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ORIGINAL RESEARCH

Diameter Reduction Determined Through Carotid Ultrasound Associated With Cardiovascular and All-Cause Mortality: A Single-Center Experience of 38 201 Consecutive Patients in Taiwan

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BACKGROUND: Few studies have evaluated the prognostic significance of diameter-based carotid sonographic measurements for mortality. We investigated whether a reduction in diameter of different carotid anatomical segments is associated with cardiovascular and all-cause mortality in a hospital-based cohort with universal health care.

METHODS AND RESULTS: We conducted a retrospective cohort study of 38 201 patients who underwent carotid duplex ultrasound at a medical center in Taiwan. Carotid sonographic parameters were the diameter reduction percentage in carotid bifurcation, the internal carotid artery, the common carotid artery, and the external carotid artery and the overall carotid atherosclerotic burden score, determined by summing the scores from all segments. The vital status was ascertained by linking data to National Death Registry until 2017. During a median follow-up of 4.2 years, 5644 participants died, with 1719 deaths attributable to cardiovascular diseases. The multivariable-adjusted hazard ratios (HRs; 95% CIs) for cardiovascular mortality were 1.33 (1.16–1.53), 1.58 (1.361.84), and 1.89 (1.58, 2.26) for participants with 30% to <40%, 40% to <50%, and ≥50% reduction in carotid bifurcation diameter, respectively, compared with participants with <30% diameter reduction (*P* for trend <0.001). The corresponding HRs (95% CIs) for all-cause mortality were 1.25 (1.16–1.34), 1.42 (1.31–1.54), and 1.60 (1.45–1.77), respectively. Diameter reduction at other carotid sites and the carotid atherosclerotic burden score exhibited the same dose–response relationship.

CONCLUSIONS: This study suggests that reduction in carotid artery diameter, which can be determined through routinely available sonography, is an independent risk factor for all-cause and cardiovascular mortality.

Key Words: atherosclerosis ■ carotid artery diameter ■ electronic health records ■ mortality

Atherosclerosis is a progressive systemic disease in middle-aged people and has an estimated prevalence of 44% to 63% in different populations.[1–4] Atherosclerosis severity is commonly evaluated using non-invasive measures, such as brachial-ankle pulse-wave velocity for arterial stiffness, multidetector computed tomography for coronary calcification, and duplex ultrasonography for carotid intima–media thickness (IMT).[5,6] Plaques, which occur when the atherosclerosis burden becomes severe, cause carotid artery stenosis.[7] High-grade carotid stenosis (ie, >50%), quantified through the peak systolic velocity (PSV) in

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CLINICAL PERSPECTIVE

What Is New?

- Carotid artery diameter reduction determined through sonography may indicate atherosclerotic burden. However, the long-term prognostic implications of diameter-based carotid sonographic measurements remain undetermined.
- Our study revealed an exposure-response relationship between the reduction in diameter of various carotid anatomical segments (carotid bifurcation, internal carotid artery, external carotid artery, and common carotid artery) determined by ultrasonography and the all-cause and cardiovascular mortality.
- Our proposed summary measure of overall atherosclerotic burden over multiple carotid segments was associated with increased risk of all-cause and cardiovascular mortality in an exposure-response manner.

What Are the Clinical Implications?

- The diameter-reducing percentage of carotid arteries and the proposed summary measures can be determined through regular carotid ultrasonography in real-world healthcare settings.
- Our observations suggested that the straightforward diameter approach has the potential utility to inform long-term prognosis for both all-cause and cardiovascular mortality.

Nonstandard Abbreviations and Acronyms

CABS	carotid atherosclerotic burden score
CCA	common carotid artery
CMUH	China Medical University Hospital
FRS	Framingham Risk Score
ICA	internal carotid artery
IMT	intima–media thickness
PSV	peak systolic velocity

the internal carotid artery (ICA),[8,9] has been linked to all-cause mortality,[10] adverse cardiovascular outcomes such as peripheral artery occlusive disease[11] and major or fatal stroke,[7,12] and composite outcomes of myocardial infarction and non-stroke vascular death.[13]

Current guidelines recommend using the PSV in the ICA to quantify carotid stenosis[14] because the PSV is strongly correlated with the stenosis severity defined by contrast angiography.[15] However, this consensus approach is based on studies conducted almost 3 decades ago,[16] and evidence shows significant variability in the relationship between Doppler velocity criteria and the percentage of angiographic stenosis.[17] Furthermore, stenosis in other anatomical areas of the carotid artery system has prognostic value.[18] For example, carotid bifurcation atherosclerosis has been identified as a risk factor for cerebrovascular insufficiency, myocardial infarction, and vascular death.[18–20]

Studies have shown that diameter measurement can serve as a reliable indicator of stenosis.[21,22] The narrowest diameter of a residual stenotic lumen was strongly correlated with 2-dimensional area–based measurements even for asymmetric and irregular lesions.[21] In addition, carotid bifurcation narrowing identified through B-mode imaging is a valid stenosis measurement, with arteriography being the gold standard.[22] However, the long-term prognostic implications of diameter-based carotid sonographic parameters remain undetermined. With the advent of a big data medical ecosystem that integrates both structured clinical information and unstructured clinical imaging, we can evaluate the relationships between the reduction in diameter of various carotid anatomical segments and the risks of all-cause and cardiovascular mortality, which were ascertained using the National Death Registry of Taiwan.

METHODS

Data Source and Study Population

Anonymized data that support findings of this study are available from the corresponding author upon reasonable request from qualified investigators. In this retrospective cohort study, we obtained data from the Clinical Research Data Repository of China Medical University Hospital (CMUH); this repository comprises validated and integrated electronic health records from various clinical sources to unify trackable patient information generated during the healthcare process (Data S1). We analyzed original carotid ultrasound reports from routine clinical practice and self-paid physical examination services for 42 216 patients who underwent a carotid duplex ultrasound examination between 2008 and 2016. In our standard protocol, carotid ultrasound examination is always performed bilaterally, and scan findings of the right and left carotid arteries are documented in a single report for each patient. For patients with >1 carotid duplex ultrasound study, we included only the first carotid ultrasound record and defined the index date as the date of the first examination. Patients aged <40 or >90 years at the index date (n=4005) and with missing data on sex (n=10) were excluded. The baseline characteristics of the study patients during the 1 year before the index date were collected from the Clinical Research Data Repository of CMUH (Data S2,

Table S1). The protocol was approved and informed consent was waived by the Big Data Center of CMUH and the Research Ethical Committee and Institutional Review Board of CMUH (CMUH105-REC3-068 and CMUH107-REC2-124).

Carotid Imaging

The bilateral segments of extracranial carotid arteries were scanned using a GE Vingmed Ultrasound Vivid 7 equipped with a 5- to 10-MHz linear array transducer. All examinations were performed following the standard vascular laboratory protocol of carotid imaging at CMUH, in which data routinely recorded include the diameter reduction percentage obtained through B-mode ultrasonography and flow velocity measures estimated through pulse-wave Doppler spectrum analysis. Carotid bifurcation, the common carotid artery (CCA), the ICA, and the external carotid artery were evaluated thoroughly through both longitudinal and transverse approaches by registered sonography technicians, and the narrowest portion of the carotid arteries was identified (Figure S1). Plaque was identified as a focal protrusion of the vascular wall encroaching upon the arterial lumen. The color-coded B-mode was used for plaque identification in case of non-calcified lesions. Acoustic shadowing without presence of plaque was considered artefactual. In the data analysis, the maximum diameter reduction percentages, one each from the left and the right arteries, were used for the analysis and classified into 4 categories—0% to <30%, 30% to <40%, 40% to <50%, and ≥50% for each carotid artery segment. To observe the relationship between the overall atherosclerosis burden and mortality, we assigned a score to each chosen segment according to the stenosis degree: 0=0% to <30%; 1=30% to <40%; 2=40% to <50%, and 3=≥50%. An overall carotid atherosclerotic burden score (CABS) was then determined by summing of scores from all segments.

Outcomes

The outcomes were cardiovascular and all-cause mortality determined from Taiwan's National Death Registry, a data set systematically maintained by the Health and Welfare Data Science Center of the Ministry of Health and Welfare. Death registration is mandatory in Taiwan. The follow-up period started on the index date and ended on death or December 31, 2017, whichever occurred first. Deaths were attributed to cardiovascular disease if the cause of death included 1 of the following: hypertensive disease, rheumatic or ischemic heart disease, cerebrovascular disease, arteriolosclerosis, and aortic aneurysm and dissection (see Table S1 for diagnosis codes).

Statistical Analysis

Continuous variables were expressed as the median and interquartile range and compared across the categories of diameter reduction by using the nonparametric Kruskal–Wallis test. Categorical variables were expressed as frequency (percentage) and compared using the Chi-square test. Cox proportional hazard models were used to estimate the associations between diameter reduction percentage and risk of mortality from all causes and cardiovascular diseases. The models yielded hazard ratios (HRs) with 95% s CIs for each category of diameter reduction percentage by using 0% to 29% as a reference. Model 1 included adjustments for age and sex. Model 2 included additional adjustments for diabetes, hypertension, cardiovascular disease, stroke, estimated glomerular filtration rate, hemoglobin level, and the use of statins and antiplatelets at baseline. In the cardiovascular mortality analysis, we used the Fine–Gray model, which yielded the subdistribution of HRs, to account for competing risks.[23] Furthermore, we characterized dose–response relationships between the CABS and risks of death from cardiovascular disease and all causes by using a restricted cubic spline model with 3 knots located at the 75th, 85th, and 95th percentiles of the diameter reduction percentage. Exploratory subgroup analysis was conducted to evaluate the potential interaction between the diameter reduction percentage in the carotid bifurcation, CABSs, and the following cardiovascular risk factors and diseases: age (≤65 versus >65 years), sex, diabetes, hypertension, stages of chronic kidney disease (1 and 2 versus 3, 4, and 5), cardiovascular diseases, and stroke. The statistical significance of the effect modification was examined using the likelihood ratio test comparing models with and without the interaction term.

To evaluate clinical implications, we performed an additional analysis to explore whether the predictions of all-cause and cardiovascular mortality risk could be improved using the measurement of diameter reduction percentage. Furthermore, several sensitivity analyses were performed to test the robustness of the main study results (Data S3 and Data S4).

We used SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) for statistical analyses. All analyses were 2-sided, and the significance level was set to 0.05.

RESULTS

Baseline Characteristics of Study Patients

Overall, 38 201 patients with complete bilateral ultrasound examination data were eligible for inclusion in the analysis; the mean (median) follow-up was 4.4 (4.2)

Table 1. Baseline Demographic and Clinical Characteristics Based on Diameter Reduction Percentage in Carotid Bifurcation

	Diameter reduction in the carotid bifurcation (n=38 201)					
	0%–<30% (n=25 970, 68.0%)	30%–<40% (n=6982, 18.3%)	40%–<50% (n=3612, 9.4%)	≥50% (n=1637, 4.3%)	*P* value*	*P* for trend†
Age, y, mean (SD)	59.7 (11.7)	69.6 (10.8)	72.0 (10.0)	74.5 (9.1)	<0.001	<0.001
Female sex, n (%)	11 977 (46.1)	3092 (44.3)	1575 (43.6)	717 (43.8)	0.002	<0.001
Diabetes, n (%)	3010 (11.7)	1810 (26.0)	1164 (32.3)	573 (35.0)	<0.001	<0.001
Hypertension, n (%)	6349 (24.8)	2955 (42.5)	1695 (47.0)	829 (50.6)	<0.001	<0.001
Cardiovascular disease‡, n (%)	3668 (14.3)	1859 (26.7)	1170 (32.5)	635 (38.8)	<0.001	<0.001
Stroke, n (%)	3886 (14.96)	2027 (29.0)	1113 (30.8)	542 (33.1)	<.0001	<.0001
Stage of chronic kidney disease, n (%), median (Q1, Q3)						
1 to 2:eGFR≧60 mL/min per 1.73 m^2	18 689 (87.1)	4052 (67.4)	1873 (58.8)	757 (51.3)	<0.001	
3 to 5:eGFR<60 mL/min per 1.73 m^2	2773 (12.9)	1960 (32.6)	1315 (41.2)	720 (48.7)	<0.001	
Total cholesterol, mg/dL	191 (165, 218)	181 (154, 212)	177 (151, 208)	176 (147, 203)	<0.001	<0.001
HDL cholesterol, mg/dL	43.6 (36.1, 53.2)	40.1 (33.2, 48.8)	39.6 (32.6, 47.8)	38.7 (32.2, 47.1)	<0.001	<0.001
LDL cholesterol, mg/dL	116 (94, 140)	110 (87, 136)	107 (84, 134)	106 (82, 130)	<0.001	<0.001
Triglyceride, mg/dL	112 (78, 163)	115 (81, 169)	115 (80, 169)	115 (82, 167)	<0.001	<0.001
eGFR, mL/min per 1.73 m^2	89.7 (74.1, 100.2)	73.6 (53.1, 89.4)	66.4 (45.1, 84.9)	60.9 (42.6, 80.0)	<0.001	<0.001
Hemoglobin, g/dL	14.1 (12.9, 15.3)	13.4 (12.0, 14.7)	13.0 (11.4, 14.3)	12.7 (11.1, 14.0)	<0.001	<0.001
Antihypertensive medication, n (%)	8817 (34.4)	3609 (51.9)	2122 (58.8)	1019 (62.2)	<0.001	<0.001
Lipid-modifying medication, n (%)	4000 (15.6)	1936 (27.8)	1199 (33.3)	606 (37.0)	<0.001	<0.001
Statin	3664 (14.3)	1800 (25.9)	1117 (31.0)	570 (34.8)	<0.001	<0.001
Fibrate	496 (1.9)	208 (3.0)	139 (3.9)	58 (3.5)	<0.001	<0.001
Anti-platelet, n (%)	8442 (32.9)	4083 (58.7)	2427 (67.3)	1221 (74.6)	<0.001	<0.001
Diameter reduction (%), median (Q1, Q3)						
Carotid bifurcation	27.6 (25.8, 28.9)	34.9 (32.5, 37.3)	43.7 (41.7, 46.3)	55.6 (52.4, 60.5)	<0.001	<0.001
ICA	35.0 (30.8, 41.0)	38.3 (33.0, 45.8)	42.1 (35.9, 51.5)	49.4 (40.2, 62.8)	<0.001	<0.001
CCA	33.0 (29.7, 37.4)	35.3 (31.2, 40.0)	38.0 (33.7, 43.7)	42.4 (36.2, 49.3)	<0.001	<0.001
ECA	35.8 (31.8, 40.4)	37.7 (33.3, 42.8)	39.7 (34.8, 46.7)	44.3 (37.9, 54.9)	<0.001	<0.001
CABS	0 (0, 0)	2 (1, 3)	4 (3, 6)	7 (5, 9)	<0.001	<0.001
0	23 129 (89.1)	0 (0.0)	0 (0.0)	0 (0.0)	<0.001	…
1	1717 (6.6)	3316 (47.5)	0 (0.0)	0 (0.0)		
2–3	971 (3.7)	2419 (34.7)	1433 (39.7)	114 (7.0)		
≥4	153 (0.6)	1247 (17.9)	2179 (60.3)	1523 (93.0)		
ICA_{max}/CCA_{dist} PSV ratio, median (IQR)	1.37 (1.11–1.71)	1.55 (1.25–1.96)	1.65 (1.31–2.11)	1.88 (1.43–2.61)	<0.001	<0.001
ICA_{max} PSV (cm/s), n (%)						
≤125	24 217 (93.4)	6279 (89.9)	2975 (82.4)	1062 (64.9)	<0.001	…
126–230	1675 (6.5)	610 (8.7)	493 (13.7)	384 (23.5)		
>230	35 (0.1)	93 (1.3)	143 (4.0)	191 (11.7)		

Variables are presented as mean (SD) unless indicated otherwise. CABS indicates carotid atherosclerotic burden score; CCA, common carotid artery; ECA, external carotid artery; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; ICA, internal carotid artery; IQR, interquartile range; LDL, low-density lipoprotein; PSV, peak systolic velocity; Q1, first quartile; and Q3, third quartile.

**P* values were calculated using the Kruskal–Wallis test for continuous variables and Chi-square test for categorical variables.

†*P* values for trends were calculated using Spearman correlation for continuous variables and the Cochran–Armitage trend test for binary variables.

‡Cardiovascular diseases include coronary artery disease, myocardial infarction, and heart failure.

years. The mean age at their first ultrasound examination was 63.3 (SD, 12.5) years, and 45.4% of the patients were women (Table 1). The median percentage of diameter reduction in the ICA, CCA, and external carotid artery and the CABS and PSV were greater when the diameter reduction in carotid bifurcation was greater (Table 1). Patients with greater diameter reduction in carotid bifurcation were older and more likely to have diabetes, hypertension, cardiovascular disease, stroke, and advanced chronic kidney disease and to use lipid-lowering medications and antiplatelets. Levels of estimated glomerular filtration rate and hemoglobin decreased with an increase in the diameter reduction in carotid bifurcation.

Reduction in Carotid Artery Diameters and Mortality Risk

During the follow-up period, 5644 patients died, with 1719 of the deaths attributable to cardiovascular disease. All-cause mortality rose markedly from 19.31 per 1000 person-years in patients with 0% to 29% diameter reduction in carotid bifurcation to 106.76 per 1000 person-years in those with ≥50% diameter reduction in carotid bifurcation. The association remained significant in a dose–response manner after the potentially confounding factors were controlled for (Models 1 and 2, Table 2). In Model 2, the adjusted HRs (95% CIs) for all-cause mortality were 1.25 (1.16–1.34), 1.42 (1.31–1.54), and 1.60 (1.45–1.77) in patients with 30% to <40%, 40% to <50%, and ≥50% diameter reduction in carotid bifurcation compared with patients with <30% diameter reduction (*P* for trend <0.001). Diameter reduction at other carotid sites exhibited a similar linear relationship after multivariable adjustments were made (Table 2, Model 2).

In all unadjusted and adjusted models with death from non-cardiovascular causes as a competing risk, the relative incidence of cardiovascular death gradually increased with diameter reduction in carotid bifurcation, the ICA, the CCA, and the external carotid artery and an increase in the CABS (Table 2).

We also found exposure–response associations of the CABS with all-cause mortality and cardiovascular mortality (Table 2, Model 2). In the restricted cubic spline model, the CABS exhibited linear relationships with all-cause and cardiovascular mortality (Figure 1).

Diameter Reduction in Carotid Bifurcation, CABS, and Mortality Risk in Stratified Analysis

Stratified analyses revealed increased risks of all-cause and cardiovascular mortality associated with the diameter reduction percentage in carotid bifurcation and CABS in all patient groups (Figures 2 and 3). The adjusted HRs for cardiovascular mortality across the categories of diameter reduction were significantly greater in women than in men (*P* for interaction=0.011; Figure 2B). Furthermore, we discovered significant interactions between reduction in carotid bifurcation diameter and cardiovascular risk factors in terms of cardiovascular mortality. The adjusted HRs were higher in patients without diabetes, advanced chronic kidney disease, cardiovascular diseases, and stroke (Figure 2B). The association between CABS categories and cardiovascular mortality was significantly stronger in those without diabetes and stroke, but no statistical interaction was observed between CABS with other cardiovascular comorbidities (Figure 3B).

Assessment of Model Performance in Predicting All-Cause and Cardiovascular Mortality

In the Framingham Risk Score (FRS) model predicting all-cause mortality, the C statistic (95% CI) for all patients was 0.80 (0.79–0.81) (Figure S2A). The C statistic improved when the diameter-based carotid artery measurements were added, with the greatest improvement for the models into which the CABS (c=0.83, *P*<0.001) was added followed by those to which carotid bifurcation diameter reduction (c=0.82, *P*<0.001) was added. Compared with FRS, the C statistics for cardiovascular mortality (c=0.79) increased most by addition of CABS or carotid bifurcation diameter reduction (c=0.82, *P*<0.001 for both; Figure S2B). The calibration plots of predicted versus observed survival indicated better model fit for the FRS plus CABS model than the model of FRS only or the FRS model with addition of other carotid artery measurements (Figure S3).

Sensitivity Analysis

First, in the coarsened exact matching sample, the association between diameter reduction in carotid bifurcation and all-cause and cardiovascular mortality in the original sample was similar to that in the matched sample (Tables S2 and S3). Second, the regression analyses using the data set for which the multiple imputation technique was applied to deal with missing data revealed similar results (Table S4), indicating that the missing data did not affect our findings. Third, the results of regression analyses including patients aged <40 years or >90 years and those excluding patients who self-paid for carotid ultrasound examinations did not reveal a material change in findings (Tables S5 and S6). Fourth, in the subset of patients (n=14 530) with data for body surface area,[24] greater diameter reduction in carotid arteries and greater levels of CABS remained significantly associated with increased all-cause and cardiovascular mortality after additionally adjusted for body surface

Table 2. HRs (95% CIs) for Death from All Causes and Cardiovascular Disease in Association with Diameter Reduction Percentage

			Crude model	Model 1	Model 2
	No. of deaths/No. of subjects	Mortality*	HR (95% CI)	HR (95% CI)	HR (95% CI)
All-cause mortality					
Diameter reduction in carotid bifurcation					
0%–<30%	2284/25 970	19.31	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30%–<40%	1636/6982	56.17	2.91 (2.73–3.10)	1.58 (1.48–1.68)	1.25 (1.16–1.34)
40%–<50%	1115/3612	81.80	4.22 (3.93–4.53)	2.00 (1.86–2.16)	1.42 (1.31–1.54)
≥50%	609/1637	106.76	5.49 (5.02–6.00)	2.32 (2.11–2.54)	1.60 (1.45–1.77)
P for trend			<0.001	<0.001	<0.001
Diameter reduction in ICA					
0%–<30%	3371/30 720	24.55	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30%–<40%	825/3363	60.26	2.45 (2.27–2.64)	1.42 (1.32–1.54)	1.15 (1.06–1.25)
40%–<50%	674/2159	79.77	3.23 (2.98–3.51)	1.62 (1.49–1.77)	1.35 (1.23–1.47)
≥50%	774/1959	105.71	4.27 (3.95–4.62)	2.03 (1.87–2.20)	1.50 (1.38–1.64)
P for trend			<0.001	<0.001	<0.001
Diameter reduction in CCA					
0%–<30%	3607/31 891	25.36	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30–<40%	1119/3909	71.07	2.79 (2.61–2.99)	1.57 (1.47–1.69)	1.26 (1.17–1.36)
40–<50%	632/1761	95.96	3.76 (3.45–4.09)	1.96 (1.80–2.13)	1.45 (1.33–1.59)
≥50%	286/640	128.90	5.03 (4.46–5.67)	2.41 (2.13–2.72)	1.77 (1.56–2.02)
P for trend			<0.001	<0.001	<0.001
Diameter reduction in ECA					
0–<30%	4437/34 984	28.63	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30–<40%	528/1614	85.83	2.99 (2.73–3.27)	1.49 (1.36–1.63)	1.23 (1.11–1.36)
40–<50%	409/990	117.33	4.06 (3.67–4.49)	2.01 (1.81–2.22)	1.46 (1.31–1.63)
≥50%	270/613	126.38	4.37 (3.87–4.94)	2.03 (1.80–2.30)	1.50 (1.31–1.72)
P for trend			<0.001	<0.001	<0.001
CABS					
0	1717/23 129	16.21	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1	857/5033	39.39	2.43 (2.24–2.64)	1.43 (1.31–1.55)	1.16 (1.06–1.27)
2–3	1214/4937	60.47	3.72 (3.46–4.00)	1.82 (1.69–1.97)	1.41 (1.30–1.53)
≥4	1856/5102	97.57	5.99 (5.61–6.40)	2.49 (2.32–2.68)	1.65 (1.52–1.78)
P for trend			<0.001	<0.001	<0.001
Cardiovascular mortality†					
Diameter reduction in carotid bifurcation					
0%–<30%	617/25 970	5.22	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30%–<40%	502/6982	17.24	3.07 (2.73–3.46)	1.66 (1.47–1.88)	1.33 (1.16–1.53)
40%–<50%	369/3612	27.07	4.59 (4.03–5.22)	2.17 (1.89–2.49)	1.58 (1.36–1.84)
≥50%	231/1637	40.50	6.57 (5.65–7.64)	2.75 (2.34–3.24)	1.89 (1.58–2.26)
P for trend			<0.001	<0.001	<0.001
Diameter reduction in ICA					
0%–<30%	939/30 720	6.84	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30%–<40%	266/3363	19.43	2.65 (2.31–3.04)	1.56 (1.35–1.79)	1.24 (1.07–1.44)
40%–<50%	226/2159	26.75	3.53 (3.05–4.08)	1.81 (1.55–2.10)	1.45 (1.23–1.70)
≥50%	288/1959	39.33	5.00 (4.38–5.70)	2.42 (2.10–2.79)	1.69 (1.44–1.97)
P for trend			<0.001	<0.001	<0.001

(*Continued*)

Table 2. Continued

			Crude model	Model 1	Model 2
	No. of deaths/No. of subjects	Mortality*	HR (95% CI)	HR (95% CI)	HR (95% CI)
Diameter reduction in CCA					
0%–<30%	1021/31 891	7.18	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30%–<40%	392/3909	24.90	3.20 (2.85–3.60)	1.81 (1.60–2.04)	1.41 (1.24–1.60)
40%–<50%	202/1761	30.67	3.74 (3.21–4.35)	1.96 (1.67–2.29)	1.50 (1.27–1.77)
≥50%	104/640	46.87	5.42 (4.43–6.63)	2.62 (2.12–3.24)	1.66 (1.31–2.10)
P for trend			<0.001	<0.001	<0.001
Diameter reduction in ECA					
0%–<30%	1304/34 984	8.41	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30%–<40%	158/1614	25.68	2.72 (2.30–3.21)	1.35 (1.14–1.61)	1.11 (0.92–1.33)
40%–<50%	161/990	46.19	4.70 (3.99–5.54)	2.32 (1.96–2.75)	1.68 (1.40–2.01)
≥50%	96/613	44.94	4.45 (3.61–5.49)	2.10 (1.69–2.60)	1.53 (1.21–1.93)
P for trend			<0.001	<0.001	<0.001
CABS					
0	438/23 129	4.14	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1	237/5033	10.89	2.51 (2.15–2.94)	1.48 (1.26–1.75)	1.22 (1.02–1.45)
2–3	393/4937	19.57	4.34 (3.79–4.97)	2.15 (1.86–2.49)	1.65 (1.41–1.93)
≥4	651/5102	34.22	7.12 (6.31–8.03)	2.99 (2.61–3.44)	1.94 (1.67–2.26)
P for trend			<0.001	<0.001	<0.001

Model 1 was adjusted for age and sex (n=38 201). Model 2 was additionally adjusted for diabetes, hypertension, cardiovascular disease, stroke, estimated glomerular filtration rate, hemoglobin, and use of statins and antiplatelet agents at baseline (n=28 218). CABS indicates carotid atherosclerotic burden score; CCA, common carotid artery; ECA, external carotid artery; HR, hazard ratio; and ICA, internal carotid artery.

*Mortality=number of patients/person-years×1000.

†Estimated using the Fine–Gray model to consider the competing risks of death from other causes.

area, although the shape of dose-response associations changed slightly (*P* for trend <0.001 for all carotid artery measurements, Table S7). The increased risk of cardiovascular mortality was most pronounced when the third level was compared against the first level (ie, referent level) of diameter reduction in the carotid bifurcation and of CABS. For example, the HR (95% CI) of cardiovascular mortality was 1.16 (0.84–1.59) in patients with CABS 1 and increased appreciably to 2.32 (1.77–3.02) and 2.01 (1.53–2.64) in patients with CABS 2–3 and ≥4 (CABS 2–3 and ≥4), respectively, as compared with those with CABS 0. In addition, we noted that the HRs in the higher 2 categories of CABS increased after additionally adjusting for body surface area.

DISCUSSION

Our findings suggest the potential utility of the percentage of luminal diameter reduction obtained during routine carotid duplex sonography examinations for the assessment of cardiovascular risks. First, consistency was observed between the diameter reduction percentage and stenosis degree based on PSV measurements. In addition, the 4 categories of diameter reduction exhibited a consistent dose–response relationship with cardiovascular risk factors and medication use history. These observations suggested that the diameter-based measures could appropriately reflect a patient's cardiovascular risk profile. Second, the diameter reduction percentage in all 4 carotid sites and the CABS were associated with risks of mortality from all causes and cardiovascular disease. The associations were attenuated but remained significant after adjustments were made for cardiovascular risk factors.

In our analysis, the rationale for using the categories 0% to <30%, 30% to <40%, 40% to <50%, and ≥50% diameter reduction in carotid arteries was 2-fold. First, rather than aiming to perform carotid stenosis classification based on velocity criteria,[9] which is an approach developed to identify patients with ischemic stroke history who may benefit from carotid endarterectomy, we aimed to evaluate whether diameter-based ultrasound parameters can serve as indicators of unfavorable cardiovascular prognosis. Diameter reduction of <50% was particularly focused on because in the literature, implications of low to mild carotid stenosis in cardiovascular risks have not been well documented. Second, when grading carotid stenosis by using ultrasound methods, morphological information obtained through B-mode imaging was recommended as the main criteria for 0% to 40% stenosis but was less relevant than velocity criteria for severe stenosis.[25]

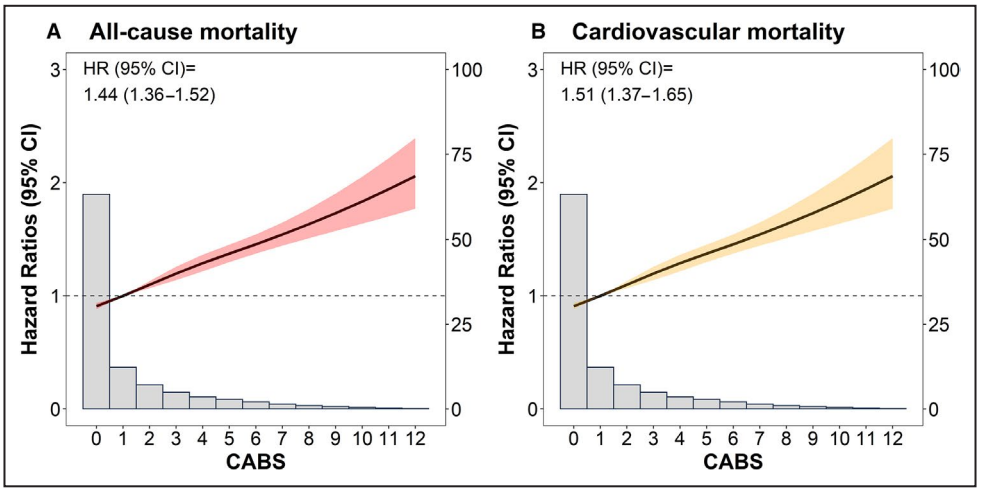

Figure 1. Dose–response relationship between the CABS and death from (A) all causes and (B) cardiovascular diseases.
Solid black lines represent adjusted hazard ratios based on the restricted cubic spline model, with 3 knots located at the 75th, 85th, and 95th percentiles of the carotid atherosclerotic burden score distribution. The reference was set at the 75th percentile of the diameter reduction percentage for each carotid site. Red and orange shaded areas represent 95% CIs. Gray bars indicate the frequency distribution of diameter reduction percentage. Models were adjusted for age, sex, diabetes, hypertension, cardiovascular disease, stroke, estimated glomerular filtration rate, hemoglobin level, and use of statins and antiplatelet agents at baseline. CABS indicates carotid atherosclerotic burden score; and HR, hazard ratio.

Diameter reduction percentage is one of the measurements representing morphological features.

Several non-invasive measures–such as coronary artery calcification, the IMT of the CCA, and the ankle-brachial index—have been used as markers of atherosclerotic burden.[5,6,26] In one population-based study, coronary artery calcification scoring had higher predictive ability than the CCA IMT and ankle-brachial index, particularly in an intermediate risk group stratified using FRS categories.[27] Another study conducted in the same population revealed that although coronary artery calcification scoring, CCA IMT and ankle-brachial index provided complementary information, the ankle-brachial index had the greatest predictive value on stroke risk.[28] In both studies, the overall predictive ability of the IMT was lower than that of the other 2 measures.[27,28] Similarly, the Multi-Ethnic Study of Atherosclerosis showed that coronary artery calcification and carotid plaque improved predictions of coronary heart disease and stroke to a greater degree than did a large CCA IMT.[29] Growing evidence shows that for cardiovascular risk prediction, carotid plaque is a better indicator than the IMT alone, particularly when the IMT is measured in plaque-free areas, and IMT measurements at multiple carotid segments allowing for the inclusion of plaque are more useful than the IMT at the CCA only.[30,31] Notably, the calculation of percentage of local diameter reduction in our study included both the IMT and plaque thickness components.

The scoring system proposed herein, the CABS, aims to summarize the total atherosclerotic burden over multiple carotid segments. Atherosclerosis is regarded as a systemic disease of large arteries.[3] Once atherosclerosis has been identified in a susceptible vascular system, other vessels can be assumed to be affected given the diffuse characteristics of the disease. Furthermore, the atherosclerotic process has a focal nature, and its occurrence is not uniform among vessels. Making measurements at multiple sites should increase the detection sensitivity and thus help evaluate the atherosclerotic burden. This is evidenced by our observations, which showed an exposure–response trend between the CABS and increased cardiovascular mortality risk and that the CABS improved predictions of cardiovascular mortality risk.

Carotid ultrasound is usually used in patients with ischemic stroke or transient ischemic attack to prevent secondary stroke. Other common indications for carotid ultrasounds include carotid bruit, follow-up for asymptomatic carotid stenosis or carotid disease, and multiple cardiovascular risk factors.[32] Therefore, our study subjects, who had undergone carotid duplex ultrasound, are likely to overrepresent those considered less healthy or at a high risk of cardiovascular events. However, our main findings were not materially different in the analysis restricted to patients without any of the following conditions at baseline: cardiovascular disease, stroke, chronic kidney disease, hypertension, and diabetes (Table S8). This indicated that the

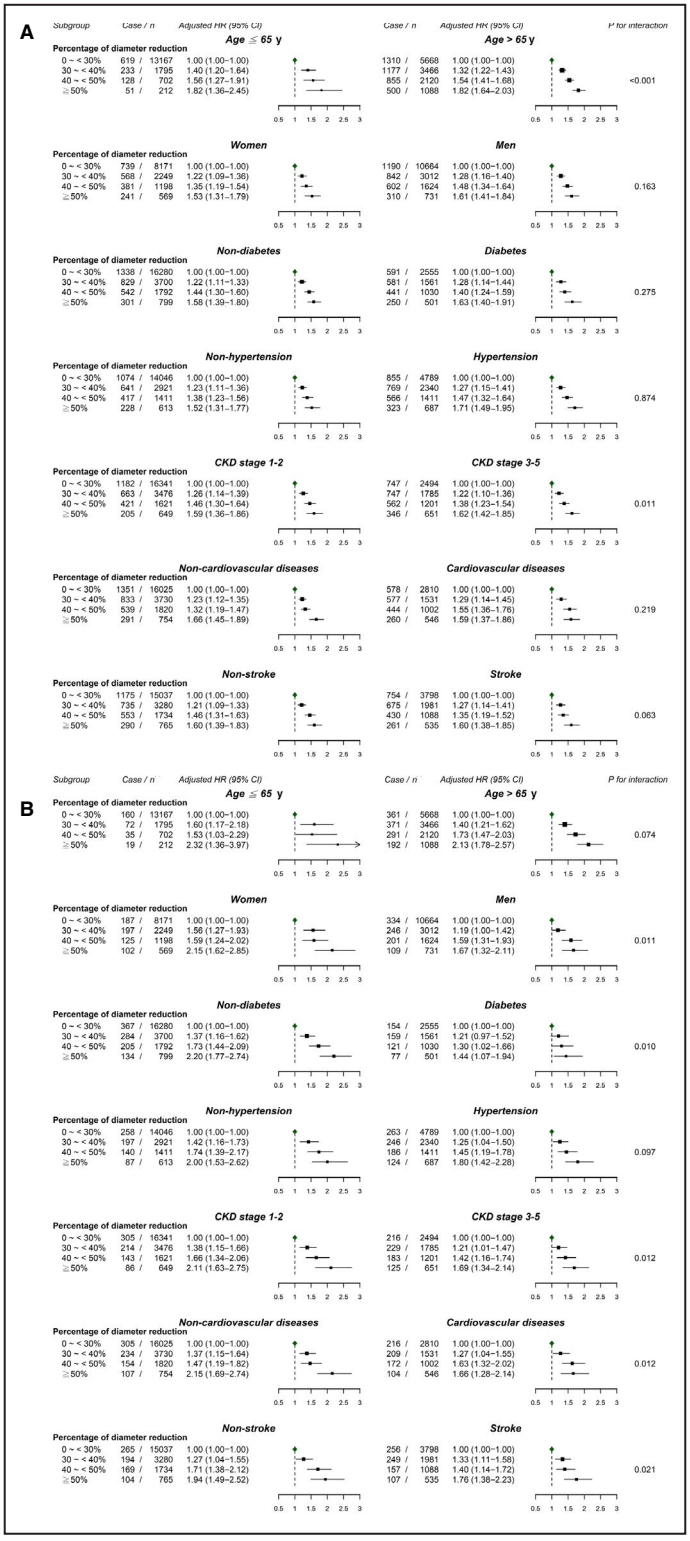

Figure 2. Hazard ratios (95% CIs) for death from (A) all causes and (B) cardiovascular diseases in association with the diameter reduction percentage in carotid bifurcation.

Models were adjusted for age, sex, diabetes, hypertension, cardiovascular disease, stroke, estimated glomerular filtration rate, hemoglobin level, and use of statins and antiplatelet agents at baseline, except for stratifying variables. CKD indicates chronic kidney disease; and HR, hazard ratio.

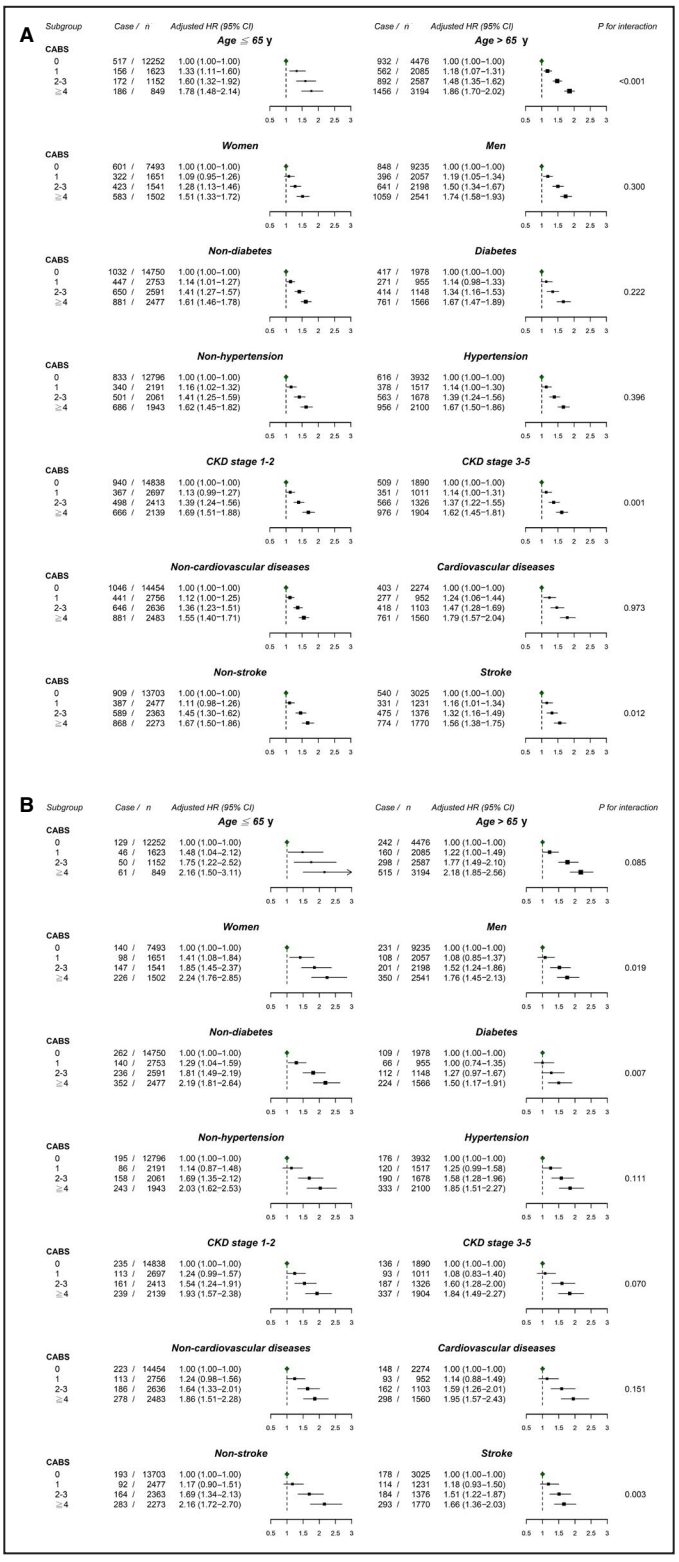

Figure 3. Hazard ratios (95% CIs) for death from (A) all causes and (B) cardiovascular disease in association with the carotid atherosclerotic burden score.

Models were adjusted for age, sex, diabetes, hypertension, cardiovascular disease, stroke, estimated glomerular filtration rate, hemoglobin, and use of statins and antiplatelet agents at baseline, except for stratifying variables. CABS indicates carotid atherosclerotic burden score; CKD, chronic kidney disease; and HR, hazard ratio.

percentage of luminal diameter reduction may have prognostic implications in terms of cardiovascular diseases in patients at a low cardiovascular risk.

Stratified analyses showed that sex modified the association between diameter reduction in carotid arteries and cardiovascular mortality risk. Other studies have shown that carotid artery diameters are associated with body and neck size and differ based on sex.[24,33] However, the sex difference was not completely explained by body and neck size.[24] Further studies are needed to clarify the reasons for the sex differences in the associations observed in our analysis.

Strengths and Limitations

The strengths of our study are its large sample, high-quality data management, and low level of loss to follow-up, which was achieved through data linkage to a national death registry. Carotid ultrasonography is a non-invasive, non-radiative, easily accessible, and low-cost imaging tool for atherosclerosis diagnosis but is dependent on technician experience.[34] The carotid measurement data used in this study were collected from routine examination in our vascular laboratory by various sonographers. A low learning threshold required to apply this straightforward approach based on diameter measurement should facilitate wide acceptance and application in daily practice.

This study has important limitations. First, this was a retrospective observational analysis of electronic health records, which may suffer from misclassification, missing data, and confounding. To deal with these issues, we conducted several sensitivity analyses including multiple imputation for missing data, coarsened exact matching, and subgroup analysis (Tables S2 through S8). However, although we collected detailed patients' characteristics including comorbidities, biochemical measures and medication use and adjusted for the potential confounding factors, unmeasured confounding by variables not available in our data set may still have existed. Second, we used a single measurement of carotid ultrasonography for each patient; however, the potential for misclassification was probably minimized through the use of categorical variables to represent carotid stenosis severity. Third, we could not assess diagnostic accuracy because information from digital subtraction angiography and other imaging studies was unavailable in the data set. However, our focus was to use a straightforward diameter-based approach that can be applied routinely in real-world healthcare settings for prognosis assessment rather than to define high-grade carotid stenosis requiring surgery or stenting. Fourth, whether the carotid ultrasound exams were performed for diagnostic, or screening purpose was unclear because the information on the actual reason for each carotid imaging study was not available in our data set. Of all study subjects, 8836 (23.1%) received self-paid carotid ultrasound examinations (self-paid physical examination services), which were likely to be performed for screening rather than diagnostic purposes. In the sensitivity analysis in which these patients were excluded, we found that the dose-response relationship between percentage of carotid artery diameter reduction and the mortality remained at similar strength to that in the main analysis (Table S6). These observations suggested that the reasons for carotid ultrasound exams probably did not have substantial impact on our main findings. Fifth, the methods for IMT images in our data set included both manual and semi-automated measurements. In addition, there was a considerable amount of missing values if the CCA was not free from atherosclerotic plaque because the semi-automated technique restricted the IMT measurement within plaque-free area. Therefore, we lacked reliable data to compare directly the performance of percentage of carotid artery diameter reduction and IMT in the risk prediction. This limitation also demonstrated the technical difficulties in IMT measurements. Sixth, the percentage of diameter reduction would not be recorded in the reports of carotid imaging when its value was <20%, which was considered low risk. Therefore, we were unable to perform additional analysis to determine the best cutoff points, which need to be verified with further studies. Seventh, this was an analysis of a single hospital's electronic health records, which may not be nationally representative. Our findings must be verified using other data sources and in other populations.

CONCLUSIONS

In the electronic health records analysis of 38 201 consecutive patients in Taiwan, the percentage of carotid artery diameter reduction determined through sonography was associated with all-cause and cardiovascular mortality in an exposure–response manner. The dose–response relationship was found in all patient groups stratified by cardiovascular risk factors, cardiovascular diseases, and stroke. Furthermore, our analysis indicated that our proposed summary measure of overall atherosclerotic burden—namely, the CABS—could predict prognoses. These observations can be verified with further studies, thus demonstrating the potential utility of the straightforward diameter approach in cardiovascular disease–related preventive care.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Data S1–S4
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SUPPLEMENTAL MATERIAL

Data S1. Data source

Clinical Research Data Repository (CRDR) of China Medical University Hospital (CMUH) includes data regarding administration, demography, diagnosis, medical and surgical procedures, prescriptions, laboratory measurements, physiological monitoring, hospitalization, Registry for Catastrophic Illness Patients, and National Death Registry for 2,750,901 patients who sought care at CMUH between 2003 and 2017.[35-36] In Taiwan, patients diagnosed as having diseases classified as catastrophic by the Ministry of Health and Welfare can apply for a catastrophic illness certificate. Relevant documents such as diagnosis certificates are reviewed; if approved, patients are exempted from copayment for medical care.[37]

Data S2. Definition of baseline characteristics

Clinical information obtained from the CRDR of CMUH within 1 year prior to the index date was used to compile baseline cardiovascular comorbidities, relevant biochemical measures, and medication use including lipid-lowering drugs, glucose-lowering drugs, antihypertensive agents, and antiplatelets. A history of diabetes mellitus and hypertension was indicated based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes and the use of glucose-lowering or antihypertensive agents. A history of cardiovascular disease was defined as having ICD-9-CM diagnosis codes for coronary artery disease, myocardial infarction, or heart failure (see Table S1 for ICD-9 codes). A history of

stroke was determined if a patient had a catastrophic illness certificate for stroke. Chronic kidney disease stage was determined using estimated glomerular filtration rate (eGFR) measured within the 1-year window and closest to the index date (stage 1: eGFR of ≥90; stage 2: eGFR of 60 to 89; stage 3: eGFR of 30 to 59; stage 4: eGFR of 15 to 29; stage 5: eGFR of <15). The eGFR was estimated on the basis of serum creatinine (Scr) using the abbreviated Chronic Kidney Disease Epidemiology Collaboration equation (eGFR = 141 × min (Scr/κ, 1)α × max (Scr/κ, 1) -1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black]).[38]

Data S3. Assessment of model performance in predicting all-cause and cardiovascular mortality

We performed additional analysis to explore whether the risk prediction of all cause and cardiovascular mortality can be improved relative to the well-known cardiovascular risk prediction tool, the Framingham Risk Score (FRS) model.[39] The FRS variables included age, sex, smoking status, high-density lipoprotein, total cholesterol, systolic blood pressure, diabetes, the use of angiotensin converting enzyme inhibitors at baseline. The data analyses were performed on a subset of data in which information on FRS variables was available except smoking status, which were imputed under the missing at random assumption (n=10228). We compared metrics for discrimination, C statistics,[40] and the calibration plots (the rms package in R; we calculated 7-year survival because only 1% of study subjects were followed up for more than 7 years) using the FRS versus the model adding the carotid artery

measurements to the FRS predictors. The FRS model was developed to predict incident cardiovascular disease,[39] and its application in prediction of cardiovascular mortality has been validated in Asians.[41] For FRS, we adapted the originally developed predictors and coefficients, which included age, sex, total cholesterol, high-density lipoprotein cholesterol, smoking, systolic blood pressure, treatment for hypertension, and diabetes.[39] A Cox proportional hazard model where the FRS was analyzed as a continuous variable was used to calculate the predicted risk of all cause and cardiovascular mortality. The measurements of percentage of diameter reduction were defined by the cutoffs shown in Table 2. The model performance was assessed in the patients overall and stratified by cardiovascular disease, as the FRS model is originally developed for patients without cardiovascular disease.

Data S4. Sensitivity analysis

First, we created matched pairs of participants with ≥30% and 0% to 30% diameter reduction at the carotid bifurcation using a coarsened exact matching (CEM) method,[42] in which we coarsened three variables, age, sex and diabetes, and compared the mortality between the groups. The multivariate imbalance measure L1, developed by Iacus et al., was used to check the balance on variables.[42] L1 is a relative measure ranging from 0 to 1. A smaller L1 in the matched sample than in the original unmatched sample indicates a better multivariate balance in the matched sample. Second, in the multiple regression analysis (Table 2, model 2), 26% of patients were excluded due to missing data on clinical and laboratory measurements. We

performed multiple imputation using the MICE package in R to deal with missing data on the baseline variables and repeated the regression analysis using the imputed data set. Third, we re-ran the Cox models after including patients aged less than 40 or over 90 years to assess if the main results change. Fourth, the Cox models were repeated after excluding patients who self-paid for carotid ultrasound exams, as these patients may be healthier than patients who received clinically indicated carotid ultrasound exams. Fifth, previous studies indicated that body surface area was associated with carotid artery diameter and may be associated with mortality.[24, 43] Therefore, in a subset of patients (n=14530) with data for body surface area, we performed a regression analysis additionally adjusted for body surface area.

Table S1. Diagnostic codes.

Category	Name	ICD-9-CM codes
Comorbidity	Cardiovascular disease	410-414, 425-428, 441-442, 458, 250.7, 429.1-429.3, 443.9, 785.4, V43.4
Comorbidity	Stroke	430-438
Comorbidity	Diabetes	250
Comorbidity	Hypertension	401-405
Outcome variable	Deaths from cardiovascular disease (hypertension disease rheumatic or ischemic heart disease, cerebrovascular disease, arteriolosclerosis, and aortic aneurysm and dissection)	390-392, 393-398, 410-414, 420-429; 401-405; 430-438; 440

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification

Table S2. Baseline characteristic after coarsened exact matching.

		Diameter reduction in carotid bifurcation		P-value
	N	0~<30% (n= 10235)	≥30% (n= 10235)	
Age at entry (year), median (IQR)	20470	70.0 (61.8, 76.8)	70.1 (61.8, 76.9)	0.699
Sex, n (%)	20470			1
Female		4435 (43.3)	4435 (43.3)	
Male		5800 (56.7)	5800 (56.7)	
Diabetes, n (%)	20414*	2453 (24.03)	2453 (24.03)	1

P values are calculated by the Wilcoxon rank sum test for continuous variables and chi-square test for categorical variables.

Multivariate L_1 distance of the original population: $L_1 = 0.402$; matched population: $L_1 = 0.04$

*Patients without any electronic health records in the previous year were considered as those with missing data on diabetes..

Table S3. Hazard ratios (95% confidence intervals) for mortality from all causes and cardiovascular disease in the original study cohort and the coarsened exact matching sample.

	Original- Model 2			CEM- Model 2		
	N	**Case**	**HR (95% CI)**	**N**	**Case**	**HR (95% CI)**
All-cause mortality						
Diameter reduction in carotid bifurcation						
0~<30%	25970	2284	1.00 (Ref)	10235	1683	1.00 (Ref)
≥30%	12231	3360	1.37 (1.29, 1.46)	10235	2475	1.30 (1.21, 1.39)
Cardiovascular mortality*						
Diameter reduction in carotid bifurcation						
0~<30%	25970	617	1.00 (Ref)	10235	458	1.00 (Ref)
≥30%	12231	1102	1.51 (1.34, 1.70)	10235	802	1.42 (1.25, 1.61)

CEM, coarsened exact matching; CI, confidence interval; HR, hazard ratio.

The model in the original unmatched sample was adjusted for age, sex, diabetes, hypertension, cardiovascular disease, stroke, baseline eGFR, hemoglobin, and use of statins and antiplatelets (n = 28,218)

The model for the CEM sample was adjusted for diabetes, hypertension, cardiovascular disease, stroke, baseline eGFR, hemoglobin, and use of statins and antiplatelets (n = 15,185)

*Estimated using Fine-Gray model to take into account the competing risks of death from other causes.

Table S4. Hazard ratios (95% confidence intervals) for mortality from all causes and cardiovascular diseases in the original data set and multiple imputation data set.

	All-cause mortality		Cardiovascular mortality*	
	Original dataset (n=28218) HR (95% CI)	Multiple imputation dataset (n=38201) HR (95% CI)	Original dataset (n=28218) HR (95% CI)	Multiple imputation dataset (n=38201) HR (95% CI)
Diameter reduction in carotid bifurcation				
0~<30%	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	1.25 (1.16, 1.34)	1.26 (1.18, 1.35)	1.33 (1.16, 1.53)	1.32 (1.17, 1.50)
40~<50%	1.42 (1.31, 1.54)	1.44 (1.33, 1.55)	1.58 (1.36, 1.84)	1.60 (1.39, 1.84)
≥50%	1.60 (1.45, 1.77)	1.58 (1.44, 1.74)	1.89 (1.58, 2.26)	1.85 (1.57, 2.19)
Diameter reduction in ICA				
0~<30%	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	1.15 (1.06, 1.25)	1.17 (1.08, 1.26)	1.24 (1.07, 1.44)	1.27 (1.10, 1.47)
40~<50%	1.35 (1.23, 1.47)	1.34 (1.23, 1.46)	1.45 (1.23, 1.70)	1.48 (1.27, 1.72)
≥50%	1.50 (1.38, 1.64)	1.50 (1.38, 1.63)	1.69 (1.44, 1.97)	1.75 (1.51, 2.03)
Diameter reduction in CCA				
0~<30%	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	1.26 (1.17, 1.36)	1.26 (1.18, 1.35)	1.41 (1.24, 1.60)	1.46 (1.29, 1.65)
40~<50%	1.45 (1.33, 1.59)	1.47 (1.35, 1.61)	1.50 (1.27, 1.77)	1.50 (1.27, 1.76)
≥50%	1.77 (1.56, 2.02)	1.83 (1.62, 2.08)	1.66 (1.31, 2.10)	1.84 (1.48, 2.30)
Diameter reduction in ECA				
0~<30%	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	1.23 (1.11, 1.36)	1.24 (1.13, 1.36)	1.11 (0.92, 1.33)	1.13 (0.95, 1.34)
40~<50%	1.46 (1.31, 1.63)	1.49 (1.34, 1.66)	1.68 (1.40, 2.01)	1.74 (1.46, 2.06)
≥50%	1.50 (1.31, 1.72)	1.53 (1.35, 1.74)	1.53 (1.21, 1.93)	1.56 (1.25, 1.94)
CABS				
0	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1	1.16 (1.06, 1.27)	1.19 (1.09, 1.29)	1.22 (1.02, 1.45)	1.22 (1.03, 1.43)
2-3	1.41 (1.30, 1.53)	1.40 (1.30, 1.52)	1.65 (1.41, 1.93)	1.66 (1.43, 1.91)
≥ 4	1.65 (1.52, 1.78)	1.66 (1.54, 1.79)	1.94 (1.67, 2.26)	1.99 (1.72, 2.29)

CABS, carotid atherosclerotic burden score; CCA, common carotid artery; CI, confidence interval; ECA, external carotid artery; HR, hazard ratio; ICA, internal carotid artery.

The models were adjusted for age, sex, diabetes, hypertension, cardiovascular disease, stroke, estimated glomerular filtration rate, hemoglobin, and use of statins and antiplatelet agents at baseline.

*Estimated using Fine-Gray model to take into account the competing risks of death from other causes.

Table S5. Hazard ratios (95% confidence intervals) for death from all causes and cardiovascular disease in association with percentage of diameter reduction in the analysis including patients aged less than 40 years or over 90 years (n=42,206).

	No. of deaths / No. of subjects	Mortality*	Crude model HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
All-cause mortality					
Diameter reduction in carotid bifurcation					
0~<30%	2383 / 29602	17.66	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	1715 / 7168	57.64	3.26 (3.06, 3.47)	1.57 (1.47, 1.67)	1.24 (1.16, 1.34)
40~<50%	1186 / 3728	85.18	4.79 (4.47, 5.14)	1.99 (1.85, 2.14)	1.41 (1.31, 1.53)
≥50%	656 / 1708	112.18	6.29 (5.76, 6.85)	2.31 (2.11, 2.52)	1.60 (1.45, 1.76)
P for trend			<0.001	<0.001	<0.001
Diameter reduction in ICA					
0~<30%	3548 / 34516	22.97	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	872 / 3453	62.41	2.70 (2.51, 2.91)	1.42 (1.31, 1.53)	1.15 (1.06, 1.25)
40~<50%	704 / 2215	81.86	3.54 (3.26, 3.84)	1.60 (1.48, 1.74)	1.34 (1.22, 1.46)
≥50%	816 / 2022	109.39	4.71 (4.37, 5.09)	2.00 (1.85, 2.16)	1.49 (1.36, 1.62)
P for trend			<0.001	<0.001	<0.001
Diameter reduction in CCA					
0~<30%	3800 / 35711	23.83	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	1175 / 4024	73.12	3.05 (2.86, 3.26)	1.54 (1.44, 1.65)	1.23 (1.15, 1.32)
40~<50%	662 / 1806	98.83	4.11 (3.78, 4.46)	1.92 (1.76, 2.08)	1.44 (1.32, 1.58)
≥50%	303 / 665	132.66	5.49 (4.88, 6.17)	2.32 (2.06, 2.61)	1.72 (1.52, 1.96)
P for trend			<0.001	<0.001	<0.001
Diameter reduction in ECA					
0~<30%	4662 / 38869	27.04	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	557 / 1667	88.42	3.25 (2.97, 3.55)	1.46 (1.33, 1.60)	1.22 (1.11, 1.35)
40~<50%	436 / 1032	121.68	4.44 (4.02, 4.90)	1.95 (1.76, 2.15)	1.45 (1.30, 1.61)
≥50%	285 / 638	130.43	4.76 (4.22, 5.36)	2.00 (1.77, 2.26)	1.46 (1.29, 1.67)
P for trend			<0.001	<0.001	<0.001
CABS					
0	1793 / 26689	14.66	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1	907 / 5180	40.65	2.77 (2.56, 3.00)	1.43 (1.32, 1.56)	1.16 (1.06, 1.27)
2-3	1279 / 5068	62.38	4.24 (3.94, 4.55)	1.80 (1.67, 1.94)	1.39 (1.28, 1.50)
≥ 4	1961 / 5269	101.15	6.85 (6.42, 7.30)	2.47 (2.30, 2.65)	1.63 (1.51, 1.76)
P for trend			<0.001	<0.001	<0.001
Cardiovascular mortality					

	No. of deaths / No. of subjects	Mortality*	Crude model HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Diameter reduction in carotid bifurcation					
0~<30%	643 / 29602	4.76	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	527 / 7168	17.71	3.44 (3.06, 3.86)	1.66 (1.47, 1.87)	1.33 (1.17, 1.52)
40~<50%	400 / 3728	28.73	5.28 (4.66, 5.98)	2.19 (1.91, 2.51)	1.60 (1.38, 1.85)
≥50%	248 / 1708	42.41	7.42 (6.40, 8.59)	2.68 (2.28, 3.15)	1.82 (1.53, 2.16)
P for trend			<0.001	<0.001	<0.001
Diameter reduction in ICA					
0~<30%	991 / 34516	6.42	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	281 / 3453	20.11	2.90 (2.54, 3.31)	1.54 (1.34, 1.77)	1.24 (1.07, 1.44)
40~<50%	239 / 2215	27.79	3.88 (3.37, 4.47)	1.81 (1.56, 2.10)	1.44 (1.23, 1.69)
≥50%	307 / 2022	41.15	5.52 (4.86, 6.27)	2.40 (2.09, 2.76)	1.68 (1.44, 1.95)
P for trend			<0.001	<0.001	<0.001
Diameter reduction in CCA					
0~<30%	1078 / 35711	6.76	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	417 / 4024	25.95	3.52 (3.14, 3.94)	1.79 (1.59, 2.02)	1.40 (1.23, 1.59)
40~<50%	214 / 1806	31.95	4.10 (3.54, 4.75)	1.93 (1.65, 2.25)	1.49 (1.26, 1.75)
≥50%	109 / 665	47.72	5.78 (4.75, 7.04)	2.48 (2.01, 3.05)	1.58 (1.26, 1.99)
P for trend			<0.001	<0.001	<0.001
Diameter reduction in ECA					
0~<30%	1375 / 38869	7.97	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	168 / 1667	26.67	2.95 (2.52, 3.47)	1.33 (1.13, 1.58)	1.10 (0.92, 1.31)
40~<50%	172 / 1032	48.00	5.09 (4.34, 5.97)	2.23 (1.89, 2.63)	1.62 (1.35, 1.93)
≥50%	103 / 638	47.14	4.88 (3.98, 5.97)	2.08 (1.69, 2.56)	1.49 (1.19, 1.87)
P for trend			<0.001	<0.001	<0.001
CABS					
0	456 / 26689	3.73	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1	249 / 5180	11.16	2.84 (2.43, 3.31)	1.48 (1.26, 1.73)	1.20 (1.01, 1.42)
2-3	417 / 5068	20.34	4.97 (4.35, 5.67)	2.15 (1.87, 2.49)	1.66 (1.42, 1.94)
≥ 4	696 / 5269	35.90	8.20 (7.28, 9.22)	3.00 (2.62, 3.44)	1.94 (1.67, 2.25)
P for trend			<0.001	<0.001	<0.001

CABS, carotid atherosclerotic burden score; CCA, common carotid artery; CI, confidence interval; ECA, external carotid artery; HR, hazard ratio; ICA, internal carotid artery.

*Mortality = no. of case/person-years × 1000.

†Estimated using Fine-Gray model to take into account the competing risks of death from other causes.

Model 1 was adjusted for age and sex (n = 42,206)

Model 2 was additionally adjusted for diabetes, hypertension, cardiovascular disease, stroke, estimated glomerular filtration rate,

hemoglobin, and use of statins and antiplatelet agents at baseline (n = 31,307)

Table S6. Hazard ratios (95% confidence intervals) for death from all causes and cardiovascular disease in association with percentage of diameter reduction in the analysis excluding patients who self-paid for carotid ultrasound examinations (n=29,365).

	No. of deaths / No. of subjects	Mortality*	Crude model HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
All-cause mortality					
Diameter reduction in carotid bifurcation					
0~<30%	2171 / 18065	27.50	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	1606 / 6302	62.20	2.26 (2.12, 2.41)	1.49 (1.40, 1.59)	1.23 (1.14, 1.32)
40~<50%	1100 / 3411	86.78	3.15 (2.93, 3.38)	1.88 (1.75, 2.03)	1.41 (1.30, 1.52)
≥50%	603 / 1587	110.54	4.00 (3.66, 4.38)	2.19 (2.00, 2.40)	1.61 (1.46, 1.78)
P for trend			<0.001	<0.001	<0.001
Diameter reduction in ICA s					
0~<30%	3246 / 22337	33.93	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	811 / 3088	65.88	1.94 (1.79, 2.09)	1.36 (1.26, 1.47)	1.14 (1.05, 1.24)
40~<50%	661 / 2047	83.31	2.45 (2.25, 2.66)	1.53 (1.40, 1.66)	1.32 (1.20, 1.44)
≥50%	762 / 1893	108.97	3.19 (2.95, 3.46)	1.90 (1.75, 2.06)	1.50 (1.37, 1.63)
P for trend			<0.001	<0.001	<0.001
Diameter reduction in CCA					
0~<30%	3470 / 23410	34.67	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	1104 / 3641	76.49	2.20 (2.06, 2.36)	1.50 (1.40, 1.61)	1.25 (1.16, 1.35)
40~<50%	624 / 1689	100.31	2.88 (2.65, 3.14)	1.86 (1.70, 2.02)	1.44 (1.32, 1.58)
≥50%	282 / 625	131.54	3.77 (3.34, 4.26)	2.27 (2.01, 2.56)	1.77 (1.55, 2.02)
P for trend			<0.001	<0.001	<0.001
Diameter reduction in ECA					
0~<30%	4282 / 26252	38.36	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	524 / 1544	90.44	2.35 (2.15, 2.58)	1.46 (1.33, 1.60)	1.24 (1.12, 1.36)
40~<50%	407 / 966	120.46	3.12 (2.82, 3.46)	1.93 (1.74, 2.14)	1.48 (1.33, 1.66)
≥50%	267 / 603	127.52	3.30 (2.92, 3.74)	1.94 (1.71, 2.20)	1.50 (1.31, 1.72)
P for trend			<0.001	<0.001	<0.001
CABS					
0	1619 / 15533	23.76	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1	836 / 4377	45.23	1.90 (1.75, 2.07)	1.32 (1.22, 1.44)	1.11 (1.01, 1.22)
2-3	1194 / 4526	65.99	2.77 (2.57, 2.99)	1.68 (1.56, 1.81)	1.35 (1.25, 1.47)
≥ 4	1831 / 4929	100.67	4.22 (3.95, 4.51)	2.26 (2.11, 2.43)	1.60 (1.48, 1.74)
P for trend			<0.001	<0.001	<0.001
Cardiovascular mortality					

	No. of deaths / No. of subjects	Mortality*	Crude model HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Diameter reduction in carotid bifurcation					
0~<30%	603 / 18065	7.64	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	498 / 6302	19.29	2.37 (2.10, 2.67)	1.56 (1.38, 1.76)	1.30 (1.13, 1.48)
40~<50%	367 / 3411	28.95	3.39 (2.98, 3.86)	2.02 (1.76, 2.31)	1.55 (1.33, 1.80)
≥50%	230 / 1587	42.16	4.74 (4.07, 5.52)	2.57 (2.19, 3.01)	1.88 (1.58, 2.24)
P for trend			<0.001	<0.001	<0.001
Diameter reduction in ICA					
0~<30%	925 / 22337	9.67	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	263 / 3088	21.36	2.08 (1.82, 2.39)	1.47 (1.28, 1.69)	1.21 (1.04, 1.41)
40~<50%	224 / 2047	28.23	2.68 (2.31, 3.10)	1.70 (1.46, 1.98)	1.42 (1.20, 1.66)
≥50%	286 / 1893	40.90	3.74 (3.27, 4.27)	2.26 (1.97, 2.60)	1.67 (1.43, 1.95)
P for trend			<0.001	<0.001	<0.001
Diameter reduction in CCA					
0~<30%	1005 / 23410	10.04	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	390 / 3641	27.02	2.52 (2.24, 2.83)	1.72 (1.52, 1.94)	1.39 (1.22, 1.59)
40~<50%	200 / 1689	32.15	2.84 (2.44, 3.31)	1.84 (1.57, 2.15)	1.48 (1.25, 1.75)
≥50%	103 / 625	48.05	4.04 (3.30, 4.95)	2.45 (1.98, 3.02)	1.65 (1.31, 2.09)
P for trend			<0.001	<0.001	<0.001
Diameter reduction in ECA					
0~<30%	1286 / 26252	11.52	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	157 / 1544	27.10	2.12 (1.80, 2.51)	1.31 (1.10, 1.55)	1.10 (0.91, 1.32)
40~<50%	160 / 966	47.35	3.59 (3.04, 4.23)	2.21 (1.87, 2.61)	1.68 (1.40, 2.01)
≥50%	95 / 603	45.37	3.36 (2.72, 4.14)	1.99 (1.61, 2.47)	1.52 (1.21, 1.92)
P for trend			<0.001	<0.001	<0.001
CABS					
0	426 / 15533	6.25	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1	237 / 4377	12.82	1.97 (1.68, 2.31)	1.38 (1.17, 1.62)	1.17 (0.98, 1.39)
2-3	388 / 4526	21.45	3.17 (2.76, 3.64)	1.94 (1.68, 2.24)	1.57 (1.35, 1.83)
≥ 4	647 / 4929	35.57	4.97 (4.39, 5.61)	2.68 (2.35, 3.06)	1.87 (1.62, 2.17)
P for trend			<0.001	<0.001	<0.001

CABS, carotid atherosclerotic burden score; CCA, common carotid artery; CI, confidence interval; ECA, external carotid artery; HR, hazard ratio; ICA, internal carotid artery.

*Mortality = no. of case/person-years × 1000.

†Estimated using Fine-Gray model to take into account the competing risks of death from other causes.

Model 1 was adjusted for age and sex (n = 29,365)

Model 2 was additionally adjusted for diabetes, hypertension, cardiovascular disease, stroke, estimated glomerular filtration rate,

hemoglobin, and use of statins and antiplatelet agents at baseline (n = 20,103)

Table S7. Hazard ratios (95% confidence intervals) for death from all causes and cardiovascular disease in the model 2 and further adjusted for body surface area.

	Model 2*		Model 2 + BSA† adjusted	
	No. of deaths / No. of subjects	HR (95% CI)	No. of deaths / No. of subjects	HR (95% CI)
N		**28218**		**14530**
All-cause mortality				
Diameter reduction in carotid bifurcation				
0~<30%	2284 / 25970	1.00 (Ref)	729 / 10014	1.00 (Ref)
30~<40%	1636 / 6982	1.25 (1.16, 1.34)	494 / 2470	1.17 (1.03, 1.32)
40~<50%	1115 / 3612	1.42 (1.31, 1.54)	392 / 1390	1.34 (1.17, 1.52)
≥50%	609 / 1637	1.60 (1.45, 1.77)	233 / 656	1.38 (1.18, 1.62)
P for trend		<0.001		<0.001
Diameter reduction in ICA				
0~<30%	3371 / 30720	1.00 (Ref)	1079 / 11753	1.00 (Ref)
30~<40%	825 / 3363	1.15 (1.06, 1.25)	287 / 1257	1.12 (0.98, 1.28)
40~<50%	674 / 2159	1.34 (1.23, 1.47)	217 / 759	1.28 (1.10, 1.48)
≥50%	774 / 1959	1.50 (1.38, 1.64)	265 / 761	1.41 (1.23, 1.63)
P for trend		<0.001		<0.001
Diameter reduction in CCA				
0~<30%	3607 / 31891	1.00 (Ref)	1181 / 12269	1.00 (Ref)
30~<40%	1119 / 3909	1.26 (1.17, 1.36)	379 / 1382	1.26 (1.11, 1.42)
40~<50%	632 / 1761	1.45 (1.32, 1.59)	194 / 638	1.19 (1.02, 1.40)
≥50%	286 / 640	1.77 (1.56, 2.02)	94 / 241	1.47 (1.18, 1.82)
P for trend		<0.001		<0.001
Diameter reduction in ECA				
0~<30%	4437 / 34984	1.00 (Ref)	1436 / 13305	1.00 (Ref)
30~<40%	528 / 1614	1.23 (1.11, 1.35)	186 / 624	1.13 (0.97, 1.32)
40~<50%	409 / 990	1.46 (1.31, 1.63)	136 / 374	1.31 (1.10, 1.57)
≥50%	270 / 613	1.50 (1.31, 1.71)	90 / 227	1.32 (1.06, 1.64)
P for trend		<0.001		<0.001
CABS				
0	1717 / 23129	1.00 (Ref)	543 / 9046	1.00 (Ref)
1	857 / 5033	1.16 (1.06, 1.27)	268 / 1807	1.18 (1.01, 1.37)
2-3	1214 / 4937	1.41 (1.29, 1.53)	409 / 1752	1.48 (1.29, 1.70)
≥ 4	1856 / 5102	1.64 (1.52, 1.78)	628 / 1925	1.52 (1.33, 1.73)
P for trend		<0.001		<0.001
Cardiovascular mortality‡				
Diameter reduction in carotid bifurcation				
0~<30%	617 / 25970	1.00 (Ref)	175 / 10014	1.00 (Ref)
30~<40%	502 / 6982	1.33 (1.16, 1.52)	151 / 2470	1.34 (1.07, 1.69)
40~<50%	369 / 3612	1.58 (1.36, 1.83)	130 / 1390	1.66 (1.29, 2.14)
≥50%	231 / 1637	1.88 (1.58, 2.25)	75 / 656	1.55 (1.14, 2.10)
P for trend		<0.001		<0.001

	Model 2*		Model 2 + BSA† adjusted	
	No. of deaths / No. of subjects	**HR (95% CI)**	**No. of deaths / No. of subjects**	**HR (95% CI)**
Diameter reduction in ICA				
0~<30%	939 / 30720	1.00 (Ref)	277 / 11753	1.00 (Ref)
30~<40%	266 / 3363	1.24 (1.06, 1.44)	95 / 1257	1.36 (1.06, 1.74)
40~<50%	226 / 2159	1.45 (1.23, 1.70)	70 / 759	1.47 (1.12, 1.93)
≥50%	288 / 1959	1.68 (1.44, 1.97)	89 / 761	1.60 (1.22, 2.09)
P for trend		<0.001		<0.001
Diameter reduction in CCA				
0~<30%	1021 / 31891	1.00 (Ref)	301 / 12269	1.00 (Ref)
30~<40%	392 / 3909	1.41 (1.23, 1.60)	130 / 1382	1.57 (1.26, 1.95)
40~<50%	202 / 1761	1.49 (1.26, 1.77)	69 / 638	1.62 (1.22, 2.15)
≥50%	104 / 640	1.66 (1.31, 2.10)	31 / 241	1.58 (1.05, 2.37)
P for trend		<0.001		<0.001
Diameter reduction in ECA				
0~<30%	1304 / 34984	1.00 (Ref)	396 / 13305	1.00 (Ref)
30~<40%	158 / 1614	1.11 (0.92, 1.33)	56 / 624	1.14 (0.85, 1.53)
40~<50%	161 / 990	1.68 (1.40, 2.01)	48 / 374	1.52 (1.11, 2.08)
≥50%	96 / 613	1.52 (1.21, 1.92)	31 / 227	1.38 (0.95, 2.00)
P for trend		<0.001		0.006
CABS				
0	438 / 23129	1.00 (Ref)	116 / 9046	1.00 (Ref)
1	237 / 5033	1.21 (1.02, 1.45)	62 / 1807	1.16 (0.84, 1.59)
2-3	393 / 4937	1.65 (1.41, 1.93)	151 / 1752	2.32 (1.77, 3.02)
≥ 4	651 / 5102	1.94 (1.66, 2.26)	202 / 1925	2.01 (1.53, 2.64)
P for trend		<0.001		<0.001

BSA, body surface area; CABS, carotid atherosclerotic burden score; CCA, common carotid artery; ECA, external carotid artery; HR, hazard ratio; ICA, internal carotid artery.

*Model 2 was the fully adjusted model (i.e., the model 2 of Table 2) in which age, sex, diabetes, hypertension, cardiovascular disease, stroke, estimated glomerular filtration rate, hemoglobin, and use of statins and antiplatelet agents at baseline were included (n = 28 218).

†BSA was calculated using the following formula: BSA (m^2)=0.20247× height (m)$^{0.7256}$×weight (kg)$^{0.425}$

‡Estimated using the Fine–Gray model to consider the competing risks of death from other causes.

Table S8. Hazard ratios (95% confidence intervals) for death from all causes and cardiovascular disease in association with diameter reduction percentage among patients without any of the following conditions at baseline: cardiovascular disease, stroke, chronic kidney disease, hypertension, and diabetes (n=17,673).

	No. of deaths / No. of subjects	Mortality*	Crude model HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
All-cause mortality					
Diameter reduction in carotid bifurcation					
0~<30%	537 / 14749	7.73	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	203 / 1927	23.57	3.08 (2.62, 3.62)	1.31 (1.11, 1.55)	1.18 (0.94, 1.49)
40~<50%	122 / 741	39.50	5.19 (4.27, 6.32)	1.64 (1.33, 2.01)	1.45 (1.09, 1.93)
≥50%	41 / 256	38.94	5.16 (3.76, 7.09)	1.41 (1.02, 1.95)	1.26 (0.80, 1.97)
P for trend			<0.001	<0.001	0.015
Diameter reduction in ICA					
0~<30%	682 / 16112	9.03	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	89 / 829	24.64	2.77 (2.22, 3.45)	1.16 (0.93, 1.46)	0.82 (0.58, 1.16)
40~<50%	66 / 439	35.55	3.99 (3.10, 5.14)	1.24 (0.95, 1.60)	1.10 (0.77, 1.59)
≥50%	66 / 293	51.86	5.80 (4.50, 7.46)	1.63 (1.26, 2.12)	1.43 (1.01, 2.03)
P for trend			<0.001	<0.001	0.112
Diameter reduction in CCA					
0~<30%	697 / 16406	9.08	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	122 / 844	32.55	3.63 (2.99, 4.39)	1.51 (1.24, 1.84)	1.51 (1.15, 1.99)
40~<50%	52 / 320	38.89	4.34 (3.27, 5.75)	1.52 (1.14, 2.02)	1.59 (1.08, 2.34)
≥50%	32 / 103	78.46	8.84 (6.20, 12.60)	2.76 (1.93, 3.95)	2.15 (1.24, 3.71)
P for trend			<0.001	<0.001	<0.001
Diameter reduction in ECA					
0~<30%	807 / 17133	10.10	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	48 / 318	34.45	3.44 (2.57, 4.61)	1.09 (0.81, 1.47)	1.33 (0.89, 1.99)
40~<50%	33 / 143	60.48	6.17 (4.35, 8.74)	1.98 (1.39, 2.81)	1.77 (1.05, 2.98)
≥50%	15 / 79	42.19	4.25 (2.55, 7.08)	1.15 (0.69, 1.92)	0.75 (0.39, 1.48)
P for trend			<0.001	0.009	0.485
CABS					
0	447 / 13840	6.85	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1	144 / 1726	18.11	2.66 (2.20, 3.21)	1.28 (1.06, 1.56)	1.13 (0.87, 1.47)
2-3	155 / 1293	28.03	4.17 (3.47, 5.00)	1.48 (1.22, 1.80)	1.41 (1.09, 1.83)
≥ 4	157 / 814	45.53	6.78 (5.65, 8.13)	1.72 (1.41, 2.10)	1.49 (1.13, 1.97)
P for trend			<0.001	<0.001	0.001
Cardiovascular mortality					

	No. of deaths / No. of subjects	Mortality*	Crude model HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Diameter reduction in carotid bifurcation					
0~<30%	98 / 14749	1.41	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	36 / 1927	4.18	2.87 (1.96, 4.20)	1.10 (0.74, 1.64)	1.18 (0.66, 2.11)
40~<50%	29 / 741	9.39	6.26 (4.14, 9.48)	1.76 (1.13, 2.73)	1.55 (0.79, 3.02)
≥50%	13 / 256	12.35	8.44 (4.74, 15.04)	2.07 (1.13, 3.77)	1.62 (0.65, 4.07)
P for trend			<0.001	0.003	0.134
Diameter reduction in ICA					
0~<30%	112 / 16112	1.48	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	24 / 829	6.64	4.37 (2.82, 6.79)	1.82 (1.16, 2.83)	1.01 (0.44, 2.33)
40~<50%	17 / 439	9.16	5.90 (3.54, 9.85)	1.77 (1.01, 3.08)	1.31 (0.53, 3.26)
≥50%	23 / 293	18.07	11.39 (7.28, 17.81)	3.21 (2.03, 5.09)	2.36 (1.22, 4.57)
P for trend			<0.001	<0.001	0.030
Diameter reduction in CCA					
0~<30%	121 / 16406	1.58	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	30 / 844	8.00	4.86 (3.26, 7.24)	1.94 (1.31, 2.89)	1.29 (0.63, 2.65)
40~<50%	12 / 320	8.98	5.38 (2.97, 9.74)	1.82 (1.00, 3.32)	1.75 (0.73, 4.17)
≥50%	13 / 103	31.87	18.62 (10.47, 33.11)	5.19 (2.79, 9.63)	4.50 (1.82, 11.15)
P for trend			<0.001	<0.001	0.003
Diameter reduction in ECA					
0~<30%	153 / 17133	1.91	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
30~<40%	9 / 318	6.46	3.16 (1.61, 6.19)	0.95 (0.48, 1.87)	1.41 (0.54, 3.63)
40~<50%	9 / 143	16.50	7.94 (4.01, 15.71)	2.29 (1.15, 4.56)	2.14 (0.72, 6.41)
≥50%	5 / 79	14.06	7.00 (2.94, 16.67)	1.80 (0.76, 4.25)	1.51 (0.53, 4.31)
P for trend			<0.001	0.030	0.138
CABS					
0	77 / 13840	1.18	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1	20 / 1726	2.52	2.08 (1.27, 3.41)	0.94 (0.57, 1.55)	0.72 (0.33, 1.56)
2-3	33 / 1293	5.97	4.85 (3.23, 7.30)	1.57 (1.02, 2.42)	1.11 (0.56, 2.20)
≥ 4	46 / 814	13.34	10.62 (7.37, 15.30)	2.49 (1.67, 3.73)	1.88 (1.04, 3.39)
P for trend			<0.001	<0.001	0.083

CABS, carotid atherosclerotic burden score; CCA, common carotid artery; CI, confidence interval; ECA, external carotid artery; HR, hazard ratio; ICA, internal carotid artery.

*Mortality = no. of case/person-years × 1000.

†With competing risk analysis for death from noncardiovascular deaths.

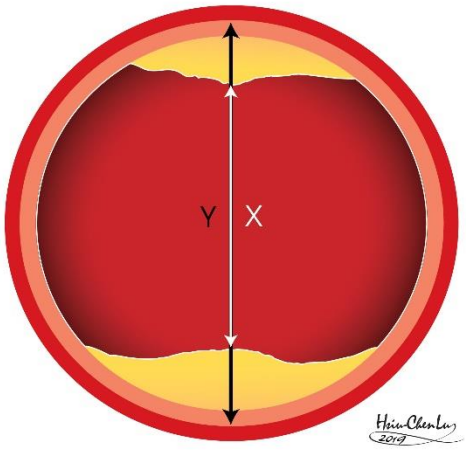
Model 1 was adjusted for age and sex (n = 17,673).

Model 2 was additionally adjusted for diabetes, hypertension, cardiovascular disease, stroke, estimated glomerular filtration rate,

hemoglobin, and use of statins and antiplatelet agents at baseline (n = 11,385).

Figure S1. Reference image indicating (a) the definition of percentage of diameter reduction and (b) the carotid anatomical segments measured in the present study. BIF, carotid bifurcation; CCA, common carotid artery; ECA, external carotid artery; ICA, internal carotid artery. Percentage diameter reduction was measured as (1−x/y) × 100%, where the arterial lumen diameter (x) were identified by intima-lumen interfaces and outer contours (y) were identified by media-adventitia interfaces.

(a) Determination of percentage of diameter reduction



(b) Carotid anatomical segments

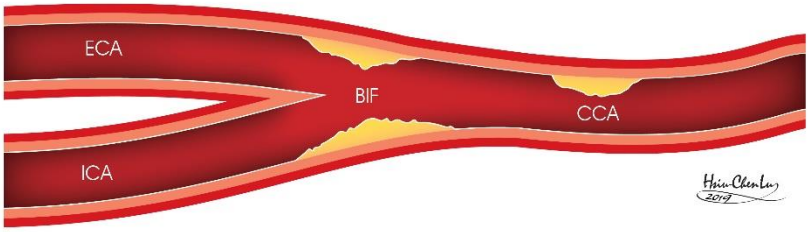
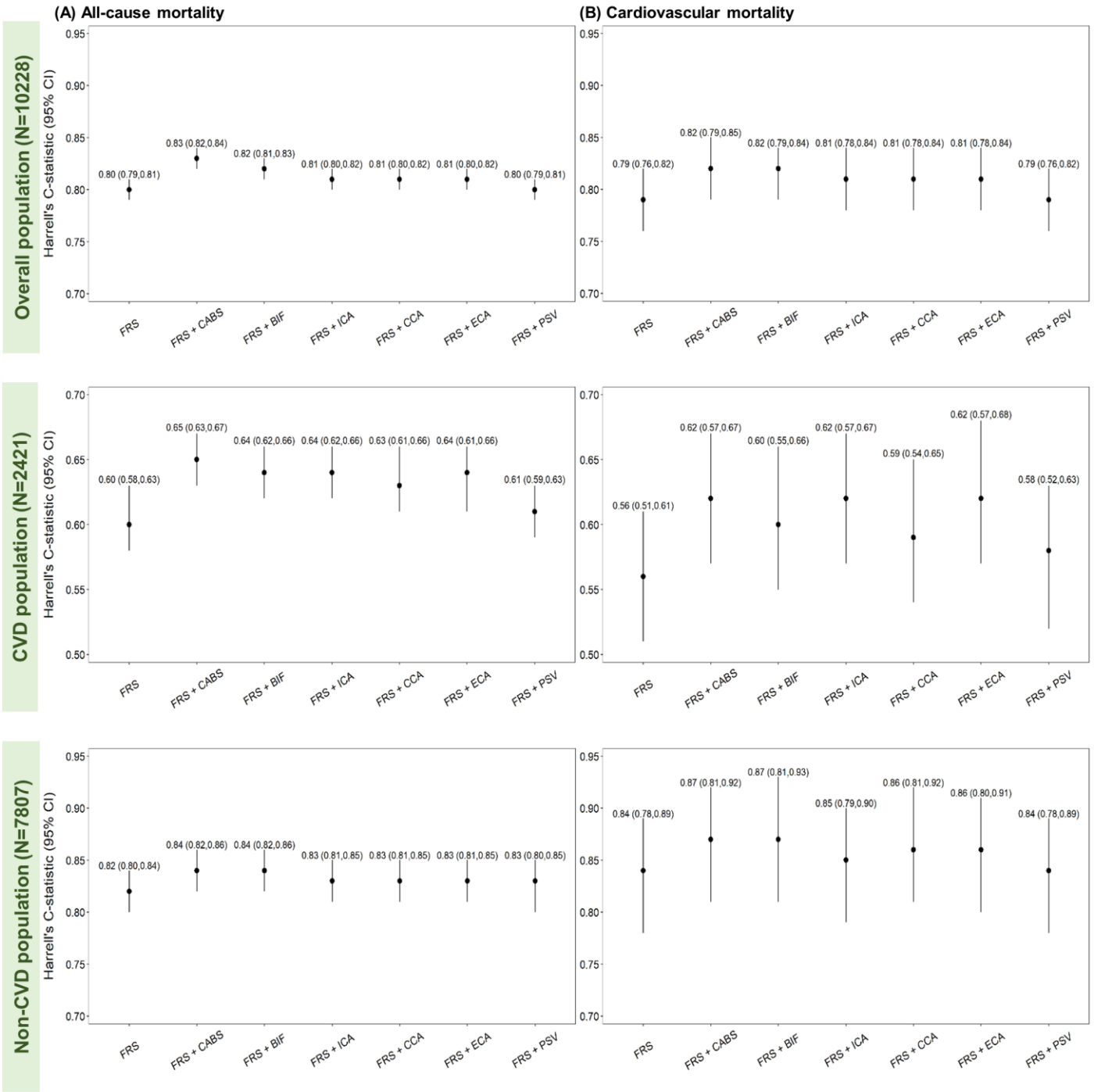


Figure S2. C statistics of model including FRS only, and models including FRS plus CABS, percentage of diameter reduction in various carotid sites (category variables), or PSV, for prediction of death from (a) all causes and (b) cardiovascular diseases. BIF indicates carotid bifurcation; CABS, carotid atherosclerotic burden score; CCA, common carotid artery; CI, confidence interval; ECA, external carotid artery; FRS, Framingham Risk Score; ICA, internal carotid artery; PSV, peak systolic velocity. The analysis was based on an imputed dataset (n=10228). P values were listed in the table below



The *P* values comparing C statistics of the models adding carotid artery parameters to FRS only model

	Overall population		CVD population		Non-CVD population	
	All-cause mortality	Cardiovascular mortality	All-cause mortality	Cardiovascular mortality	All-cause mortality	Cardiovascular mortality
FRS	Ref	Ref	Ref	Ref	Ref	Ref
FRS+CABS	<0.001	<0.001	0.003	0.022	<0.001	0.015
FRS+BIF	<0.001	<0.001	<0.001	0.017	<0.001	0.019
FRS+ICA	<0.001	0.004	0.038	0.178	<0.001	0.085
FRS+CCA	<0.001	0.003	0.006	0.049	<0.001	0.199
FRS+ECA	<0.001	0.004	0.025	0.145	<0.001	0.059
FRS+PSV	0.055	0.971	0.589	0.816	0.117	0.771

Figure S3. Calibration plots of predicted and observed (a) all-cause and (b) cardiovascular survival probability of predicted survival at 7-years according to models including FRS only, and models of FRS plus CABS, percentage of diameter reduction in various carotid sites (category variables), or PSV (based on an actual database, n=4004). BIF indicates carotid bifurcation; CABS, carotid atherosclerotic burden score; CCA, common carotid artery; CI, confidence interval; ECA, external carotid artery; FRS, Framingham Risk Score; ICA, internal carotid artery; PSV, peak systolic velocity.