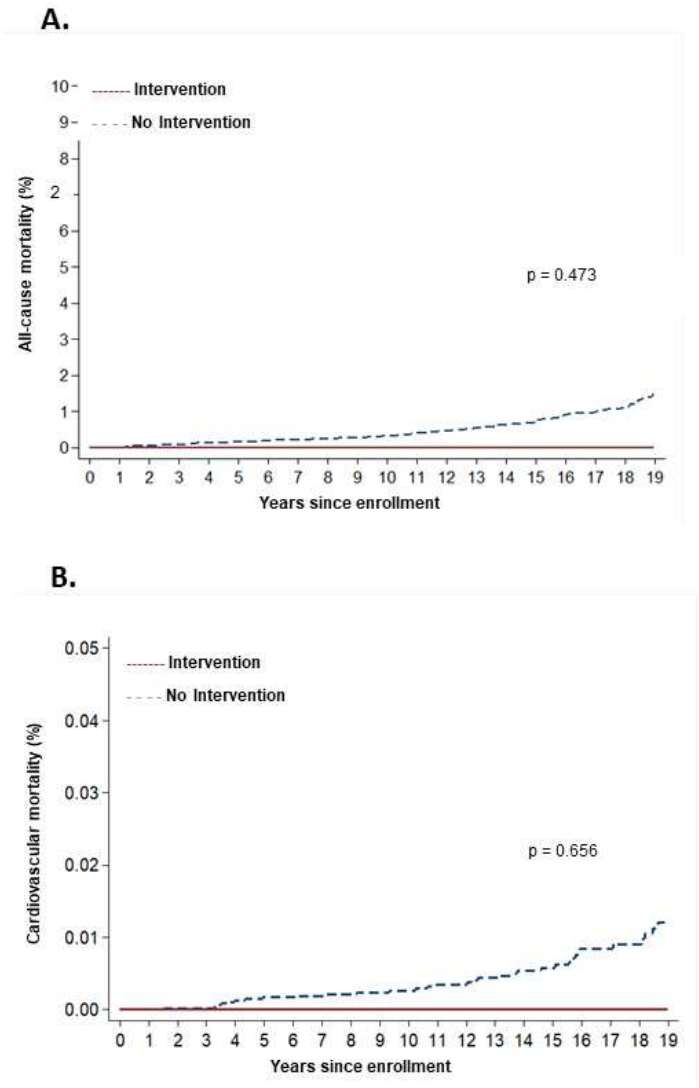
Cardiac arrest	
I46 (I46.0-I46.9)	Cardiac arrest
Stroke	
I60 (I60.0-I60.9)	Subarachnoid hemorrhage
I61 (I61.0-I61.9)	Intracerebral hemorrhage
I62 (I62.0-I62.9)	Other nontraumatic intracranial hemorrhage
I63 (I63.0-I63.9)	Cerebral infarction
I64 (I64X)	Other cerebral infarction
Heart Failure (same as above covariate)	
I11.0	Hypertensive heart disease with (congestive) heart failure
I13.0	Hypertensive heart and renal disease with (congestive) heart failure
I13.2	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
I50 (I50.0-I50.9)	Heart failure
Myocardial Infarction (Heart Attack)	
I21 (I21.0-I21.9)	Acute myocardial infarction
I22 (I22.0-I22.9)	Subsequent myocardial infarction
I23 (I23.0-I23.9)	Certain current complications following acute myocardial infarction
I25.2	Old myocardial infarction

Supplemental Table 5. Demographics and comorbidities of patients with incident valve disease receiving valvular interventions

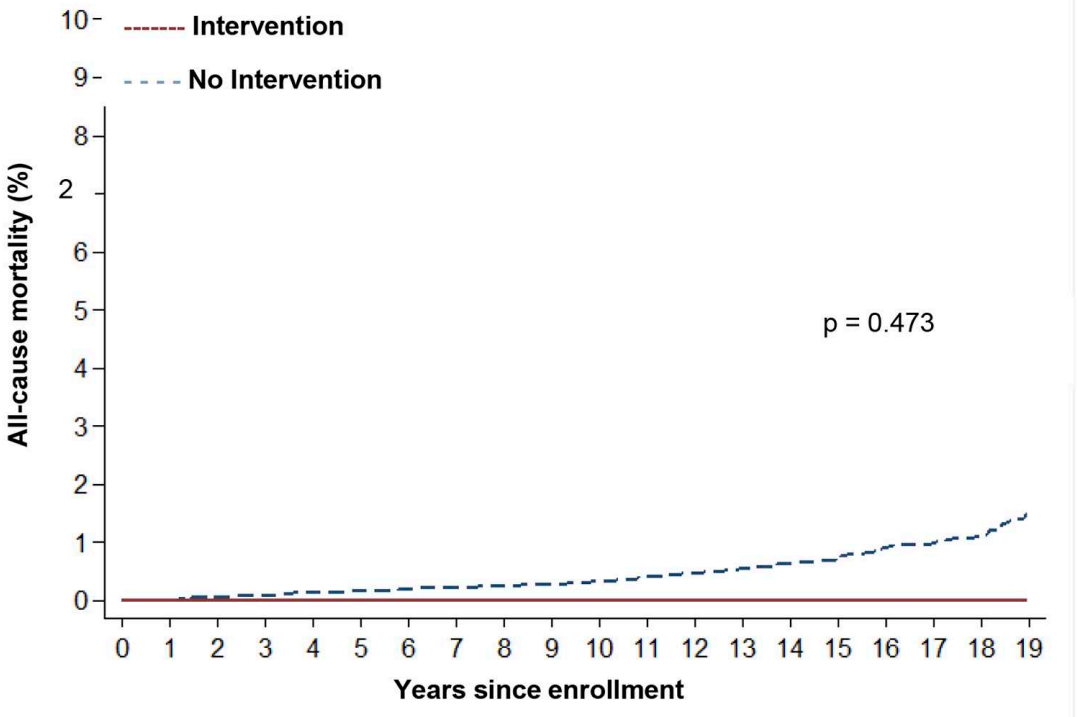
	No Intervention (N = 13289)	Any intervention (N = 309)	P value
Female, n (%)	5899 (44)	81 (26)	<0.001
BMI >30 kg/m^2, n (%)	4322 (33)	96 (31)	0.57
SBP (mmHg)	145 ± 21	147 ± 22	0.20
Smoking (%)	500 (4)	13 (4)	0.69
Dyslipidemia, n(%)	1761 (13)	94 (30)	<0.001
Diabetes, n (%)	1491 (11)	36 (12)	0.82
CAD, n (%)	1964 (15)	105 (34)	<0.001
CHF, n (%)	1780 (13)	21 (6)	<0.001
Rheumatic fever, n(%)	891 (7)	0	<0.001
Infective endocarditis, n (%)	966 (7)	8 (3)	0.0016
Atrial fibrillation and flutter, n (%)	3725 (28)	115 (37)	<0.001
Pulmonary hypertension, n(%)	313 (2)	7 (2)	0.91

Values are expressed as mean ± SD or n (%); BMI, body mass index; SBP, systolic blood pressure; CAD, coronary artery disease; CHF, congestive heart failure.

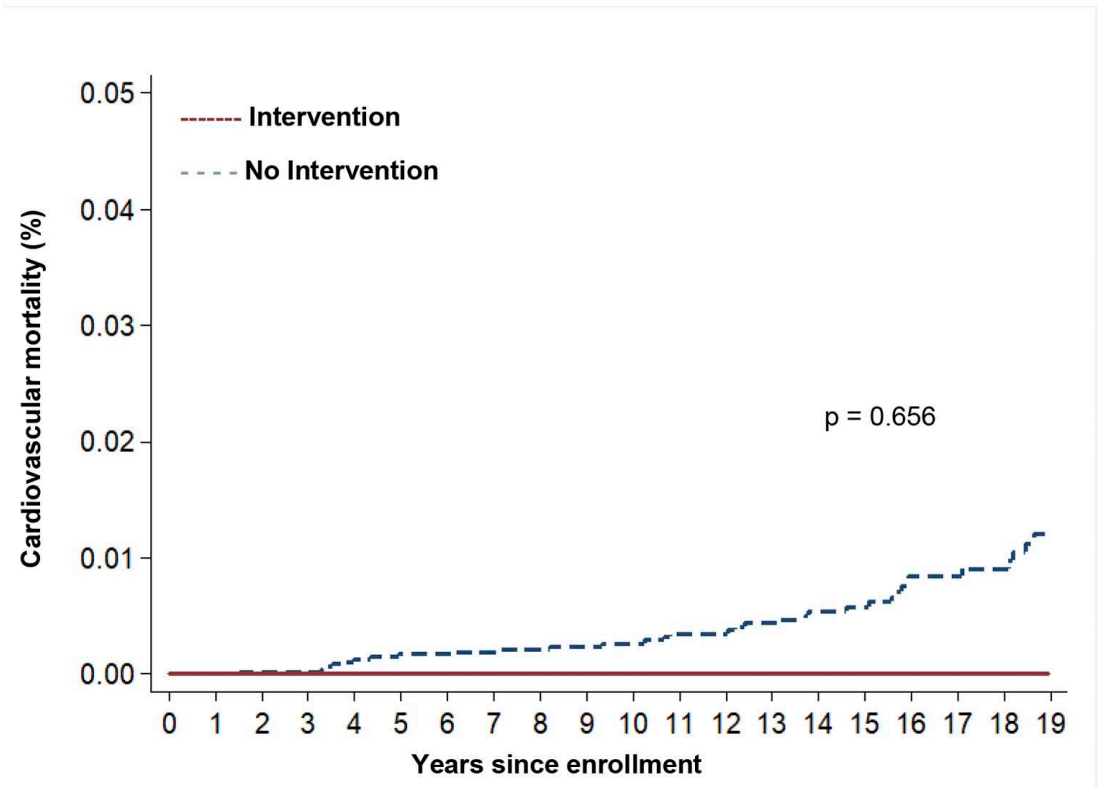
Supplemental Figure 1. Cumulative mortality among patients with valvular heart disease (VHD) receiving interventions. Kaplan-Meier survival curves for all-cause (a) and cardiovascular (b) mortality among patients with VHD who did and did not receive valvular interventions. Models were adjusted for age, sex, systolic blood pressure, obesity, smoking, dyslipidemia, diabetes, coronary artery disease, congestive heart failure and valvular interventions.



A.


Intervention
No Intervention
All-cause mortality (%)
p = 0.473
Years since enrollment

B.


Intervention
No Intervention
Cardiovascular mortality (%)
p = 0.656
Years since enrollment