Carotid Stiffness Is Associated With Incident Stroke

A Systematic Review and Individual Participant Data Meta-Analysis

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ABSTRACT

BACKGROUND Carotid stiffening is considered a key element in the pathogenesis of stroke. However, results of studies evaluating the association between carotid stiffness and incident stroke have been inconsistent.

OBJECTIVES This study investigated whether carotid stiffness (as determined by ultrasonography) is associated with incident stroke and whether this association is independent of aortic stiffness as estimated by carotid-femoral pulse wave velocity (cfPWV). Additionally, we evaluated the incremental value of carotid stiffness for stroke risk prediction beyond Framingham risk factors and cfPWV.

METHODS This study included a systematic review and meta-analyses of aggregate and individual participant data (IPD), the latter of which was obtained by requesting individual-level data of all cohort studies with available data on carotid stiffness and cfPWV.

RESULTS Ten studies (n = 22,472) were included in the aggregate data meta-analysis and 4 (n = 4,540) in the IPD meta-analysis. After adjusting for cardiovascular (CV) factors, the aggregate data meta-analysis showed that greater carotid stiffness (per SD) was associated with stroke (hazard ratio: 1.18; 95% confidence interval: 1.05 to 1.33). In addition, carotid stiffness was associated with total CV events and CV and all-cause mortality, but not with coronary heart disease events. In the IPD meta-analysis, additional adjustment for cfPWV did not materially change these associations. Carotid stiffness did improve stroke risk prediction beyond Framingham and cfPWV (integrative discrimination improvement: 0.4 percentage point [95% confidence interval: 0.1 to 0.6 percentage point] and continuous net reclassification improvement: 18.6% [95% confidence interval: 5.8% to 31.3%]).

CONCLUSIONS Carotid stiffness is associated with incident stroke independently of CV factors and aortic stiffness. In addition, carotid stiffness improves stroke risk prediction beyond Framingham and aortic stiffness. (J Am Coll Cardiol 2015;66:2116–25) © 2015 by the American College of Cardiology Foundation.

S troke is 1 of the leading causes of disability and mortality worldwide (1). The global burden of stroke has greatly increased in the last decades, and will continue to increase in the coming years (1,2). Therefore, effective prevention strategies need to be developed, which requires a better understanding of stroke risk factors (1).

Aging and cardiovascular disease (CVD) risk factors lead to stiffening of the common carotid artery (3), which can be quantified noninvasively by measuring local distensibility (3,4). Stiffening of carotid arteries impairs their cushioning function, increasing pressure and flow pulsatility, which transmit distally into the cerebral circulation and, thus, may increase stroke risk (5,6). Carotid stiffening also may lead to stroke through development of (rupture-prone) atherosclerotic carotid plaques (7). However, results of studies on the association between carotid stiffness and incident stroke have been inconsistent; 1 study (8) reported a statistically significant association between carotid stiffness and incident stroke, but 3 smaller studies (6,9,10) did not.

We therefore performed a systematic review and aggregate data meta-analysis of cohort studies on the association between carotid stiffness and incident stroke. Carotid-femoral pulse wave velocity (cfPWV), a measure of aortic stiffness (3), is the most often used arterial stiffness measurement and is associated with incident CVD (11,12). Therefore, we performed an individual participant data (IPD) meta-analysis from cohorts with measures of both carotid stiffness and cfPWV, evaluating whether the association between carotid stiffness and stroke (if any) is independent of cfPWV. Additionally, to evaluate whether carotid stiffness has any potential of being used as a risk predictor of stroke, we quantified the incremental value of carotid stiffness for stroke risk prediction beyond Framingham stroke risk score factors and cfPWV. Finally, we evaluated the association between carotid stiffness and other cardiovascular outcomes than stroke, including coronary heart disease (CHD) events, nonfatal and fatal cardiovascular events, and all-cause mortality.

METHODS

This review is reported in accordance with the preferred reporting items for systematic reviews and meta-analyses (Online Appendix A) (13).

Two independent reviewers (T.T.vS., S.S.) selected all relevant studies based on title and abstract, retrieved selected full texts, performed an eligibility assessment, extracted data, and assessed risk of bias (described later). Any disagreements between the reviewers were resolved by consensus. A third independent reviewer was available to solve any persisting disagreements.

We identified relevant studies through a search of MEDLINE, Embase, and Scopus from inception to August 7, 2015, without any language restriction (search terms are in Online Appendix B). We further identified studies by reviewing the reference lists of all relevant papers identified and by discussion with experts in the field to identify unpublished data.

For the systematic review and aggregate data meta-analysis, we considered eligible all prospective cohort studies in humans (of any age) that investigated the association between carotid stiffness and incident stroke (nonfatal and/or fatal), CHD events and/or total cardiovascular events, and/or all-cause mortality. We selected all studies that measured common carotid artery properties (diameter and distention) by ultrasound, together with brachial or local carotid pulse pressure (PP), and calculated carotid artery distensibility coefficient (DC), Young's elastic modulus (YEM), compliance coefficient (CC), or beta-stiffness index (SI). DC represents arterial stiffness (the lower the DC, the greater the stiffness) (3,4). (Formulas used for index calculation are in Online Appendix C.) The other indexes are closely related to the DC: higher YEM represents greater

ABBREVIATIONS AND ACRONYMS

CC = compliance coefficient

cfPWV = carotid-femoral pulse wave velocity

DC = distensibility coefficient

IDI = integrated discrimination improvement

IPD = individual participant data

NRI = net reclassification index

PP = pulse pressure

SI = beta-stiffness index

YEM = Young's elastic modulus

stiffness of the arterial wall material; lower CC represents lower arterial buffering capacity; and higher SI represents greater stiffness and takes into account the nonlinear relation between pressure and carotid artery diameter (3,4).

DATA EXTRACTION AND STATISTICAL ANALYSIS. We used a pre-designed data extraction form to collect information on the following: study size, location, population characteristics, measures of arterial stiffness, follow-up duration, type and number of events, reported risk estimates, and variable(s) that were adjusted for in the analyses. In the case of multiple publications (6,14-16), we included the most up-to-date or comprehensive information. For the aggregate data meta-analysis, additional information for 2 studies (17,18) was requested from corresponding authors but not provided.

Risk of bias was evaluated with the Newcastle-Ottawa Scale (NOS) (Online Appendix D) (19). The scale includes items on participant selection; validity of measurements; whether or not results were adjusted for age, sex, and blood pressure; and duration and completeness of follow-up.

For the IPD meta-analysis, we requested individual-level data of all studies eligible for the aggregate data meta-analysis with available data on cfPWV. All 4 eligible studies provided the requested data. Individual data from these studies were collected and harmonized using PASW statistics version 21 (SPSS Inc., Chicago, Illinois).

In both the aggregate data and IPD meta-analysis, outcome definitions were used as reported in the originally published papers (Online Table 1). Stroke included nonfatal and fatal cerebral infarction and intracerebral hemorrhage; CHD events included nonfatal and fatal acute myocardial infarction, angina pectoris, coronary artery bypass grafting, percutaneous coronary intervention, and sudden death; total cardiovascular events included nonfatal and fatal CHD events, stroke, congestive heart failure (HF), and peripheral arterial disease; cardiovascular mortality included all fatal cardiovascular events (as defined earlier); and all-cause mortality included death from any cause.

All statistical analyses were performed with Cochrane Review Manager version 5.2 (The Cochrane Collaboration, London, United Kingdom) and R statistical software version 2.15 (R Foundation for Statistical Computing, Vienna, Austria).

AGGREGATE DATA META-ANALYSIS. Results were pooled for the association between 1 SD greater carotid stiffness and incident stroke. Additionally, we evaluated the association of carotid stiffness with CHD events, total cardiovascular events, and cardiovascular and all-cause mortality. Results were included for lower DC or, if not available, higher YEM, lower CC, or higher SI. For studies that reported results on carotid stiffness calculated with brachial as well as local PP, we included the results on carotid stiffness calculated with brachial PP in the main analysis, because these were available in the largest number of participants. In a sensitivity analysis, results were pooled for carotid stiffness calculated with local PP. All included studies calculated hazard ratios (HRs), except 1 study (20) that calculated an odds ratio. We treated this odds ratio as an HR. Pooled HRs were calculated using the random-effects inverse variance method. For each study, we included the fully adjusted value for the HR. Heterogeneity between studies was investigated with Higgins I^2 statistic.

IPD META-ANALYSIS. Missing values on covariates were imputed using the expectation maximization method (single imputation) for each cohort separately. The percentage of missing values on covariates was minimal (total 2.0%). We first used a 2-stage analysis approach (21) with estimates of association calculated separately within each study before pooling across studies by the random-effects inverse variance method. We used Cox proportional hazard models with 1 SD lower carotid DC as the determinant and incident stroke as the outcome. Additionally, we evaluated the association of carotid stiffness with CHD events, total cardiovascular events, and cardiovascular and all-cause mortality. The associations were first adjusted for the following potential confounders (selected based on previously published data and previous knowledge): age, sex, mean arterial pressure, heart rate, body mass index, total/high-density lipoprotein (HDL) cholesterol ratio, triglycerides, current smoking, diabetes, prior CVD, and the use of antihypertensive and lipid-modifying medication (model 1), and additionally for cfPWV (model 2). We used interaction terms to explore whether any association with incident stroke differed according to age, sex, hypertension, and/or diabetes. We also evaluated the association between the individual elements of the stiffness indexes (PP, distension, and diameter) and stroke. To investigate whether carotid plaques mediate the association between carotid stiffness and any of the outcomes, results were additionally adjusted for presence of carotid plaques. We also tested for any potential differences in the results dependent on the method used to measure travel distance in calculating cfPWV (Online Appendix E).

We then evaluated whether carotid stiffness has any potential use as a risk predictor of stroke. We used the integrated discrimination improvement (IDI) and the continuous (category-free) net reclassification index (NRI) to quantify the incremental value of carotid DC for prediction of stroke risk beyond Framingham risk score factors and cfPWV. These indexes quantify any reclassification, irrespective of (clinically relevant) cutoffs. We used a 1-stage approach (21). These analyses were done in individuals without a prior CVD (at baseline) and limited to a time horizon of 10 years. We first fitted a Cox proportional hazards model to the data using the Kaplan-Meier estimate (22) on the basis of cfPWV and the Framingham stroke risk score factors (23) age, sex, systolic blood pressure, total and HDL cholesterol, current smoking, diabetes, use of antihypertensive medication, and left ventricular hypertrophy. This "base" model was then extended by carotid DC, and the base and extended model were compared using the IDI and continuous NRI. Additionally, we calculated the (change in) C-statistic, a measure of risk discrimination (24). Confidence intervals for the IDI, NRI, and C-statistic were calculated by bootstrapping (1,000 repetitions). Finally, we evaluated the incremental value of carotid DC beyond Framingham cardiovascular risk score factors (25) (i.e., age, sex, systolic blood pressure, total and HDL cholesterol, current smoking, diabetes, and use of antihypertensive medication) and cfPWV for risk prediction of CHD events, total cardiovascular events, and cardiovascular and all-cause mortality.

Additional information on methods is in the Online Appendix F.

RESULTS

STUDY CHARACTERISTICS. Of 3,939 references initially identified, 10 were included (6,8-10,15,20,26–29) in the aggregate meta-analysis (**Figure 1**). Of these 10 studies, 4 (6,8-10) evaluated stroke (n = 17,662 with 898 events), 5 (6,8-10,27) CHD events (n = 21,080 with 2,113 events), 10 (6,8-10,15,20,26–29) any cardiovascular events (n = 22,214 individuals with 3,010 events), 7 (6,9,10,15,26,28,29) cardiovascular mortality (n = 8,534 with 806 events), and 5 (6,10,15,26,29) all-cause mortality (n = 5,991 with 2,062 events). For the Rotterdam Study (10) and the study from Blacher et al. (15), the original investigators were able to provide an update of previously published results with unpublished data on a higher number of participants and longer follow-up duration. The updated results of the Rotterdam Study were based on 4,713
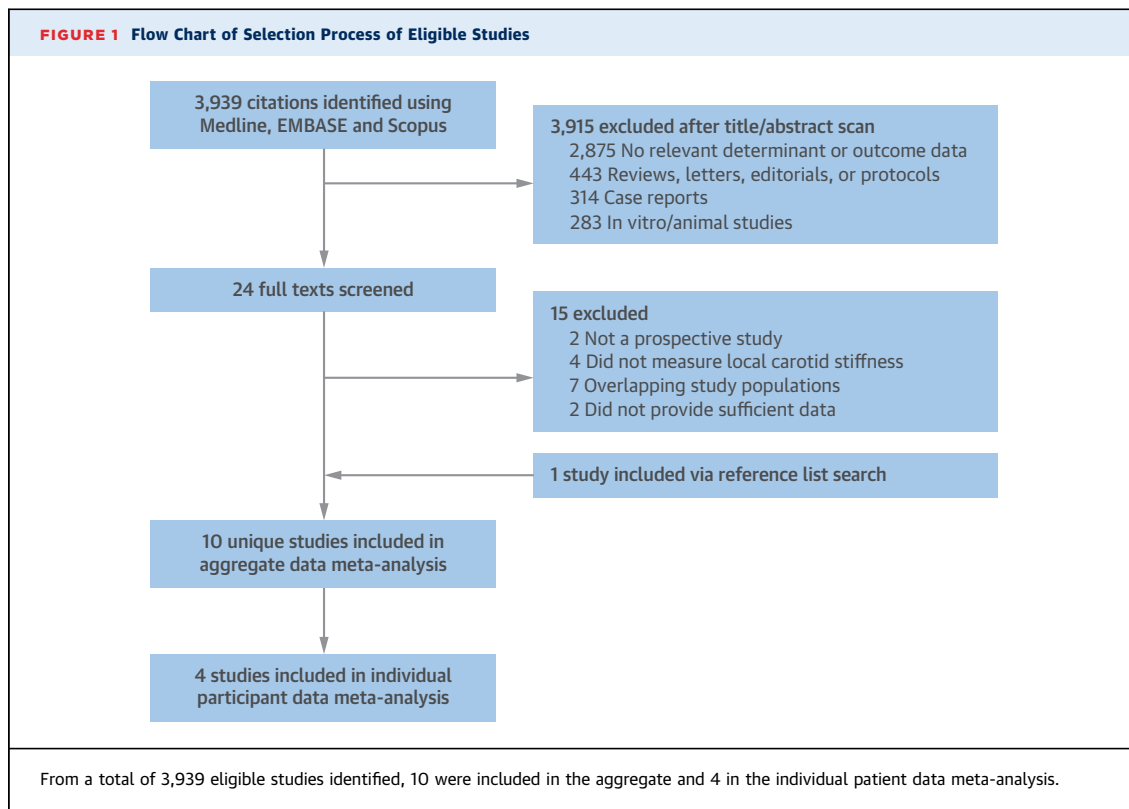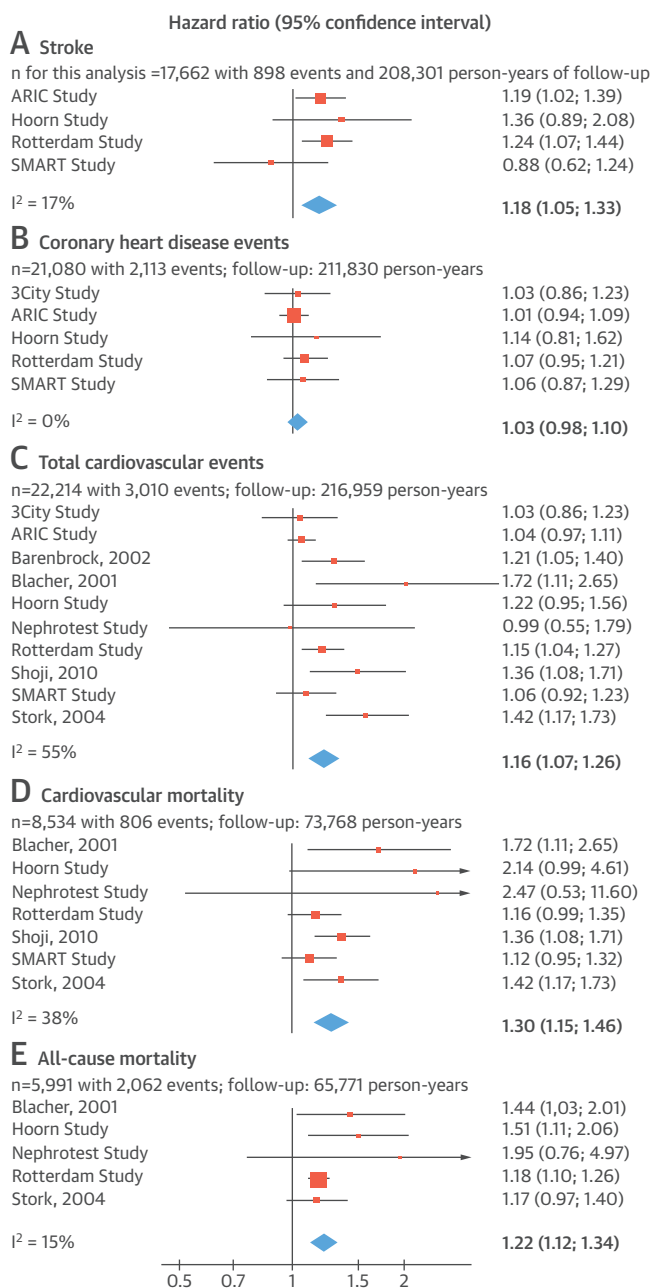

FIGURE 1 Flow Chart of Selection Process of Eligible Studies

From a total of 3,939 eligible studies identified, 10 were included in the aggregate and 4 in the individual patient data meta-analysis.

FIGURE 2 Aggregate Data Meta-Analysis Results

Forest plots mark the association between 1 SD greater carotid stiffness and incident stroke **(A)**, coronary heart disease events **(B)**, total cardiovascular events **(C)**, cardiovascular mortality **(D)**, and all-cause mortality **(E)**. For each study, the hazard ratio was pooled for 1 SD lower carotid distensibility coefficient; if not available, the hazard ratio was pooled for 1 SD higher Young's elastic modulus (SMART Study [9], 3-City Study [27], and Stork et al. [29]) or 1 SD higher beta-stiffness index (Shoji et al. [28]). ARIC = Atherosclerosis Risk In Communities; SMART = Second Manifestations of Arterial Disease.

individuals and a median follow-up duration of 12.0 years (previously published results [10] were based on n = 2,835 and 4.1 years of follow-up), and the updated results of Blacher et al. (15) were based on 156 individuals and a median follow-up duration of 5.1 years (previously published results [15] were based on n = 110 and 4.4 years follow-up). The studies included were conducted in the general population (6,8,10,27,29), or in individuals with chronic kidney disease (15,20,26,28) or prior CVD (9). The follow-up duration ranged from 2.8 to 13.8 years (full study characteristics are provided in the Online Tables 1 to 3).

Four studies (Blacher et al. [15], Rotterdam [10], Hoorn [6], and Nephrotest [26]) had data available on cfPWV and were included in the IPD meta-analysis. Of these, Rotterdam and Hoorn had data available on incident stroke (n = 4,075 with 351 events) and all 4 had data available on total cardiovascular events (n = 4,395 with 763 events). A detailed description of the assessment of cfPWV by each study is provided in Online Appendix E.

Risk of bias among the included studies (Online Table 4) was low (mean NOS score: 7 of 8).

AGGREGATE DATA META-ANALYSIS. Greater carotid stiffness (per SD) was associated with a higher stroke incidence (**Figure 2A**). In addition, greater carotid stiffness was associated with a higher incidence of total cardiovascular events and with greater cardiovascular and all-cause mortality, but not with CHD events (**Figures 2B to 2E**). The statistical heterogeneity between studies was low to moderate (range of I^2 was 0% to 55%) (**Figures 2A to 2E**). Results did not materially change when data were pooled of studies that calculated carotid stiffness with local PP, after exclusion of studies with a relatively high risk of bias, or when data were pooled of studies that obtained carotid stiffness data by echo tracking (Online Figure 1). Also, results were qualitatively similar for each carotid stiffness index, except for carotid CC, which was not statistically significantly associated with stroke or any other outcome (Online Figure 1).

IPD META-ANALYSIS. After adjustment for potential confounders, lower carotid DC (per SD) was associated with higher stroke incidence (**Table 1A**); further adjustment for cfPWV did not materially change this association. Additionally, lower carotid DC was associated with a higher incidence of total cardiovascular events and greater cardiovascular and all-cause mortality, but not with CHD events (Online Table 5). We found no interaction between carotid DC and incident stroke according to sex, age, hypertension,

TABLE 1 Individual Participant Data Meta-Analysis Results

Models	Carotid DC (per 1 Lower SD)*
A. Cox regression analysis	Hazard ratio (95% CI)
Model 1†	1.24 (1.05 to 1.47)
Model 1† + cfPWV	1.24 (1.05 to 1.46)
B. Risk improvement analysis‡	Effect estimate (95% CI)
IDI, percentage point	0.4 (0.1 to 0.6)
Continuous NRI, %	18.6 (5.8 to 31.3)
C-statistic base model	0.747 (0.710 to 0.784)
C-statistic extended model	0.750 (0.713 to 0.787)
Change in C-statistic	0.003 (−0.003 to 0.009)

*Carotid DC as the determinant and incident stroke as the outcome; number of participants for this analysis = 4,075 with 351 events and 47,881 person-years of follow-up. †Model 1: Results adjusted for age, sex, mean arterial pressure, heart rate, body mass index, smoking habits, diabetes, triglycerides, total/high-density lipoprotein cholesterol ratio, prior cardiovascular disease, and use of lipid-modifying and antihypertensive medication. ‡Base model for risk improvement analysis included Framingham stroke risk score factors and cfPWV. Model was extended by carotid distensibility coefficient (DC) (per 1 lower SD).

cfPWV = carotid-femoral pulse wave velocity; CI = confidence interval; IDI = integrated discrimination improvement; NRI = net reclassification index.

or diabetes (p for interaction >0.24). After additional adjustment for presence of carotid plaques, results did not materially change (Online Table 6). Higher PP, lower distension, and greater carotid diameter were associated with a higher stroke incidence, although results for lower distension and greater diameter were not statistically significant (Online Figure 2). The baseline stroke risk was high as estimated by the base model (including Framingham stroke risk score factors and cfPWV) for individuals included in the IPD meta-analysis (i.e., 50.2% of individuals included had an estimated stroke risk >5.0%). This was due to the inclusion of older individuals (6,10) and/or individuals with diabetes (6) or chronic kidney disease (15,26). When carotid DC was added to the base model, the IDI and continuous NRI for incident stroke improved significantly; the C-statistic also improved, but not significantly (Table 1B). In addition, the IDI and continuous NRI improved significantly for cardiovascular mortality (0.3 percentage points [95% confidence interval: 0.1 to 0.5 percentage points] and 17.5% [95% confidence interval: 3.2% to 31.7%], respectively) and all-cause mortality (0.6 percentage points [95% confidence interval: 0.4 to 0.9 percentage points] and 19.0% [95% confidence interval: 12.3% to 25.7%], respectively), but not for CHD events (−0.0 percentage points [95% confidence interval: −0.1 to 0.1 percentage points] and 3.9% [95% confidence interval: −7.3% to 15.1%], respectively) and total cardiovascular events (0.1 percentage points [95% confidence interval: −0.2 to 0.3 percentage points] and 5.0% [95% confidence interval: −4.6% to 15.0%], respectively) (Online Table 5). The C-statistic

did not significantly improve for any of these outcomes (Online Table 5).

DISCUSSION

The present systematic review and meta-analysis of aggregate and individual participant data showed that greater carotid stiffness was associated with a higher stroke incidence. This association was independent of age, sex, blood pressure, and other CVD risk factors, and did not materially change after adjustment for aortic stiffness (measured as cfPWV). Additionally, estimation of carotid stiffness modestly improved stroke risk prediction beyond Framingham stroke risk score factors and cfPWV, as indicated by a statistically significant improvement of the IDI and continuous NRI (**Central Illustration**). Finally, carotid stiffness was associated with a higher incidence of total cardiovascular events and greater cardiovascular and all-cause mortality, but not with CHD events.

This is the first systematic review and meta-analysis on the association between carotid stiffness and incident CVD and mortality. The findings agree with and extend previous observational studies (6,8,20,26) reporting an association between carotid stiffness and incident CVD (6,8,20,26), including stroke (8). The aggregate data meta-analysis enabled us to examine these associations in greater detail with enhanced power, and the IPD meta-analysis allowed us to do a comprehensive range of additional analyses, including adjustment for cfPWV and quantification of stroke risk improvement beyond Framingham risk score factors and cfPWV.

METHODOLOGICAL ISSUES. Some methodological issues warrant consideration. First, the results were consistent across different study populations notwithstanding differences in methods to quantify carotid stiffness, and were not related to the risk of bias of included studies, which strengthens the findings' validity. Second, the results were consistent for all carotid stiffness indexes, except for carotid CC, which was not statistically significantly associated with stroke. To further explore this finding, we evaluated the association between individual elements of the stiffness indexes (PP, distension, and diameter) and stroke. The results showed that greater carotid diameter, lower distension, and higher PP were each associated with a higher stroke incidence. The association between greater carotid diameter and incident stroke echoes previous studies (30,31), and may reflect arterial remodeling in response to atherosclerosis or increased arterial stiffness (14). However, a

CENTRAL ILLUSTRATION Carotid Stiffness and Incident Stroke: Meta-Analyses Indicate Associations
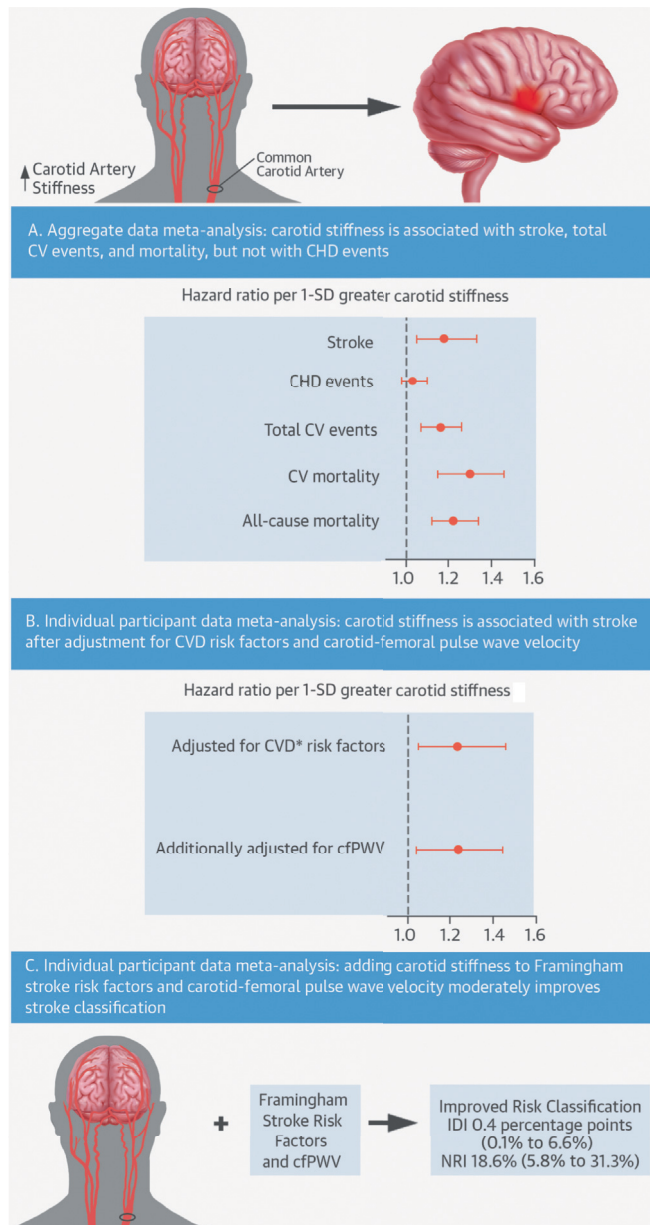
van Sloten, T.T. et al. J Am Coll Cardiol. 2015; 66(19):2116–25.

Meta-analyses were performed to determine associations between carotid stiffness and stroke. **(A)** An aggregate data meta-analysis (10 studies; n = 22,472) found an association between carotid stiffness and incident cardiovascular (CV) events and mortality. An individual participant data (IPD) meta-analysis (4 studies; n = 4,540) was done with all studies with available data on carotid stiffness and carotid-femoral pulse wave velocity (cfPWV), finding associations after adjusting for such factors **(B)**, and demonstrating that the addition of carotid stiffness to Framingham risk factors and cfPWV improves stroke risk classification **(C)**. *Results adjusted for age, sex, mean arterial pressure, heart rate, body mass index, smoking habits, diabetes, triglycerides, total/high-density lipoprotein cholesterol ratio, prior cardiovascular disease (CVD), and use of lipid-modifying and antihypertensive medication. CHD = coronary heart disease; IDI = integrated discrimination improvement; NRI = net reclassification index.

greater carotid diameter is associated with higher values of carotid compliance (under the same operating pressure); this may explain why we did not find an association between (lower) carotid CC and stroke. Third, the present study had insufficient power to formally test the potential influence of publication bias (32). Nevertheless, a broad systematic search was done to identify all relevant studies, and we were able to include published as well as unpublished data. This limits the possibility of the presence of (substantial) publication bias.

UNDERLYING MECHANISMS. The present study showed that greater carotid stiffness is associated with a higher stroke incidence, independently of aortic stiffness, supporting the concept that carotid stiffening is important in the pathogenesis of stroke (6). We speculated that the underlying mechanism may be that stiffening of the carotid artery (or other elastic arteries for which the carotid artery may serve as a proxy) leads to a higher pulsatile pressure and flow load on the brain (3,4,32). This increased load can penetrate distally into the cerebral microcirculation and may directly cause cerebral ischemia and hemorrhage (5,33,34). Also, the increased pulsatile load may induce a hypertrophic remodeling response and rarefaction of small cerebral arteries which, in turn, may lead to chronic ischemia. Furthermore, carotid artery stiffening may lead to stroke through local development of rupture-prone atherosclerotic plaques. Indeed, previous studies (7,35) have shown that arterial stiffness is associated with presence (7,35) and a rupture-prone phenotype (7) (e.g., intraplaque hemorrhage) of atherosclerotic plaques in the internal carotid artery. In the present study, the association between carotid stiffness and stroke did not materially change after adjustment for presence of carotid plaques. However, no information was available with regard to the phenotype of these plaques, and this issue requires further study.

In the present study, carotid stiffness, in contrast to aortic stiffness (as determined by cfPWV) (11,12), was not associated with incident CHD events. A possible explanation for these observations may be that stiffening of the aorta, but not of the carotid artery, leads to a higher left ventricular load and reduced diastolic coronary perfusion (3,4).

Furthermore, carotid stiffness was associated with total (nonfatal and fatal) cardiovascular events and with all-cause mortality not explained quantitatively by stroke. This suggests that carotid artery stiffening additionally increases the risk of diseases other than stroke. For example, it is conceivable that it is associated with risk of congestive HF, as stiffening of the carotid artery could act as a proxy for stiffening of the proximal elastic segment of the aorta, which increases cardiac afterload and is associated with HF risk (36,37). Carotid stiffness also may be a marker of biological aging and thus associated with mortality of age-related diseases other than CVD (6). These possibilities require further investigation.

CLINICAL RELEVANCE. The observation that carotid stiffness was associated with incident stroke independently of aortic stiffness could hold clinical relevance, with carotid stiffness becoming a potential separate target for stroke risk-lowering therapy. CVD risk factors have different effects on stiffening of elastic versus muscular arteries (38,39). This may be attributed to the marked differences in these arteries' architecture and suggests that stiffness of elastic arteries may be specifically targeted; no effective clinical therapy currently available does so now.

In the present study, carotid stiffness improved risk prediction of stroke beyond Framingham stroke risk score factors and cfPWV, as indicated by improvement of IDI and continuous NRI. This finding provides proof of principle that carotid stiffness can have additional value as a risk predictor of stroke, although such improvement was modest; moreover, in high-risk populations, such as those included in the current analyses, such an improvement may not be clinically relevant (40). Nevertheless, the current data provide a framework for investigating whether assessment of carotid stiffness can improve stroke risk prediction in younger individuals and in those at intermediate risk for stroke, in whom improvement of risk prediction may be of greater importance (41).

STUDY LIMITATIONS. In this study, (unavoidable) survival bias may have led to an underestimation of the associations observed. Additionally, the association between cfPWV and incident cardiovascular events is weaker in older compared with younger individuals (11). The present meta-analysis included relatively older study populations. It therefore remains to be seen whether carotid stiffness is also associated with incident stroke independently of cfPWV in younger populations. Finally, we could not evaluate the association between carotid stiffness and stroke subtypes, although it is likely that carotid artery stiffening increases the risk of both ischemic and hemorrhagic stroke (5,33,34).

CONCLUSIONS

The present study showed that greater carotid stiffness is associated with a higher incidence of stroke independently of cfPWV and modestly improved risk prediction of stroke beyond Framingham stroke risk score factors and cfPWV. This identifies carotid stiffness as a potential separate target for stroke prevention strategies.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Carotid stiffness is independent of aortic stiffness and conventional cardiovascular factors in predicting incident stroke.

TRANSLATIONAL OUTLOOK: Further studies are needed to quantify the predictive value of carotid stiffness in patients at intermediate risk and to assess whether interventions that reduce arterial stiffness can reduce stroke risk.

REFERENCES

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. Lancet 2014;383:245–54.

2. Ovbiagele B, Goldstein LB, Higashida RT, et al. Forecasting the future of stroke in the United States: a policy statement from the American Heart Association and American Stroke Association. Stroke 2013;44:2361–75.

3. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006;27:2588–605.

4. Safar ME, O'Rourke MF, editors. Volume 23. Arterial stiffness in hypertension. In: Birkenhäger WH, Reid JL, senior editors. Handbook of Hypertension. Amsterdam, the Netherlands: Elsevier, 2006:63–8.

5. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. J Appl Physiol (1985) 2008;105:1652–60.

6. van Sloten TT, Schram MT, van den Hurk K, et al. Local stiffness of the carotid and femoral artery is associated with incident cardiovascular events and all-cause mortality: the Hoorn study. J Am Coll Cardiol 2014;63:1739–47.

7. Selwaness M, van den Bouwhuijsen Q, Mattace-Raso FU, et al. Arterial stiffness is associated with carotid intraplaque hemorrhage in the general population: the Rotterdam study. Arterioscler Thromb Vasc Biol 2014;34:927–32.

8. Yang EY, Chambless L, Sharrett AR, et al. Carotid arterial wall characteristics are associated with incident ischemic stroke but not coronary heart disease in the Atherosclerosis Risk In Communities (ARIC) study. Stroke 2012;43:103–8.

9. Dijk JM, Algra A, van der Graaf Y, Grobbee DE, Bots ML. Carotid stiffness and the risk of new vascular events in patients with manifest cardiovascular disease. The SMART study. Eur Heart J 2005;26:1213–20.

10. Mattace-Raso FU, van der Cammen TJ, Hofman A, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation 2006;113:657–63.

11. Ben-Shlomo Y, Spears M, Boustred C, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol 2014;63:636–46.

12. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 2010;55:1318–27.

13. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.

14. van Dijk RA, Dekker JM, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD. Brachial artery pulse pressure and common carotid artery diameter: mutually independent associations with mortality in subjects with a recent history of impaired glucose tolerance. Eur J Clin Invest 2001;31:756–63.

15. Blacher J, Guerin AP, Pannier B, Marchais SJ, London GM. Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. Hypertension 2001;38:938–42.

16. Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM. Carotid arterial stiffness as a predictor of cardiovascular and all-cause mortality in end-stage renal disease. Hypertension 1998;32:570–4.

17. Duprez D, Jacobs DR, Lutsey PL, et al. Small artery elasticity, but neither carotid artery elasticity nor aorta distensibility, predicts cardiovascular events in an asymptomatic—results of the Multi-Ethnic Study of Atherosclerosis (abstr). J Am Coll Cardiol 2010;55 Suppl 1:A133. E1252.

18. Haluska BA, Jeffries L, Carlier S, Marwick TH. Measurement of arterial distensibility and compliance to assess prognosis. Atherosclerosis 2010;209:474–80.

19. Wells GA SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed January 5, 2015.

20. Barenbrock M, Kosch M, Joster E, Kisters K, Rahn KH, Hausberg M. Reduced arterial distensibility is a predictor of cardiovascular disease in patients after renal transplantation. J Hypertens 2002;20:79–84.

21. Pennells L, Kaptoge S, White IR, Thompson SG, Wood AM, for the Emerging Risk Factors Collaboration. Assessing risk prediction models using individual participant data from multiple studies. Am J Epidemiol 2014;179:621–32.

22. Steyerberg EW, Pencina MJ. Reclassification calculations for persons with incomplete follow-up. Ann Intern Med 2010;152:195–6, author reply 196–7.

23. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke 1991;22:312–8.

24. Harrell FEJ. Regression Modeling Strategies: With Application to Linear Models, Logistic Regression, and Survival Analysis. New York, New York: Springer Publishing, 2001:16–26, 483–9.

25. D'Agostino RB Sr., Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743–53.

26. Karras A, Haymann JP, Bozec E, et al. Large artery stiffening and remodeling are independently associated with all-cause mortality and cardiovascular events in chronic kidney disease. Hypertension 2012;60:1451–7.

27. Leone N, Ducimetiere P, Gariepy J, et al. Distension of the carotid artery and risk of coronary events: the three-city study. Arterioscler Thromb Vasc Biol 2008;28:1392–7.

28. Shoji T, Maekawa K, Emoto M, et al. Arterial stiffness predicts cardiovascular death independent of arterial thickness in a cohort of hemodialysis patients. Atherosclerosis 2010;210:145–9.

29. Stork S, van den Beld AW, von Schacky C, et al. Carotid artery plaque burden, stiffness, and mortality risk in elderly men: a prospective, population-based cohort study. Circulation 2004;110:344–8.

30. Baldassarre D, Hamsten A, Veglia F, et al. Measurements of carotid intima-media thickness and of interadventitia common carotid diameter improve prediction of cardiovascular events: results of the IMPROVE (Carotid Intima Media Thickness [IMT] and IMT-Progression as Predictors of Vascular Events in a High Risk European Population) study. J Am Coll Cardiol 2012;60:1489–99.

31. Polak JF, Sacco RL, Post WS, Vaidya D, Arnan MK, O'Leary DH. Incident stroke is associated with common carotid artery diameter and not common carotid artery intima-media thickness. Stroke 2014;45:1442–6.

32. Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. Stat Med 2001;20:641–54.

33. Tzourio C, Laurent S, Debette S. Is hypertension associated with an accelerated aging of the brain? Hypertension 2014;63:894–903.

34. Brisset M, Boutouyrie P, Pico F, et al. Large-vessel correlates of cerebral small-vessel disease. Neurology 2013;80:662–9.

35. Zureik M, Temmar M, Adamopoulos C, et al. Carotid plaques, but not common carotid intima-media thickness, are independently associated with aortic stiffness. J Hypertens 2002;20:85–93.

36. Coutinho T, Borlaug BA, Pellikka PA, Turner ST, Kullo IJ. Sex differences in arterial stiffness and ventricular-arterial interactions. J Am Coll Cardiol 2013;61:96–103.

37. Tartiere-Kesri L, Tartiere JM, Logeart D, Beauvais F, Cohen Solal A. Increased proximal arterial stiffness and cardiac response with moderate exercise in patients with heart failure and preserved ejection fraction. J Am Coll Cardiol 2012;59:455–61.

38. Paini A, Boutouyrie P, Calvet D, Tropeano AI, Laloux B, Laurent S. Carotid and aortic stiffness: determinants of discrepancies. Hypertension 2006;47:371–6.

39. Stehouwer CD, Henry RM, Ferreira I. Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease. Diabetologia 2008;51:527–39.

40. Pencina MJ, D'Agostino RB, Pencina KM, Janssens AC, Greenland P. Interpreting incremental value of markers added to risk prediction models. Am J Epidemiol 2012;176:473–81.

41. Lloyd-Jones DM. Cardiovascular risk prediction: basic concepts, current status, and future directions. Circulation 2010;121:1768–77.

KEY WORDS arterial stiffness, cardiovascular disease, risk classification

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