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Sex-related differences in coronary and carotid vessel geometry, plaque composition and shear stress obtained from imaging

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ABSTRACT

Atherosclerosis manifests itself differently in men and women with respect to plaque initiation, progression and plaque composition. The observed delay in plaque progression in women is thought to be related to the hormonal status of women. Also features associated with the vulnerability of plaques to rupture seem to be less frequently present in women compared to men. Current invasive and non-invasive imaging modalities allow for visualization of plaque size, composition and high risk vulnerable plaque features. Moreover, image based modeling gives access to local shear stress and shear stress-related plaque growth. In this review, current knowledge on sex-related differences in plaque size, composition, high risk plaque features and shear stress related plaque growth in carotid and coronary arteries obtained from imaging are summarized.

1. Introduction

Cardiovascular disease is one of the leading causes of death, being responsible for approximately a third of global deaths [1]. Acute cardiovascular events are most often proceeded by atherosclerotic plaque rupture and are associated with a high plaque burden and a particular, well-defined rupture-prone plaque composition [2–8]. These rupture-prone plaques are also called vulnerable plaques and in coronary arteries typically contain a large lipid pool covered by a thin fibrous cap, have a high plaque burden, are positively remodeled and are highly inflamed [3,5] In carotid arteries vulnerable plaques most often contain intraplaque hemorrhage and also the plaque volume itself is associated with cardiovascular events [4].

Interestingly, atherosclerosis manifests itself differently in women compared to men, regarding atherosclerotic plaque size, composition and rupture risk. Atherosclerotic plaques in coronary arteries from women are generally smaller and contain less lipid and calcium compared to plaques observed in men [9,11]. In addition, women present more often with non-obstructive coronary artery disease because of microvasculature abnormalities leading to ischemia or myocardial infarction compared to men [12]. These differences in plaque composition are also directly linked to the difference in the risk of a cardiovascular event [11].

Most sex-related differences in carotid artery atherosclerosis have been recognized from studies on carotid endarterectomy specimen, which consistently show that carotid artery plaques from women appear to be more stable and are more homogeneous than those of men [10, 13–15]. Particularly, plaques derived from women exhibited predominantly fibrous characteristics. In women, atheromatous plaques, i.e. plaques that contain more than 40% fat, seem to be present in 22% of the plaques, whereas in men, this may be as high as 40%. Also in terms of inflammatory aspects of the plaques, macrophage infiltration is often less prevalent in women than in men (14% versus 21%), and the expression of proinflammatory cytokines and protease activity seems to be generally lower in women than in men [10].

Atherosclerotic plaques can be visualized with various invasive and non-invasive imaging modalities, including ultrasound, intravascular ultrasound (IVUS), optical coherence tomography (OCT), magnetic resonance imaging (MRI) and computed tomography (CT), each with their own advantages and disadvantages. To identify the presence of vulnerable plaques in coronary arteries and the link with future events, researchers predominantly concentrated on the identification of plaques with a large lipid rich necrotic core, a thin fibrous cap, or the so called thin cap fibroatheroma (TCFA), and large plaque burden [3,16–18]. In carotid arteries, the focus has been mostly on identifying plaques with intraplaque hemorrhage or large plaque volume, that demonstrated to

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positively correlate with risk of stroke or transient ischemic attack [4]).

Blood flow pattern characteristics and shear stress have gained considerable interest in the prediction of cardiovascular risk [19,20]. Shear stress is a frictional force caused by the blood flow on the vessel wall, that regulates endothelial cell function [21,22]. At regions of low or disturbed shear stress, found at branch points and curved sections of arteries, the resulting effect on endothelial function is responsible for the initiation of atherosclerosis. Similarly, plaque progression is also most pronounced at sites where the endothelium is exposed to low or disturbed blood flow [23,24].

This paper gives an overview of the existing knowledge on sex-related differences in plaque composition in coronary and carotid arteries of patients as can be assessed with the different invasive and non-invasive imaging modalities and the sex-specific effect of shear stress on the growth and vulnerability of atherosclerotic plaques.

2. Carotid arteries

Rapid advances in imaging modalities over the past two decades allow for accurate visualization (and quantification) of carotid atherosclerotic plaques. In addition to simple quantification of plaque thickness and the degree of stenosis using ultrasound, visualizations of plaque morphology and plaque composition have become possible using computed tomography (CT) and magnetic resonance imaging (MRI) (Fig. 1). In line with the increasing evidence on sex differences in cardiovascular disease, advances in imaging of carotid atherosclerosis have revealed sex-specific characteristics for carotid plaque composition and morphology. See Supplementary Table S1 for an overview of the differences among men and women.

2.1. Ultrasound and angiography

Ultrasound is a radiofrequency based non-invasive imaging method that allows visualization of the carotid artery intima medial thickness (cIMT) and the artery geometry. The use of contrast, i.e. gas filled bubbles, during ultrasound imaging (contrast-enhanced ultrasound (CEUS)) increases the ability to detect irregularities on the surface of plaques, including ulcerations. The irregularities visualized through CEUS align well with histopathological findings of vulnerable plaques [25]. Angiography allows visualization of the vessels by x-ray imaging using x-ray contrast agents.

The earliest reports on sex-related differences in vessel size and geometry are based on ultrasound measurements [26]. In an asymptomatic cohort, the size of the common carotid artery was measured, demonstrating that the size of the carotid artery increased with age, with a similar growth rate observed in men and women. A meta-analysis on plaque distribution in the carotid artery of men and women, demonstrated a similar asymmetric pattern of plaque in men and women with the most plaque at the postural medial wall of the bifurcation and internal carotid segments and the anterolateral wall of the common carotid segment [27]. Even though the distribution of plaque was similar in men and women, carotid arteries of men showed a higher intima media thickness compared to women. As expected, patients with a higher age proved to have thicker walls compared to younger patients [27] (Fig. 2). In addition, a recent study of 7908 asymptomatic middle-aged Chinese participants (58±9 years, 62% women), revealed a lower overall cIMT, as well as left and right cIMT in women compared to men. However, the annual cIMT progression rate was not statistically different among men (-5.21 (-46.88– 38.46) μm/year) and women (-9.80 (-46.67–35.71) μm/year). After adjustment for general risk factors, women demonstrated a much lower plaque progression rate compared to men (β=-15.48 (-20.2– -10.74) μm/year). Interestingly, sex-specific differences in risk factors for plaque progression were observed; for women, smoking and alcohol drinking were significantly related to plaque progression, while in men, hypertension and anti-hypertensive medication were associated with progressive disease [28].

In terms of geometry, angiography showed in a large cohort of patients that women tend to have a greater outflow to inflow area ratio, and their internal carotid arteries seem to be relatively larger compared to the common carotid artery and external carotid artery when compared to men [29].

2.2. CT/MRI

CT- or MRI-based characteristics of carotid atherosclerosis are, in our view, the most promising in terms of potential clinical application. Amongst the most commonly used plaque characteristics are measures of plaque size, which include wall thickness (1-dimensional), wall area (2-dimensional), and wall volume (3-dimensional). Findings from a recent meta-analysis show that all of these plaque measurements are more likely to be larger in men than in women [mean difference (95% confidence interval (CI)) between men and women for maximum wall thickness = 0.44 (0.27–0.61); for wall area = 0.70 (0.59–0.81); and for wall volume = 0.71 (0.46–0.96)] [30]. This seems to be fully driven by the fact that men tend to have larger arteries, as the normalized wall

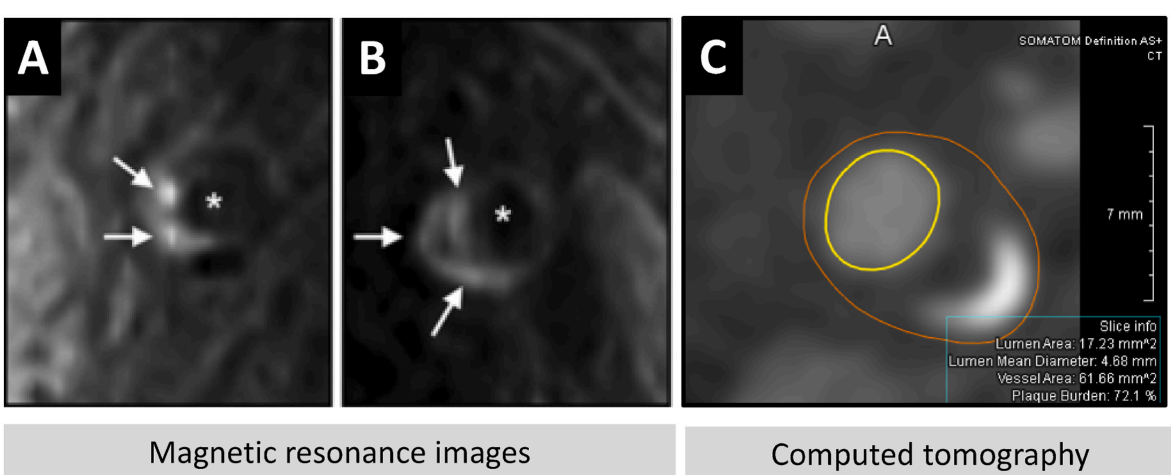

Fig. 1. Images of carotid plaque.
Two examples of magnetic resonance images (A), (B) of Internal carotid artery plaque Asterisk: lumen. Arrow: intraplaque hemorrhage (high signal intensity on the T1w-GRE image). Adapted from [79] (C) Example of a carotid plaque visualized with computed tomography; yellow line: lumen contour; red line: outer wall boundary.

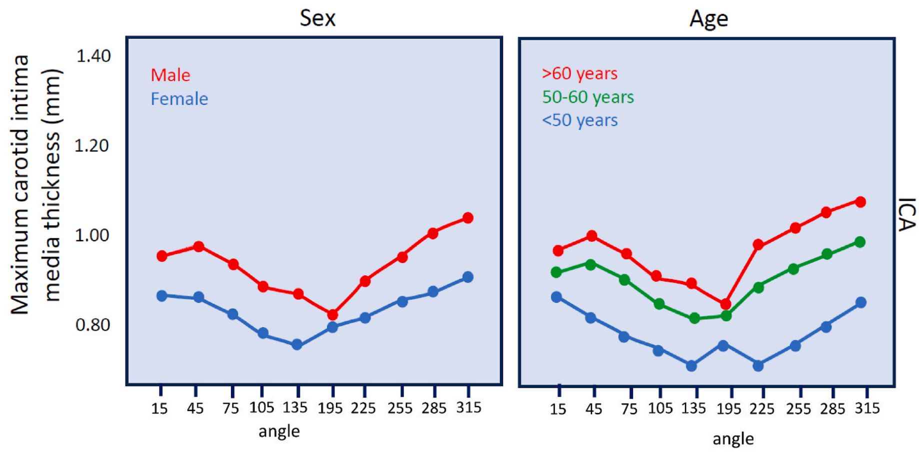

Fig. 2. Circumferential distribution of maximum carotid intima media thickness in internal carotid artery based on ultrasound.
Circumferential distribution (angle in degrees) of maximum carotid intima media thickness (mm) based on ultrasound in internal carotid artery (ICA) stratified for age and sex. Adapted from Ref. [27].

index (accounting for the total vessel size) did not differ between men and women (Fig. 3A) [30].

One of most direct indicators of plaque vulnerability is ulceration of the surface of carotid atherosclerotic plaques [31,32], which might relate to localized ruptures in the fibrous cap. Ulceration can trigger the activation of platelets and the coagulation cascade and thereby increases the risk of thrombus formation and embolism [33,34]. With use of contrast-enhanced CT, ulceration can be visualized as contrast is

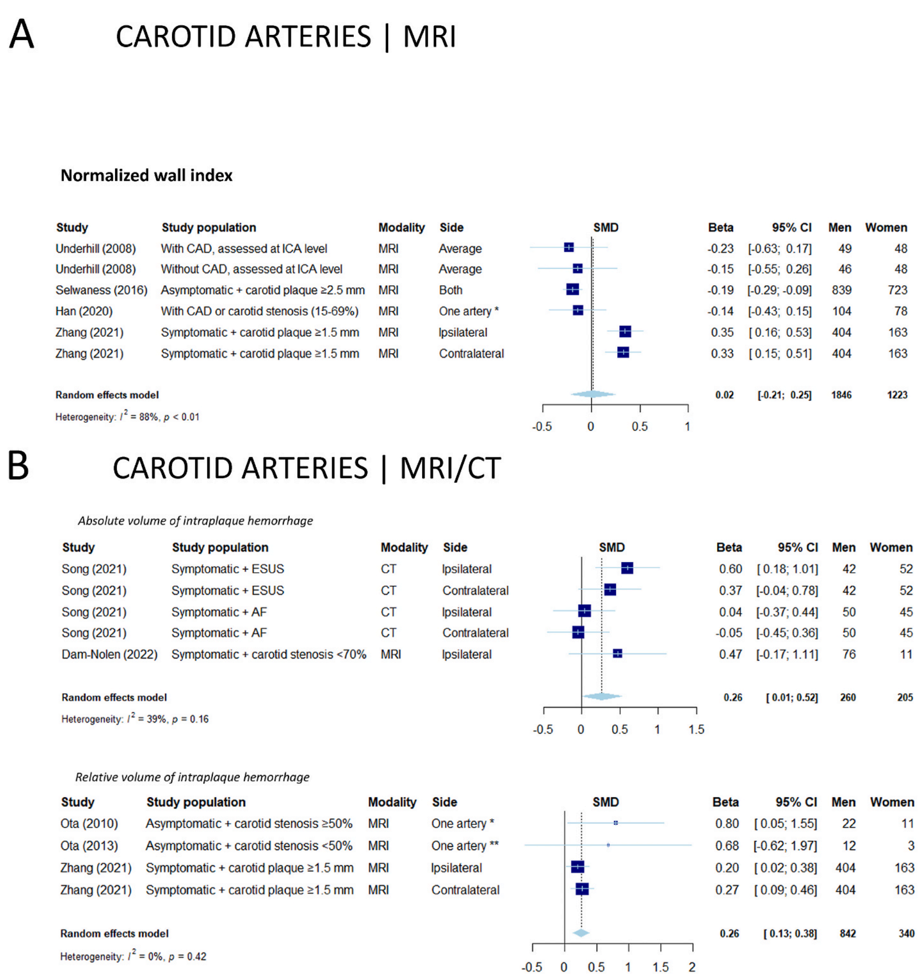

Fig. 3. Forest plot of meta-analysis on sex-related differences in wall thickness and intra plaque hemorrhage in carotid arteries.
Forest plot of meta-analysis on the association between (A) sex and normalized wall thickness and (B) sex and absolute volume of intra plaque hemorrhage (upper panel) and relative volume of intraplaque hemorrhage (lower panel) in carotid arteries. The size of the box which represents the beta, is proportional to the weight of the study. The diamond is the result of the random-effect eta-analysis. Abbreviations: CAD = coronary artery disease; CI = confidence interval; ICA = internal carotid artery; MRI = magnetic resonance imaging; SMD = standardized mean difference. * most severly stenotic side; ** = side with stenosis <50%. Adapted from [30].

observed in the resulting cavities with in the plaque. Contrast-enhanced MRI is an alternative imaging modality for the visualization of plaque ulceration. A recent meta-analysis, consisting of 3517 stroke and transient ischemic attack patients from three studies, showed that plaque ulcerations are significantly more prevalent in men than in women [odds ratio (OR) (95% CI) = 1.81 (1.30–2.51)] [30] identifying different pathological mechanisms are responsible for stroke risk in men and women.

The presence and amount of calcification in carotid atherosclerosis is by far the most extensively studied characteristic. Following the research field on coronary atherosclerosis, in which calcification is currently used as screening tool for the presence of coronary heart disease, calcification in the carotid arteries has been linked to the risk of ischemic stroke. The best image modality for evaluation of calcification is non-contrast CT [35]. Its unprecedented capability to detect and quantify calcification, firmly positioned non-contrast CT cardiovascular imaging [36] as a suitable tool for the initial detection of atherosclerotic disease in otherwise asymptomatic individuals. Presence of carotid artery calcification is related to a 40% increased risk of first-ever stroke [37]. Carotid artery calcification is also related to the total atherosclerotic burden [38]. However, despite the presence of calcification indicating an elevation of stroke risk, calcification itself may have a stabilizing effect on the plaque and thus reduce plaque vulnerability among patients with known atherosclerotic disease [39,40]. The complexity around size and location of carotid plaque calcification makes it difficult to draw generalizable conclusions on its effect on an individual's risk of stroke. For example, where multiple small regions of calcification are present within one plaque, the interactions of calcified and noncalcified areas may enhance strain thereby promoting vulnerability to ulceration [41], while a single large deep-seated area of calcification may reduce strain and thereby the risk of plaque disruption. Sex differences in calcification further add to this complexity. Carotid plaques in men more frequently tend to contain larger volumes of calcification compared to women [mean difference between men and women (95% CI) = 0.37 (0.25–0.48)] [30]. However, the amount of calcification relative to the total plaque volume seems to be comparable across men and women. The implications of these differences are yet to be determined.

The final and, in our view, highly promising imaging feature of carotid atherosclerosis is the presence of intraplaque hemorrhage (IPH), which is thought to reflect a recent rupture of intraplaque neovessels or rupture of the fibrous cap. It thereby presents one of the strongest indicators of plaque vulnerability. Intraplaque hemorrhage is commonly seen in patients with symptomatic and asymptomatic carotid atherosclerosis and the strongest predictor of first ever stroke [HR for risk of stroke in presence of IPH (95% CI) = 2.42 (1.3–4.5)] [42] and of recurrent stroke [HR for risk of stroke recurrence in presence of IPH (95% CI) from a recent meta-analysis: 10.2 (4.6–22.5)] [43]. A recent meta-analysis demonstrated that presence of IPH is more common in men than in women [OR for presence of IPH comparing men to women (95% CI) = 2.52 (1.74–3.66)] [30]. Regarding the amount of IPH, both absolute and relative volumes of IPH were significantly higher in men compared to women [mean difference between men and women (95% CI) = 0.26 (0.01–0.52) and 0.26 (0.13–0.38) for absolute and relative IPH volumes respectively] [30] (Fig. 3B). The relationship between IPH and other plaque features, including calcification and extracellular lipid core volumes to determine plaque phenotype, may add further prognostic information.

2.3. Carotid artery shear stress

In addition to investigations of the morphological characteristics of carotid atherosclerosis, increasing interest is pointed towards the sex-specific role of blood flow and biomechanics on the vessel wall at the site of atherosclerotic plaques. Ultrasound analysis first identified sex-specific differences in flow and shear stress [26], demonstrating that the *peak* wall shear stress in the common carotid artery is considerably higher in men than in women, particularly in the first six decades of life [26]. After the sixth decade, this difference in peak wall shear stress was disappeared. Interestingly, the *mean* wall shear stress was similar for men and women and slightly decreased with age. The latter descend reached statistically significance in women [26]. Since plaque growth has been associated with the *mean* wall shear stress, it is unclear how the differences in peak wall shear stress could perhaps contribute to the observed differences in plaque initiation and progression in men and women. If so, these data suggest that the higher peak wall shear stress in men, presumably protective to prevent plaque growth, are most likely counteracted by the hormonal status of men.

Many questions remain unanswered with regard to sex specific differences in the geometry of the carotid artery, the shear stress, and their consequences for plaque growth. It also remains unclear whether these differences are congenital or acquired, genetically programmed or affected by the additional influence of sex hormones.

3. Coronary arteries

Imaging of coronary arteries is performed using both invasive and non-invasive imaging techniques. Invasive techniques allow for detailed analysis of the coronary artery lumen and wall, whereas the non-invasive techniques give an approximation of the geometry, tortuosity presence of local stenosis and calcium load in the total coronary tree (Fig. 4). See (Supplementary Table 2) for an overview of the differences among men and women.

3.1. Invasive imaging (ultrasound)

The PROSPECT study (Providing Regional Observation to Study Predictors of Events in the Coronary Tree), using intravascular ultrasound to image the coronary arteries of patients undergoing percutaneous coronary intervention (PCI) demonstrated that non-culprit plaques in coronary arteries from women have a smaller lumen area (7.0 [5.4–8.8] *vs.* 8.1 [6.1–10.6] mm^2/mm), outer vessel area (13.9 [10.6–16.9] *vs.* 16.0 [12.3–20.5] mm^2/mm) and plaque area (6.6 [5.1–8.3] *vs.* 7.7 [5.8–10.0] mm^2/mm), but similar plaque burden (55.6 [49.1–63.2] *vs.* 55.3 [49.1–61.8] %) as compared to non-culprit plaques in coronary arteries from men [11]. Similar differences in coronary plaque dimensions were reported by the study that combined data from the AtheroRemo-IVUS (Inflammation and Vascular Wall Remodeling in Atherosclerosis - Intravascular Ultrasound) and third Integrated Biomarker and Imaging (IBIS-3) studies and PREDICTION trial [9,44] However, normalization for body surface area eliminated the observed differences in total plaque volume, as BSA is smaller in women than men (4.5 (0.6) *vs.* 4.5 (0.6); $p = 0.19$) [9].

Virtual histology-IVUS (VH-IVUS), i.e. radiofrequency-based assessment of plaque composition, showed that he absolute volumes of fibrous tissue, fibro fatty tissue, necrotic core and dense calcium were smaller in non-culprit coronary plaques from women compared to men [9], also after normalization for BSA [9], while the percentage of the various plaque components was similar in men and women [9] (Fig. 5). Tthe number and percentage of the different plaque phenotypes (fibrotic PIT, thCFA, TCFA) of non-culprit lesions in acute coronary syndrome patients did not differ among men and women [9,11]. However, in culprit lesions of a cohort of 280 Korean, ST elevation myocardial infarction female patients showed a lower percentage fibro-fatty tissue and more dense calcium but no difference in percentage necrotic core based on VH-IVUS, compared to men after prospensity matching [45].

Since atherosclerotic plaque growth is accelerated in women after menopause and age is the greatest determinant of plaque growth/presence, stratification of data according to age is important. The general observation that vessels and plaques in coronary arteries are smaller in women than in men was true across all age categories [46]. Regarding plaque composition, non-culprit lesions in female ACS patients younger

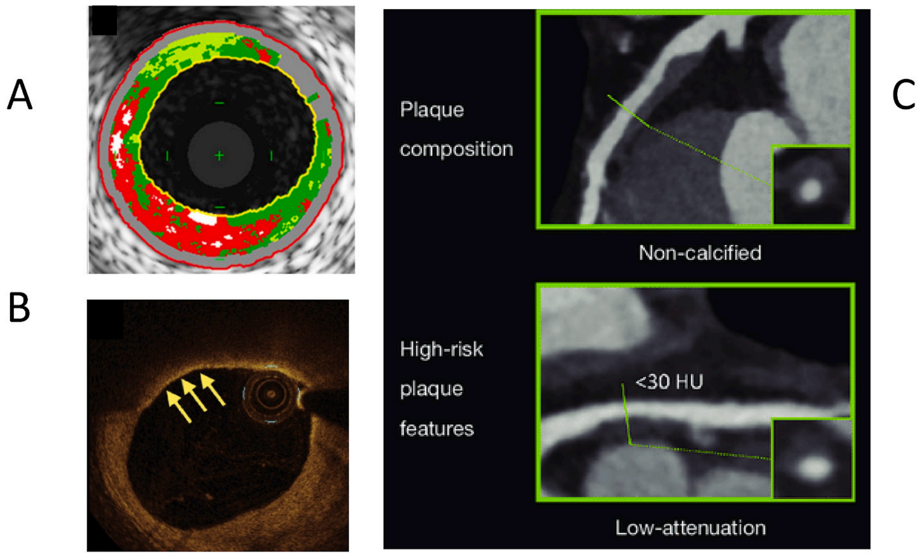

Fig. 4. Images of coronary plaque using invasive and non-invasive imaging.
(A) Intravascular ultrasound virtual histology (VH-IVUS) [80], red = necrotic core, white = calcium, light green = fibrofatty, green = fibrous tissue, (B) optical coherence tomography (OCT), arrow heads indicate location of lipids [81], (C) computed tomography (CT) [82], with non-calcified plaque and a low attenuation plaque.

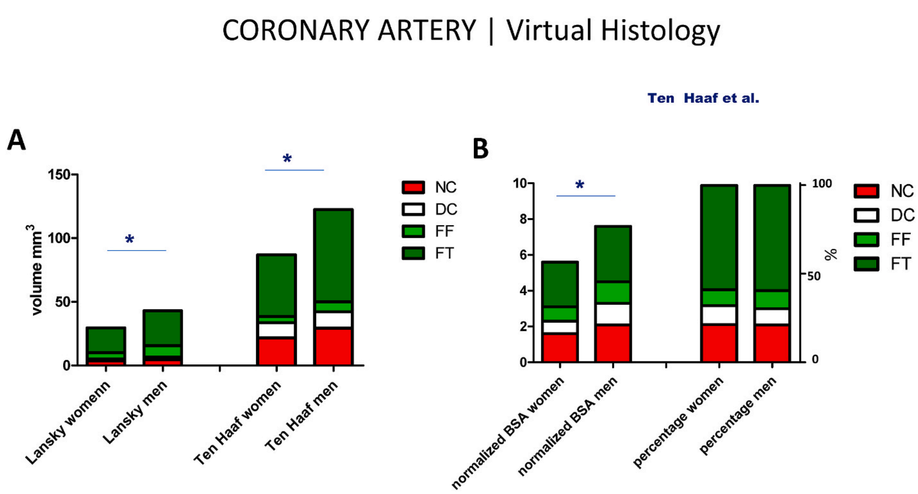

Fig. 5. Coronary artery plaque composition data based on virtual histology.
Bar graph on absolute volumes (A) and volumes normalized for BSA or plaque volume (right axis) (B) of necrotic core (NC), dense calcium (DC), fibrofatty (FF) and fibrous tissue (FT) in men and women in the study by Lansky et al. [11] and ten Haaf et al. [9]. *$p < 0.05$.

than 65 years were more often fibrotic than non-culprit lesions from younger male patients (<65 years). The frequency of other plaque phenotypes (PIT, thCFA, TCFA) did not differ among younger men and women. For patients older than 65 years, no difference in the frequency of plaque phenotype or high risk lesion characteristics was observed [45, 46], although the percentage of plaque area comprising the necrotic core seems to be higher in women. This likely reflects an acceleration of necrotic core development post menopause, given the propensity for the development of more fibrotic plaques in younger women [45,46].

Sex-related differences in plaque progression rate was studied in a cohort of patients that participated in a number of lipid lowering or best medical treatment studies [47]. No differences in plaque progression rate in terms of total atheroma volume, percent atheroma volume and atheroma volume progression in the 10 mm most affected by atherosclerosis were observed among men and women. Even after correction for general known risk factors, no differences were observed, implying that risk factor modification in women is equally effective as in men [47].

3.2. Near infrared spectroscopy (NIRS)

Near infrared spectroscopy showed a similar lipid load in coronary non-culprit lesions from men and women with acute coronary syndrome, as can be expressed as the lipid core burden index (LCBI) at the region of interest, i.e. the lumen surface area containing lipid relative to total lumen surface area * 1000 (F: 50±46 *vs.* M: 73±93), as well as in the worst 4 mm (maxLCBI4mm, F: 220±163 *vs.* M: 283±203) and 10 mm segments (maxLCBI10mm, F: 145±117 *vs.* M: 193±170) [9]. After adjustment for clinical risk factors and age, coronary arteries from men displayed a significant higher LCBI being 20 larger than in women (8, 29), higher maxLCBI10mm being 48 larger than in women (10, 74) and higher maxLCBI4mm being 62 larger than in women (3, 104) [9]. In a combined cohort of stable angina and acute coronary syndrome patients, a higher LCBI was also observed in coronary arteries from men compared to women ([48 (21–95) *vs.* 27 (9–59), $p < 0.003$]) [48].

In a Japanese ACS population, LCBI and maxLCBI4mm were much higher in both the culprit and non-culprit arteries, but also (culprit lesions: 544.7±29.9 *vs.* 501.7±19.1; non-culprit lesions 288.8±26.7 vs. 272.7±18.9) not different in coronary arteries of men and women, even after adjustment for clinical risk factors. With the introduction of the lipid burden density index that corrects the maxLCBI4mm for the local plaque volume, significant higher values were found in coronary arteries of women both for culprit and non-culprit lesions even after adjustment for clinical risk factors [49].

3.3. Optical coherence tomography (OCT)

Optical coherence tomography is a light based high-resolution intravascular imaging technique and allows for visualization of very detailed small features in plaques such as fibrous cap thickness, the presence of (foam cell) macrophages and vasovasorum [50]. OCT is limited by the relatively poor penetration of light through lipid rich plaque components excluding the visualization of the outer vessel wall in lipid-rich plaques, thus the lipid presence is expressed as angle or lipid arc [50].

The majority of studies on acute coronary syndrome patients demonstrated that women are generally older, but both the culprit and non-culprit lesions in women display similar distribution in plaque phenotype (%lipid rich plaque, %TCFA, %fibrous plaques, %fibrous calcific plaques) [51–54]. A meta-analysis based on 6 papers using high risk plaque characteristics in non-culprit lesions, demonstrated that cap thickness is higher (8.2 μm 95% CI (3.4–13 μm), $p < 0.001$) and lipid arc lower (-26° 95% CI (-50°– -2°), p=0.031) in women compared to men [51,52,55] while in culprit lesions no differences in cap thickness (-1 μm 95%CI (-12–10 μm), p = 0.86) and lipid arc (3.2° 95% CI (-23–29, p=0.81) were observed [53,54,56] (Fig. 6).

Although in general plaque phenotype in culprit lesions is not so different among men and women, stratification to age showed clear differences. Women with increasing age showed an increasing number of lipid rich plaques, TCFAs and plaques containing macrophages, cholesterol crystal and calcifications, while in men the frequency in plaque phenotypes was similar across all age categories [53].

Clinical events result from thrombus formation in the coronary arteries because of either plaque rupture (44%), plaque erosion (31%) or calcified nodule (8%) [57]. Optical coherence tomography can excellently distinguish the different etiologies of atherothrombosis [53,57]. Plaque erosion is observed in men and women in all age categories, but with the highest prevalence in the lowest age categories [58]. In young women, the percentage of cases observed with plaque erosion ranged from 36% to 74%, but this large range is most likely influenced by the low number of cases studied [53,58,59]. With increasing age, the underlying cause of coronary events in women shifted from plaque erosion to plaque rupture and calcified nodule in a small percentage of cases [53,58,59]. For young men, plaque erosion is observed in around 50–55% of the cases with a slightly lower frequency in plaque rupture (47%) [58,59]. Across the different age categories, the frequency in plaque rupture remained the same; plaque erosion decreased and calcified noduled increased with increasing age [53,58].

The question rises on whether women have other vulnerable plaque features that are most predictive for future cardiovascular events compared to men. Indeed, in women a minimum lumen area <3.5 mm^2 and the presence of macrophages was associated with clinical events after adjustment for risk factors. In men, a maximum lipid arc >180° was observed as a significant predictor. The vulnerable plaque features that men and women shared was fibrous cap thickness <75 μm and inflammatory content as characterized by macrophage arc >67° [53].

3.4. MRI/CT

In general clinical practice, magnetic resonance imaging of coronary arteries is not often performed because of the low resolution, problems with scanning planning and motion-related image degradation. With advances in MRI data acquisition and post-processing, interest is gaining in the assessment of coronary plaque composition next to lumen stenosis [60].

CT is an excellent imaging modality to identify the presence of calcium in coronary arteries. This is quantified as coronary calcium score (CAC) and has shown to have an excellent predictive power for long-term myocardial infarction risk [61]. In multiple studies, it has been demonstrated that women, compared to men, at similar ages with similar risk factors, have lower CAC scores [62–64] and are more likely to have a zero calcium score [64]. In women, the presence of any calcium has already a 1.3 times higher risk on cardiovascular events compared to men [65] and points to a need for female-specific CAC cut-off values to determine their event risk [66].

Coronary computed tomography angiography offers the possibility to assess a number of features of coronary artery plaque and high risk plaque features. Data from the SCOT-HEART, PARADIGM, ICONIC study demonstrated that coronary plaques in females are smaller in terms of length, volume and burden compared to men [67–69]. Women have approximately a 9-year delay in developing plaque compared to men [70]. Visual assessment of adverse plaque features proved that positive remodeling, low-attenuation plaque, spotty calcification, and napkin

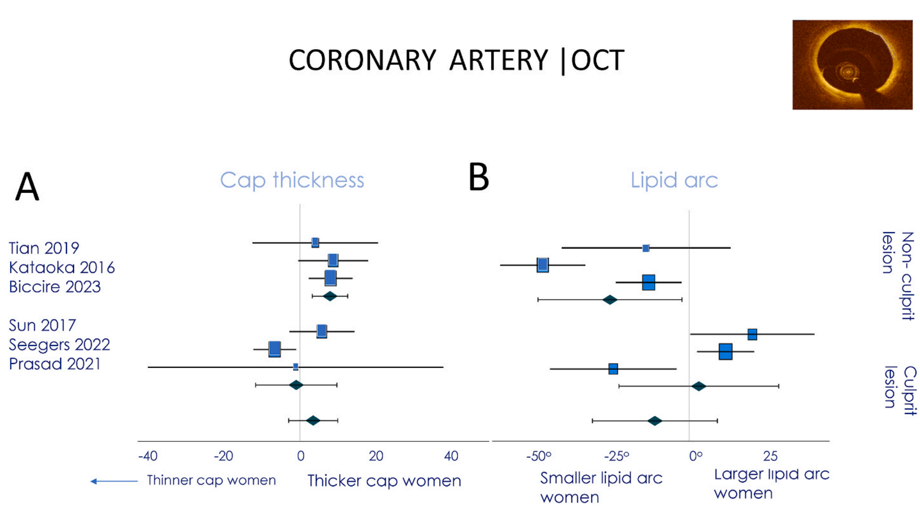

Fig. 6. Forest plot of meta-analysis on sex-related differences in cap thickness lipid arc based on OCT.
Forest plot of meta-analysis on the association between (A) sex and cap thickness and (B) sex and lipid arc in culprit (CL) and non culprit (NCL) lesions based on optical coherence tomography (OCT) [51–56].

ring sign are less or equally frequent in women compared to men [64,69, 70]. Women also show lower absolute volumes in fibrous, fibro-fatty, calcium and necrotic core, but after correction for plaque size, the plaque composition is much more similar to men with calcium relatively higher in women [69,71]. Interestingly, plaques from women and men who underwent myocardial infarction were similar in terms of plaque burden, area stenosis, plaque length, high risk plaque features, such as low attenuation and remodeling index, non-calcified plaque burden. However, the total calcified plaque burden was smaller in women compared to men [64,69], which reflects the general observation that women with lower CAC are at increased risk compared to men. In culprit lesions, no difference in plaque composition among men and women at different age categories was observed [69].

In general, the Progression of Atherosclerotic Plaque Determined by Computed tomographic Angiography Imaging (PARADIGM) Registry reported that the annual plaque progression rate in coronary arteries from women was slower compared to that in coronary arteries from men, which was mainly driven by the slower progression of non-calcified tissue, with no clear difference in calcium progression [70]. Women were also associated with less development of high risk plaque features, including low attenuation plaques and spotty calcification [70]. Once male and female patients were matched based on baseline plaque volume, no differences in total plaque progression rates were observed anymore, with females showing a higher calcium and a slower non-calcified tissue progression rate compared to men [70]. In a much smaller cohort, differences in non-calcified and fibrous progression rate were only observed in women younger than 55 compared to age-matched men [71].

3.5. *FLOW/SS*

Not much information is available on sex-related differences in flow, shear stress and shear-stress related plaque growth in human coronary arteries. In one study, data from the PREDICTION study were retrospectively stratified according to the sex of the patient resulting in 95 women and 384 men [44]. They reported that coronary flow and shear stress at plaque regions was similar in men and women. However, shear stress normalized to patient-specific flow was higher in women (1.50 ± 0.03 *vs.* 1.64 ± 0.07 Pa s/ml). Also, no differences in stress-related plaque burden growth were observed comparing coronary arteries from women and men ($\beta = -0.62 \pm 0.13$ *vs.* $\beta = -0.68 \pm 0.05$, $p = 0.62$). After stratification for age, differences in shear stress related plaque growth were apparent, with the largest difference for the lowest age category <55 years (F: $\beta = -2.02 \pm 0.61$ *vs.* M: $\beta = -0.33 \pm 0.10$; $p = 0.007$). Men showed hardly any change over time, whereas women showed a continuous change in magnitude of ESS-dependent plaque growth over the different age categories ($p < 0.001$). The clearest significant trend was the reduction in magnitude of ESS-related plaque growth (β) up till 75 years of age [44].

4. Discussion

Atherosclerosis is a multifactorial disease in which sex-hormones play an important role. In this review, plaque size and composition were compared for men and women in coronary or carotid arteries as assessed with various invasive and non-invasive imaging modalities. In both carotid and coronary arteries, sex-related differences are observed in the absolute morphology and atherosclerotic plaque size and composition. A large range in observations were described with differences more pronounced when stratified for age or clinical status. After normalization for body surface area or plaque size, differences in plaque composition mostly disappeared. Culprit lesions that are responsible for the cardiovascular events were more similar in men and women compared to non-culprit lesions. See Fig. 7 for an overview of the sex-related differences in atherosclerotic plaque morphology and composition.

Sex hormones are known to influence various pathways associated with atherosclerosis plaque initiation and progression mainly because of their involvement in endothelial function [72]. Estrogen is thought to protect the endothelium and thereby protect women from atherosclerotic plaque build up in the years before menopause. After menopause a sharp decline in estrogen concentration is observed and women are at a higher risk for cardiovascular disease development and at risk for cardiovascular events. Similarly in males, testosterone declines with age, with 30% over 50 years having low bioavailable testosterone [73]. Low testosterone to oestradiol ratio is a risk factor for vulnerable atherosclerotic plaque composition and outcome in men [74], highlighting the inter-relationship between sex, sex hormones, aging and changes in plaque biology that might predispose growth and development of a vulnerable plaque phenotype in both sexes. In that respect, imaging studies on specific patient groups with, for instance, polycystic ovary syndrome, who have much higher testosterone levels, might help

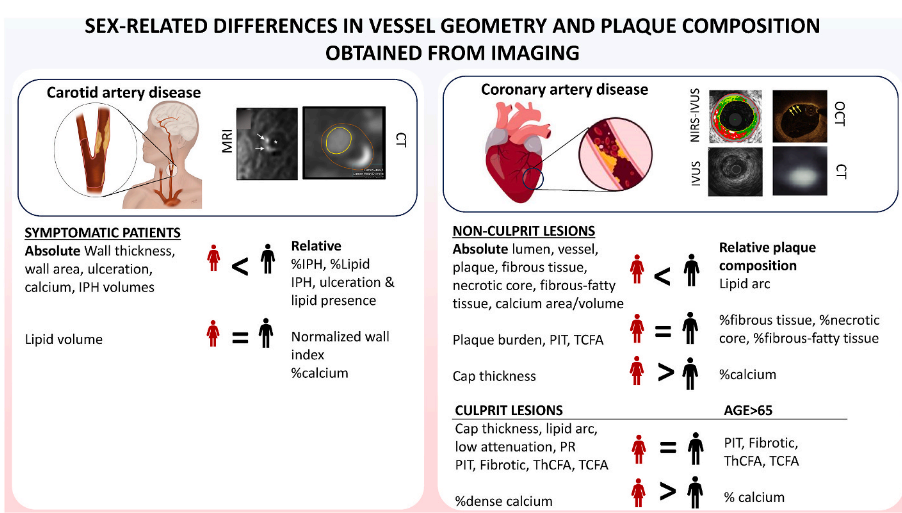

Fig. 7. Overview of sex-related differences in plaque size and composition in carotid and coronary arteries as obtained with imaging.
Overview of sex-related differences in plaque size and composition in carotid (left panel) and coronary arteries (right panel) as obtained with imaging including magnetic resonance imaging (MRI), near infrared spectroscopy-intravascular ultrasound (NIRS-IVUS), optical coherence tomography (OCT), intravascular ultrasound (IVUS); computed tomography (CT); IPH: intraplaque hemorrhage; PR: positive remodeling; PIT: pathological intima thickening; ThCFA: thickcap fibroatheroma; TCFA: thin cap fibro atheroma.

unravel the individual contribution of sex-hormones to plaque composition.

However, it is not clear whether the trajectory from disease free to an event-causing lesion is similar in men and women [70]. Interestingly, none of the studies on sex-related differences in plaque composition included the status of female patients (pre, peri or post-menopause) or the concentration of sex hormones to further investigate the underlying mechanisms. On top of that, most of the studies were of cross sectional nature, not allowing to study the complex interplay between sex-hormones, inflammation and plaque progression.

Furthermore, only papers that stratified the data based on sex were included in this review, ignoring the influence of social and cultural (gender-related) differences between men and women that may also influence the composition of atherosclerotic plaques.

OCT-imaging data on the prevalence of plaque erosion and plaque rupture in acute coronary syndrome patients demonstrated a high incidence of erosions also in younger men (50–55%), which in in contrast with data from histology of sudden death patients showing a much lower prevalence of plaque erosion compared to plaque rupture both in young (<50 years, 16.9% *vs.* 64.7%) and older men (>50 years, 16.9% *vs.* 76.6%) [75]. The prevalence of erosion in young women was even more pronounced in histology studies compared to OCT studies (77.1% *vs.* (35.7%–74%). Interestingly, in women, smoking was mostly associated with erosion [75]. The differences observed between OCT and pathology studies might be related to the patient presentation comparing acute coronary syndrome patients with sudden death patients. These data might suggest that male patients die less often from coronary plaque erosion compared to female patients.

Various imaging modalities were used to study differences in plaque composition among plaques in coronary and carotid arteries of men and women. Each imaging modality has its advantages and disadvantages with respect to spatial and temporal resolution, penetration depth, contrast of tissues. For that reason, studies using CT mostly focused on calcium that can be accurately identified with CT, IVUS studies included measures of vascular remodeling, MRI studies were assessing intraplaque hemorrhage, and OCT demonstrated differences in cap thickness and lipid angle. Thereby, some bias in reporting the different high risk plaque features might be related to the image modality and should be taken into consideration when interpreting the obtained data on sex-related differences. Molecular imaging to identify inflammation has been proven to have prognostic value both in coronary and carotid arteries. However, hardly any study up till now investigated differences in plaque phenotype among men and women.

Pathology in carotid arteries differs from coronary artery pathology with regard to the prevalence of different plaque components and characteristics of plaque vulnerability and thus the options to visualize and identify vulnerable lesions. Lesion components associated with vulnerability in the carotid artery include: fibrous cap thickness <165 μm, inflammatory macrophages, size of the necrotic core, and previous IPH [76]. Inflammation plays also a major role in plaque vulnerability in coronary arteries, but occupies only for 2–5% the lesion, making that plaque component less relevant for imaging. In coronary arteries, plaque burden, necrotic core and lumen size are associated with events [77] and are therefore more often used to identify plaques and patients at risk of cardiovascular events. These differences in the prevalence of plaque components, but also the size of the vessels, the location, pulsatile movement of coronary arteries opposed to carotid arteries make certain imaging modalities more suitable to identify sex-related differences in vulnerable plaque components in carotid arteries compared to coronary arteries.

Women are in general smaller in length and have a lower weight than men coming with smaller vessels, which results in a lower body surface area (BSA). To take these size differences into account, some studies used the BSA or the plaque size to account for these differences and normalized the data accordingly. Unfortunately not all studies used these normalizations so that studies are hard to compare and interpret.

Although plaques in coronary arteries of women are smaller, show less often lipids and have a thicker cap, plaques that resulted in a coronary events were very similar to men according to high risk features. This might indicate that mechanisms underlying coronary events are similar in men and women [78]. Further studies are needed to investigate the role of sex hormones independent from the plaque composition in the risk of cardiovascular events.

4.1. Conclusion

Based on (non)-invasive imaging techniques, plaques of men and women were evaluated and clear differences in plaque size and composition were reported that largely varied with age and clinical status. Although the differences in plaque composition are more clear in carotid arteries with less vulnerability in plaques observed for females compared to males, in coronary arteries less often high risk plaque features, including higher cap thickness and smaller necrotic core, were observed in non-culprit coronary plaques of females. However, culprit coronary lesions were more similar in men and women in terms of relative plaque composition. Interestingly, calcium score is lower in female patients compared to male patients that experience coronary cardiovascular events. This information might urge for new guidelines in clinical decision making.

Key point box 1

Future research | Open questions on sex-related differences in carotid artery plaque composition

- None of the studies included the hormonal status of the participants in the study or the concentrations of sex-hormones, which could help interpret the data
- Data are lacking on sex-related differences in carotid artery composition in culprit lesion *versus* non-culprit lesions
- Only few data are available on sex-related differences in carotid artery inflammation based on molecular imaging
- Although age is recognized as risk factor for cardiovascular disease, data are lacking on sex-related differences in carotid artery composition stratified for age
- Although sex is recognized as risk factor, data are lacking on sex-related differences in carotid artery plaque progression and changes in plaque composition over time

Key point box 2

Future research | Open questions on sex-related differences in coronary artery plaque composition

- None of the studies included the hormonal status of the participants in the study or the concentrations of sex-hormones, which could help interpret the data
- Data are lacking on sex-related differences in coronary artery inflammation based on molecular imaging
- Only few data are available on sex-related differences in coronary artery composition in culprit lesions
- Only few data are available on sex-related differences in coronary artery plaque progression and changes in plaque composition over time

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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