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Efficacy of the coronary computed tomography to improve cardiovascular risk stratification in postmenopausal women

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TABLE DES MATIERES

ABBREVIATIONS

ACE: angiotensin converting enzyme

APS: Anti-Phospholipid Syndrome

BMI: Body Mass Index

CAC: Coronary Artery Calcium

CAD: Coronary Artery Disease

CAD RADS: Coronary Artery Disease Reporting and Data System

CCT scan: Coronary Computed Tomography Scanner

CCTA: Coronary Computed Tomography Angiography

CNIL: National Commission for Information and Liberties

CVD: Cardio Vascular Disease

DBP: Diastolic Blood Pressure

ESC: European Society of Cardiology

HDL: High-Density Lipoprotein

HELLP: Hemolysis Elevated Liver Enzymes Low Platelet count

LDL: Low-Density Lipoprotein

MACE: Major Adverse Cardiovascular Events

MI: Myocardial Infarction

MHT: Menopausal Hormone Therapy

NASCET: The North American Symptomatic Carotid Endarterectomy Trial

SBP: Systolic Blood Pressure

SD: Standard Deviation

ABSTRACT

Introduction: Clinical assessment of cardiovascular risk in postmenopausal women is still challenging. The aim of this study is to evaluate the efficacy of the coronary computed tomography angiography to improve cardiovascular risk stratification in postmenopausal women.

Methods: We included postmenopausal unselected women who referred for a cardiovascular evaluation at Lille University Hospital, in primary or secondary CVD prevention, who underwent a CCTA, between January 1, 2013 and March 31, 2021. They were classified in three group according to the CADRADS.

Results: We included 151 postmenopausal women with a mean age of 58 years-old. According to ESC SCORE, 42% were at moderate risk, 46% at high risk, and 6% at very high risk of CVD. According to SCORE 2, 54% were at low risk, and 34% at moderate risk of CVD. A coronary artery atherosclerotic disease (CAD) was detected in 53% women, which was obstructive in 9% of cases. Women with a CAD were significantly more likely to have high CAC score, dyslipidaemia, a peripheral atherosclerosis and to be older. CCTA improved risk stratification and permitted to reclassify appropriately 23 % and 46% of our patients to a higher risk group compared to ESC and SCORE 2 scores respectively.

Conclusion: Our findings suggested that traditional methods underestimate CVD risk in postmenopausal women. CCTA might be a tool of choice to improve CVD risk and to guide primary prevention therapies in this population.

INTRODUCTION

Historically, atherosclerotic cardiovascular diseases (CVD) were more often reported in men compared to women, explaining why men were over-represented in CVD prevention clinical trials (1). However, over the past three decades, CAD became the first cause of death in women in France (2,3). An increased incidence of CVD has been specially observed in younger women. Indeed, in women under 65 years-old, hospitalization rates for myocardial infarction increased by 25.2% over the period 2002-2013 (4,5). This increased prevalence of CVD in women might be explained by a change in women's lifestyle and a lack of knowledge of the sex specificities risk factors for CVD, leading to disparities in care and often less aggressive treatment (1).

Hormonal changes throughout a woman's life cycle have a potential impact on their risk of CVD. Women produce oestrogen which may have cardio protective effects that could explain why women typically develop coronary artery disease (CAD) several years later than men (1,6). Peri menopause period is associated with huge changes in women which may notably enhanced the risk of CVD. Indeed, we observed a decrease in oestrogen levels during menopause that alters the lipid profile which becomes more atherogenic with increased levels of LDL-C and decrease levels in HDL-C (1). Menopause is also associated with an increase abdominal and visceral fat, increasing abdominal circumference which increased the cardiovascular risk.

Since the increase in CAD during menopause is associated with a decrease in the production of oestrogen, the benefit of menopausal hormonal therapy (MHT) to reduce CVD risk has been evaluated. Beside its effects on vasomotor symptoms,

favourable effects of MHT on CAD prevention were reported in previous cohorts and case controls studies. Meta-analyses of those observational studies reported a pooled estimated benefit of approximately 40% decrease in CAD in the early 2000s (7, 8, 9). Those data were later challenged by the publication of randomized trials: HERS in secondary prevention (10) and WHI in primary prevention (11). Along with the significant drop in prescription of MHT, these studies showed an increased in CVD risk for two types of MHT, particularly in the first year of use. It became of major importance to properly screen menopausal women for, even minimal, CAD before the introduction of any MHT.

It is now well-established that traditional CAD risk stratification tools are not accurate for risk stratification in women. Thus, it has been previously demonstrated that the American score Framingham underestimated the real risk of CAD in women (3,12). In a study including 2500 women, (mean age 55 years-old), 90% of women were classified at “low risk”, but 84% of them had significant coronary calcifications (13). Several parameters might explain this underestimation of the women CVD risk by those scores. First, inception and validation cohorts were composed by a predominance of male participants; second those scores did not take into account the reproductive history of women, which is of importance to estimate their CVD risk. Those sex specific risk factors include, pre-eclampsia, pregnancy hypertension, gestational diabetes and premature menopause (3,14,15,16). Among them, pre-eclampsia and HELLP syndrome confers the highest for CVD risk (17). In addition to a 4-fold increased risk of subsequent hypertension, preeclampsia 2-fold increased the risk of developing CAD over the 5 to 15 years after pregnancy (16,17). Moreover, symptoms of CAD are often atypical in women and may be misleading. Thus, diagnosis and prevention of CAD in women is challenging and classical tools

insufficiently predict CVD risk in women, whereas an appropriate stratification of women might allow to identify those who would most benefit from aggressive management o CVD risk to reduce the CAD burden in the future.

The coronary computed tomography scanner (CCT scan) is now established as the first-line non-invasive diagnostic imaging in the initial assessment of patient at low to intermediate risk of CVD. The coronary artery calcium (CAC) allows quantification of the coronary calcium load, an indirect reflection of atherosclerosis and have a high sensitivity for the detection of CAD. The negative predictive value of CAC was close to 100%: in case of a CAC of 0, diagnosis of CAD can be ruled out (18, 19, 20). The South Bay Heart Watch study showed that the CAC score allowed a better stratification of intermediate risk subjects compared to the Framingham score (18, 21). Non-obstructive CAD is twice as common in women, whereas men tend to have an obstructive form of the disease (17). In women, in case of a positive CAC score, the risk of cardiovascular mortality is 1.3 times higher than in men (22).

However, hypodense lipido-necrotic plaques are undetectable without contrast product injection, whereas those plaques are more likely to cause an acute coronary event. Calcified plaques are more stable and less at risk of an acute event. The coronary tomography angiography (CCTA), thanks to an injection of contrast product, makes it possible to detect all the plaques, calcified or not and quantify the eventual degree of stenosis which can be a powerful screening tool. The CCTA can visualize three aspects of CAD: coronary artery stenosis, coronary artery plaque formation (presence, calcifications, volume), and markers of instability such as expansive vascular remodelling, spotty calcifications, atheroma size. Two randomized trials have analysed the ability of CCTA to diagnose stable CAD. In the SCOT – HEART

and PROMISE trials, the CCTA resulted in a higher rate of detection of CAD than standard care (SCOT HEART) or functional testing (PROMISE trial) (23,24). Accuracy of CCTA for CVD risk stratification has been evaluated in several clinical settings, such as before surgery, in patient with diabetes, renal disease, chronic non obstructive CAD or smoker (25). To our knowledge, the ability of CCTA findings to enhance risk stratification of CVD in post-menopausal women has not been yet studied.

The aim of our study was to describe frequency of asymptomatic coronary atherosclerotic lesions in a cohort of post-menopausal women, and to evaluate the interest of CCTA findings to improve CVD risk assessment in postmenopausal women.

METHODS

Study design and population

This study was an epidemiological, observational, monocentric, transversal study of all unselected menopausal women followed in outpatient care or hospitalized at Lille University Hospital for a cardiovascular assessment at menopause, between January 1st, 2013, and March 31th, 2021.

Since 2013, a clinical care pathway has been created - “heart, arteries and women”- at Lille University Hospital. The objective was to improve the women’s care and the coordination between the different specialties. Women were addressed by gynaecologist, cardiologist or by their general practitioner.

Inclusion criteria of this study were: i) all consecutive menopausal women ii) who referred for a cardiovascular evaluation of menopause in our center, iii) in primary or secondary CVD prevention, iiii) who underwent a CCTA.

Data and samples collection

Data studied were collected retrospectively from electronic medical records by using the Sillage software. Medical history data were collected by the cardiologist at the day of hospitalization or consultation.

For each patient, cardiovascular risk factors were collected: age, arterial hypertension, treated or not, defined by systolic blood pressure higher than 140mmHg and/or diastolic blood higher greater than 90mmHg; diabetes defined by fasting blood sugar above 1.26g/L twice and/or glycated haemoglobin above 7%; smoking defined as active or quit smoking for less than three years; dyslipidaemia defined according to the ESC by a total cholesterol higher than 1,9g/L and/or HDL cholesterol lower than 0,45g/L and/or LDL cholesterol higher than 1,15g/L and/or triglycerides higher than 1,5g/L; sleep apnea syndrome defined by apnea/hypopnea index higher than five confirmed by polysomnography; systemic or inflammatory disease like anti-phospholipid syndrome (APS), systemic sclerosis, rheumatoid arthritis, systemic lupus erythromatosus, ankylosing spondylitis and cryoglobulinemia; cardiovascular heredity defined by CAD, stroke or sudden death in a first degree relative under 55 years old in male and under 65 years old in female; BMI and abdominal circumference has been measured

Gyneco-obstetric history were recorded: age of menopause defined by the amenorrhea more than 1 year or a history of hysterectomy with oophorectomy; menopausal vasomotor symptoms (hit flashes, night sweats …), early menopause

defined by age of menopause before 45 years old, gestational diabetes defined by diabetes beginning or diagnosed during pregnancy, and vascular placental insufficiency which reunited pregnancy-induced hypertension, pre-eclampsia and HELLP syndrome; time since menopause was the time between the year of menopause and the year of performing the CCT scan.

Women's cardiovascular risk was stratified according to ESC score which classified women into four groups (low risk, moderate, high, and very high risk) and according to SCORE 2 risk who estimate the cardiovascular risk at 10 years (26, 27)

Cardiovascular treatment (platelet aggregation inhibitor, anticoagulant, statin, ACE inhibitor, angiotensin II receptor antagonists, beta-blocker, thiazide diuretics, spironolactone, calcium channel blockers, alpha blocker, central antihypertensive) and MHT were reported.

Complementary examinations were carried out in hospital or in outpatient care. Blood samples were obtained by venous punction at the entrance for hospitalized women and in town for women in outpatient care, including: complete lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides), fasting blood glucose, glycated haemoglobin, serum creatinine. The 24-hour blood pressure measurement was carried out using an electronic blood pressure monitor (Ultralite – Spacelabs healthcare 90217A) during hospitalization or before the consultation. Ultrasound of the supra-aortic trunks and the arteries of the legs looked for the presence of peripheral atherosclerosis. A significant stenosis on the supra-aortic trunks were defined by a stenosis higher than 50% with the NASCET method. And for the legs, a significant stenosis was defined by a stenosis higher than 50% hemodynamically. we have grouped the presence of plaque, non-significant stenosis, and significant

stenosis on the ultrasound of the supra-aortic trunks and the legs to form the category of peripheral atherosclerosis.

CCTA imaging

CCTA were performed at the university hospital of Lille (SOMATON definition flash, Siemens 2014). Only two were performed in another center. Patients received a premedication, if the heart rate > 65bpm, with 2 breaths of nitro derivatives (Natispray) and intravenous betablockers (5mg atenolol). Images were obtained by helical acquisition on the cardiac mass at arterial time with prospective cardiac synchronization. The coronary artery calcium score was measured using the scoring system (in units) described by Agatston et al (28). Epicardial coronary calcifications are considered if ≥ 3 pixels and ≥ 130 HU. With injection of iodinated contrast, the CT angiographic examination was performed, and the CAD RADS were obtained. Thereafter, women were classified into three groups according to the Coronary Artery Disease Reporting and Data System (CAD-RADS) (29):

- Group 1: CADRADS 0= absence of CAD
- Group 2: CADRADS 1-2= non-obstructive CAD
    - CADRADS 1: 1%-24% of stenosis, minimal stenosis, or plaque without stenosis
    - CADRADS 2: 25%-49% of stenosis
- Group 3: CADRADS ⩾ 3 = obstructive CAD
    - CADRADS 3: 50%-69% of stenosis
    - CADRADS 4A: one or two vessels, 70-99% of stenosis

- CADRADS 4B: Left main artery > 50% or three vessels ⩾ 70%
- CADRADS 5: total occlusion

Statistical analysis

First, descriptive analysis was performed. For numerical parameters, the normality of the distribution was assessed using the Shapiro-Wilk test. In case of normality, the parameter was reported as mean ± standard deviation (SD), by the median and quartile otherwise.

Comparisons of the 3 subgroups were then performed. Groups were compared with non-parametric tests: Chi squared test or Fischer exact test was used for qualitative variables and Kruskal-Wallis test for quantitative variables.

All statistical analyses were performed using SAS Software (Cary NC, USA), V 9.4. A p value < 0.05 was considered as statistically significant.

Ethical standards

A declaration of the data file was made to the National Commission for Information and Liberties (CNIL) in February 2015 and accepted under the reference DEC2015-9.

All patients were receiving writing information about the use of their medical data collected during consultation, hospitalisation, and complementary examinations for research purpose. None of them objected to the use of their medical data. Moreover, each consultation or hospitalisation letter contained the following quote: "Your medical data collected during the consultation or hospitalisation may be used anonymously, unless you object, for medical research purposes. In this context, they

may be transmitted to other research organisations, in accordance with the "Data Protection Act" of 6 January 1978 as amended. You can obtain this data by contacting the secretariat corresponding to your place of consultation or hospitalisation". Writing informed consent were not required by French law for non-interventional clinical studies.

RESULTS

Baseline characteristics of the study population

Study population

Between January 1st,2013 and March 31th, 2021, 903 women were followed in our clinical care pathway “heart, arteries and women”. Among these patients 156 underwent a CCT scan. Four were excluded because they were not menopausal. Overall, 151 women were included in our study (*figure 1*). Two CCT scan were not injected, and the main data (CADRADS) was missing in the reports for three patients.

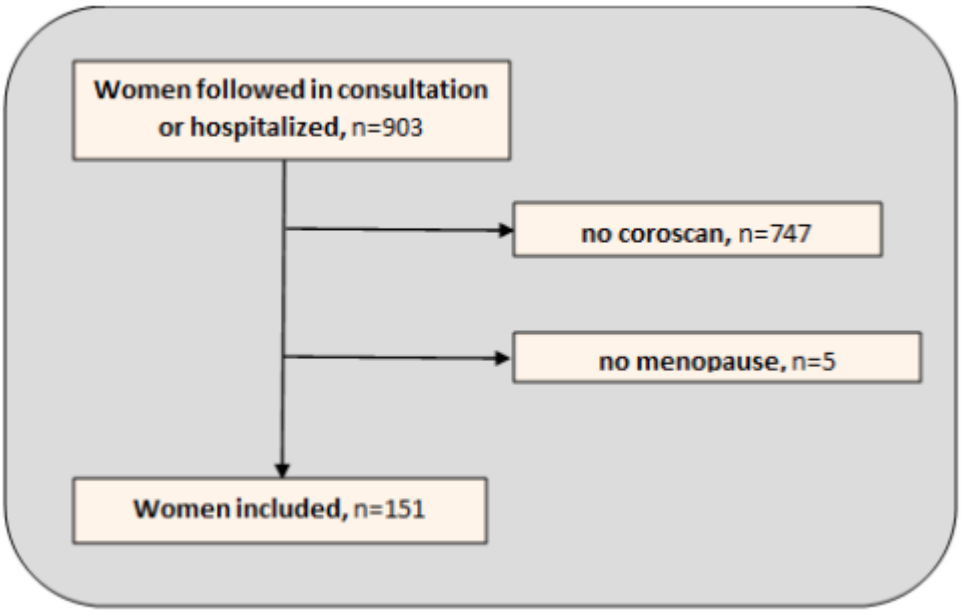

Figure 1. Flow chart of the study population

Demographical and clinical characteristics of the study population

Main characteristics of the study population were described in *table 1.* Mean age of the patient was 58,0 (± 6,77) years.

The median age of menopause was 51 [49-51] years, 5 had history of premature menopause, and median duration of menopause was 6 years [2-13] at inclusion. Eighty-nine (63%) patients had vasomotor symptoms. Forty-one (27%) were treated by MHT (17 in group 2 and 2 in group 3).

Table 1: Demographical and clinical characteristics of the study population

Characteristics	**Over all (n = 151)**	**Group 1 (n=66)**	**Group 2 (n=67)**	**Group 3 (n=13)**	**P value**
Age (Years), mean (± SD)	58 (± 6,7)	56 (± 5,8)	60 (±6,8)	60 (±7,7)	0,0012
CVD risk factors					
HBP, n (%)	93 (61%)	31 (47%)	47 (70%)	10 (77%)	0.0105
Daytime SBP (mmHg), mean (SD)	125(±12)	124 (±13)	126 (±11)	127 (±10	0,7343
Daytime DBP (mmHg), median [Q1-Q3]	77 [72-81]	77 [72-82]	77 [72-81]	77 [70-80]	0,7092
Night-time SBP (mmHg), median [Q1-Q3]	107 [99-115]	106 [98-115]	108 [102-114]	104 [99-115]	0,6412
Night-time DBP (mmHg), median [Q1-Q3]	63 [59-70]	63 [59-69]	64 [60-70]	62 [57-68]	0,8713
Diabetes, n (%)	21 (14%)	6 (9%)	13 (19%)	2 (15%)	0.2366
Current smoker, n (%)	44 (29%)	20 (30%)	22 (33%)	2 (15%)	0.4547
Dyslipidemia, n (%)	98 (66%)	36 (54%)	46 (72%)	13 (100%)	0.0030
total cholesterol, median [Q1-Q3]	2,15 [1,88-2,43]				
HDL cholesterol, median [Q1-Q3]	0,60 [0,5-0,71]	0,62 [0,53-0,79]	0,55 [0,48-0,69]	0,58 [0,52-0,62]	0,0858
LDL cholesterol, median [Q1-Q3]	1,32 [1,05-1,58]	1,28 [1,08-1,60]	1,38 [1,03-1,56]	1,42 [0,91-1,72]	0,9106
BMI, median [Q1-Q3]	25,7 [22,9-29,4]	24,9 [22,5-28,3]	26,7 [22,9-30,8]	26,6 [25,2-28,9]	0,4515
Obstetrics and gynecology history					
Age of menopause, median [Q1-Q3]	51 [49-53]	51 [48-53]	50,5 [50-60]	52 [50-54]	0,8146
Time since menopause, median [Q1-Q3]	6 [2-13]	4 [2-9]	8 [4-15]	4 [2-17]	0,0207
MHT, n (%)	41 (27%)	20(30%)	17 (25%)	2 (15%)	0.5096
Climteric syndrome, n (%)	89 (63%)	51 (81%)	29 (47%)	6 (50%)	0.0004
Vascular placental insufficiency, n (%)	21 (14%)	6 (9%)	12 (18%)	3 (23%)	0.2258
Gestational	11 (7%)	5 (7%)	4 (6%)	1(7%)	0,927

diabetes, n (%)					
Complementary examination					
CAC Score, median [Q1-Q3]	0 [0-39]	0 [0-0]	20 [1,5-51,7]	185 [96-381]	< 0,0001
Percentile, median [Q1-Q3]	0 [0-81]	0 [0-0]	74 [53-86]	92 [85-99]	< 0,0001
peripheral atherosclerosis, n (%)	45 (30%)	9 (14%)	24 (36%)	9(69%)	< 0,0001
Treatment, n (%)					
Platelet aggregation inhibitor	26 (17%)	8 (12%)	12 (18%)	3 (23%)	0.4925
ACE inhibitor	15 (10%)	7 (11%)	8 (12%)	0 (0%)	0.4282
Angiotensin II receptor antagonists	31 (20%)	6 (9%)	20 (30%)	5 (38%)	0.0039
Beta-blocker	27 (18%)	7 (11%)	14 (21%)	4 (31%)	0.1134
Statin	50 (33%)	15 (23%)	24 (36%)	8 (61%)	0.0162
Thiazide diuretics	19 (13%)	4 (6%)	11 (16%)	2 (15%)	0.1701
Spironolactone	22 (15%)	9 (14%)	7 (10%)	4 (31%)	0.1510
Anticoagulant	1 (0,66%)	0 (0%)	1 (1,5%)	0 (0%)	0.5521
Calcium channel blockers	30 (20%)	7 (11%)	18 (27%)	4(31%)	0.04
Risk score, n (%)					
ESC SCORE					0,0164
Very high risk	9 (6%)	1 (1,5%)	5 (8%)	1 (8%)	
High risk	68 (46%)	23 (35%)	38 (58%)	5 (42%)	
Moderate risk	72 (48%)	42 (64%)	23 (35%)	6 (50%)	
SCORE 2					< 0,0001
Low risk	83 (54%)	46 (82%)	30 (51%)	7 (70%)	
Moderate risk	42 (34%)	10 (18%)	29 (49%)	3 (30%)	

P value < 0.005, Chi squared test or Fischer exact test for qualitative variables and Kruskal-Wallis test for quantitative variables.

ACE= angiotensin converting enzyme, BMI= Body Mass Index, CAC= Coronary Artery Calcium, ESC= European Society of Cardiology, SBP= Systolic Blood Pressure, MHT= Menopausal Hormone Therapy, DBP= Diastolic Blood Pressure, SD= Standard Deviation, HDL= High-Density Lipoprotein, LDL= Low-Density Lipoprotein

Regarding obstetrical history, 21 (14%) had history of vascular placental insufficiency (8 (5%) pre-eclempsia, 15 (9%) gestational hypertension and no HELLP syndrome), and 11 (7%) had history of gestational diabetes.

CVD risk factors were distributed as follow: 93 (61%) had history of hypertension, 98 (66%) of dyslipidaemia, 21 (14%) of diabetes, and 44 (29%) were current smoker or former smoker for less than 3 years. Twenty-seven (19%) had familial history of premature CVD. Height women were in secondary prevention (2 had a CAD and a history of stroke and 6 had a history of stroke or transient ischemic attack only). Median level of total cholesterol was 2,15 g/L [1,88-2,43], and median level of LDL cholesterol was 1,32g/L [1,05-1,58]. The median BMI of our population was above the normal range at 25,7kg/m2 [22,9-29,4].

CVD risk assessment using clinical scores

According to ESC SCORE, none of the women were classified at low risk, 72 (42%) at moderate risk, 68 (46%) at high risk and 9 (6%) at very high risk of CVD.

According to SCORE 2 risk, 83 (54%) women were classified at low risk, 42 (34%) at moderate risk, and only was at high-risk.

CCTA findings

Overall, 66 (45%) women had no atherosclerotic lesions on CCTA (Group 1), 67 (46%) women had non-obstructive atherosclerotic lesion (group 2), and 13 (9%) had significant atherosclerotic lesions (group 3).

Among the 8 patients in secondary prevention, one was in group 1, 4 were in group 2 and 1 was in group 3. We did not have CADRADS for 2 patients.

Median CAC score was 0 [0-39]: median CAC score was 0, 20, 185 respectively in groups 1,2 and 3 (*figure 2*). Nine (6%) women had a non-significant CAD (group 2) with a CAC at 0. None had significant stenosis (group 3) and a CAC score of 0.

Among 73 women with CAC score at 0, 64 (87,7%) were in group 1, 9 (12,3%) were in the group 2 and no in group 3. Among the 46 patients with a low CAC score (CAC 1-100), 9% were in group 3.

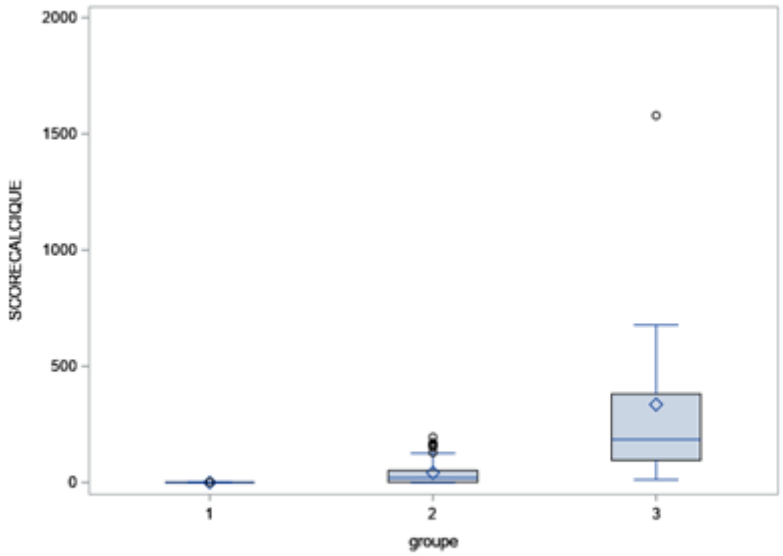

Figure 2. Distribution of CAC score by group

Factor associated with CCTA findings

Patients in group 1 were more likely to have climacteric syndrome compared to patients in group 2 and 3. The difference was significant (81% versus 47%, and 50%) (*p=0.0004*)

Patients in group 3 were more likely to have a higher CAC score (0 versus 20, and versus 185, p < 0,0001), a dyslipidaemia (54% versus 72%, and 100%, p=0,003), a peripheral atherosclerosis (14% versus 36%, and 69%, p<0,001) and to be treated

with angiotensin II receptor antagonist (9% versus 30%, and 38% p=0,0039) compared to others. They were also older in group 2 and 3 than in group 1 (60 years in both group 2 and 3 versus 56 in group 1, p=0,0012). These differences were significant. Other factors such as diabetes, hypertension, vascular placental insufficiency and gestational diabetes tended to be more common in groups 2 and 3 without significant differences. There was no difference in LDL cholesterol between the groups (*figure 3*).

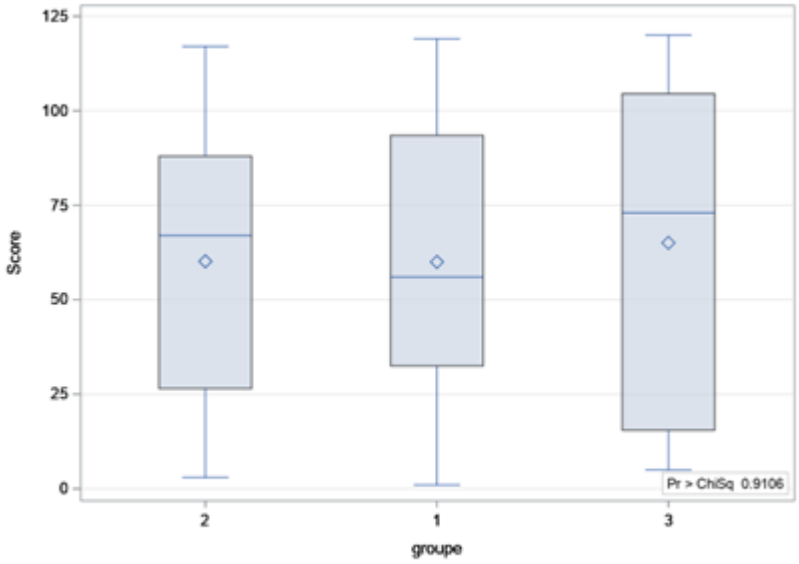

Figure 3. Distribution of LDL cholesterol (g/L) by group

Reclassification based on ESC score

Among the 72 patients classify at moderate according to ESC score, 23 (32%) had non-obstructive CAD (group2) and 6 (8%) had obstructive CAD (group 3) and were reclassify at high risk of CVD. Among the 68 patients classify at high risk according to ESC score, 5 (7%) had obstructive CAD (group 3) and were reclassify at very high risk of CVD.

Overall, CCTA assessment allowed to reclassify 34 (23%) women, in whom CVD risk was underestimated by clinical score calculation.

Reclassification based on SCORE 2

Among the 83 patients classify at low according to SCORE 2, 30 (36%) had non-obstructive CAD (group2) and 7 (8%) had obstructive CAD (group 3), and were reclassify at higher risk of CVD. Among the 42 patients classify at moderate, 29 (69%) had non-obstructive CAD (group2) and 3 (7%) had obstructive CAD (group 3).

Overall, CCTA assessment allowed to reclassify 69 (46%) women, in whom CVD risk was underestimated by clinical score calculation.

Other imaging assessments

Peripheral atherosclerosis was found in 30% (n=45), two patients had significant stenosis in the supra-aortic trunks, one with significant coronary stenosis. In comparison with the group 1, peripheral atherosclerosis was strongly more significant in group 2 and 3 ($p<0.0001$) (*Table 1*).

Only six patients had a positive trans thoracic stress echocardiography and none of them were in group 3.

DISCUSSION

An asymptomatic CAD was detected by CCTA in more than half (53%) of our postmenopausal women, which was obstructive in 9% of cases. Women with a CAD were significantly more likely to have high CAC score, dyslipidaemia, a peripheral atherosclerosis and to be older. Detection of CAD by CCTA improved risk

stratification and permitted to reclassify appropriately 23 % and 46% of our patients to a higher risk compared to ESC and SCORE 2 scores respectively.

The baseline characteristics of our patients were similar to that previously reported by studies which enrolled postmenopausal women. Indeed, frequencies of CVD risk factors were consistent with the evolution of CVD risk factors' repartition in women described those last years with two thirds of hypertensive patients and about 30% of smokers (3,30). The rates of pre-eclampsia and gestational hypertension were also similar to the general population (5-10% gestational hypertension and 3-7% pre-eclampsia). The average age of onset of menopause in our study was consistent with findings from the Study of Women's Health Across the Nation (SWAN) which estimated onset of natural menopause at a median age of 51.4 year (31).

Previous data on the prevalence of coronary atherosclerosis in the post-menopausal women are rare. The prevalence of CAD (53%) in our population was similar than reported in previous study. Waqas and al. found a plaque prevalence of 51,6% in women (32). The CCTA allowed the detection of obstructive CAD in 9% of women who could benefit from additional coronary angiography, but it also allowed the detection of non-obstructive CAD in 46% of cases. For women, the detection of atherosclerotic plaque, even nonobstructive CAD, is critical for risk stratification (33,34). From CONFIRM registry, there was an association between increase major adverse cardiovascular events (MACE) risk and nonobstructive CAD among 2,056 women ($p < 0.001$) (33,34). We know from the PROMISE trial that, at 2 years follow-up, high-risk atherosclerotic plaque was a stronger predictor of MACE in women with

a four-fold higher risk of MACE for women with versus without high-risk atherosclerotic plaque (36).

The CAC score correlated significantly with the degree of stenosis, as women in group 3 had a significantly higher CAC score compared to group 1 and 2, with a median CAC at 185 [96-381] (*figure 2*). This is consistent with previous observations in general population (36, 37). However, we found discrepancies between CCTA and CAC score findings. Indeed, among the 46 patients with a low CAC score (CAC 1-100), 9% had an obstructive CAD. Noncalcified plaques have been suggested as a sign of more vulnerable form of coronary atherosclerosis prone to cause events. Whereas the prevalence of participants with only noncalcified plaques was low (6%) in our study, women are more likely to have non-calcified plaques than men (32). This finding supported the fact that CCTA and CAC score provided complementary data on coronary atherosclerosis.

We reported an association between the presence of peripheral atherosclerosis and both non-obstructive and obstructive CAD on CCTA, which highlighted the systemic feature of atherosclerosis.

In our study, the degree of stenosis was associated with classical CVD risk factors such as age and dyslipidaemia. However, we did not find an association with the sex specific risk factors such as history of gestational diabetes, placental vascular insufficiency, and early menopause. This might be due to the small number of patients with those characteristics. In our study, patients without CAD on CCTA had a higher frequency of climacteric syndrome. Our findings are conflicting with previous studies that showed an increased CVD risk in patients with vasomotor symptoms

(38). In addition, the type of menopause might also have an influence on CVD risk, e.g., bilateral oophorectomy increases the risk compared to natural menopause.

In our study, the use of MTH was not associated with the presence of an asymptomatic CAD on CCTA. Among 41 women under MHT, 2 (5%) were classified in group 3. In daily practice, based on professional experience and previous studies, we do not introduce or continue a MHT in case of CADSRADS higher than 3. Previous randomised trials that found a higher CVD risk with MHT involved the combination of two oral therapies, one of which was an oestrogen whenever the mode of administration, whereas it may have an impact on CAD. The use of transdermal oestrogen therapy and an oral progestin did not show an increased risk. (3).

Others non-conventional CVD risk factors might influence CVD risk in women, such as depression and autoimmune diseases (e.g. lupus, rheumatoid arthritis) (39) Due to lack of data, we did not analyse this factor that need to be analysed in larger scale studies.

Thanks to CCTA, 23% of post-menopausal women could be reclassified as being at higher cardiovascular of CVD risk according to ESC score and 46% according to SCORE 2 and in particular women at moderate risk for whom CCTA has the greatest benefit. This highlights that ESC score underestimates the CVD risk of menopausal women less than the SCORE 2. Our findings also confirmed that CVD risk stratification by using only clinical risk score systems is not completely satisfactory in postmenopausal women. Accuracy of CAC score to reclassified women has been previously evaluated. The utility of CCTA has also been evaluated in diabetics. The absence of CAD on CCTA allowed to safely exclude future events

and on the other side the presence of CAD allowed to identify high-risk patients who required aggressive risk factor modification (40). Similar findings were reported in the PROMISE study. CCTA improved risk stratification in patients with stable chest pain and stable chest pain and non-obstructive CAD ref. Anoop N Koshy *and al.* showed that CCTA conferred incremental risk for perioperative of MACE in patients undergoing non-cardiac surgery (41).

Daniel Matos *and al.* showed that the inclusion of CAC scoring in the MESA score resulted in the reclassification of 46% patients on a population of 467 consecutive patients undergoing CCTA for suspected obstructive CAD in Portugal of which 53% were women (42). Women with CAC score of 0 had a lower 15-year mortality of 5% compared to 23.5% for women with CAC score ≥ 400. Thus, CAC was effective in identifying high-risk women who were otherwise deemed as low-intermediate risk by Framingham risk score (43). But our study shows that using the CAC score alone does not identify all high or very high-risk women who may benefit from more aggressive therapy. To our knowledge, we reported here for the first time the accuracy of CCTA findings to reclassify CVD risk of postmenopausal women. In addition to clinical information, CCTA might be helpful to select patient who may benefit for targeted aggressive prevention strategies.

Maybe due to the underestimation of the CVD risk by clinical scores, women in group 3 were not significantly more treated to control their CVD risk factors compare to women in group 1 or 2, and their mean LDL cholesterol level did not differ from group 1 or 2 (*figure 3*). Moreover, the mean LDL-c level was above the LDL-c target level according to 2019 ESC/EAS guidelines for the management of dyslipidemia (44). Those findings support the observation already made that women are often

insufficiently treated and receiving less aggressive therapies compared to men (1), especially regarding statins and anti-platelet therapies (45). A better assessment of CVD risk by the CCTA might help to identify those patients and to improve primary prevention. Others factors might include ignorance of clinicians due to more frustrating symptoms, which are often confused with menopausal symptoms. WISE study concluded that the typical angina classification missed 65% of women who actually had CAD (46). Women are also less adherent to statins and have more side effects (45). However, the benefit of statin therapy to prevent CAD was strongly demonstrated. The interest of the use of statins has already been demonstrated in the JUPITER study which highlighted a 44% reduction in cumulative events (47). Furthermore, a large meta-analysis of 22 statin treatment trials with >174 000 participants (27% women) showed that statin treatment has similar efficacy in preventing primary and secondary major cardiovascular events and cardiovascular disease mortality in women and men (48). Menopause is the ideal window for the implementation of preventive measures. Given the health and economic implications of cardiovascular disease, it is necessary to continue efforts to control risk factors and to move towards a preventive approach to management. A CAC score > 100 Agatson units or a CAC score that is > 75th percentile, when adjusted for age and gender, has been suggested by the 2018 ACC/AHA lipid guidelines as a threshold for initiating statin therapy but using the CCT alone would not identify all women who might be eligible for lipid-lowering therapy. Among randomized controlled imaging-guided trials, CCTA has been consistently associated with reduced MI in both acute and stable chest pain populations. This is due to changes in preventive therapies, such as aspirin and statins, made possible by the CCTA (49). In SCOT-HEART study (23), patients who underwent CCTA had a fourfold increase in the use of aspirin or

statin therapy. Early treatment of these women is a real public health issue, as women have a poorer prognosis and more serious outcomes than men after myocardial infarction (MI), percutaneous coronary intervention and coronary artery bypass surgery. In Framingham heart study the one-year mortality following an MI was 44% in women versus 27% in men (50).

Limitations and strength

Our study has several limitations. First, its monocentric design in a tertiary care center might limit extrapolation to the whole population of menopausal women. Women who referred to our clinical care pathway were at high socio-economic level and were mainly active women in their health inducing a potential recruitment bias. Second, the relatively small sample size of our study might underpower the statistical analysis for some parameters, such as analysis of sex specific risk factors. Finally, data were analysed retrospectively. However, data derived from data collected prospectively. Our study had also strengths, to our knowledge this is the first study which reported CCTA findings in postmenopausal women . Moreover, the reading of the CCTA was centralized and well-standardised with a clear report and a classification by the CADRADS who is a standardized findings communication method and clinical decision aid.

CONCLUSION

In conclusion, CCTA assessment showed an asymptomatic CAD in 53% post-menopausal women, which was obstructive in 9% of cases. The mains risk factors associated with the presence of asymptomatic CAD were age, concomitant peripheral atherosclerosis, a higher CAC score, and dyslipidaemia. CCTA allowed to optimise CVD risk stratification in about 23% and 46% of cases according to ESC

score and to SCORE 2 respectively, that highlighted the underestimation of CVD risk in menopausal women by only traditional methods. CCTA might be a tool of choice to guide primary prevention therapies in this population. Further studies are needed to evaluate prognostic value of CCTA findings in postmenopausal women, interest of CCTA follow-up, and effect of treatment modifications after CCTA assessment on future CVD events. Moreover, menopause is the ideal window for the implementation of preventive measures. Given the health and economic implications of cardiovascular disease, it is necessary to continue efforts to control risk factors and to move towards a preventive approach to management.

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Date de soutenance: 30 Septembre 2022

Titre de la thèse: Efficacy of the coronary computed tomography angiography to improve cardiovascular risk stratification in post-menopausal women.

Thèse - Médecine – Lille 2022

Cadre de classement : *cardiologie et médecine vasculaire*

DES + FST/option : *Médecine Vasculaire*

Mots-clés : *cardiovascular risk stratification, menopause women, prevention, CCTA*

Résumé :

Introduction: Clinical assessment of cardiovascular risk in middle aged women is still challenging. The aim of this study is to evaluate the efficacy of the coronary computed tomography angiography to improve cardiovascular risk stratification in postmenopausal women.

Methods: We included postmenopausal unselected women who referred for a cardiovascular evaluation of menopause at Lille University Hospital, in primary or secondary CVD prevention, who underwent a CCTA, between January 1, 2013 and March 31, 2021. They were classified in three group according to the CADRADS.

Results: Population included 151 postmenopausal women with a mean age of 58 years. According to ESC SCORE 42% were at moderate risk, 46% at high risk and 6% at very high risk of CVD. According to SCORE 2 risk 54% were as low risk, 34% at moderate risk. An CAD was detected in 53% women which was obstructive in 9% of cases. Women with a CAD were significantly more likely to have high CAC score, dyslipidaemia, a peripheral atherosclerosis and to be older. CCTA improved risk stratification and permitted to reclassify appropriately 23 % and 46% of our patients to a higher risk compared to ESC and SCORE 2 scores respectively.

Conclusion: Traditional methods underestimate CVD risk in menopausal women. CCTA might be a tool of choice to improve CVD risk and to guide primary prevention therapies in this population.

Composition du Jury :

Président : Pr Claire MOUNIER VEHIER

Assesseurs : Pr François PONTANA, Dr Guillaume LEDIEU

Directeur de thèse : Dr Cécile YELNIK