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Differential association of flow velocities in the carotid artery with plaques, intima media thickness and cardiac function

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ABSTRACT

Background and aims: We aimed to determine the association of carotid intima media thickness (CIMT), carotid plaques, and heart function with peak systolic velocity (PSV) of the common (CCA) and internal carotid artery (ICA) in a cross-sectional study.
Methods: In the population-based Hamburg-City-Health-Study participants between 45 and 74 years were recruited. Cardio-vascular risk factors were assessed by history, blood samples, and clinical examination. CIMT, plaques, and PSV were determined by carotid ultrasound. Serum N-terminal brain natriuretic peptide (NT-proBNP) was determined as a biomarker for cardiac dysfunction, and left ventricular ejection fraction (LVEF) was quantified by echocardiography. Participants with carotid stenosis were excluded. Data were analyzed by multivariate linear regression.
Results: We included 8567 participants, median age was 62 years, 51.8% were women. Median CIMT was 0.75 mm, NT-proBNP 80 pg/ml, LVEF 58.5%, and 30.4% had carotid plaques. For women PSV decreased in decades from 89 to 73 cm/s in CCAs and 78 to 66 cm/s in ICAs, and for men from 91 to 76 cm/s in CCAs and from 70 to 66 cm/s in ICAs. Corrected for age, sex, red blood cell count, and blood pressure, in CCAs lower PSV was associated with carotid plaques ($p < 0.001$; $\beta = -0.03$), lower CIMT ($p = 0.005$; $\beta = 0.007$), higher levels of log-transformed NT-proBNP ($p < 0.001$; $\beta = -0.01$), and lower LVEF ($p < 0.001$; $\beta = 0.01$). In ICAs, lower PSV was independently associated with lower CIMT ($p < 0.001$; $\beta = 0.02$) and lower EF ($p = 0.001$; $\beta = 0.007$).
Conclusions: Markers of cardiac dysfunction and plaques are associated with lower and CIMT with higher flow velocities in the carotid arteries.
Clinical Trial Registration: http://www.clinicaltrials.gov, NCT03934957.

Introduction

Carotid plaques and intima media thickness (CIMT) are simple and reliable measures of carotid arteriopathy [1], which can be amended by further parameters such as carotid diameter, pulse-wave, end-diastolic velocity, and peak-systolic velocity (PSV). Carotid diameter was connected to heart and renal failure [2], and pulse wave velocity to cognitive decline [3]. End-diastolic velocity was positively associated with cardio-vascular events [4] [–] [6] and negatively as part of the pulsatility index with CIMT [7]. More controversially wall tension and shear stress were associated with

Abbreviations: PSV = peak systolic velocity, CCA = common carotid artery; ICA = internal carotid artery, SBP = systolic blood pressure; DBP = diastolic blood pressure, BP = blood pressure; LVEF = left ventricular ejection fraction, NT-proBNP = N-terminal brain natriuretic peptide; CIMT=Carotid intima media thickness, RBC = red blood cell count.

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plaque presence in dependance of age and hypertension [8] [–] [10]. Being less dependent on distal occlusive disease than end diastolic velocity the relevance of direct values of PSV has been increased by its reliability in estimating stenoses [11]. Knowledge about its dynamic and impact aside from classification of haemodynamically relevant stenosis is scarce. Though pilot studies demonstrated an association of higher PSV with higher scores in Mini-Mental State Examination [5,12], little is known about the factors determining or influencing PSV beyond increased values in the context of carotid stenosis. Environmental factors appear to have a stronger influence on PSV than genetic factors [13], but there is little evidence about the separate influence of haemodynamically not significant carotid stenoses, CIMT, and cardiac dysfunction on peak systolic velocities of the carotid arteries. We therefore aimed to analyze the association of PSV with measures of haemodynamically not significant carotid arteriopathy and markers of cardiac dysfunction in the common carotid artery (CCA) and internal carotid artery (ICA).

Materials and methods

Data sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request and where necessary after approval of the ethics committee by the corresponding author within 24 months after publication.

Study population

From February 2016 on we started to enroll registered residents of the metropolitan region of Hamburg between the age of 45 and 74 years in the single center observational population-based Hamburg City Health Study. Due to recruitment process some participants were above 75 years when examined. Overall, the study has a long-term prospective design with the aim to determine and characterize risk and prognostic factors of chronic diseases. It comprises multiple laboratory, physical, imaging, and patient-reported assessments. Written informed consent was obtained from all participants. The study was approved by the Ethics Committee of the Hamburg chamber of physicians. Its study design has been published [14], and the study is registered at clinicaltrials.gov, NCT03934957. The study was carried out following the Helsinki Declaration of the World Medical Association and according to the principles of good clinical and good scientific practice. Of the first cohort of 10000 participants, we included all subjects with available baseline data measured between February 2016 and November 2018 in our cross-sectional analysis. We excluded participants with relevant stenoses of the common, internal, or external carotid arteries.

Carotid ultrasound & echocardiography

Carotid ultrasound was performed using a Siemens SC2000® with a 7.5-MHz linear array transducer. Measurements of ultrasound parameters were made according to recommendations by the European Stroke Organisation [15]. In the B-Mode, we measured CIMT in a longitudinal view of the left and right CCA >1 cm proximal of the carotid bulbus for three times within a distance of 1 cm on the far wall and calculated the mean for further analyses. Plaques were defined as a circumscribed focal thickening of the intima media >1.5 mm and measured in CCAs and proximal ICAs. PSV of the CCA and ICA were measured by pulsed-wave doppler in the central segment between origin and bifurcation of the CCA and distal beyond the bifurcation in the ICA close to the jaw angle using duplex-mode with angle correction. For further statistical analyses the mean value of both sides was used. Stenoses were defined as systolic flow velocities above 200 cm/s in the common, internal, and external carotid artery. Concerning the external carotid artery consensus is scant and we chose the definition of haemodynamically relevant stenosis pragmatically [16]. Transthoracic echocardiography was performed using a Siemens SC2000® with a 2.0-MHz linear array transducer. Left ventricular ejection fraction (LVEF) was determined using the two-dimensional biplane method of disks summation as recommended by the European Association of Cardiovascular Imaging [17,18]. Medical technical assistants underwent three months of training before examining participants and followed a standard operating procedure for carotid ultrasound and echocardiogram. Inconclusive and pathologic findings, like stenoses, underwent a regular and risk-based quality check and were inspected by physicians experienced in carotid ultrasound.

Laboratory measurements from blood samples

N-terminal pro brain natriuretic peptide (NT-proBNP) was assessed by immunoassay using Siemens Atellica®, and Roche Cobas e411®. Red blood cell count (RBC) was assessed by fluorescence-activated cell sorting with Siemens Advia®.

Questionnaire and physical measures

We determined demographics and history of cardiovascular risk factors by a pen and pencil questionnaire. Blood pressure was physically examined during visits. Systolic and diastolic blood pressure were measured twice on the right arm and the mean values were used for further analyses.

Statistics

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 assessing the association of Carotid arteriopathy and heart function with PSV in the CCA and ICA, we used multivariate regression models. We fitted two separate models for the dependent variable PSV in CCAs and ICAs containing as independent predictors the numeric cofactors age, CIMT, RBC, logarithmic NT-proBNP, LVEF, systolic and diastolic blood pressure (BP) and the binary cofactors sex and presence of plaque(s). Systolic BP subtracted by diastolic BP was included as pulse pressure (PP) in the multivariate models to minimize confounding by collinearity. Confounding factors were chosen hypothetical based on literature. NT-proBNP was log-transformed oriented on its distribution in descriptive analysis. The models were built from participants with available data, participants with missing values were excluded from multivariate analyses. Associations were considered significant for p-values <0.05. All statistical analyses were carried out using R-studio statistical package 1.1.453 (http://www.r-project.org/).

Results

Participants' characteristics

We included 8567 participants with available values of PSV in CCAs or ICAs, 51.8% were female and their median age was 62 (IQR:55; 69) years. Median CIMT was 0.75 mm (IQR:0.67; 0.84), plaques were detected in 30.4% of the participants. In CCAs median PSV was 83 cm/s (IQR:72; 96), and in ICAs 70 cm/s (IQR:60; 82).

Median LVEF was 58.5% (IQR:55.6; 61.9), and NT-proBNP was 80 pg/ml (IQR:44; 146).

Categorized by age in decades between 45 and 75+ years, female participants between 45 and 54 years had a median PSV of 89 cm/s in CCAs and 78 cm/s in ICAs, which decreased ($p < 0.001$) stepwise to 73 cm/s in CCAs and 66 cm/s in ICAs at the age of 75 years and older (Table 1A). Male participants between 45 and 54 years had a median PSV of 91 cm/s in CCAs and 70 cm/s in ICAs, which decreased ($p < 0.001$) as well to 76 cm/s in the CCA and 66 cm/s in ICAs at the age of 75 years and older (Table 1B).

Association of characteristics with peak systolic velocities

Concerning the CCA, the model included 5984 participants (Fig. 1A). Lower PSV was associated with carotid plaques ($p < 0.001$; $\beta = -0.034$, CI: 0.044,-0.023) and higher log NT-proBNP levels ($p < 0.001$; $\beta = -0.015$, CI: 0.020,-0.010). Higher PSV showed an association with higher CIMT ($p = 0.002$; $\beta = 0.008$, CI:0.003,0.013) and higher LVEF ($p < 0.001$; $\beta = 0.012$, CI:0.008,0.017). Of further confounders, age ($p < 0.001$; $\beta = -0.053$, CI: 0.058,-0.047) and female sex ($p < 0.001$; $\beta = -0.044$, CI: 0.054,-0.034) predicted lower PSV. Pulse pressure ($p < 0.001$; $\beta = 0.011$, CI:0.006,0.016) was positively associated with higher PSV.

Concerning the ICA the model comprised 7667 participants (Fig. 1B). Higher PSV was associated with higher CIMT ($p < 0.001$; $\beta = 0.017$, CI:0.012,0.022) and higher LVEF ($p < 0.001$; $\beta = 0.010$, CI:0.005,0.014). The presence of plaques ($p = 0.829$; $\beta = -0.001$, CI: 0.011,0.009), and levels of log NT-proBNP ($p = 0.780$; $\beta = -0.001$, CI: 0.006,0.004) had no influence on PSV in ICAs. Of further confounders age ($p < 0.001$; $\beta = -0.041$, CI: 0.046,-0.035) predicted lower PSV, while female sex ($p < 0.001$; $\beta = 0.035$, CI:0.026,0.045) and pulse pressure ($p < 0.001$; $\beta = 0.018$, CI:0.013,0.022) were associated with higher PSV.

Equally fitted models containing solely carotid plaque or CIMT are shown in the supplemental material (Tables I and II for CA and Tables III and IV for ICA).

Discussion

Our study provides novel insights in the relations of carotid plaques and CIMT to peak flow velocity in the carotid arteries. Carotid plaques were independently associated with lower PSV. In contrast, CIMT revealed an association with higher PSV. LVEF as a measure of cardiac output showed a positive association with PSV. In accordance, higher NT-proBNP as a measure of cardiac dysfunction was associated with lower PSV. RBC correlated negatively with PSV.

The population-based cohort represents mid to old aged participants with cardio-vascular risk factors but not being severely ill [19]. The distribution of carotid plaques and amount of CIMT is comparable to similar risk groups [20]. Reference values of PSV from population-based cohorts are scarcely reported, and if so only of small samples or for a different purpose [13,21]. Herein reported ICA/CCA ratios of velocities match our results of PSV in women, but do not support the age dependent decrease in men [21]. Another study reported a relation of old age to a low PSV similar to our findings, and discussed multifaceted reasons, e.g., decreased elastin in the media [22], and altered cardiac function [23]. The steeper decrease of PSV in women's ICAs with increasing age might be related to a loss of a initially more effective autoregulation [24]. Higher values of PSV measured after stenoses of ICAs [25] support this assumption. It might as well contribute to the different impact of female sex on PSV in ICAs and CCAs.

PSV in CCAs and ICAs was independently associated with higher CIMT, a marker of general atherosclerotic wall-changes, and LVEF. The association of CIMT with higher PSV may be explained by a systemic endothelial damage leading to a disturbed autoregulation through changes in diameter [26,27]. The impact of haemodynamic parameters of heart function, as LVEF and systolic BP, on carotid arteries' PSV stand in line with reported physiologically analyses [28].

Lower PSV in CCAs was associated with presence of carotid plaques and higher values of NT-proBNP. Though CIMT and plaques are both markers of arteriopathy, both predict cardiovascular events [29,30] and share a common incidence [31], the association of plaques with low PSV stands in contrast to the one of CIMT with high PSV. It is, however, not contradictory. Plaques are by definition circumscribed and were most commonly measured close to the carotid bulbus [15]. They are related to non-aligned scatter flow [32,33], and instead of CIMT to low shear stress, which are both associated with lower flow velocities and localization close to the carotid bulbus [27,34,35]. The carotid bulbus is the area of most frequent plaque development and detection. The reason for this is the bifurcation that separates the previous undirected flow of the proximal CCA with a consecutive loss of axial alignment, scatter-flow, and decrease in wall shear stress [34]. Wall shear stress in the carotid bulbus is dependent from flow velocity [27]. That plaque presence is associated with lower PSV in CCAs and not in ICAs reflects that the CCA is the feeding vessel of the carotid sinus and determines its flow velocity and wall shear stress more directly than the ICA's correlates with it. This is based in the ICA's location distal to the bifurcation which confounds flow velocity by its anatomy and hemodynamics of the external carotid artery. Changes in wall structure with a transition zone in the proximal ICA

Table 1A
Characteristics of female participants.

Female	Age categories				Total
	45–54 years	55–64 years	65–74 years	75+ years	(missing)
N	1091	1547	1546	256	8567
PSV in CCA (cm/s, median [IQR])	89 [79,101]	82 [73,94]	78 [66,89]	73 [62,82]	83 [55,69] (4)
PSV in ICA (cm/s, median [IQR])	78 [68,90]	74 [64,85]	70 [59,82]	66 [57,78]	70 [60,82] (47)
CIMT (mm, median [IQR])	0.67 [0.61,0.73]	0.71 [0.65,0.79]	0.78 [0.70,0.86]	0.84 [0.74,0.91]	0.75 [0.67,0.84] (82)
Presence of plaque (%)	90 (8.3)	303 (19.6)	596 (38.9)	123 (49.2)	2584 (30.4%) (63)
Plaque diameter (mm, median [IQR])	1.88 [1.64,2.26]	2.04 [1.72,2.42]	2.10 [1.75,2.54]	2.08 [1.78,2.47]	2.14 [1.80,2.54]
NT-proBNP (pg/dl, median [IQR])	68 [42,111]	81 [50,132]	129 [80,222]	186 [112,286]	80 [22,146] (219)
LVEF (%, median [IQR])	59.1 [56.4,62.5]	59.6 [56.5,62.9]	59.2 [56.3,62.7]	59.1 [56.0,62.1]	58.5 [55.6,61.9] (2058)
SBP (mmHg, median [IQR])	125.0 [115.1135.5]	131.0 [120.5142.3]	141.5 [130.0,156.0]	145.0 [130.5155.5]	136.5 [125.0,150.0] (296)
DBP(mmHg, median [IQR])	79.5 [73.5,86.5]	80.5 [74.5,86.9]	80.5 [74.5,87.5]	80.0 [74.0,87.5]	81.5 [75.5,88.0] (297)
RBC (10^6/µl, median [IQR])	4.54 [4.34,4.73]	4.58 [4.37,4.78]	4.59 [4.38,4.82]	4.59 [4.36,4.82]	4.73 [4.48,5.01] (245)

Table 1B
Characteristics of male participants.

Male	Age categories				Total
	45–54 years	55–64 years	65–74 years	75+ years	(missing)
N	912	1346	1560	309	8567
PSV in CCA (cm/s, median [IQR])	91 [79,104]	87 [74,99]	79 [68,92]	76 [66,86]	83 [55,69] (4)
PSV in ICA (cm/s, median [IQR])	70 [60,80]	67 [58,77]	66 [56,78]	66 [55,76]	70 [60,82] (47)
CIMT (mm, median [IQR])	0.69 [0.62,0.78]	0.76 [0.68, 0.85]	0.81 [0.73,0.91]	0.88 [0.78,1.00]	0.75 [0.67,0.84] (82)
Presence of plaque (%)	128 (14.0)	400 (29.9)	746 (48.4)	198 (64.9)	2584 (30.4%) (63)
Plaque diameter (mm, median [IQR])	2.03 [1.79,2.34]	2.11 [1.82, 2.50]	2.23 [1.90,2.66]	2.23 [1.86,2.63]	2.14 [1.80,2.54]
NT-proBNP (pg/dl, median [IQR])	35 [22,58]	51 [30, 87.5]	97 [55.75,180]	162 [82.25,296.25]	80 [22,146] (219)
LVEF (%, median [IQR])	57.7 [55.4,60.7]	57.9 [55.3,61.2]	57.3 [54.5 60.5]	56.9 [53.9,60.7]	58.5 [55.6,61.9] (2058)
SBP (mmHg, median [IQR])	134.5 [125.0,144.5]	137.5 [127.0,150.5]	143.00 [131.0,156.0]	143.5 [129.5157.5]	136.5 [125.0,150.0] (296)
DBP(mmHg, median [IQR])	83.5 [78.5,90.5]	84.5 [78.5,91.0]	82.0 [76.0,88.0]	79.5 [73.0,87.5]	81.5 [75.5,88.0] (297)
RBC (10^6/µl, median [IQR])	5.03 [4.79,5.24]	4.96 [4.73,5.19]	4.85 [4.60,5.11]	4.82 [4.57,5.07]	4.73 [4.48,5.01] (245)

Abbreviations: CIMT= Carotid intima media thickness; PSV = peak systolic velocity; CCA = common carotid artery; ICA = internal carotid artery; N = number; IQR = interquartile range; NT-proBNP = n-terminal pro brain natriuretic peptide; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure; DBP = diastolic blood pressure; RBC = red blood cell count.

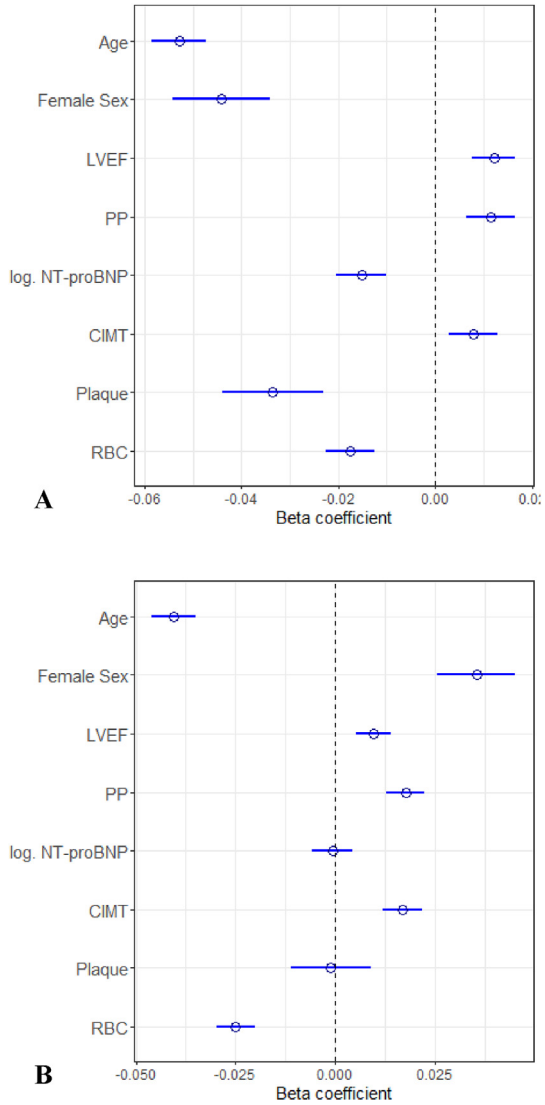

Fig. 1. Factors associated with peak systolic velocity in common (**A**) and internal (**B**) carotid arteries in a model of multivariate regression. Abbreviations: CIMT= Carotid intima media thickness; NT-proBNP = n-terminal pro brain natriuretic peptide; LVEF = left ventricular ejection fraction; PP = pulse pressure (systolic blood pressure - diastolic blood pressure); RBC = red blood cell count. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

additionally explain our findings of CCAs' PSV being associated with plaque and ICAs' PSV not [36].

The same directed association of plaques, low LVEF, and high NT-proBNP concentration with PSV supports plaques' more distinct clinical and genetic connection to cardiovascular events and ischemic cardiomyopathy compared to CIMT [37,38], which is closer associated with stroke [39]. Therefore CIMT's association with high PSV and plaques' with low PSV represents one physiological bridge between their pathogenesis and concomitant clinical manifestation.

Impaired cardiac function indicated by higher levels of NT-proBNP predicted low PSV in CCAs as well. NT-proBNP is a subclinical marker sensitive for myocardial stress caused by volume load [40]. Its independent association suggests an additive value of PSV to haemodynamics measured by echocardiogram and BP in estimating cardiac function.

We considered RBC as a cofactor in respect to blood viscosity and further studies suggesting an influence on vascular structure and flow velocity [41–43]. Its correlation with lower PSVs stands in line with the literature and might be explained due to autoregulatory mechanisms to guarantee a steady oxygen transport.

While the assumption, that heart function and different factors of arteriopathy have a distinct association with flow velocity is physiologically plausible, we have to acknowledge the limitation that our study had a cross-sectional design. Therefore, we can only report associations with no possibility to inference on causality. Longitudinal studies are needed, to determine the time course and possible causality of the observed association between PSV, arteriopathy, and cardiac dysfunction. Concerning heart function, this population-based study is focused on values within the normal range and not able to predict the effect of pathologic findings.

Our study provides novel information about the interaction of PSV measured in the CCA and ICA with carotid plaques, CIMT, and cardiac function. An increased CIMT and higher LVEF predicts a higher PSV, while presence of plaques and higher NT-proBNP concentrations are associated with lower PSV in CCAs apart from BP, RBC, age, and sex. The difference in associations with carotid plaques and CIMT and its link to heart function suggests a benefit of considering PSV in clinical context, on the one hand, and both markers of carotid arteriopathy individually on the other.

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Author contributions

D. Leander Rimmele conceptualized the study, contributed to acquisition and analysis of data; and drafted the manuscript. Katrin Borof contributed to analysis of data and revised the manuscript for intellectual content. Jan-Per Wenzel contributed to acquisition of data and revised the manuscript for intellectual content. Märit Jensen, Christian A. Behrendt, Christoph Waldeyer, Renate B. Schnabel, Tanja Zeller, E. Sebastian Debus, Stefan Blankenberg, and Christian Gerloff revised the manuscript for intellectual content. Götz Thomalla conceptualized and drafted the study design and revised the manuscript for intellectual content.

Submission declaration statement

All authors had access to all data in the study and have read and approved the final version of the manuscript. The material in the manuscript has not been published or is under consideration for publication elsewhere.

Declaration of competing interest

DLR, KB, JPW, MJ, CAB, CW, TZ, and ESD have nothing to report. RBS has received speaker honoraria from Bristol-Myers Squibb/Pfizer. RBS has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No 648131), from the European Union's Horizon 2020 research and innovation programme under the grant agreement No 847770 (AFFECT-EU) and German Center for Cardiovascular Research (DZHK e.V.) (81Z1710103); German Ministry of Research and Education (BMBF 01ZX1408A) and ERACoSysMed3 (031L0239). SB has received research funding from Abbott Diagnostics, Bayer, SIEMENS, Singulex and Thermo Fisher. He received honoraria for lectures from Abbott, Abbott Diagnostics, Astra Zeneca, Bayer, AMGEN, Medtronic, Pfizer, Roche, SIEMENS, Thermo Fisher and as member of Advisory Boards for consulting for Bayer, Novartis and Thermo Fisher. CG reports personal fees from Amgen, Bayer Vital, Bristol-Myers Squibb, Boehringer Ingelheim, Sanofi Aventis, Abbott, and Prediction Biosciences outside the submitted work. GT 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

Supplementary data related to this article can be found at https://doi.org/10.1016/j.athplu.2021.07.020.

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