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Association Between Carotid Atherosclerosis and Atrial Fibrillation, Cardiac, and Renal Function

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WHAT THIS PAPER ADDS

In a large population based cohort the association between carotid atherosclerosis (CA) measured by carotid ultrasound and atrial fibrillation, N-terminal pro-brain natriuretic peptide (NT-proBNP), and estimated glomerular filtration rate (eGFR) as markers of cardiac and renal dysfunction was studied. CA was defined by carotid intima media thickness $\geq$ 1 mm or presence of plaques to combine risk profiles. CA was associated with higher concentrations of NT-proBNP considering renal function and cardiovascular risk factors, atrial fibrillation only in consideration of age and sex, and eGFR had no association. These results imply a link between heart function and CA beyond traditional risk factors and add information to risk stratification by carotid ultrasound in middle age to old people.

Objective: The aim was to analyse whether the association between carotid atherosclerosis (CA) and atrial fibrillation (AF), heart function, and renal function is mediated by traditional risk factors.

Methods: In the prospective, single centre, long term, population based Hamburg City Health Study citizens, between 45 and 74 years of age were studied by cross sectional analysis of the first cohort. Laboratory values, blood pressure, heart rhythm, and body mass index (BMI) were examined. Carotid intima media thickness (CIMT) and plaques were assessed by carotid ultrasound, and CA was defined as either CIMT ≥ 1 mm or presence of plaques or both. N-terminal pro-brain natriuretic peptide (NT-proBNP), and glomerular filtration rate (eGFR) were quantified as measures of heart and renal function. Association between CA and AF, NT-proBNP, and eGFR was analysed by multivariable linear and logistic regression.

Results: Of the first 10 000 participants, carotid ultrasound was available for 9 466 (95%). Of these, 2 937 (31%) had carotid plaques, 643 (7%) had CIMT ≥ 1 mm, and 412 (4%) presented with both, so that 3 168 (34%) had CA. Participants with CA had AF more frequently (9.6% *vs*. 4.3%; $p < .001$), higher levels of NT-proBNP (median 100 *vs.* 73 pg/mL; $p < .001$), and lower eGFR (82.8 *vs.* 87.1 mL/min; $p < .001$) than those without CA. Adjusted for age and sex, CA was associated with AF ($p = .01$; OR 1.29) and higher NT-proBNP levels ($p < .001$; $\beta = 0.12$), but not with eGFR. After further adjustment for vascular risk factors and history of cardiovascular diseases, CA remained associated with NT-proBNP ($p < .001$; $\beta = 0.10$), but additionally adjusted for NT-proBNP ($p < .001$; OR 2.80) not with AF.

Conclusion: CA is independently associated with higher levels of NT-proBNP, through common risk factors and NT-proBNP with AF, and not with renal function. CA's association with a marker of cardiac dysfunction beyond known common risk factors supports the value of carotid ultrasound in defining patients' cardiovascular risk profile. The measures of CA, i.e., CIMT and carotid plaque, had an equally directed and additive influence.

Keywords: Carotid atherosclerosis, Carotid intima media thickness, Carotid plaque, Brain natriuretic peptide, Renal function, Atrial fibrillation
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INTRODUCTION

Atherosclerosis is the most frequent underlying predisposition for stroke, myocardial infarction (MI), and heart failure. Through these diseases, atherosclerosis is the main cause of death and morbidity in developed countries.[1] Known risk factors leading to atherosclerosis additional to

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age comprise hypertension, hypercholesterolaemia, smoking, and diabetes as well as autoimmune disorders or genetic factors.[1–3] Early stages of atherosclerosis can be detected by carotid ultrasound by measuring the carotid intima media thickness (CIMT) and carotid plaques.[4,5] Both CIMT and plaques are associated with cardiovascular risk factors and inflammatory markers[6,7] as well as with end organ damage.[8,9] In particular, impaired heart and renal function due to atherosclerosis have been reported.[8,10] However, the specificity of carotid atherosclerosis (CA) reflecting organ dysfunction consecutive to systemic atherosclerosis in consideration of risk factors is still under discussion. The association between CIMT and renal function may be mainly due to hypertension underlying both CIMT and renal dysfunction.[11] The association between CIMT and plaques and atrial fibrillation (AF) is also controversially discussed against the effect of common underlying risk factors.[12] Heart failure itself has been associated with CIMT.[13] The independent connection between carotid atherosclerosis and biomarkers of heart failure, however, has not been described yet.[14] A previously reported interaction between CIMT and N-terminal pro-brain natriuretic peptide (NT-proBNP) was related to underlying risk factors.[15,16] The association between carotid plaques and NT-proBNP was only shown in the context of a small cohort with cryptogenic stroke.[17]

The aim was to study whether the association between CA and AF, NT-proBNP as a marker of cardiac dysfunction, and estimated glomerular filtration rate (eGFR) as a marker of renal function is mediated by traditional risk factors in a cross sectional analysis of a middle to old age population based cohort. Due to the complex pathogenesis of atherosclerosis involving multiple heterogeneous risk factors, and the relationship between myocardial infarction and stroke with each other, the association between CA and AF and NT-proBNP was hypothesised to be independent.

MATERIALS AND METHODS

Study population

The Hamburg City Health Study (HCHS) is a single centre observational population based study with a long term prospective design with the aim of determining and characterising risk and prognostic factors of chronic diseases. Residents of the metropolitan region of Hamburg aged 45 — 74 years are invited to participate. Participants lacking knowledge of the German language to understand study documents and without an adequate translator, and participants not able to travel to the study centre or cooperate due to physical or psychological disability are excluded. Enrolment started in February 2016.

HCHS comprises multiple laboratory, physical, imaging, and patient reported assessments. All participants were intended to be examined by carotid ultrasound, 12 lead electrocardiogram (ECG), blood sample analysis of NT-proBNP and creatinine concentrations and eGFR, and were asked for history of diagnosed AF. The complete design of the HCHS has been published previously.[18] HCHS is registered at clinicaltrials.gov, NCT03934957. The study was approved by the Ethics Committee of the Hamburg Chamber of Physicians (PV5131). All participants have provided written informed consent. The first cohort of 10 000 participants who were studied between February 2016 and November 2018 was included.

Carotid ultrasound

Carotid ultrasound was performed using a Siemens SC2000 with a 7.5 MHz linear array transducer. In the B mode CIMT and plaques were assessed following the criteria of the European Stroke Organisation.[19] CIMT was measured in a longitudinal view of the left and right common carotid artery 1.0 cm proximal to the carotid bulb three times within a distance of 1.0 cm on the far wall and the mean calculated for further analyses. Plaques were defined as focal thickening of the intima media $>$ 1.5 mm.[19,20] CA was defined as CIMT $\geq$ 1 mm and or presence of atherosclerotic plaques in the carotid.[21–23] Stenoses were defined separately from CA haemodynamically as systolic flow velocities above 200 cm/second in the common, internal, or external carotid artery. Medical assistants underwent three months of training before examining participants and followed a standard operating procedure. Non-conclusive and pathological findings, like stenoses, underwent a quality check and were inspected by physicians experienced in carotid ultrasound.

Laboratory measurements from blood samples

Lipids (total cholesterol, high density lipoprotein [HDL]), glycated haemoglobin (HbA1C), high sensitivity C reactive protein (hsCRP), and creatinine were assessed photometrically, and NT-proBNP, thyroid stimulating hormone (TSH), and interleukin 6 (IL-6) by immunoassays using Siemens Atellica and Roche Cobas e411. The eGFR was calculated by the chronic kidney disease Epi formula,[24] low density lipoprotein LDL cholesterol by the Friedewald formula, and non-HDL cholesterol by the difference in the mentioned lipid concentrations.

Questionnaire and physical measures

The history of cardiovascular risk factors was determined in interviews with participants in the study centre comprising questions for smoking, hypertension, diabetes, AF, prior stroke, prior MI, and heart failure. Medication was brought along and assessed during the visit. For all participants, as part of the study protocol, blood pressure (BP), height and weight, and 12 lead ECG (Schiller, Baar, Switzerland) were examined by medical assistants during visits and supervised by physicians. ECG was recorded at rest on a two minute rhythm strip with automatic pre-analysis. Systolic and diastolic BP were measured twice on the right arm and the mean was taken for further analyses.

Hypertension was defined by antihypertensive medication and/or participant's statement and/or measured values above 140/90 mmHg.[25] Diabetes was defined by participant's statement and or fasting blood glucose above 126 mg/dL and or non-fasting blood glucose above 200 mg/

dL.[26] Dyslipidaemia was defined by an LDL concentration above 129 mg/dL and or statin medication.[27] Smoking was defined by participant's statement about current smoking. For multivariable regression analysis AF was defined by typical findings from 12 lead ECG and/or participant's statement of a positive diagnosis in medical history. In the descriptive analysis the two components were distinguished.

All measured characteristics of this study are shown in Table 1. The measures included as cofactors in the three different multivariable models are age, sex, hypertension, dyslipidaemia, smoking, body mass index (BMI), prior MI, reported heart failure, HbA1c, NT-proBNP (log transformed), heart rate, TSH (log transformed), and eGFR. Detailed build up of the models is described below.

Statistics

Participants with and without CA were compared, and the association between CA, CIMT, and plaques with each parameter was tested by linear and logistic uni- and bivariable analysis. Categorical variables were tested using the chi squared test and are presented as count and percentage. Continuous variables are presented as median and interquartile range and a Mann–Whitney U test was performed to test for association. For the identification of predictors of target organ damage, multivariable linear and logistic regression models were fitted for AF, NT-proBNP as a biomarker of heart failure, and for calculated eGFR as a biomarker of renal function. Models containing either CA or CIMT and presence of plaque were built separately for sex, age, and additional risk factors. The risk factors included in the models were chosen based on knowledge of the literature about their potential influence on the outcome parameter. Risk factors in all models comprised hypertension, smoking, BMI, MI, and HbA1c.[28] For AF, oriented on the Cohorts for Heart and Ageing Research in Genomic Epidemiology (CHARGE) AF score, reported heart failure was added, and amended for the score for NT-proBNP. For NT-proBNP as outcome parameter, dyslipidaemia, TSH, and heart rate were added due to their reported association with both CA and heart function, and eGFR due to its renal metabolism relevant for NT-proBNP concentrations.[29–32] Heart rate was included instead of AF in the model, because of the expected small percentage of participants with AF and similar evidence for overlapping associations with CA and heart function.[33] For eGFR as outcome

Table 1. Characteristics of 9 466 participants of the Hamburg City Health Study with and without carotid atherosclerosis defined as carotid intima media thickness (CIMT) ≥1 mm or detection of plaque on carotid ultrasound examination

	CIMT < 1 mm and no plaque (n = 6 298)	CIMT ≥ 1 mm or plaque (n = 3 168)	p
Age – years	59 (53–67)	68 (62–73)	<.001
Female sex	3 526 (56.0)	1 324 (41.8)	<.001
BMI – kg/m^2	25.7 (23.3–28.8)	26.6 (24.1–29.6)	<.001
Smoking	1 148 (18.3)	712 (22.6)	<.001
Hypertension	3470 (58.4)	2451 (79.6)	<.001
Systolic BP – mmHg	134.5 (123.5–147.5)	141.5 (129.0–156.2)	<.001
Diastolic BP – mmHg	81.5 (75.5–88.0)	81.5 (75.0–88.5)	.79
Antihypertensive medication	1 546 (25.9)	1467 (47.8)	<.001
Diabetes	354 (6.2)	374 (12.6)	<.001
HbA1c –%	5.5 (5.3–5.7)	5.6 (5.4–5.9)	<.001
Dyslipidaemia	4 286 (71.0)	2 364 (77.3)	<.001
LDL-C – mg/dL	121 (98–145)	119 (90–145)	<.001
Statin medication	612 (10.3)	810 (26.4)	<.001
Cholesterol – mg/dL	209 (183–237)	206 (174–236)	<.001
HDL-C – mg/dL	63 (51–78)	59 (48–73)	<.001
Non-HDL-C – mg/dL	143 (117–170)	143 (113–171)	.20
Atrial fibrillation	244 (4.3)	276 (9.6)	<.001
Heart rate – per min	68.5 (62.0–75.5)	69.5 (62.5–77.5)	<.001
Heart failure	123 (2.0)	137 (4.4)	<.001
NT-proBNP – pg/mL	73 (40–130)	100 (55–194)	<.001
Prior myocardial infarction	101 (1.6)	184 (5.9)	<.001
Prior stroke	122 (1.9)	167 (5.3)	<.001
eGFR – mL/min	87.1 (76.8–95.4)	82.8 (70.6–91.3)	<.001
hsCRP – mg/mL	0.11 (0.06–0.24)	0.14 (0.07–0.30)	<.001
IL-6 – pg/mL	1.51 (1.09–2.14)	1.85 (1.37–2.64)	<.001
TSH – μU/mL	1.18 (0.83–1.67)	1.14 (0.78–1.63)	.001
Carotid plaque	0 (0.0)	2937 (93.2)	<.001
Carotid plaque diameter – mm	–	2.17 (1.83–2.59)	–
Carotid stenosis	0 (0.0)	89 (2.9)	<.001

Data are presented as n (%) or as median (interquartile range). BMI = body mass index; NT-proBNP = N-terminal pro-brain natriuretic peptide; eGFR = estimated glomerular filtration rate; hsCRP = high sensitivity C reactive protein; HbA1c = glycated haemoglobin A1c; IL-6 = interleukin 6; TSH = thyroid stimulating hormone; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; BP = blood pressure.

parameter, dyslipidaemia and reported heart failure were added. Oriented on their distribution in univariable analyses, NT-proBNP, TSH, hsCRP, IL-6, LDL, and non-HDL cholesterol were log transformed. All statistical analyses were carried out using R-studio statistical package 1.1.453 (http://www.r-project.org/).

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Participant characteristics and group comparison

Of the first 10 000 participants, carotid ultrasound was available for 9 466 (95%) participants. Of these, 2 937 (31%) had carotid plaques, and 643 (7%) had a CIMT ≥ 1 mm. Given that 412 patients had both carotid plaque and a CIMT ≥ 1 mm, 3 168 (34%) were defined as having CA. Participants in the CA group were significantly older, predominantly male, and had a higher BMI (Table 1). Hypertension was more frequent in the group with CA and as part of its definition measured systolic BP was elevated. Diabetes was more frequent as well. LDL and total cholesterol concentrations were lower, and more participants in the atherosclerosis group took statins. Participants with CA also reported current smoking, heart failure, AF, prior MI, and stroke more frequently. With regards to further laboratory values, participants with CA had higher serum concentration of Hb1AC and NT-proBNP, and lower eGFR. AF was reported in 521 cases, detected on ECG in 169 with an overlap of 129 (total 561).

Association between carotid atherosclerosis and risk factors and atrial fibrillation

In a multivariable model including age and sex comprising 8 550 participants, CA was associated with higher odds of AF ($p = .010$; odds ratio [OR] 1.27). In a second model including risk factors oriented on the CHARGE-AF score comprising 7 460 participants, the association between CA and AF was no longer significant ($p = .69$) (Fig. 1A).

Association between carotid atherosclerosis and risk factors and N-terminal pro-brain natriuretic peptide

In a multivariable model including age and sex comprising 9 213 participants, CA was associated with higher odds of log NT-proBNP ($p < .001$; $\beta = 0.12$). The association remained significant in a second model including BMI, prior MI, hypertension, log. TSH, dyslipidaemia, smoking, HbA1c, heart rate, and eGFR comprising 7 783 participants ($p < .001$; $\beta = 0.10$). Further parameters associated with log NT-proBNP were female sex ($p < .001$; $\beta = 0.42$), higher age ($p < .001$; $\beta = 0.35$), prior MI ($p < .001$; $\beta = 0.62$), hypertension ($p < .001$; $\beta = 0.14$), current smoking ($p = .014$; $\beta = 0.06$), lower HbA1c ($p < .001$; $\beta = -0.05$), lower BMI ($p < .001$; $\beta = -0.04$), lower heart rate ($p < .001$; $\beta = -0.09$), and lower eGFR ($p < .001$; $\beta = -0.1$) (Fig. 1B).

Association between carotid atherosclerosis and risk factors and estimated glomerular filtration rate

CA showed no significant association with eGFR, neither in a simple model with sex and age as confounders comprising 7 301 participants ($p = .27$), nor in a model including comprehensive cardiovascular risk factors comprising 6 944 participants ($p = .38$).

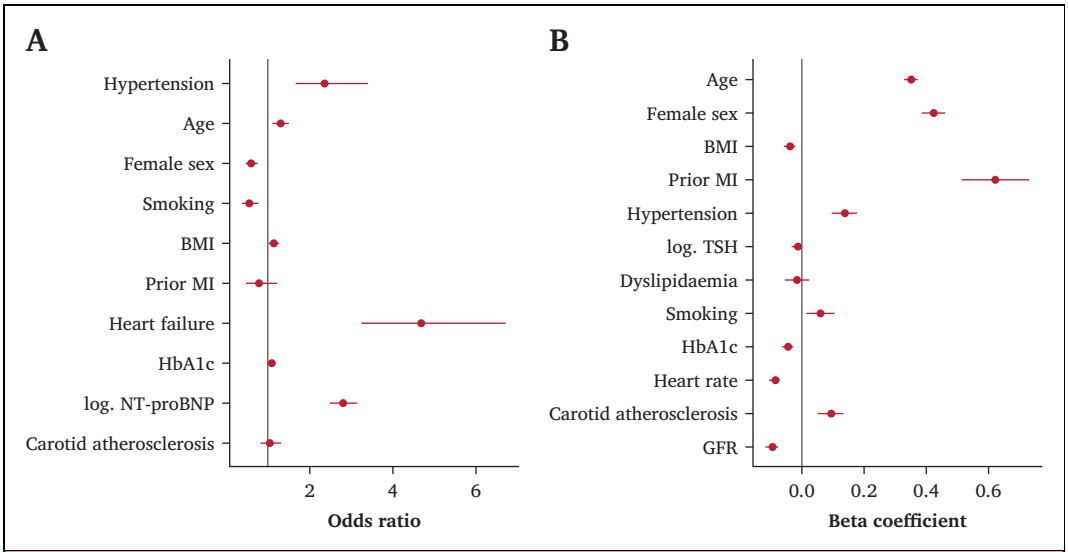

Figure 1. Prediction of (A) atrial fibrillation and (B) logarithmic N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration by carotid atherosclerosis and risk factors in multivariable regression model of 9 466 participants of the Hamburg City Health Study examined with carotid ultrasound. Carotid atherosclerosis was defined as carotid intima media thickness (CIMT) ≥ one mm or presence of carotid plaque. The factors are presented with their coefficient estimate (odds ratio and beta coefficient). TSH = thyroid stimulating hormone; BMI = body mass index; HbA1c = glycated haemoglobin A1c; MI = myocardial infarction.

DISCUSSION

The prediction of unfavourable major events is receiving increasing attention by the cardiovascular community. While medical innovation, device evolution, and improved best medical treatment have led to changing patient selection during recent years, new challenges have been introduced to everyday clinical practice. The clinical value of risk prediction scores may improve by variables that are easy to collect and valid.

CIMT and carotid plaques are mainly related to cardiovascular disease. Yet one study suggests an association with the future development of heart failure independent of cardiovascular risk factors and cardiovascular disease.[13] An association between CA and NT-proBNP as shown in the study supports CA's relevance for cardiac dysfunction and adds a new aspect. The population based association between NT-proBNP and CA independent of traditional risk factors and prior MI is a novel observation. Concerning risk stratification, these results suggest that patients with CA are more vulnerable to cardiac dysfunction than are those without apart from cardiovascular risk factors or disease. The results imply that a "subclinical impairment" is present at the time of measurement. NT-proBNP is a marker for volume stress and is certainly not specific. The data suggest to further investigate CA's association with cardiomyopathies or extrinsic haemodynamic challenges apart from cardiovascular disease.

In the population based cohort of middle age to old participants, atherosclerosis of the carotid arteries was present in about one third defined by carotid plaque or CIMT thickening $\geq$ 1 mm. CIMT and plaque presence were merged to combine the supposed cerebral[34] and myocardial[35] focused risk prediction of the population as CA to a general risk profile. Except for LDL, all common cardiovascular risk factors were increased in participants with CA. These results stand in line with previous studies which underline the association between CA and higher age, male sex, increased inflammatory markers, and the presence of cardiovascular risk factors.[6,36] Lower LDL concentrations in participants with CA in the cohort may be explained by a rate of more than twice as many participants on statin treatment in this group. In particular, the high proportion of plaques in the CA group, which have been shown to persist under lipid lowering treatment,[37] gives reason for this estimation. The homogeneous distribution of cardiovascular risk factors between groups supports the chosen criteria for CA and the suggested additive value of assessing plaques combined with CIMT[38,39] with the cut off at 1 mm.[21] Higher levels of BP in the group with CA, though with a median still in the normal range, further support the suggested impact of pre-hypertension on subclinical carotid damage.[40]

In order to study the association between CA and organ dysfunction over and above the impact of known cardiovascular risk factors, statistical models were calculated with eGFR, AF, and NT-proBNP as dependent variables, reflecting renal dysfunction and atrial and ventricular cardiac dysfunction, respectively. CA was not associated with renal dysfunction, while typical cardiovascular risk factors predicted lower eGFR. It is concluded that the previously reported association between CIMT and chronic kidney disease reflects an effect of common underlying risk factors, mostly hypertension.[8,11] Though differences in entity and value for risk prediction between CIMT and plaques are discussed, they had an equally directed influence with additive value on the analysed organ functions.[35,39,41]

The association between CIMT and plaques and AF is controversial. CIMT's contribution to the CHARGE AF score has been estimated as present, but minor.[12] In a small cohort of cryptogenic stroke patients, carotid plaques were associated with AF after adjustment for factors of the CHA2DS2-VASc score.[17] In this cohort, CIMT and plaques were not significantly associated with AF after adjusting for age and sex, and risk factors oriented on the CHARGE-AF score. Factors of this score were used due to its reported superiority compared with the CHA2DS2-VASc score and amended for NT-proBNP.[42] The choice of factors may explain the lack of the reported association between CA and AF. In particular, NT-proBNP, which independently contributed to the prediction of AF, may be the connecting factor between CA and AF.

Appropriate results were found for the association between CA and levels of NT-proBNP as a circulating biomarker of cardiac dysfunction. CA showed a significant independent association with higher NT-proBNP levels, even after adjustment for typical cardiovascular and heart failure risk factors,[43] including TSH[31,32,44] and renal function.[29] The impact of low BMI,[45] female sex,[46] hypertension,[47] prior MI,[48] and low HbA1c[49] on higher NT-proBNP levels confirms results of previous studies and the reliability of the model. The significance of low heart rate may be a consequence of medication but can be interpreted in various ways.[50] The association between carotid plaques and NT-proBNP in a large population based cohort after adjustment of confounding factors extends the observation made in a few cryptogenic stroke[17] patients and for CIMT in the one on hypertensive subjects.[16] It suggests reconsidering CA's association with cardiac dysfunction beyond traditional cardiovascular risk factors.[14]

Measuring CA by ultrasound provides a unique window into systemic atherosclerosis, and is highly correlated with coronary atherosclerosis and ischaemic heart disease.[10,13,35] In addition to routinely assessed cardiovascular risk factors, common genes have been identified connecting CIMT and plaques with heart disease.[51] This genetic link between CIMT, carotid plaques, and heart disease might provide an explanation for the association with biomarker levels of heart failure beyond typical risk factors. The more distinct impact of plaques than CIMT on heart disease supports the findings of a large meta-analysis of genome wide association studies, in which the genetic pattern associated with plaque was more frequent in patients with coronary heart disease and the pattern for CIMT more frequent in patients with a history of stroke.[51] The association between CA and NT-proBNP in a population based cohort has so far not been described and adds novel and confirmatory information to

the reported association between CA and heart failure.[13,15] This association means that a tendency to cardiac dysfunction is present and amplifies the described value concerning possible development of heart failure.[13] However, while the assumption that atherosclerosis contributes to the pathophysiology is biologically plausible, the cross sectional design is a limitation of the study. Therefore, associations with no possibility of inference on causality can be reported. Longitudinal studies are needed to determine the time course and possible causality of the observed association between CA and cardiac dysfunction.

In conclusion the study confirms and further characterises the strong association between CA and cardiovascular risk factors. With regard to organ dysfunction, CA is independently associated with NT-proBNP, through common risk factors and NT-proBNP with AF, but not with renal function. In particular, the association between CA and a marker of cardiac dysfunction beyond known common risk factors supports the value of carotid ultrasound in defining the patient's cardiovascular risk profile. The individual measures of carotid atherosclerosis, i.e., CIMT and carotid plaque, appear to have an equally directed and additive influence.

CONFLICT OF INTEREST

D.L.R., K.B., M.J., C.A.B., B.C., and E.S.D. have nothing to report. C.G. reports personal fees from Amgen, Bayer Vital, Bristol-Myers Squibb, Boehringer Ingelheim, Sanofi Aventis, Abbott, and Prediction Biosciences outside the submitted work. G.T. reports receiving consulting fees from Acandis, grant support, and lecture fees from Bayer, lecture fees from Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, and Daiichi Sankyo, and consulting fees and lecture fees from Stryker outside the submitted work.

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APPENDIX A. SUPPLEMENTARY DATA

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