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Combination of carotid intima-media thickness and plaque for better predicting risk of ischaemic cardiovascular events in Chinese subjects

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ABSTRACT

Background Several indices of carotid atherosclerosis have been studied to investigate their associations with the risk of cardiovascular disease. However, the best index of carotid atherosclerosis that predicts the risk of cardiovascular disease remains unclear.

Objective To investigate the index that best reflects the relationship between carotid atherosclerosis and subsequent ischaemic cardiovascular disease (ICVD) events.

Design An observational longitudinal study with a 5-year follow-up.

Participants 1734 Chinese subjects (623 men, 1111 women) aged 43–79 years at baseline.

Main outcome measures ICVD events, including coronary heart disease and ischaemic stroke.

Results Carotid intima-media thickness (IMT) at baseline was significantly associated with the risk of ICVD among participants without carotid plaque (multivariable adjusted HR=1.59, 95% CI 1.04 to 2.45) but not among those with plaque (HR=1.04, 95% CI 0.78 to 1.39). However, the total area of plaques (HR=1.29, 95% CI 1.08 to 1.55), the number of plaques (HR=1.14, 95% CI 1.02 to 1.27) and the number of segments with plaque (HR=1.45, 95% CI 1.09 to 1.93) were all significantly associated with ICVD in participants with plaque. Thus, carotid IMT and the number of segments with plaque were combined to establish a summary index—the total burden score (TBS) of carotid atherosclerosis—which was shown to improve the prediction of the 5-year risk of ICVD significantly compared with IMT or the number of segments with plaque alone. The c-statistics and net reclassification index showed that TBS improved the risk prediction by increases of 6.0% and 17.1%, respectively, compared with the conventional risk score.

Conclusion The TBS could significantly improve the prediction of ICVD risk and should be used in clinical practice and future studies.

INTRODUCTION

Cardiovascular disease (CVD) including coronary heart disease (CHD) and stroke often occur in individuals without prior symptoms.[1 2] Identification of individuals with a high risk of cardiovascular disease for early intervention remains a serious public health challenge.[1] Non-invasive tests for subclinical atherosclerosis have recently become available and are becoming widely promoted for risk assessment in asymptomatic patients.

B-mode ultrasound is a relatively inexpensive and safe technique that can visualise the lumen and walls of the carotid artery non-invasively. Carotid intima-media thickness (IMT), the number of plaques (NP), the number of segments with plaque (NS) and the total area of plaques (TA) have all been reported to be predictors of subsequent cardiovascular events.[2–5] However, the question of how to compare and summarise the effects of these different indices remains largely unknown in clinical practice. In addition, more research is needed to evaluate the incremental value for IMT and plaque to predict the risk of CHD and stroke as well as traditional risk factors.[6] We therefore conducted a longitudinal cohort follow-up study in a general Chinese population to compare the predictive ability of carotid IMT and plaque indices and to further develop a summary index of carotid atherosclerosis to better predict ischaemic cardiovascular disease (ICVD) events.

METHODS

Study population

The study sample was taken from the original cohort of rural Beijing participants in the People's Republic of China-United States of America (PRC-USA) Collaborative Study of Cardiovascular and Cardiopulmonary Epidemiology. A detailed description of the goals, design and methods of the PRC-USA study has been published elsewhere.[7 8] Briefly, a clustered random sample of 2313 participants was selected from all 11 villages of the Shijingshan district of Beijing in autumn 1993 and autumn 1994 for the PRC-USA study's third survey. Of the 2313 participants, 39 participants died, 71 were excluded because of a history of CHD and/or stroke and the remaining 2203 participants were invited for examination using carotid ultrasonography in 2002 and in 2005. Of the total 2203 eligible participants, 1734 (1202 included in 2002 and 532 included in 2005; response rate 79%, 623 men and 1111 women) consented and underwent the baseline carotid artery ultrasound examination and thus were used in the data analysis.

Peking University Health Science Center ethics committee approved the examination and follow-up in 2007 and the Cardiovascular Institute and Fuwai Hospital ethics committee approved all the previous studies. Written informed consent was obtained from all participants in all surveys and examinations.

Risk factor measurement

The baseline examination included all major conventional cardiovascular risk factors measured using the same standard protocols as those in the

PRC-US study.[8 9] Current smoking was defined as having smoked at least one cigarette per day for at least the past year. Hypertension was defined as mean systolic blood pressure (SBP) ≥140 mm Hg and/or mean diastolic blood pressure (DBP) ≥90 mm Hg or the use of antihypertensive drugs in the past 2 weeks. Diabetes mellitus was defined as a fasting blood glucose ≥7.0 mmol/l or current use of insulin or oral hypoglycaemic medication. Body mass index was calculated as kg/m^2.

Follow-up and definition of cardiovascular events

Follow-up for total deaths and cardiovascular events was conducted by re-surveying the cohort in 2005 and 2007 according to a standardised protocol. The follow-up data for CHD and stroke events were first collected by investigators using a standardised form at each follow-up survey via face-to-face interviews (88.2%). If participants were absent the investigators completed the forms by telephone (11.8%). Suspected events were further investigated with a repeat visit of the doctor to the patient or family or the hospital if applicable to collect clinical data needed for diagnosis (including symptoms, personal history, ECG, enzyme tests, brain CT scan or autopsy findings). The vital information for assessing events was provided by the patients or family members (86%), primary care physicians (10%) or relatives or friends (4%). If a participant died or reported an incidence of cardiovascular events during the follow-up, the participant's death certificate, hospital records including medical history, findings from physical and laboratory examinations, discharge diagnosis and autopsy findings (if applicable) were reviewed and abstracted by trained staff using a standardised form. The final diagnosis was made by independent adjudication committees which reviewed the medical history and death certificates using prespecified criteria from the WHO MONICA project[10] and the PRC-USA Collaborative Study.[8]

The coronary events were defined as an occurrence of first non-fatal or fatal myocardial infarction (MI) during the follow-up. Criteria used to define MI were adapted from diagnostic criteria developed by the PRC-USA Collaborative Study and have been described in detail elsewhere.[8]

During the follow-up period the incidence of first non-fatal or fatal stroke was defined using the WHO MONICA criteria[10]: rapidly developing signs of focal or global disturbance of cerebral function lasting >24 h (unless interrupted by surgery or death) with no apparent non-vascular cause. The definition of ischaemic stroke included cerebral thrombosis and cerebral embolism. Intracerebral haemorrhage, subarachnoid haemorrhage, transient ischaemic attacks and silent brain infarctions (cases without clinical symptoms or signs) were not included, neither were events associated with trauma, blood disease or malignancy. All of the stroke cases underwent brain CT scans.

The incidence of ICVD was defined as the composite of coronary events or ischaemic stroke events. If an individual had more than one event, the first event was used. If an individual had both CHD and ischaemic stroke, only one ICVD event was included.

Ultrasound protocol

The protocol for carotid atherosclerosis measurements at baseline examinations in 2002 and 2005 were the same and have been published elsewhere.[11] In short, measurements were made in magnified longitudinal views. IMT was measured at the far wall of three 10-mm segments of bilateral carotid artery: the proximal common carotid artery, the distal common carotid artery and the bifurcation. In every segment, separate measurements were attempted at three points (0, 5 and 10 mm), provided these points were in the absence of plaque (see figure S1 in online supplement). The overall average value of the IMT at the 18 points was calculated and used in the analysis.

To assess the presence of plaques, the near and far walls of the common carotid arteries and the bifurcation were scanned longitudinally and transversely. A carotid plaque was defined as a localised thickness of IMT ≥1.3 mm or a focal raised lesion of ≥0.5 mm, with or without flow disturbance (see figure S2 in online supplement). First, NP was counted in the bilateral carotid arteries in the scanning area, and NS reflected the total number of segments where a plaque was detected (range 0–4, left- and right-sided common carotid artery and bifurcation). The plaque was then measured by tracing the perimeter with a cursor on the screen and the cross-sectional area of the plaque was computed by the software in the duplex scanner (see figure S2 in the online supplement); the total cross-sectional area of all the plaques was summed to give the TA.

Reproducibility study

We randomly selected 40 participants from the cohort and invited them to attend the reproducibility study. The intraclass correlation coefficients for inter-observer and intra-observer reproducibility of IMT were 0.96 (95% CI 0.88 to 0.99, p<0.001) and 0.98 (95% CI 0.97 to 0.99, p<0.001), and the inter-observer and intra-observer reproducibility for the presence of plaque was 85% and 95%, respectively.[11]

Statistical analysis

The t test and χ^2 test were used to compare the baseline characteristics between participants who had and had not developed ICVD events during the follow-up period.

Cox proportional hazards regression analysis was used to calculate unadjusted, age-, sex- and multivariable-adjusted HRs of ICVD events in groups with various degrees of carotid atherosclerosis measured by different indices. For IMT we divided the participants into four quartile groups and took the lowest quartile as the reference. For NP the participants were divided into four groups (0, 1, 2 and ≥3 plaques) using the group with no plaque as the reference. For NS we divided the participants with plaque into four groups (0, 1, 2 and ≥3 segments with plaque) and the group with no plaque was used as the reference. For TA we divided the participants with plaque into three tertile groups according to their TA and took the group with no plaque as the reference. The p value for trend was calculated using Cox proportional hazards regression analysis with the indices of carotid atherosclerosis as continuous variables.

To explore if the presence of plaque affected the association of IMT with the cardiovascular risk, we further divided the study population into two groups: those without plaque and those with plaque. The same analysis was repeated for IMT as had been used for the whole study population.

For the participants with carotid plaque we used backward stepwise regression analysis to assess which plaque index was best related to the risk of ICVD (backward: LR; removal: 0.05). Subsequently, to explore whether the three plaque indices could be substituted for each other, we forced one index into the model and then determined whether the two others could still remain in the model using stepwise regression.

For estimating the 10-year risk of ICVD we applied the Chinese scoring sheet previously published,[9] which is now widely accepted and used in China (see figure S3 in the online supplement). The conventional risk factors employed in this scoring system include age, SBP, diabetes mellitus, body mass

index, current smoking status and total cholesterol.[12 13] We used the conventional risk score and total burden score (TBS) to fit two risk prediction models: the model using the conventional risk score alone and the model using the conventional risk score plus TBS.

We used two strategies to determine whether the TBS made an additional contribution to predicting the risk of ICVD. Receiver operating characteristic curve analysis was used to compare the two models in their ability to predict the 5-year ICVD risk and equality of the area under the curves (AUC, or c-statistics) was tested using the algorithm proposed by Hanley *et al*.[14]

We also used the net reclassification improvement (NRI) index proposed by Pencina *et al*[15] to determine whether the addition of TBS to the conventional model could significantly increase its ability to predict the 5-year ICVD risk. Reclassification tables were constructed separately for participants who did and did not develop events using <3%, 3–10% and >10% 5-year ICVD risk categories, according to the Third Adult Treatment Panel.[16] The absolute 5-year risk of ICVD was predicted with a Cox regression model developed by Framingham investigators.[17]

Statistical analyses were performed with SPSS Version 13.0 software. All analyses are two-sided with a p value of 0.05 indicating statistical significance.

RESULTS

Baseline characteristics

During a mean follow-up of 4 years (total of 6984 person-years) there were 63 new cases of ischaemic stroke events (29 for men and 34 for women), 23 CHD events (9 for men and 14 for women) and 81 ICVD events (36 for men and 45 for women). The incidence rate was 9.8 per 1000 person-years for ischaemic stroke events (13.0 for men and 8.1 for women), 3.6 per 1000 person-years for CHD events (4.0 for men and 3.4 for women) and 12.6 per 1000 person-years for ICVD events (16.1 for men and 10.7 for women). The analyses of the baseline characteristics of the study participants showed that the mean age, SBP, carotid IMT, NP, NS and TA, and the prevalence of current smoking, hypertension and presence of plaque at baseline were all significantly higher in cases of new ICVD events than in non-cases (see figure S4 in online supplement).

Association of baseline carotid IMT with the risk of new ICVD events

Table 1 shows that HRs of new ICVD events increased significantly with the increase in baseline carotid IMT in all participants. However, further analysis shows that the trend only existed for participants without any plaque and not for those with plaque (table 2). The interaction between IMT and the presence of plaque was examined using the Cox regression model and no statistical significance was found.

Association of baseline carotid plaque indices with the risk of new ICVD events

In all participants the three plaque indices were significantly associated with the risk of ICVD (table 1). Among participants with plaque, the three plaque indices were still significantly associated with the risk of ICVD even after adjustment for multiple variables (table 2). To identify the best ICVD

Table 1 HRs of ICVD events in relation to carotid IMT, total area, number of plaques and number of segments with plaque among all participants

		HR (95% CI)		
Ultrasound variables	**Events/sample size**	**Unadjusted**	**Age- and sex- adjusted**	**Multivariable- adjusted***
IMT (mm) in quartiles				
Quartile 1 (<0.66)	9/434	1.00	1.00	1.00
Quartile 2 (0.66–0.71)	14/392	1.75 (0.76 to 4.04)	1.53 (0.66 to 3.55)	1.31 (0.56 to 3.08)
Quartile 3 (0.72–0.78)	25/445	3.00 (1.40 to 6.43)	2.39 (1.09 to 5.22)	2.04 (0.92 to 4.50)
Quartile 4 (≥0.79)	33/463	4.56 (2.18 to 9.55)	3.06 (1.37 to 6.81)	2.30 (1.02 to 5.21)
p for trend		<0.001	0.004	0.041
Per 1 SD (0.10) increase	81/1734	1.56 (1.30 to 1.88)	1.37 (1.11 to 1.70)	1.27 (1.02 to 1.59)
Total area (mm^2) of plaques				
No plaque	31/1043	1.00	1.00	1.00
Tertile 1 (<12.0)	13/240	1.79 (0.94 to 3.42)	1.56 (0.81 to 3.02)	1.51 (0.78 to 2.92)
Tertile 2 (12.0–29.9)	12/208	2.33 (1.20 to 4.54)	1.90 (0.95 to 3.78)	1.71 (0.85 to 3.44)
Tertile 3 (≥30.0)	25/243	4.44 (2.61 to 7.53)	3.19 (1.74 to 5.83)	2.70 (1.47 to 4.96)
p for trend		<0.001	<0.001	<0.001
Per 1 SD (31.3) increase	81/1734	1.36 (1.24 to 1.50)	1.28 (1.15 to 1.43)	1.23 (1.10 to 1.38)
Number of plaques				
0	31/1043	1.00	1.00	1.00
1	19/335	2.04 (1.16 to 3.62)	1.77 (0.98 to 3.18)	1.63 (0.91 to 2.95)
2	6/167	1.40 (0.58 to 3.35)	1.10 (0.45 to 2.70)	1.03 (0.42 to 2.54)
≥3	25/189	5.57 (3.28 to 9.45)	4.03 (2.21 to 7.35)	3.46 (1.89 to 6.35)
p for trend		<0.001	<0.001	<0.001
Per 1 plaque increase	81/1734	1.27 (1.17 to 1.37)	1.21 (1.11 to 1.32)	1.17 (1.07 to 1.28)
Number of segments with plaque				
0	31/1043	1.00	1.00	1.00
1	20/380	1.91 (1.09 to 3.34)	1.63 (0.91 to 2.90)	1.52 (0.85 to 2.72)
2	15/203	2.99 (1.61 to 5.54)	2.20 (1.13 to 4.30)	2.04 (1.04 to 3.98)
≥3	15/108	5.87 (3.16 to 10.89)	4.23 (2.15 to 8.33)	3.51 (1.76 to 7.01)
p for trend		<0.001	<0.001	<0.001
Per 1 segment increase	81/1734	1.70 (1.43 to 2.01)	1.53 (1.26 to 1.86)	1.44 (1.19 to 1.75)

*Adjusting for age, sex, diabetes mellitus, hypertension, body mass index, current smoking status and total and HDL cholesterol levels.
ICVD, ischaemic cardiovascular disease; IMT, intima-media thickness.

Table 2 HRs of ICVD events in relation to carotid IMT, total area, number of plaques and number of segments with plaque in participants with or without plaque

		HR (95% CI)		
Ultrasound variables	**Events/sample size**	**Unadjusted**	**Age- and sex- adjusted**	**Multivariable- adjusted***
Among 1043 participants without any plaque				
IMT (mm) in quartiles				
Quartile 1 (<0.63)	4/255	1.00	1.00	1.00
Quartile 2 (0.63–0.68)	7/285	1.61 (0.47 to 5.51)	1.46 (0.43 to 5.02)	1.35 (0.39 to 4.66)
Quartile 3 (0.69–0.74)	8/234	2.25 (0.68 to 7.48)	1.87 (0.55 to 6.35)	1.81 (0.52 to 6.27)
Quartile 4 (≥0.75)	12/269	3.64 (1.17 to 11.29)	2.63 (0.79 to 8.72)	2.41 (0.71 to 8.22)
p for trend		0.002	0.027	0.034
Per 1 SD (0.10) increase	31/1043	1.82 (1.25 to 2.64)	1.59 (1.06 to 2.40)	1.59 (1.04 to 2.45)
Among 691 participants with plaque				
IMT (mm) in quartiles				
Quartile 1 (<0.72)	10/178	1.00	1.00	1.00
Quartile 2 (0.72–0.77)	14/160	1.67 (0.74 to 3.77)	1.59 (0.70 to 3.59)	1.54 (0.68 to 3.49)
Quartile 3 (0.78–0.84)	11/176	1.22 (0.52 to 2.87)	1.08 (0.45 to 2.59)	1.00 (0.41 to 2.43)
Quartile 4 (≥0.85)	15/177	2.06 (0.92 to 4.60)	1.76 (0.76 to 4.06)	1.38 (0.59 to 3.21)
p for trend		0.170	0.368	0.754
Per 1 SD (0.10) increase	50/691	1.20 (0.92 to 1.56)	1.14 (0.86 to 1.50)	1.04 (0.78 to 1.39)
Total area (mm^2) of plaques				
Tertile 1 (<12.0)	13/240	1.00	1.00	1.00
Tertile 2 (12.0–29.9)	12/208	1.28 (0.58 to 2.80)	1.24 (0.56 to 2.74)	1.20 (0.54 to 2.65)
Tertile 3 (≥30.0)	25/243	2.42 (1.23 to 4.74)	2.23 (1.09 to 4.54)	1.91 (0.93 to 3.95)
p for trend		<0.001	0.001	0.006
Per 1 SD (43.2) increase	50/691	1.38 (1.17 to 1.62)	1.35 (1.14 to 1.61)	1.29 (1.08 to 1.55)
Number of plaques				
1	19/335	1.00	1.00	1.00
2	6/167	0.70 (0.27 to 1.70)	0.66 (0.26 to 1.65)	0.70 (0.27 to 1.76)
≥3	25/189	2.70 (1.48 to 4.90)	2.50 (1.33 to 4.70)	2.30 (1.21 to 4.35)
p for trend		0.001	0.003	0.014
Per 1 plaque increase	50/691	1.19 (1.08 to 1.32)	1.18 (1.06 to 1.31)	1.14 (1.02 to 1.27)
Number of segments with plaque				
1	20/380	1.00	1.00	1.00
2	15/203	1.55 (0.79 to 3.03)	1.45 (0.73 to 2.89)	1.45 (0.73 to 2.90)
≥3	15/108	3.05 (1.56 to 5.97)	2.81 (1.40 to 5.64)	2.43 (1.20 to 4.93)
p for trend		0.001	0.002	0.010
Per 1 segment increase	50/691	1.62 (1.23 to 2.13)	1.57 (1.18 to 2.09)	1.45 (1.09 to 1.93)

*Adjusting for age, sex, diabetes mellitus, hypertension, body mass index, current smoking status and total and HDL cholesterol levels.
ICVD, ischaemic cardiovascular disease; IMT, intima-media thickness.

risk-associated variable of the three tested, we then put all of them into a backward stepwise regression. The results showed that only NS remained significant in the final model. However, if we forced NP or TA into the model, the other two variables did not remain significant in the model (data not shown).

Combination of the impact of IMT and plaque on the risk of ICVD

Based on the above results, we created a new way to categorise the level of each individual's carotid atherosclerosis by combining IMT and NS. We first divided the study participants according to the presence of any carotid plaque. Then, for those who did not have any plaque, we further divided them into four quartile groups by their mean IMT (table 3). For those who had any carotid plaque, we divided them into three groups according to NS (1, 2 or ≥3). We then used the new variable as six dummy variables, together with the conventional risk score, to fit a multivariable Cox proportional hazard model (table 3). We named the scores as the TBS of carotid atherosclerosis and assigned an appropriate score to each level of the new variable with reference to the corresponding regression coefficients by using the quantity of risk from every conventional risk score increase as 1 standard unit of risk and gave it an incremental score of 1 (table 3).

Comparison of TBS with IMT and NS in association with the risk of new ICVD events

Backward stepwise regression analysis was used to explore whether this new summary index was better related to the risk of ICVD than either IMT or NS alone. The results showed that only TBS remained in the final model. When IMT or NS was forced into the model, TBS still remained significant and the forced variable was insignificant (data not shown).

Additive value of TBS in the prediction of ICVD risk

To test the additional contribution of TBS in predicting the 5-year risk of ICVD events, we first fit two models—the model using only the conventional risk score and the model using the conventional risk score plus TBS. The equations for calculating the 5-year risk of ICVD are $E_1=1-0.953^{\exp(0.193\times(\text{conventional risk score}-7.3))}$ and $E_2=1-0.953^{\exp(0.172\times(\text{sum of conventional risk score and total burden score}-9.88))}$, respectively.

We then compared the receiver operating characteristic curves and the corresponding AUCs between the models (figure 1). TBS resulted in a significant increase in AUC from 0.724 (95% CI 0.675 to 0.773) for the model using only the conventional risk score to 0.784 (95% CI 0.738 to −0.829) for the model using the conventional risk score plus TBS (p<0.01). However, neither

Table 3 Regression coefficients (β) and HRs of the simplified Cox proportional hazard model for 5-year risk of ICVD, and translation of β into total burden score

Variables in the model	N	β	HR (95% CI)	Total burden score
Conventional risk score (per 1 score increase)	1734	0.274	1.32 (1.24 to 1.41)	1 (Ref)
Combined carotid atherosclerosis categories				
No plaque and IMT<0.63 mm	255	Ref	1.00	0
No plaque and 0.63≤IMT≤0.68 mm	285	0.271	1.31 (0.38 to 4.50)	1
No plaque and 0.69≤IMT≤0.74 mm	234	0.510	1.67 (0.50 to 5.59)	2
No plaque and IMT ≥0.75 mm	269	0.786	2.19 (0.69 to 7.02)	3
1 segment with plaque	380	0.834	2.30 (0.85 to 5.73)	3
2 segments with plaque	203	1.263	3.54 (1.12 to 11.14)	5
≥3 segments with plaque	108	1.785	5.96 (1.86 to 19.13)	7

ICVD, ischaemic cardiovascular disease; IMT, intima-media thickness.

IMT nor plaque indices resulted in significant increases (data not shown). We further used the NRI method to evaluate the additive value of TBS, IMT and NS. The NRIs were 0.073 (95% CI 0.061 to 0.086) for IMT, 0.120 (95% CI 0.104 to 0.136) for NS and 0.171 (95% CI 0.153 to 0.188) for TBS (see figure S5 in the online supplement) The NRI for TBS was significantly greater than those for IMT or NS.

DISCUSSION

Since Pignoli first used B-mode ultrasound to evaluate human carotid atherosclerosis in 1986,[18] carotid atherosclerosis measured by non-invasive ultrasound has been suggested to be the 'window' for atherosclerosis in other arteries. In the past 10 years a number of longitudinal studies in Europe and the USA have been done to estimate the relation between preclinical atherosclerosis and coronary heart disease and stroke. Most of these studies focused on carotid IMT.[5 19–23] Lorenz *et al* recently published a meta-analysis after reviewing data from 37 197 participants followed for a mean of 5.5 years and concluded that carotid IMT is a strong predictor of future CVD events[24]: the age- and sex- adjusted relative risks of MI and stroke were 1.26 (95% CI 1.21 to 1.30) and 1.32 (95% CI 1.27 to 1.38), respectively, per 1 SD of common carotid IMT.

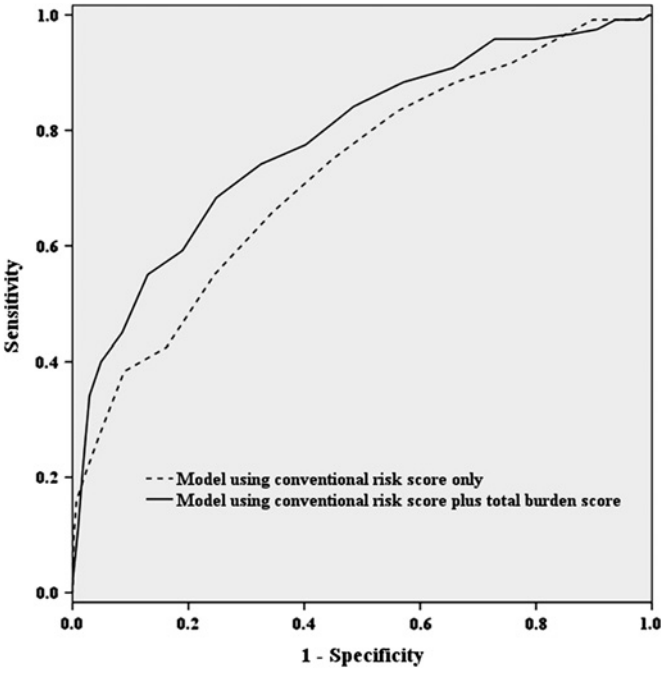

Figure 1 Receiver operating characteristic (ROC) curves and corresponding areas under the curve (AUCs) comparing the discriminative power of the conventional risk score alone and the conventional risk score plus total burden score. The total burden score resulted in a significant increase in AUC from 0.724 (95% CI 0.675 to 0.773) for the model using only the conventional risk score to 0.784 (95% CI 0.738 to 0.829) for the model using the conventional risk score plus total burden score (p<0.01).

Compared with carotid IMT, the presence and severity of carotid plaque are less frequently studied in relation to CVD.[2 3 25] In 2002 Spence suggested that the plaque area could be an alternative to IMT.[26] In his cohort study of 1686 patients with stroke, transient ischaemic attack or asymptomatic carotid stenosis he found that the combined 5-year risk of stroke, MI and vascular death increased by quartiles of TA.[4] Another prospective population-based study among 6226 participants aged 25–84 years with no previous MI found that TA was associated significantly with CVD.[27]

The present study confirmed the above findings from previous studies that carotid IMT, TA, NP and NS were all significantly associated with the risk of ICVD events.[2–5] However, our study found that the association of carotid IMT with the risk of ICVD existed only in participants who had not developed carotid plaque. On the other hand, we know that carotid plaque indices cannot help to differentiate the risk of ICVD events among participants who have not yet developed any carotid plaque. To solve this dilemma we propose that the TBS of carotid atherosclerosis—a measure derived from IMT for those who have not developed carotid plaque and from NS for those who have developed carotid plaque—be used to evaluate the impact of carotid atherosclerosis on the risk of ICVD events. Our study has shown that this new summary index provides a significantly better prediction of ICVD risk than IMT or plaque indices alone, which is additional to the conventional ICVD risk score. The c-statistics and net reclassification index showed that TBS improved the risk prediction by increases of 6.0% and 17.1%, respectively, compared with the conventional risk score, a clinically significant improvement in the risk prediction previously been reported. It implies that the TBS, as a new summary index of carotid atherosclerosis, should be used in practice for estimation of an individual's risk of cardiovascular disease.

The findings of this study that a lower TBS score (<3) was assigned to IMT and a higher score (>3) was assigned to NS strongly support a previous hypothesis that IMT and formation of plaque may reflect different stages in the pathology of atherosclerosis, the former reflecting early lesions of atherosclerosis and the latter reflecting advanced lesions.[28]

In this study we used the risk score system developed by Wu *et al*[9] to evaluate the conventional vascular risk factors, but we

did not use the Framingham score because we did not consider it appropriate for this study. First, the cardiovascular outcome-specific algorithms in the Framingham Heart Study do not all match the outcome in our study. Second, since more than 99% of participants in the Framingham Heart Study are of European descent and the CVD patterns between Western and Chinese populations are very different, the Framingham functions and scores cannot be generalised to the Chinese population. The Chinese Multi-provincial Cohort Study and the USA-PRC Study all showed that the original Framingham functions and scores overestimated the CHD risk in the Chinese population.[9 29]

This study has some limitations that need to be addressed. First, there were 469 non-responders and the results showed that the non-responders had a higher risk of CVD than the responders (see figure S6 in the online supplement). Using only the responding subgroup as the study population would be expected to dilute the association between carotid atherosclerosis and future ICVD events since the association was stronger in high-risk participants than in low-risk participants.[30] Second, we only measured the common carotid artery and bifurcation but not the internal carotid artery. This was simply because the common carotid artery and bifurcation are easier to measure than the internal carotid artery which is very difficult to visualise in many circumstances and intra-observer and inter-observer reproducibility is large.[31] Third, a longer period of follow-up accumulating more cases would probably have allowed us to look at the associations for coronary heart events and stroke events separately. Finally, the models and results in this study are only valid for the Chinese population and would need to be assessed in other populations, particularly in Western populations where coronary heart disease is much more common than stroke.

Despite these limitations, our study provides strong support for the conclusion that a summary index of the total burden of carotid atherosclerosis should and could be developed. We propose to use the TBS of carotid atherosclerosis, a combined index derived from IMT and NS, to predict the risk of ICVD events in clinical practice and in future studies.

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Patient consent Obtained.

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Heart

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