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Original article

In postmenopausal women, lower limb peripheral arterial disease, assessed by ankle-brachial index, may be a strong predictor of cardiovascular risk

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ABSTRACT

Background: Lower limb peripheral arterial disease (PAD) is a leading atherosclerotic disease in the elderly. However, awareness of the disease is poor, particularly in women.

Methods: In this retrospective, cross-sectional study, postmenopausal women referred to our Angiology Division were tested for PAD, defined as an "ankle-brachial index" (ABI) ≤0.9 or ≥1.4 (in the latter case with a "toe-brachial index" <0.7), or a history of lower limb arterial revascularization. Aim of our study was to assess cardiovascular (CV) risk profile in postmenopausal women with and without PAD, and to evaluate the role of PAD and six classic CV risk factors (CVRFs), namely age, current smoking, hypertension, dyslipidaemia, severe chronic renal failure, and diabetes in predicting CV disease (CVD), defined as coronary artery disease and/or cerebrovascular disease.

Results: Overall, 850 patients were included, 39.4% of whom with PAD. Compared with women without PAD, those with PAD were older (75.2 vs 66 years, respectively; p <0.001), and displayed higher rates of other CVRFs (p <0.001 for each). A personal history of CVD was reported in 18.8% of women with PAD and in 6.1% of those without PAD (p <0.001). At multivariate regression analysis, PAD (odds ratio [OR]: 2.15; 95% confidence interval [CI]: 1.33–3.47), and hypertension (OR: 2.20; 95%CI: 1.24–3.88) were the strongest factors associated with CVD presence.

Conclusions: PAD is a strong marker of CVD in this selected series of postmenopausal women. If confirmed in the general population, PAD screening through ABI calculation may be considered for CV risk assessment in postmenopausal women.

Abbreviations

ABI	"Ankle–brachial index"
AUC	Area Under the Curve
BMI	Body mass index
CAD	Coronary artery disease
CeVD	Cerebrovascular disease
CI	Confidence interval
CV	Cardiovascular
CVD	Cardiovascular disease
CVRF	Cardiovascular risk factor
ESC	European Society of Cardiology
ESVM	European Society of Vascular Medicine
ESVS	European Society for Vascular Surgery
MACE	Major adverse cardiovascular events
MALE	Major adverse limb events
NRI	Net Reclassification Improvement
OR	Odds ratio
PAD	Peripheral arterial disease
ROC	Receiver operating characteristic
SBP	Systolic blood pressure
SD	Standard deviation
TBI	"Toe-brachial index"

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1. Introduction

Lower limb peripheral arterial disease (PAD) is the third most common clinical manifestation of atherosclerosis after ischemic heart disease and stroke [1]. It is associated with both significant functional impairment and increased risk of major adverse cardiovascular (CV) events (MACE), major adverse limb events (MALE), and overall mortality [2,3]. According to a systematic review and meta-analysis of 2013, the burden of PAD, defined as "ankle–brachial index" (ABI) $\leq$0.9 regardless of PAD symptoms, rose by 23.5% from 2000 to 2010, with greater increases in low and middle-income countries [1]. In 2015, an update of such data reported 236.62 million people with PAD worldwide, with the highest prevalence in Europe [4]. This trend may partly result from population growth and aging [1,5], as well as increasing prevalence of CV risk factors (CVRFs).

Although impact of PAD on global health is significant, patient and clinician awareness of the disease is poor, even in countries with an advanced health-care system [6]. This is particularly the case for women. Worldwide, more than half of patients with PAD are women [4]. Notwithstanding this, women are underrepresented in clinical trials [7], and less information is available on disease characteristics in this population. Moreover, women are more likely to be asymptomatic or to have atypical symptoms, further challenging the clinical diagnosis [8,9]. Compared to men, women appear to be less likely to receive appropriate treatment such as antiplatelet agents or lipid lowering drugs [10]. Importantly, women with PAD have a 2- to 4-fold increased risk of CV mortality and morbidity compared with women without the disease [8]. CV risk in the female population increases particularly after the cessation of ovarian function at menopause [11]. The menopausal transition is associated with detrimental changes in lipids and lipoproteins, glucose and insulin metabolism, and body fat distribution, leading to increased rates of hypertension and diabetes, as well as a deterioration of vascular function [12]. Therefore, risk to develop symptomatic atherosclerosis is increased in women after menopause. Current evidence suggests that women with PAD present faster functional decline and greater mobility loss than men with PAD [13]. Furthermore, when symptomatic, women are older and show a more complex (i.e., multilevel) and severe disease [14]. Therefore, early PAD diagnosis in women is warranted but seldomly performed probably because majority of women present with asymptomatic/atypical disease [5,8]. In light of these aspects, a scientific statement published in 2012 by the American Heart Association called for greater inclusion of women in clinical trials on PAD and attention to potential sex-based differences [15].

Accordingly, the aim of our study was to evaluate CV risk profile of postmenopausal women with and without PAD, in terms of both traditional CVRFs and personal history of CVD, defined as CAD and/or CeVD. Furthermore, we sought to evaluate the role of ABI and CVRFs, as well as their combination, in predicting CVD in this clinical setting.

2. Materials and methods

2.1. Study setting and design

We performed a single center retrospective, cross-sectional study including postmenopausal women with at least one CVRF, admitted for any reason (i.e., known or suspected arterial, venous or lymphatic disease) to our outpatient Angiology Division at Lausanne University Hospital and tested for PAD during a 24-month period (February 2017-February 2019). The following data were assessed: presence of CVRFs (diabetes, hypertension, dyslipidaemia, current smoking, severe chronic renal failure, and obesity), concomitant established diagnosis of CVD, defined as CAD and/or CeVD, as well as family history of myocardial infarction.

Main study objectives were:

- Evaluate the association between CVRFs and PAD in postmenopausal women.
- Evaluate the association between either PAD or CVRFs and concomitant CVD in postmenopausal women.
- Assess the predictive value of PAD and CVRFs, as well as their combination in a new clinical score (i.e., the PAD-RiF Score), for the presence of concomitant CVD in postmenopausal women.

In this study we used anonymized secondary data; therefore, ethical approval was not required according to the Swiss law for research on humans [16].

2.2. Definitions

Menopause was defined as amenorrhea from at least 12 months in a woman over 45 years of age [17].

Patients were considered to have PAD if positive at ABI calculation or having a history of lower limb revascularization (percutaneous vascular angioplasty or artery bypass graft surgery). PAD severity was stratified according to the Fontaine classification [18]. As for the ABI calculation, measures were performed in supine position following guidelines of the European Society of Cardiology (ESC) and the European Society for Vascular Surgery (ESVS) [19], as well as those of the European Society of Vascular Medicine (ESVM) [20], using a vascular handheld 4–8 MHz Doppler instrument (Basic-2, Atys Medical, 69,510 Soucieu en Jarrest, France). ABI was calculated separately for each leg dividing the higher of the posterior tibialis or dorsalis pedis systolic blood pressure (SBP) by the higher of the right or left arm SBP. The test was considered diagnostic for PAD if ABI was $\leq$0.9 [19]. In case of abnormally high ABI (i.e., ABI $\geq$1.4), the systolic toe pressure was measured (Basic-2, Atys Medical, 69,510 Soucieu en Jarrest, France), and the "toe-brachial index" (TBI) calculated. The test was considered diagnostic for PAD if TBI was $<$0.7 [19].

The presence of CVRFs was ascertained as follows: documented diagnosis of diabetes or patient on antidiabetic treatment with no other clear indication; documented diagnosis of hypertension or patient on antihypertensive treatment with no other clear indication; documented diagnosis of dyslipidaemia or patient on lipid lowering drugs with no other clear indication; self-reported history of current smoking (if more than 100 cigarettes lifetime); presence of obesity, defined as body mass index (BMI) $>$30 kg/m^2; presence of severe chronic renal failure, defined as creatinine clearance $<$30 ml/min (according to Cockroft-Gault formula).

A diagnosis of CAD was established for any patient with a documented history of myocardial infarction, stable or unstable angina, percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery, as well as the presence of at least one coronary artery stenosis $>$70% detected by coronary angiography. Patients were considered to have CeVD if they had a documented history of transient ischemic attack, ischemic stroke, or carotid endarterectomy and/or stenting.

2.3. Statistical analysis

Patients were classified according to whether they had or not PAD. First, descriptive analysis was performed. Continuous variables were reported as mean $\pm$ standard deviation (SD). Categorical variables were reported as percentage. As for the first ones, groups were compared by using the Student's *t*-test or the Mann-Whitney test (in case of non-normal distribution). Differences between groups in terms of categorical variables were assessed by using the Chi-square test or the Kruskal-Wallis test (in case of non-normal distribution).

Multiple linear regression analyses were performed to investigate the associations found to be statistically significant in the univariable analyses between patients' baseline characteristics (CVRFs and personal history of CAD and/or CeVD) and PAD, as well as between the presence

of CVRFs and PAD and a personal history of CAD and CeVD. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported for the multivariable models.

As for the CVD prediction model combining PAD and CVRFs (PAD-RiF Score), the score, ranging 0 to 7 points, was subdivided in 4 categories, as follows: category 1 (0 points), category 2 (1–2 points), category 3 (3–4 points), and category 4 (≥5 points). Receiver operating characteristic (ROC) curves were performed for various cut-off points of the final risk score, calculating Area Under the Curve (AUC), sensitivity, specificity, Youden's Index, and Net Reclassification Improvement (NRI). The analyses above were applied to the individual components of the model (i.e., PAD, hypertension, severe chronic renal failure, dyslipidaemia, current smoking, age ≥65 years, and diabetes). Moreover, a second prediction model (Adj-PAD-RiF) was created combining the above CVRFs and PAD presence, the weight of each component being adjusted to the OR value obtained at multivariate analyses of predictors of CVD, as follows: OR 0.50–1.49 = 1 point; OR 1.50–2.49 = 2 points; OR 2.50–3.49 = 3 points. Multiple comparisons between models and their single components were made.

All statistical tests were two-tailed and conducted at a significance level of 0.05.

The analyses were performed with Stata software (version 16.0, StataCorp LLC, College Station, Texas, USA).

3. Results

3.1. Overall population

During the 24-month study period, 850 consecutive postmenopausal women with at least one CVRF were tested for PAD and were included in the analysis.

Mean age was 75 ± 11 years. Overall, 22.6% of patients were aged 45–59 years, 31.2% 60–69 years, 25.2% 70–79 years, and 21% ≥80 years (Supplementary Figure 1). Included patients consulted our Angiology Division for the following reasons: suspected PAD (25.4%); known PAD follow up (19.8%); suspected carotid artery stenosis (19.0%); varicose veins (14.5%); CV risk estimation (6.9%); rare vascular disease (3%); aortic aneurysm (2.8%); suspected venous thromboembolism (2.8%); assessment of arteriovenous haemodialysis access (1.8%); lymphatic disease (1.2%).

Overall, 167 (19.6%) patients had diabetes (80.2% of whom were on antidiabetic drugs), 489 (57.5%) had dyslipidaemia (64.2% of whom were on lipid-lowering drugs), 502 (59%) had hypertension (85.5% of whom were on anti-hypertensive drugs), 187 (22%) had a BMI consistent with obesity, 94 (11.1%) had severe chronic renal failure, 193 (22.7%) reported current smoking, and 66 (7.8%) had a family history of CAD.

Two hundred seventy-one women had an ABI ≤0.9. Additionally, 13 of 21 women with an ABI ≥1.4 had a TBI <0.7, and 45 had normal ABI but a history of revascularization. Therefore, 329 (38.7%) women were classified as having PAD. According to Fontaine's classification, PAD severity was classified as stage I in 136 (41.3%) of cases, stage IIa in 47 (14.3%) of cases, stage IIb in 55 (16.7%) of cases, stage III in 12 (3.6%) of cases, and stage IV in 31 (9.4%) of cases. In 32 women with PAD, the pain-free walking distance was not assessable because of a concomitant functional limitation not related to PAD, whereas PAD stage was not reported in 16 cases.

PAD prevalence increased with age, 28% being in the range 60–69 years, 46% in the range 70–79 years, and 70% ≥80 years. Similarly, prevalence of CAD and CeVD increased with age, although less significantly (Fig. 1). Prevalence of PAD also increased with increasing number of CVRFs (up to 79% in patients with four or more risk factors) (Fig. 2). Lastly, PAD was prevalent in women with known CVD, as 67.1% patients with CAD and 65.9% of patients with CeVD had concomitant PAD at inclusion.

3.2. Comparison between patients with and without PAD

Compared with women without PAD, those with PAD were older (75.2 vs 66.0 years, respectively; $p < 0.001$), and displayed higher rates of diabetes (29.5 vs 13.4%; $p < 0.001$), dyslipidaemia (67.8 vs 51.1%; $p < 0.001$), hypertension (80.2 vs 45.8%; $p < 0.001$), severe chronic renal failure (18.5 vs 6.2%; $p < 0.001$), and current smoking (33.7 vs 15.7%; $p < 0.001$). A family history of CAD and a personal history of CAD and CeVD were also more frequent in women with PAD. Conversely, obesity prevalence was not significantly different between the two groups (Table 1).

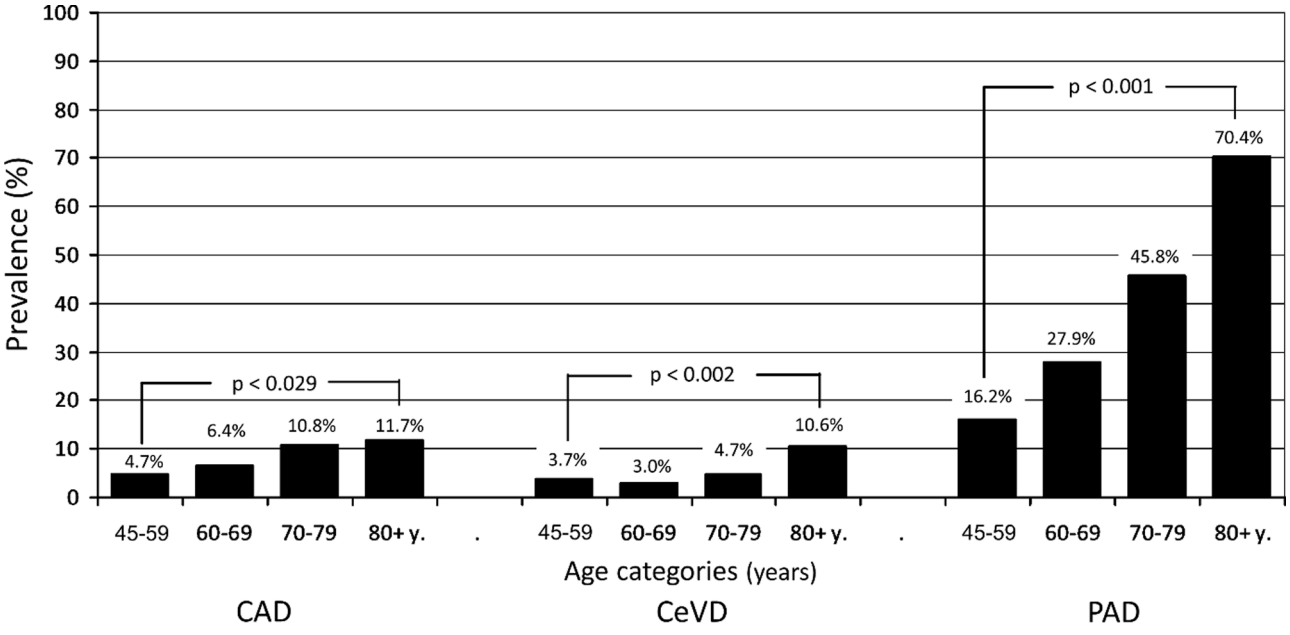

Fig. 1. Prevalence of PAD, CAD and CeVD according to age in the overall population of postmenopausal women.
CAD: coronary artery disease; CeVD: cerebrovascular disease; PAD: peripheral arterial disease.

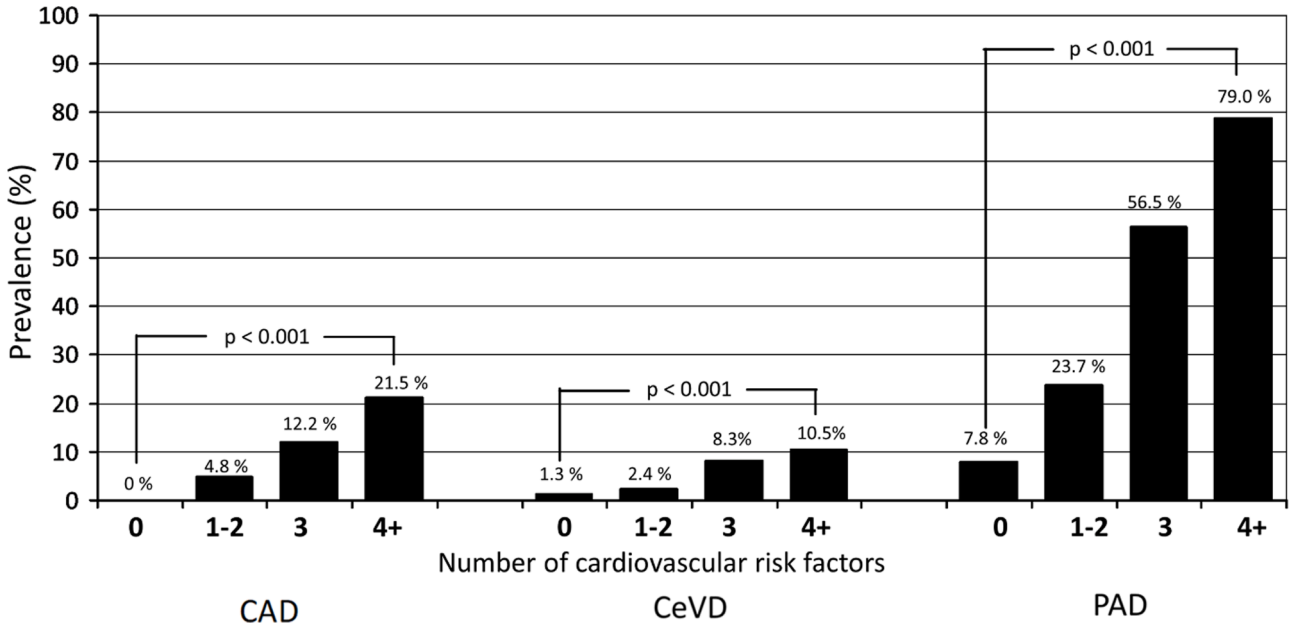

Fig. 2. Prevalence of CAD, CeVD and PAD in the overall population of postmenopausal women, according to the number of cumulated CVRFs.
CAD: coronary artery disease; CeVD: cerebrovascular disease; PAD: peripheral arterial disease.

Table 1
Patients' characteristics.

Parameters	PAD(n = 329)	No PAD(n = 521)	p-value
Age (mean ± SD)	75.2 ± 10.8	66.0 ± 9.9	<0.001
Age ≥65 years	80.9% (266)	19.1% (63)	<0.001
Diabetes,% (N)	29.5% (97)	13.4% (70)	<0.001
Dyslipidaemia,% (N)	67.8% (223)	51.1% (266)	<0.001
Hypertension,% (N)	80.2% (264)	45.8% (238)	<0.001
Obesity (BMI ≥ 30 kg/m^2),% (N)	18.8% (63)	24.1% (124)	0.069
Severe chronic renal failure,% (N)	18.5% (62)	6.2% (32)	<0.001
Current smoking,% (N)	33.7% (111)	15.7% (82)	<0.001
Family history of CAD,% (N)	4.0% (13)	10.3% (53)	<0.001
CVD (CAD + CeVD)*,% (N)	18.8% (68)	6.1% (32)	<0.001
CAD,% (N)	14.5% (48)	4.2% (22)	<0.001
CeVD,% (N)	8.8% (29)	2.9% (15)	<0.001

BMI: body mass index; CAD: coronary artery disease; CeVD: cerebrovascular disease; CVD: cardiovascular disease; PAD: peripheral arterial disease; SD: standard deviation.
* Some patients presented both CAD and CeVD.

3.3. Multiple linear regression analyses

After inclusion in a multiple linear regression model, current smoking, age ≥65 years, and hypertension were significantly and independently associated with the presence of PAD, ORs being as follows: 4.09 (95%CI: 2.61–5.89), 3.62 (95%CI: 2.55–5.59), and 2.91 (95%CI: 2.08–4.27), respectively. Severe chronic renal failure and diabetes were also independently associated with PAD, though this association was less strong. Lastly, dyslipidaemia was not significantly associated with PAD at multiple linear regression analysis (Supplementary Figure 2).

On the other hand, PAD, hypertension, severe chronic renal failure, and dyslipidaemia were found to be independently associated with known CVD at multiple linear regression analysis. Among those, hypertension and PAD displayed the strongest association, with an OR of 2.20 (95%CI: 1.24–3.88), and 2.15 (95%CI: 1.33–3.47), respectively (Fig. 3). When CAD and CeVD were considered separately, PAD, hypertension, and smoking were independently associated with CAD with an OR of 3.29 (95%CI: 1.35–8.02), 4.99 (95%CI: 1.10–22.65), and 3.00 (95%CI: 1.31–6.89), respectively. PAD was the only factor independently associated with CeVD (OR: 4.90, 95%CI: 1.40–17.15).

3.4. CVD prediction models

Overall, 299 (90.9%) patients with PAD had a PAD-RiF score of 3 or more, whereas 355 (68.1%) of women without PAD had a score of 1 or 2 (Supplementary Table 1).

Analysis of the PAD-RiF model as a predictor of CVD resulted in an AUC of 0.70 (95%CI: 0.65–0.74), optimal cut-off value being category 3, with a sensitivity and a specificity of 0.85 and 0.50, respectively (Table 2, Fig. 4). Considering any individual component of the score, PAD was the best predictor of CVD with a Youden's Index of 0.30. Compared with the PAD-RiF model, lower AUC values were found for its components. In particular, AUC was 0.64 (95%CI: 0.59–0.69) for PAD, 0.63 (95%CI: 0.59–0.67) for hypertension, 0.61 (95%CI: 0.56–0.67) for age ≥65 years, 0.60 (95%CI: 0.55–0.64) for dyslipidaemia, 0.57 (95%CI: 0.52–0.61) for severe chronic renal failure, 0.56 (95%CI: 0.51–0.61) for smoking, and 0.53 (95%CI: 0.49–0.58) for diabetes. The Adj-PAD-RiF was not superior to the PAD-RiF model in predicting CVD (NRI 0%; p = 0.990) (Table 2).

4. Discussion

Present study shows that presence of lower limb PAD, assessed by ABI calculation, was one of the best predictors of CVD in postmenopausal women referred to our Angiology Division. In this selected series, PAD prevalence increased with increasing age and number of CVRF. Moreover, PAD was a prevalent disease in women with known CVD.

If confirmed by further evidence in the general population, ABI calculation should be considered at least once in postmenopausal

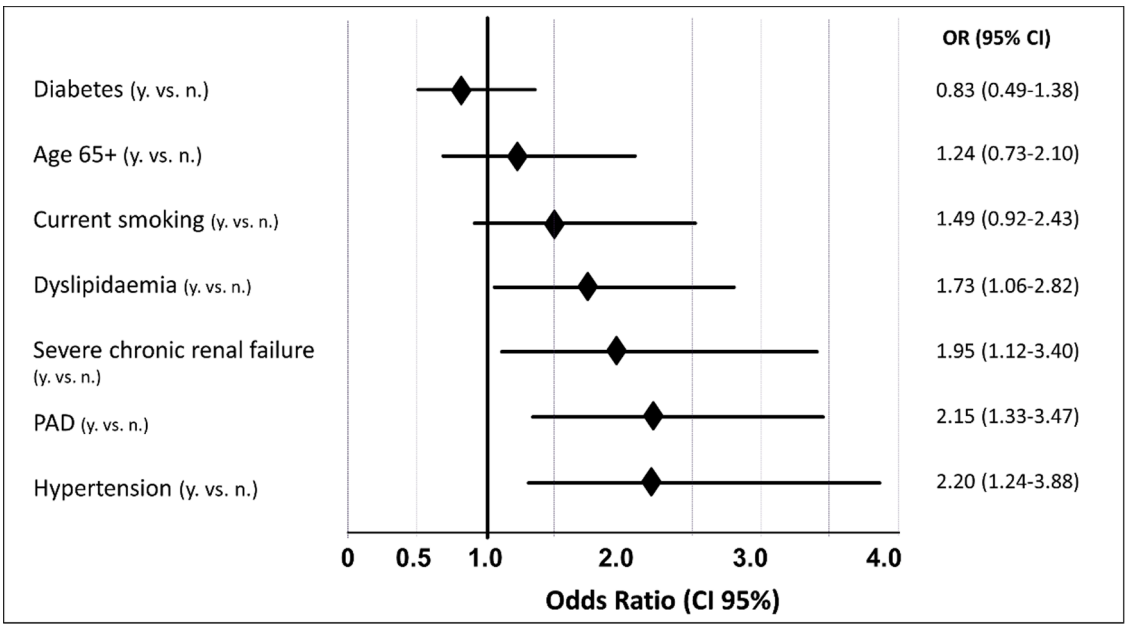

Fig. 3. Association between both PAD and major CVRFs and CVD at multiple logistic regression analysis.
CI: confidence interval; OR: odds ratio; PAD: peripheral arterial disease.

Table 2
Comparison between the PAD-RiF prediction model and its components in predicting personal history of CVD.

	PAD-RiF Score(≥3 vs <3)	Adj-PAD-RiF Score(≥3 vs <3)	PAD(y. vs. n.)	Hypertension(y. vs. n.)	Dyslipidaemia(y. vs. n.)	Severe chronic renal failure(y. vs. n.)	Age 65y+ (y. vs. n.)	Smoking(y. vs. n.)	Diabetes(y. vs. n.)
Sensibility (%)	0.85	0.81	0.65	0.82	0.75	0.23	0.76	0.33	0.25
Specificity (%)	0.50	0.54	0.65	0.44	0.45	0.91	0.37	0.79	0.81
Youden's Index	0.35	0.35	0.30	0.26	0.20	0.14	0.13	0.12	0.07
Statistical difference (p-value)	Ref.	0.990	0.012	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
NRI	Ref.	0%	−5%	−9%	−16%	−21%	−22%	−23%	−28%

NRI: net reclassification improvement; PAD: peripheral arterial disease.

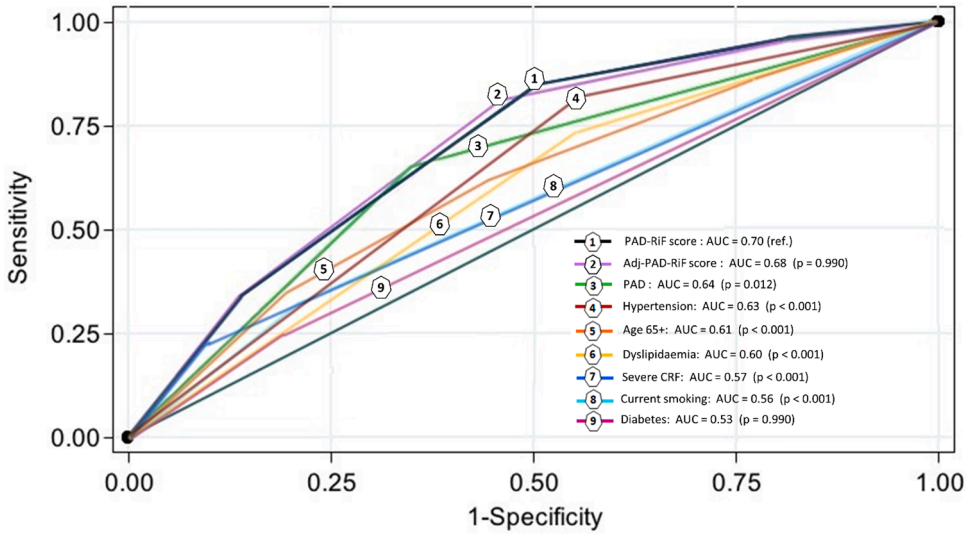

Fig. 4. Comparison between the PAD-RiF prediction model and its components in predicting personal history of CVD.
AUC: area under the curve; PAD: peripheral arterial disease; CRF: chronic renal failure.

women with at least one CVRF and ≥65 years, or in younger postmenopausal women with at least two CVRFs. In the present work, ABI values were integrated in a simple CVD prediction model (PAD-RiF) including other common CVRFs. Various CV risk calculators are available predicting patient's likelihood of experiencing a CV event over a fixed time horizon based on clinical and demographic characteristics [21]. However, none of the pubished risk scores focuses on postmenopausal women. Although tested on a relatively small, highly selected population and without external validation, the PAD-RiF model shows good predictive ability worth further exploring in the next future.

PAD is one of the main atherosclerotic diseases along with CAD and CeVD. It is strongly associated with age and its prevalence increases with increasing number of CVRFs [1]. The effect of traditional CVRFs on PAD has been found to be cumulative, with substantially greater risk the higher the number of risk factors present [22]. This was also the case in our study, where 74% of participants with PAD presented with at least four CVRFs.

Among the CVRFs, cigarette smoking is considered one of the most important contributor to PAD development [23]. In women, previous research showed that smoking was a stronger risk factor for myocardial infarction than in men during a 12-year follow-up [24]. More recent epidemiologic data found an increased risk of CV mortality and myocardial infarction in females with both smoking and diabetes compared to males [25]. Along the same line, present study showed that smoking was the CVRF most strongly associated with PAD in postmenopausal women. In our population, smoking was also independently associated with CAD. These data stress the importance of smoking habit assessment and its counselling in postmenopausal women.

In both genders, risk of intermittent claudication is known to be about twice as high in patients with diabetes. In this population, relative risk of critical limb ischemia is even higher, with a rate of major amputation being around fivefold higher than in non-diabetics [26]. Notwithstanding this, population attributable fraction of diabetes for incident PAD was estimated at 14% among US professionals [23]. This is mainly due to lower diabetic prevalence in the general population than other traditional CVRFs, and may at least partially explain why diabetes was less strongly associated with PAD in our study compared to other CVRFs. Nonetheless, it has to be noted that PAD risk increases with diabetes severity (26% for every 1% increase in hemoglobin A1c) [27], and that glycaemic control was not assessed in our study.

Hypertension has been associated in most epidemiological studies with increased PAD risk, although at levels lower than smoking and diabetes [28]. Although the relative risk associated with hypertension is modest in some studies, its high prevalence, particularly in the elderly, makes it a significant contributor to the total burden of PAD in the general population [29]. Consistently, hypertension was one of the strongest CVRFs associated with PAD in our population, as well as the main risk factor associated with personal CVD history.

Studies have shown that population attributable fraction for PAD related to hypercholesterolemia was 17% [23]. However, in our study, dyslipidaemia, although more prevalent in postmenopausal women with than without PAD, was not significantly associated with PAD. Notably, several patients included were on lipid lowering drugs, which may have mitigated the effects of this risk factor in our population. However, the significant association between hypertension and PAD despite high rates of antihypertensive drug therapy seems to contradict the latter hypothesis. As data on drugs class and dose, treatment duration, as well as control of the different CVRFs are lacking, no further conclusion can be drawn in this regard. Future research should clarify these aspects.

In our study, severe chronic renal failure was also independently associated with PAD, although less strongly than smoking, older age, and hypertension. This is in line with several published studies [30,31]. Moreover, literature suggests that there may be a 1.53-fold higher risk of PAD prevalence in younger women (<70 years old) with chronic kidney failure than age-matched men [32].

Intriguingly, no significant association was found between obesity and PAD in our population. However, evidence on this relationship is quite conflicting. Most studies show no association, and others suggest a slightly increased risk, a U-shaped relationship, or even a protective effect [29]. Reasons for such discrepancy are unclear, though it has been hypothesized that PAD in the elderly is often associated with other chronic illnesses contributing to weight loss.

Present study has some limitations. First, population included is highly selected from a single Angiology center and results may not reflect PAD characteristics in postmenopausal women in the general population. In fact, about half of included subjects had known PAD or symptoms suggestive of the disease, whereas the others underwent ABI calculation to rule out involvement of lower limb arteries in different vascular conditions. Larger studies on postmenopausal women in the general population using ABI calculation as opportunistic screening should confirm the epidemiological value of the present study and reinforce the importance of PAD as a CVRF in this specific setting. Second, several clinical information were limited and/or lacking in the setting of anonymized, secondary data analysis. In particular, neither CVRFs treatment (e.g. molecule used, drug dose, duration of treatment, etc.) nor their control (e.g. office systolic and diastolic blood pressure, hemoglobin A1c level, total cholesterol, etc.) have been extensively assessed, which may have influenced our results. Third, presence of concomitant CAD or CeVD was not actively searched for, but based on known personal history. Therefore, asymptomatic patients may have been missed. Lastly, this is a cross-sectional study and no longitudinal information can be provided, in particular regarding MACE and MALE.

However, our study has also strengths, as it allows shedding light on women, a population not often studied in the field of vascular medicine, and highlights the need for gender-specific studies. Data about women, particularly postmenopausal women, and PAD are limited although the CV risk in this cohort should be expected higher than in other populations. Indeed, in addition to traditional CVRFs, postmenopausal women carry an additional, sex-specific risk factor, represented by the loss of ovarian function and the decline of estrogen levels. Overall, our findings underline the importance of PAD in postmenopausal women as a marker of CAD and CeVD, and vice versa. Furthermore, our study confirms the relevance of several CVRFs in the setting of PAD, as well as their cumulative effect in the development of PAD and other CVDs in women.

5. Conclusions

PAD is a strong marker of CVD in this selected series of postmenopausal women referred to our Angiology Division. If confirmed by further evidence in the general population, ABI calculation may be considered to refine CV risk in postmenopausal women, allowing identifying women needing aggressive secondary CV prevention. An evaluation of the attitudes and behaviours of clinicians and their patients with PAD with a gender-specific focus is warranted in the next future, in order to enhance awareness of PAD and improve the management of CV risk profile in this specific population.

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Author contribution

AA, GB, MD, LM, and JS contributed to the conception or design of the work. AA, GB, RD, LC, MD, LM and JS contributed to the acquisition, analysis, or interpretation of data for the work. GB and AA drafted the manuscript. RD, MD, LM, and JS critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.02.002.

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