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ORIGINAL INVESTIGATIONS

Association Between Cardiovascular Risk Factors and Aortic Stenosis

The CANHEART Aortic Stenosis Study

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ABSTRACT

BACKGROUND Few longitudinal studies have delineated the association between traditional cardiovascular risk factors and development of aortic stenosis (AS).

OBJECTIVES The authors examined the association between traditional cardiovascular risk factors and incident severe AS in a large, unselected elderly population.

METHODS This observational cohort study used multiple linked health care population-based databases of individuals older than 65 years on April 1, 2002, without prior valvular disease, coronary artery disease, heart failure, cardiac arrhythmia, cerebrovascular disease, congenital heart disease, or admissions with cardiac symptoms. The relationship between hypertension (HTN), diabetes, dyslipidemia, and incident severe AS requiring hospitalization or surgical or interventional treatment was examined.

RESULTS Among 1.12 million individuals followed for a median of 13 years, 20,995 subjects developed severe AS. Overall absolute incidence was 144 per 100,000 person-years (169 and 127 per 100,000 person-years in men and women, respectively). In cause-specific hazard models, HTN (adjusted hazard ratio [HR]: 1.71; 95% confidence interval [CI]: 1.66 to 1.76), diabetes (HR: 1.49; 95% CI: 1.44 to 1.54), and dyslipidemia (HR: 1.17; 95% CI: 1.14 to 1.21) were all significantly associated with increased risk of developing severe AS (all $p < 0.001$). There was a positive dose-response relationship between the number and duration of cardiac risk factors and risk of AS. In the Fine-Gray model, all 3 risk factors were independently associated with a higher incidence of AS. The population-attributable risk of AS associated with 3 cardiac risk factors was 34.4% (95% CI: 32.8 to 36.0).

CONCLUSIONS HTN, diabetes, and dyslipidemia have independent and dose-response associations with incident AS in an unselected population of older individuals, and together accounted for approximately one-third of the incidence of severe AS. (J Am Coll Cardiol 2017;69:1523–32) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

CI = confidence interval

COPD = chronic obstructive pulmonary disease

HR = hazard ratio

HTN = hypertension

IQR = interquartile range

PAR = population-attributable risk

py = person-years

Valvular heart disease is an emerging epidemic in cardiovascular medicine. Calcific aortic stenosis (AS) is the most common indication for valve replacement in developed countries and its prevalence is expected to rise with the aging population (1-3). Left untreated, symptomatic severe AS is uniformly fatal, with an estimated annual mortality rate of 50%, and confers a worse prognosis than most metastatic cancers. Although aortic valve replacement represents a definitive treatment and transcutaneous techniques have evolved rapidly over the past decade, AS continues to be a major cause of morbidity and mortality and incurs enormous health care costs (2-5).

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The pathogenesis of degenerative AS, which is characterized by leaflet thickening, stiffening, and calcification, is not completely understood (1,6,7). Nevertheless, it is now recognized that degenerative AS is not merely an inevitable consequence of aging resulting from passive wear and tear (1,6,7). Experimental studies have revealed intricate pathogenetic mechanisms involving lipid deposition, inflammation, and osteopontin production, which are active processes also seen in atherosclerosis (6-8). Early epidemiological studies have demonstrated an association between conventional cardiovascular risk factors such as hypertension (HTN), diabetes, and dyslipidemia, and aortic sclerosis or stenosis (9-11). However, most of these studies were cross-sectional, evaluated a selected population, or used imaging endpoints (9-12). To date, there exist only limited longitudinal data from large, representative, population-wide studies (13,14); added insights into the development of AS could potentially lead to future efforts for its prevention. Accordingly, the main objective of our study was to examine the relationship between conventional cardiovascular risk factors and incident severe AS during extended follow-up in a large, unselected elderly population in Ontario. In addition, we assessed whether a dose-response relationship existed by evaluating the relationship between the number and duration of cardiac risk factors with the development of severe AS.

METHODS

DATA SOURCES. The CANHEART (Cardiovascular Health in Ambulatory Care Research Team) "big data" initiative has created large population-based cohorts through the merging of 17 individual-level data sources. It has been fully described elsewhere, with further information available on the study website (15,16). Data sources essential to this current study included the following: 1) the Ontario Registered Persons Database, a dataset of all Ontario residents eligible for the provincial universal health insurance program; 2) the Canadian Institute for Health Information Discharge Abstract Database, the Ontario Hypertension Database, and the Ontario Diabetes Database, which were used to identify prior cardiovascular risk factors and comorbidities; 3) the Ontario Drug Benefit prescription database, which was used to determine outpatient prescription drug use for patients age 65 years or older; 4) the Registrar General of Ontario Vital Statistics Database, which was used to determine cause of death of all Ontarians; and 5) the Statistics Canada census database, which was used to estimate income quintiles based on neighborhood of residence using the postal code of each individual's residency. These datasets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences in Toronto, Ontario, to ensure patient confidentiality.

STUDY COHORT. Ontario residents who were age 65 years or older as of April 1, 2002, and had a valid Ontario Health Insurance Plan number as part of universal health care were eligible for inclusion. We created an inception cohort in 2002 because of the long time severe AS takes to develop. Older individuals were included because our main goal was to evaluate calcific AS. To evaluate individuals without prior cardiac conditions, we excluded patients who had a history of valvular disease, valvular surgery,

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congenital heart disease, coronary artery disease, heart failure, arrhythmia and conduction disorders, and stroke or transient ischemic attacks based on prior hospitalization records. We also excluded patients who had previous hospitalizations for chest pain, syncope, or shock because they could be manifestations of symptomatic severe AS.

ASSESSMENT OF CARDIOVASCULAR RISK FACTORS AND TREATMENT. HTN and diabetes were assessed using previously validated Institute for Clinical Evaluative Sciences databases that have been shown to be highly accurate (17,18). The Ontario Diabetes Database and the Ontario Hypertension Database have been validated to have high specificity (97% and 95%, respectively) for identifying patients with diabetes and HTN, respectively (17,19). In a similar manner, we assessed the presence of dyslipidemia using a combination of outpatient codes from the physician billing records and hospitalization codes using the Canadian Institute for Health Information Discharge Abstract Database.

Antihypertensive medications included angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, and diuretic agents. Oral antihyperglycemic medications included metformin, sulfonylurea, thiazolidinedione, DPP-4 inhibitor, α-glucosidase inhibitor, and meglitinide. Lipid-modifying medications included statins, ezetimibe, niacin, fibrates, and bile acid sequestrants. Medication use was defined as prescription within 100 days before cohort inception.

OUTCOMES. The main outcome of our study was incident severe AS, which was defined as hospitalization for AS and/or aortic valve interventions including surgical or transcatheter aortic valve replacement. Hospitalization for AS was identified using International Classification of Disease-10th revision codes (I060, I062, I350, I352). These codes have been used previously in other population-based studies of AS (13,20). A previous study demonstrated that administrative codes have more than 85% positive predictive values for moderate to severe AS on echocardiography (13). Aortic valve interventions were identified using Canadian Classification of Health Interventions codes (1HV80, 1HV90). Our group has previously demonstrated that valve surgery codes are highly accurate in Ontario with a >95% positive predictive value (21). Complete follow-up to March 31, 2015, was available for all subjects in the cohort.

STATISTICAL ANALYSIS. Categorical variables were presented as frequencies and percentages and compared by chi-square test. Continuous variables were summarized by medians and interquartile ranges (IQRs) and compared by Mann-Whitney *U* test. We investigated the relationship between conventional cardiovascular risk factors and AS by examining both cause-specific hazard models and subdistribution hazard (Fine-Gray) models to account for the competing risk of death (22). Cause-specific hazard models are preferred when disease etiology is of interest because they quantify the effect of covariates on the event rate among those at risk of developing AS. On the other hand, examining the effect of covariates on the cumulative incidences is more informative for predicting the absolute incidence of AS and assessing disease burden in the population (22).

Cox proportional hazard cause-specific models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). The independent variables included age, sex, HTN, diabetes, dyslipidemia, and chronic obstructive pulmonary disease (COPD). Because smoking status was not consistently captured in our database, we adjusted for COPD to account for the potential clinical effect of smoking on our outcomes (23). The assessment period began from the time of cohort inception to the date of diagnosis of AS, death, or end of follow-up (March 31, 2015), whichever came first. Death was treated as a competing event. We verified the proportional hazard assumption by examining the log-log plots and Schoenfeld residuals.

In addition to modeling the association between individual cardiac risk factor and AS, we also tested for the existence of a graded response. First, we evaluated the effect of number of cardiac risk factors on the risk of developing AS by including a variable denoting the number of cardiac risk factors, thereby allowing us to test for a linear dose-response relationship between number of risk factors and the occurrence of AS. Second, we evaluated the duration of each cardiac risk factor (<5 years and ≥5 years) at baseline in cause-specific modeling. The resulting HRs were compared between different durations using *z*-test, based on the parameter estimate and standard error from cause-specific hazard models. We also stratified all of the analyses by sex to evaluate the impact of cardiac risk factors on men and women separately, and tested for interaction between sex and risk factors. We repeated all the models adjusting for additional comorbidities using the Charlson comorbidity score (24), a commonly used composite score comprising medical comorbidities for mortality prediction, and found our results were essentially identical to our original analyses. In an ancillary

TABLE 1 Baseline Characteristics of the Study Cohort

	Overall (N = 1,120,108)	No Aortic Stenosis (n = 1,099,113)	Developed Aortic Stenosis (n = 20,995)	p Value
Age, yrs	74.1 ± 6.8	74.0 ± 6.8	75.2 ± 6.2	<0.001
Median (IQR)	73 (69-78)	73 (69-78)	75 (70-79)	<0.001
Men	455,944 (40.7)	445,945 (40.6)	9,999 (47.6)	
Income quintiles				
1 (lowest)	223,372 (19.9)	219,444 (20.0)	3,928 (18.7)	<0.001
2	242,430 (21.6)	237,805 (21.6)	4,625 (22.0)	
3	225,386 (20.1)	221,306 (20.1)	4,080 (19.4)	
4	206,290 (18.4)	202,360 (18.4)	3,930 (18.7)	
5 (highest)	219,866 (19.6)	215,486 (19.6)	4,380 (20.9)	
Cardiac risk factors				
Hypertension	596,124 (53.2)	582,285 (53.0)	13,839 (65.9)	<0.001
Diabetes	169,019 (15.1)	164,604 (15.0)	4,415 (21.0)	<0.001
Dyslipidemia	220,233 (19.7)	215,324 (19.6)	4,909 (23.4)	<0.001
COPD	28,649 (2.6)	28,079 (2.6)	570 (2.7)	0.145
Peripheral vascular disease	38,081 (3.4)	37,210 (3.4)	871 (4.2)	<0.001
Renal disorder	27,837 (2.5)	27,353 (2.5)	484 (2.3)	0.091
Anemia	35,468 (3.2)	34,680 (3.2)	788 (3.8)	<0.001
Gastrointestinal hemorrhage	43,846 (3.9)	42,845 (3.9)	1,001 (4.8)	<0.001
Medication use				
Angiotensin-converting enzyme	197,515 (17.6)	191,807 (17.5)	5,708 (27.2)	<0.001
Angiotensin II receptor blockers	41,504 (3.7)	40,360 (3.7)	1,144 (5.5)	<0.001
Beta-blockers	126,508 (11.2)	123,408 (11.2)	3,100 (14.8)	<0.001
Calcium-channel blockers	152,980 (13.7)	148,452 (13.5)	4,528 (21.6)	<0.001
Diuretic agents	193,988 (17.3)	188,907 (17.2)	5,081 (24.2)	<0.001
Other lipid-lowering drugs	176,358 (15.7)	171,423 (15.6)	4,935 (23.5)	<0.001
Statin	164,380 (14.7)	159,741 (14.5)	4,639 (22.1)	<0.001
Warfarin	18,673 (1.7)	18,020 (1.6)	653 (3.1)	<0.001
Oral antihyperglycemics	79,678 (7.1)	77,386 (7.0)	2,292 (10.9)	<0.001
Insulins	13,765 (1.2)	13,328 (1.2)	437 (2.1)	<0.001

Values are mean ± SD or n (%) unless otherwise indicated.
COPD = chronic obstructive pulmonary disease; IQR = interquartile range.

TABLE 2 Incidence of Aortic Stenosis Accounting for Competing Risks, Stratified by Age, Sex, and Risk Factors (per 100,000 Person-Years)

	Overall (N = 1,120,108)	Men (n = 455,944)	Women (n = 664,164)
Overall	144.2 (142.2-146.1)	168.7 (165.5-172.0)	127.4 (125.0-129.7)
Age, yrs			
65-69	96.7 (93.8-99.6)	125.2 (120.4-130.0)	73.1 (69.7-76.5)
70-74	145.2 (141.5-148.8)	174.8 (168.7-180.9)	122.7 (118.2-127.2)
≥75	178.9 (175.6-182.3)	205.2 (199.2-211.2)	164.4 (160.5-168.5)
Previous conditions			
Hypertension	178.6 (175.6-181.5)	213.7 (208.5-219.0)	158.0 (154.5-161.5)
Diabetes	200.9 (195.1-206.8)	223.1 (214.0-232.2)	182.0 (174.5-189.6)
Dyslipidemia	171.5 (166.7-176.2)	205.6 (197.2-214.0)	150.2 (144.5-155.8)
Number of risk factors			
0	95.8 (93.2-98.5)	115.1 (110.8-119.4)	80.4 (77.2-83.6)
1	154.7 (151.7-157.8)	184.7 (179.3-190.0)	136.3 (132.6-139.9)
2	200.2 (194.9-205.4)	236.4 (227.3-245.5)	176.8 (170.5-183.2)
3	234.2 (218.7-249.6)	263.0 (237.3-288.6)	214.5 (195.3-233.7)

Values are incidence rate per 100,000 person-years (95% confidence intervals).

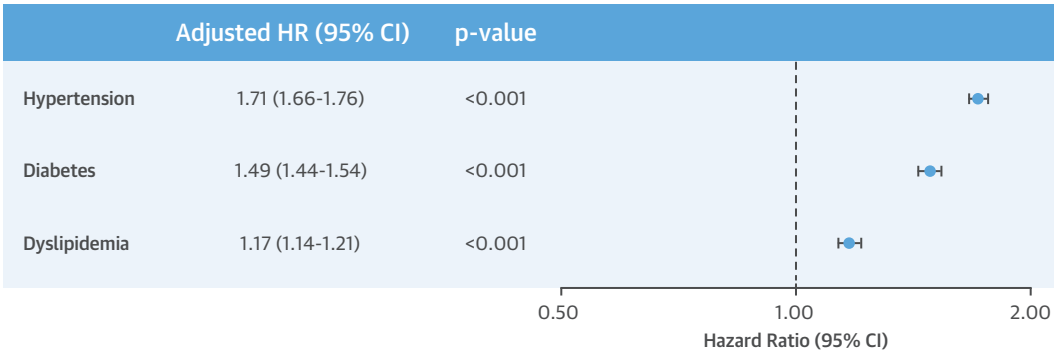
analysis, the risk factors were analyzed as time-dependent covariates.

We calculated the multivariable-adjusted population-attributable risk (PAR) for each risk factor and in combination (25), using the subdistribution HRs in the Fine-Gray model, and estimated the 95% CI according to the delta method. Statistical analysis was performed using SAS Enterprise Guide, version 9.3 (SAS Institute, Cary, North Carolina). All reported p values are 2-sided, and statistical significance was set at $p < 0.05$. This study was approved by the institutional review board at Sunnybrook Health Sciences Centre, Toronto, Canada.

RESULTS

STUDY COHORT. As of April 1, 2002, there were approximately 1.6 million residents age 65 or older in Ontario, Canada. After excluding 42,725 patients who

CENTRAL ILLUSTRATION **The Relationship Between Cardiac Risk Factors and Aortic Stenosis**



Yan, A.T. et al. J Am Coll Cardiol. 2017;69(12):1523–32.

Forest plots demonstrating cause-specific adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) for individual cardiac risk factors (hypertension, diabetes, dyslipidemia). Higher adjusted HRs indicate increased hazard for the development of aortic stenosis.

had prior congenital heart disease, valvular heart disease, or surgery and 376,195 patients who had prior coronary heart disease, heart failure, cardiac arrhythmia, or symptoms of heart disease, our study cohort consisted of 1,120,108 individuals. Over a median follow-up of 13 years (IQR: 7.9 to 13.0 years), 20,995 subjects (1.9%) developed AS and 470,938 (42.0%) died.

BASELINE CHARACTERISTICS ACCORDING TO THE DEVELOPMENT OF AS. Table 1 presents the baseline characteristics of the study cohort stratified by incident AS. At baseline, 53.2% had HTN, 15.1% had diabetes, and 19.7% had dyslipidemia. Among those with diabetes, 43.1% were on oral antihyperglycemic medications only and 8.1% were on insulin (with or without concomitant oral antihyperglycemic medications). Individuals who developed AS were older, more likely to be men, lived in a higher-income neighborhood, and had a higher prevalence of HTN, diabetes, dyslipidemia, peripheral vascular disease, and COPD. They were also more frequently taking antihypertensive, antihyperglycemic, and lipid-modifying medications. Individuals who developed AS had significantly higher mortality than those without AS (60.0% vs. 41.7%, respectively; $p < 0.001$).

INCIDENCE OF AS. The incidence of severe AS by age, cardiac risk factors, and number of risk factors is shown in Table 2 and Online Figure 1. The overall incidence of AS requiring hospitalization or intervention during follow-up was 144.2 per 100,000 person-years (py), 168.7 and 127.4 per 100,000 py in men and women ($p < 0.001$), respectively. When the cohort was stratified by the number of cardiovascular risk factors, the incidence rates were 95.8, 154.7, 200.2, and 234.2 per 100,000 py for subjects with 0, 1, 2, and 3 risk factors, respectively (p for trend <0.001) (Table 2, Online Figure 1). Men had a significantly higher incidence of AS compared with women in all subgroups.

ASSOCIATION OF CARDIOVASCULAR RISK FACTORS AND AS. The Central Illustration and Table 3 summarize the results of the cause-specific Cox proportional hazard model. For each 10-year increase in age, the adjusted HR was 1.71 for the development of AS. Women had substantially lower hazard of AS (HR: 0.65; 95% CI: 0.63 to 0.67). HTN (adjusted HR: 1.71; 95% CI: 1.66 to 1.76), diabetes (HR: 1.49; 95% CI: 1.44 to 1.54), and dyslipidemia (HR: 1.17; 95% CI: 1.14 to 1.21) were all significantly associated with developing AS (all $p < 0.001$). The adjusted HRs were 1.71 (95% CI: 1.63 to 1.79) for diabetes treated with oral antihyperglycemic medications only and 2.34 (95% CI 2.13 to 2.57) for diabetes treated with insulin. Further adjustment for chronic kidney disease in the cause-specific Cox model did not change the results. When these risk factors were analyzed as time-dependent covariates in the multivariable model, their independent associations with AS were maintained.

We also observed a positive dose-response relationship between the number and duration of cardiac risk factors and risk of AS. Compared with the group with no risk factor, the increased hazard of AS was

TABLE 3 Estimates of the Adjusted Hazard Ratios for Severe Aortic Stenosis in Prediction Models for All Individuals, Men, and Women

	Overall (N = 1,120,108)	Men (n = 455,944)	Women (n = 664,164)
Model 1: risk factors			
Age, per 10 yrs	1.75 (1.71-1.78)	1.64 (1.59-1.69)	1.84 (1.79-1.89)
Women	0.65 (0.63-0.67)	NA	NA
Hypertension	1.71 (1.66-1.76)	1.68 (1.61-1.75)	1.74 (1.67-1.82)
Diabetes	1.49 (1.44-1.54)	1.44 (1.37-1.51)	1.54 (1.47-1.61)
Dyslipidemia	1.17 (1.14-1.21)	1.17 (1.12-1.23)	1.17 (1.12-1.22)
Chronic obstructive pulmonary artery disease	1.36 (1.25-1.48)	1.36 (1.21-1.53)	1.36 (1.21-1.53)
Model 2: no. of risk factors			
Age, per 10 yrs	1.78 (1.75-1.82)	1.67 (1.62-1.72)	1.88 (1.83-1.93)
Women	0.65 (0.63-0.66)	NA	NA
1 risk factor	1.73 (1.67-1.79)	1.70 (1.62-1.78)	1.75 (1.67-1.84)
2 risk factors	2.31 (2.22-2.40)	2.25 (2.13-2.38)	2.37 (2.24-2.50)
3 risk factors	2.77 (2.57-2.98)	2.55 (2.30-2.84)	2.97 (2.69-3.28)
Chronic obstructive pulmonary artery disease	1.37 (1.26-1.49)	1.37 (1.21-1.54)	1.38 (1.23-1.55)
Model 3: duration of risk factors			
Age, per 10 yrs	1.73 (1.70-1.77)	1.63 (1.58-1.68)	1.82 (1.77-1.87)
Women	0.65 (0.63-0.66)	NA	NA
Hypertension <5 yrs	1.50 (1.45-1.57)	1.53 (1.45-1.62)	1.48 (1.40-1.57)
Hypertension ≥5 yrs	1.81 (1.75-1.87)	1.75 (1.68-1.83)	1.86 (1.78-1.94)
Diabetes <5 yrs	1.31 (1.24-1.38)	1.27 (1.18-1.37)	1.34 (1.24-1.45)
Diabetes ≥5 yrs	1.58 (1.52-1.65)	1.53 (1.45-1.62)	1.63 (1.54-1.73)
Dyslipidemia <5 yrs	1.15 (1.09-1.20)	1.16 (1.08-1.24)	1.13 (1.06-1.21)
Dyslipidemia ≥5 yrs	1.19 (1.14-1.24)	1.19 (1.12-1.26)	1.19 (1.13-1.26)
Chronic obstructive pulmonary artery disease	1.37 (1.26-1.49)	1.37 (1.22-1.55)	1.37 (1.22-1.54)

Values are adjusted hazard ratios (95% confidence intervals). Estimates for women were not available for sex-stratified models.
NA = not available.

1.73 (95% CI: 1.67 to 1.79) for 1 risk factor, 2.31 (95% CI: 2.22 to 2.40) for 2 risk factors, and 2.77 (95% CI: 2.57 to 2.98) for 3 risk factors (p for trend <0.001) (Figure 1).

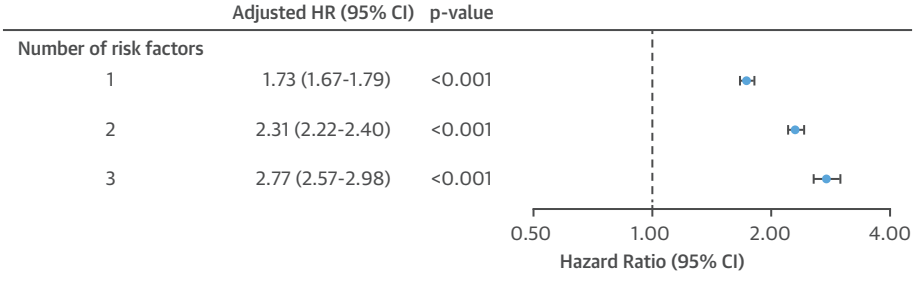
Figure 2 illustrates the relationship between duration of cardiac risk factors and incident severe AS. Longer duration of HTN and diabetes was associated with increased risk of AS. For example, the adjusted cause-specific HR for individuals with HTN for at least 5 years was 1.81 (95% CI: 1.75 to 1.87) versus 1.50 (95% CI; 1.45 to 1.57; p < 0.001) for individuals with HTN for <5 years. Similarly, individuals who had a longer duration of diabetes had significantly higher HR compared with those with shorter duration (HR: 1.58; 95% CI: 1.52 to 1.65 for ≥5 years vs. HR: 1.31; 95% CI: 1.24 to 1.38 for <5 years; p <0.001). The HRs did not differ significantly for dyslipidemia duration.

In the Fine-Gray model, all 3 cardiac risk factors were independently associated with the incidence of AS. There was also a graded response relationship between the number of risk factors and incidence of AS.

RELATIONSHIP OF CARDIAC RISK FACTORS AND AS IN MEN AND WOMEN. Although women had a lower incidence of AS compared with men, the relationship of cardiac risk factors on AS development did not differ significantly (Online Figures 2 to 4). There was no significant interaction between sex and any of the risk factors. The adjusted HRs for AS in women with HTN (HR: 1.74; 95% CI: 1.67 to 1.82), diabetes (HR: 1.54; 95% CI: 1.47 to 1.61), and dyslipidemia (HR: 1.17; 95% CI: 1.12 to 1.22) did not differ significantly from those in men with HTN (HR: 1.68; 95% CI: 1.61 to 1.75), diabetes (HR: 1.44; 95% CI: 1.37 to 1.51), and dyslipidemia (HR: 1.17; 95% CI: 1.12 to 1.23).

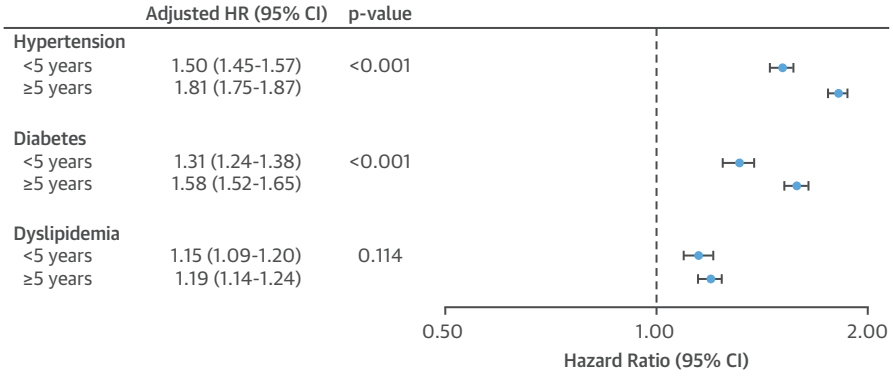
PAR OF CARDIAC RISK FACTORS. Table 4 shows the PAR of individual and combined risk factors in men and women. HTN had the highest attributable risk at 23.4%, followed by diabetes (5.6%) and dyslipidemia

FIGURE 1 The Relationship Between Number of Cardiac Risk Factors and Aortic Stenosis



Forest plots demonstrating cause-specific adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) for the number of cardiac risk factors (hypertension, diabetes, dyslipidemia). Higher adjusted HRs indicate increased hazard for the development of aortic stenosis.

FIGURE 2 The Relationship Between Duration of Cardiac Risk Factors and Aortic Stenosis



Forest plots demonstrating cause-specific adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) for individual duration of each cardiac risk factor (<5 years or ≥5 years). Higher adjusted HRs indicate increased hazard for the development of aortic stenosis. p values refer to the comparisons of hazard ratios between the 2 durations.

(4.4%). Taken together, the 3 risk factors had a PAR of 34.4% (95% CI: 32.8 to 36.0) in the entire cohort.

DISCUSSION

Using a population-based longitudinal and big data methodological approach, we were able to examine the relationship of cardiac risk factors and the development of AS. Among the 1.12 million Canadians age 65 and older who were followed for more than a decade, we found an independent and dose-response relationship between conventional cardiovascular risk factors such as HTN, diabetes, and dyslipidemia and the risk of developing severe AS. The combination of these risk factors accounted for approximately one-third of the attributable risk for AS on a population level. HTN had the highest attributed risk compared with other risk factors because of its higher prevalence in older individuals and a higher HR. Our observational study demonstrates a strong, independent, and graded association between cardiovascular risk factors and the development of AS in the elderly population, which is corroborated by prior experimental data. Together, these findings strongly implicate a pivotal causative role of cardiovascular risk factors in pathogenesis of AS and the potential impact of intensive risk factor modification in mitigating the disease burden.

Even though we included an older cohort in which more than one-half of the patients had HTN, 15% had diabetes, and 20% had dyslipidemia, the overall incidence of AS was low at 144 events per 100,000 py. In fact, the competing risk of death predominated. Not surprisingly, age had a strong association with the development of AS: each decade increase in age had a 75% increase in the hazard of AS. Accordingly, as overall life expectancy continues to increase, the burden of AS on the aging society is anticipated to soar. We also observed that although women had lower incidence of AS, the association of cardiac risk factors and development of AS in men and women was similar.

There appears to be a complex interplay between genetic and modifiable epigenetic factors in the development of calcific AS (1,6,7,26). Animal models and experimental studies have furnished valuable insights into the pathogenesis of AS and therapeutic targets (7,27). Genetically hypercholesterolemic old mice are prone to aortic calcification and dysfunction that resemble clinical AS in humans, and this disease process is accelerated by a high-fat diet (27,28). Activation of the renin-angiotensin system and receptors of the advanced glycosylation end-products, radical oxygen species, proinflammatory cytokines, and metalloproteinases are thought to modulate the pro-fibrotic and pro-calcific pathways

TABLE 4 Population-Attributable Risk of Aortic Stenosis by Cardiovascular Risk Factors

	Overall	Men	Women
Hypertension	23.4 (22.0–24.9)	22.1 (20.2–24.0)	27.1 (25.0–29.2)
Diabetes	5.6 (4.9–6.2)	4.9 (4.0–5.9)	5.3 (4.4–6.1)
Dyslipidemia	4.4 (3.7–5.2)	4.4 (3.4–5.5)	5.0 (3.9–6.0)
1 risk factor	21.2 (19.7–22.7)	19.5 (17.5–21.5)	22.6 (20.4–24.8)
1 or 2 risk factors	32.6 (31.0–34.2)	30.4 (28.2–32.6)	34.5 (32.2–36.8)
1 or 2 or 3 risk factors	34.4 (32.8–36.0)	31.9 (29.7–34.2)	36.3 (34.0–38.6)

Values are % population-attributable risk (95% confidence intervals).

culminating in AS (7). Together, these data imply common pathogenetic mechanisms in atherosclerosis and AS.

Clinical studies have also demonstrated an association between conventional cardiovascular risk factors and the spectrum of aortic valve disease, ranging from aortic sclerosis to severe calcific AS (1,29,30). Among 2,683 participants in the Framingham Heart Study's offspring cohort, inflammatory biomarkers (C-reactive protein, intercellular adhesion molecule-1, interleukin-6, and monocyte chemoattractant protein-1) were associated with calcified aortic valve or annulus on echocardiography (10). However, the association became nonsignificant after adjustment for cardiovascular disease risk factors, suggesting that the observed association between systemic inflammatory markers and valvular calcification may be mediated by shared risk factors. In a cross-sectional analysis of 5,201 elderly men enrolled in the Cardiovascular Health Study, history of HTN, smoking, low-density lipoprotein cholesterol and lipoprotein (a) levels were independently associated with AS or aortic sclerosis on echocardiography (9). In the Multi-Ethnic Study of Atherosclerosis, metabolic syndrome and diabetes were independently associated with aortic valve calcification as assessed by computed tomography (12). Using a Mendelian randomization study design, Smith et al. found that genetic predisposition to elevated low-density lipoprotein cholesterol was associated with aortic valve calcification and stenosis in 3 community-based cohorts (31), providing further support for a causal relationship.

Our study differed from prior studies in that we evaluated a large, unselected population in a longitudinal fashion and used clinical event or intervention for AS as the primary outcome. We observed positive and independent associations between number and duration of cardiovascular risk factors such as HTN, diabetes and dyslipidemia, and the development of AS. These data raise the intriguing hypothesis that aggressive risk factor modification may retard the progression of aortic sclerosis and stenosis. To date, there has been no randomized controlled trial to specifically examine whether antihypertensive or antihyperglycemic therapy can prevent the development or retard the progression of AS. Although it is unlikely that adequately powered trials with sufficient long-term follow-up will be conducted to evaluate their impact on AS, optimal management of these risk factors is warranted given the other established cardiovascular benefits (32).

In our study, we found that dyslipidemia was associated with a statistically significant but only modest increase in the hazard of AS of about 13%. This observation may explain the neutral findings of prior randomized controlled trials of statins that failed to halt the increase in aortic jet velocity or valvular calcification, or need for aortic valve surgery, given the duration of follow-up and number of events (33–35). Furthermore, experimental data suggest that there may be distinct pathogenetic mechanisms in the initiation of aortic sclerosis and the late progression of fibrocalcific AS, supporting the notion that statin efficacy may differ substantially in early versus advanced disease (36).

Both the magnitude of the associated increase in risk and the PAR of AS were highest for HTN, followed by diabetes, and then dyslipidemia. Together, these 3 risk factors accounted for 34% of the PAR of AS. By comparison, the Health Professionals Follow-up study reported that these 3 risk factors and smoking conferred a PAR of 75% for incident peripheral arterial disease in men (37). In the INTERHEART study involving 52 countries worldwide, 5 risk factors (smoking, lipids, HTN, diabetes, and obesity) constituted about 80% of the PAR of acute myocardial infarction among men and women (38). It is conceivable that genetic and other yet-to-be-elucidated factors are relatively more important in the pathogenesis of AS than atherosclerotic diseases.

STUDY LIMITATIONS. First, we used a composite endpoint of hospitalization for AS or aortic valve interventions as an outcome because echocardiographic data were not available. We believe that these are reasonable surrogates of severe AS and are unlikely to be subject to ascertainment bias. Although other groups have validated the accuracy of administrative codes for AS, they have not been validated in Ontario. It is conceivable that some patients who had developed AS might have experienced sudden cardiac death before diagnosis of AS and thus would not have been captured in our cohort. Second, we did not have physiological measures and laboratory values and we were not able to assess the association between risk factor control and AS. Furthermore, smoking status was not recorded in our databases; we used COPD as a surrogate for smoking. Although obesity is a potential modifiable risk factor, we were unable to evaluate its association with AS because measures of obesity such as body mass index or waist circumference were not available in our dataset. Because patients with coronary artery disease and AS share similar risk factors, it is possible that they received more cardiac testing such as echocardiography. However, we believe our association was unlikely an epiphenomenon because most patients with coronary artery disease would not be hospitalized or received intervention more often

for AS. Although this Ontario population-based study included subjects from diverse ethnic backgrounds, our findings may not be generalizable to other populations and developing countries in which the etiologies of AS may vary. Finally, causality cannot be inferred in this observational study alone, although several lines of experimental evidence also lend credence to a causal association between these traditional cardiovascular risk factors and AS.

CONCLUSIONS

In this large population-based longitudinal study of an elderly cohort, we found strong, independent, and graded relationships between conventional cardiovascular risk factors and both the risk and incidence of AS. These modifiable risk factors, HTN, diabetes, and dyslipidemia, together accounted for about one-third of the PAR of AS.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Hypertension, diabetes, and dyslipidemia have strong, independent, graded relationships with the incidence of severe aortic stenosis in the elderly, accounting for about one-third of the attributable risk.

TRANSLATIONAL OUTLOOK: Prospective studies are needed to determine whether risk factor management can reduce the incidence of severe aortic stenosis.

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APPENDIX For supplemental figures, please see the online version of this article.