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Simona Negrini and Arnold von Eckardstein

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Peripheral arterial disease (PAD) is a prevalent disease affecting roughly 20% of the elderly population and more than 200 million people worldwide. PAD limits quality and extent of life leading to limb ischemia and its association with a high risk of major adverse cardiovascular events (MACE). Volumes 315, 316 and 317 of *Atherosclerosis* contain several articles on methods for the diagnostics and prognostics of PAD and limb ischemia, as well as therapeutic interventions.

The accuracy of toe brachial index and ankle brachial index in the diagnosis of lower limb peripheral arterial disease: A systematic review and meta-analysis

PAD implies systemic atherosclerosis, which makes PAD a strong predictor of cardiovascular (CV) morbidity and mortality both in symptomatic and asymptomatic patients. The ankle-brachial pressure index (ABI) (the ratio between systolic blood pressures in the ankle and in the arm) remains the non-invasive technique endorsed by current guidelines to measure PAD. However, there is concern about lack of sensitivity, especially in elderly individuals, and patients suffering from renal insufficiency or diabetes. Medial arterial calcification (MAC) seems to be an explanation for such lack of sensitivity. On the other hand, toe brachial index (TBI) (the ratio between systolic blood pressures in the first toe and in the arm) is generally unaffected by MAC since collateral vessels of the toe are less prone to suffer from calcification. Herraiz-Adillo et al. aimed to compare the diagnostic accuracy of ABI and TBI for PAD in a wide spectrum of PAD populations and reference standard tests, and to examine variables influencing heterogeneity in the estimates.

Systematic searches in EMBASE, MEDLINE, Web of Science and the Cochrane Library databases were performed, from inception to January 2020. Hierarchical summary receiver operating characteristic curves (HSROC) were used to summarize the pooled test performance.

Thirty five and nine studies were included in ABI and TBI meta-analyses, respectively. The QUADAS-2 tool identified many studies with high risk of bias, especially in the “patient selection” domain. Pooled estimates for ABI in detecting 50% or greater stenosis were sensitivity = 61%, specificity = 92% and dOR = 16.5. Similarly, TBI yielded sensitivity = 81%, specificity = 77% and dOR = 13.1. In a direct comparison of seven studies jointly analyzing ABI and TBI, TBI showed better overall

diagnostic accuracy at the expense of sensitivity (82% *vs* 52%), while specificity (77% *vs* 94%) performed worse in TBI than ABI. Heterogeneity was large in sensitivity for ABI, with variables as different reference standard tests, smoking habit and PAD prevalence accounting for such variability. Similarly, gender, different index test cut-offs and sample size influenced the heterogeneity in TBI specificity.

Though ABI and TBI showed similar diagnostic performance to diagnose PAD, TBI showed far better sensitivity than ABI, especially in "challenging populations", as those with calcification.

Association of pulse wave velocity and pressure wave reflection with the ankle-brachial pressure index in Japanese men not suffering from peripheral artery disease

The ankle-brachial pressure index (ABI) is a ratio of systolic blood pressure in the ankles to that in the arms. Low ABI, caused by arterial stenosis in the lower extremities, is a simple marker of PAD and a predictor of the risk of development of cardiovascular disease (CVD). Takahashi et al. examined the cross-sectional and longitudinal association of arterial stiffness and pressure wave reflection with ABI in middle-aged Japanese subjects free of PAD.

ABI, brachial-ankle pulse wave velocity (baPWV) and radial augmentation index (rAI) were measured annually during the 9-year observation period in 3066 men with ABI ≥1.00 at baseline of the study period, and not taking any antihypertensive medication.

In the cross-sectional assessments, mediation analysis showed both direct and indirect (via the rAI) associations of baPWV with ABI as well as direct and indirect (via the heart-arm difference of systolic blood pressure) associations of rAI with the ankle-arm difference of systolic blood pressure, both at study baseline and end of study period. Mixed model linear regression analysis of the repeated-measurement data obtained over the 9-year observation period demonstrated that annual increase of baPWV and rAI was associated with ABI. When baPWV and rAI were entered into the same model, only baPWV showed a significant longitudinal association with ABI.

In middle-aged Japanese men free of PAD, arterial stiffness may contribute to ABI directly and via pressure wave reflection. Pressure wave reflection may contribute to ABI directly and, at least in part, via attenuation of peripheral pulse pressure amplification.

Costs and effects of cardiovascular risk reclassification using the ankle-brachial index (ABI) in addition to the Framingham risk scoring in women

Ankle brachial index (ABI) is a simple and cheap parameter to assess the presence of atherosclerosis. It could also help correctly reclassify the cardiovascular risk when added to the Framingham risk score (FRS). Recent evidence has demonstrated improvement in prediction

performance of ABI when added to FRS, particularly in women. However, no studies have been published yet evaluating the cost-effectiveness of this approach. Cortesi et al. attempted to fill in this gap by assessing the cost-effectiveness of ABI measurements in primary prevention in women.

The authors developed a Markov model to compare two different strategies for assessing the cardiovascular risk (low, intermediate and high) among women in the general population: 1) FRS strategy, and 2) FRS + ABI strategy; and the relative impact associated with interventions for preventing CV events in intermediate and high-risk categories.

In the base-case analysis, FRS + ABI reported an additional cost of € 110 and a gain of 0.0039 QALYs per patient, resulting in an ICER of € 27.986/QALY, when compared to FRS alone. The ICER improved to €1.641/QALY when using a lifetime horizon. The effectiveness of preventive CV disease interventions reported also a significant impact. A 32% reduction of CV events was the minimum value estimated to maintain FRS + ABI as a cost-effective strategy.

The addition of ABI to FRS is a cost-effective approach in women classified at low and intermediate risk with FRS only. This new approach gives the possibility to reclassify and allocate them into the appropriate risk group and treatment.

Sinusoidal changes in transcutaneous oxygen pressure, suggesting Cheyne-Stokes respiration, are frequent and of poor prognosis among patients with suspected critical limb ischemia

Transcutaneous oxygen pressure ($TcpO_2$) is used as a diagnostic tool in patients with suspected critical limb ischemia (CLI) to classify the risk of amputation or to estimate the probability of healing of lower limb ulcers suspected to be of vascular origin. Sinusoidal changes (SC~) in $TcpO_2$ are found in patients with Cheyne-Stokes respiration (CSR), rare in the general population and characterized by regular cycles of crescendo and decrescendo changes in breathing amplitude, followed by periods of transient apnea. Hersant et al. aimed to determine the characteristics of $TcpO_2$ changes at rest in patients with suspected CLI, define the objective criteria for SC~ $TcpO_2$ patterns (SC+), and estimate the prevalence of SC+ in these patients and its impact on the outcome.

Three hundred chest $TcpO_2$ recordings performed in a 16-month period were retrospectively analyzed. The presence/absence of SC~ $TcpO_2$ by visual analysis and the acceptable error in the regularity of peaks of the cross-correlation with ROC curve analysis, among patients with typical SC ~ $TcpO_2$ and non-sinusoidal patterns, were determined. Then, the authors defined SC+ as a minimum of five peaks, a standard deviation of $TcpO_2$ >1.25 mmHg, an error in regularity of peaks of the cross-correlation < 10%, and a cycle length between 30 and 100 s. In patients included until October 2019, the outcome, as a function of SC + or SC-, was compared with Cox models.

Mathematical detection of SC + found that 43 patients (14.3%) fulfilled all four defined criteria at chest level, but only 23 did so at limb level. In the follow-up of 207 patients, the presence of Sc~ $TcpO_2$ at the chest significantly increased the risk of mortality (hazard ratio: 2.69).

In conclusion, SC~ $TcpO_2$ is frequent, and is associated with a poor outcome in patients with suspected CLI.

Elevated levels of serum PCSK9 in male patients with symptomatic peripheral artery disease: The CAVASIC study

Increased low-density lipoprotein cholesterol (LDL-C) levels are a risk factor for PAD and the concentrations are influenced by proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 regulates the recycling of the LDL receptor to the cell membrane surface. Only a limited number of mostly small studies investigated the association between serum PCSK9 concentrations and PAD of different definition, which revealed contrasting results. Due to these heterogeneous results and definitions, Kheirkhah et al. investigated PCSK9 serum concentrations in patients with symptomatic PAD and age and diabetes-matched controls. In addition, they examined whether PCSK9 concentrations are associated with PAD independent of Lp(a) concentrations.

Serum PCSK9, Lp(a) and other lipoprotein concentrations were measured in male participants of the CAVASIC study, a case-control study of 248 patients with intermittent claudication and 251 age and diabetes-matched controls.

PAD patients had significantly higher PCSK9 concentrations when compared to controls. Logistic regression analysis with adjustment for age revealed that an increase in PCSK9 concentrations of 100 ng/mL was associated with a 1.78-fold higher risk for PAD. The association attenuated, but was still significant when adjusting additionally for age, Lp(a)-corrected LDL cholesterol, high density lipoprotein cholesterol (HDL-C), high-sensitivity-CRP, statin treatment, hypertension, diabetes mellitus and smoking. The strongest association was observed when both PCSK9 concentrations were above the median and Lp(a) concentrations were above 30 mg/dL.

These findings suggest an association of higher PCSK9 concentrations with PAD, which was independent of other lipid parameters and classical cardiovascular risk factors.

Low-density lipoprotein aggregation predicts adverse cardiovascular events in peripheral artery disease

Low-density lipoprotein (LDL) aggregation contributes to atherosclerotic plaque progression and may contribute to plaque instability. Heffron et al. aimed to determine if LDL aggregation is associated with MACE in patients with PAD undergoing lower extremity revascularization (LER).

Two hundred thirty-nine patients with PAD undergoing LER had blood collected at baseline and were followed prospectively for MACE (myocardial infarction, stroke, cardiovascular death) for one year. Nineteen age, sex and LDL-cholesterol-matched control subjects without cardiovascular disease also had blood drawn. Subject LDL was exposed to sphingomyelinase and LDL aggregate size measured via dynamic light scattering.

Mean age was 72.3 ± 10.9 years, 32.6% were female, and LDL-cholesterol was 68 ± 25 mg/dL. LDL aggregation was inversely associated with triglycerides, but not with demographics, LDL-cholesterol or other risk factors. Maximal LDL aggregation occurred significantly earlier in subjects with PAD than in control subjects. 15.9% of subjects experienced MACE over one year. The 1st tertile (shortest time to maximal aggregation) exhibited significantly higher MACE. After multivariable adjustment for demographics and CVD risk factors, the hazard ratio for MACE in the 1st tertile was 4.57 compared to tertile 3. Inclusion of LDL aggregation in the Framingham Heart Study risk calculator for recurrent coronary heart disease events improved the c-index from 0.57 to 0.63.

In the setting of very well controlled LDL-cholesterol, patients with PAD with the most rapid LDL aggregation had a significantly elevated MACE risk following LER even after multivariable adjustment. This measure further improved the specificity of an established risk prediction tool. The findings support broader investigation of this assay for risk stratification in patients with atherosclerotic cardiovascular disease.

Evaluation of sCD163 and sTWEAK in patients with stable peripheral arterial disease and association with disease severity as well as long-term mortality

The TNF-superfamily member sTWEAK and its scavenger receptor sCD163 are potentially involved in pathophysiological processes of atherosclerosis. In patients with PAD, previous research has shown that sTWEAK and the sCD163/sTWEAK ratio were independently associated with long term all-cause and cardiovascular survival. Mrak et al. assessed sTWEAK and sCD163 in a cohort of stable PAD including asymptomatic (Fontaine stage I) and intermittent claudication (Fontaine stage II) patients.

sTWEAK concentrations of 354 patients were measured using a commercially available ELISA kit. sCD163 was quantified using a multiplex bead assay. Cox proportional hazards regression was used to assess outcome after a seven-year follow-up.

Patients with intermittent claudication exhibited increased sCD163 levels in comparison to asymptomatic patients. However, sTWEAK was not related to peripheral arterial disease severity. A multivariable Cox-proportional hazard model including sTWEAK and cardiovascular risk factors (age, HbA1c, CRP, LDL-C, BMI, eGFR) revealed an inverse association with all-cause mortality and

cardiovascular mortality. Further multivariable models including sCD163 or the sCD163/sTWEAK ratio and cardiovascular risk factors showed no association with mortality.

This study highlights the use of sCD163 as a novel biomarker for PAD severity and supports sTWEAK as an independent predictor of all-cause and cardiovascular mortality even in stable peripheral arterial disease.

Polyvascular disease: A narrative review of current evidence and a consideration of the role of antithrombotic therapy

The 2017 European Society of Cardiology (ESC) guidelines defined polyvascular disease (PVD) as “clinically significant” atherosclerotic disease in at least 2 major arterial territories. It affects approximately 20% of patients with atherosclerosis and is a strong independent risk factor for ischemic outcomes. However, guidelines do not address screening or treatment for PVD, and there have been no PVD-specific trials. Weissler et al. reviewed subgroup analyses of large randomized controlled trials of more intense antithrombotic therapy to determine whether increased intensity of therapy improved ischemic outcomes in patients with PVD.

MEDLINE, MEDLINE in-Process, EMBASE, and the Cochrane Library were queried for randomized controlled trials larger than 5000 patients evaluating secondary prevention therapies in patients with coronary artery disease or lower extremity peripheral artery disease.

Thirteen trials were included ranging in size from 7243 to 27,395 patients. In 9 trials (CHARISMA, TRA 2°P–TIMI 50, PEGASUS—TIMI 54, VOYAGER PAD, TRACER, EUCLID, TRILOGY ACS, PLATO, and COMPASS), patients in the PVD subgroup treated with increased-intensity antithrombotic therapy had similar or greater relative risk reductions for ischemic events in comparison with the general trial cohorts. In four trials (DAPT, THEMIS, APPRAISE-2, and ATLAS ACS 2 TIMI 51), the PVD subgroup had an increased hazard of ischemic events with increased-intensity therapy compared with the general trial cohorts.

More intense antithrombotic therapy in patients with PVD was associated with a similar relative risk reduction for ischemic events compared with patients without PVD. Therefore, patients with PVD benefit from a larger absolute risk reduction because of their higher baseline risk. Future trials in patients with atherosclerotic cardiovascular disease should intentionally include PVD patients to adequately assess treatment options for this under-studied, under-treated population.