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CURRENT OPINION

The year in cardiology 2014: peripheral circulation

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Abstract

In 2014, the debate on the indication of revascularization in case of asymptomatic carotid disease continued, while another one regarding the use of surgery vs. stenting addressed some new issues regarding the long-term cardiac risk of these patients. Renal arteries interventions trials were disappointing, as neither renal denervation nor renal artery stenting was found associated with better blood pressure management or outcome. In contrast, in lower-extremities artery disease, the endovascular techniques represent in 2014 major alternatives to surgery, even in distal arteries, with new insights regarding the interest of drug-eluting balloons. Regarding the aorta, the ESC published its first guidelines document on the entire vessel, emphasizing on the role of every cardiologist for screening abdominal aorta aneurysm during echocardiography. Among vascular wall biomarkers, the aorta stiffness is of increasing interest with new data and meta-analysis confirming its ability to stratify risk, whereas carotid intima-media thickness showed poor performances in terms of reclassifying patients into risk categories beyond risk scores. Regarding the veins, new data suggest the interest of D-dimers and residual venous thrombosis to help the decision of anti-coagulation prolongation or discontinuation after the initial period of treatment for deep vein thrombosis.

Carotid disease

In a systematic review and meta-analysis (56 studies) for the U.S. Preventive Services Task Force,[1] the authors concluded a lack of sufficient evidence to establish incremental benefit of carotid endarterectomy (CEA), carotid stenting (CAS), or medical therapy intensification beyond current standard medical therapy, leading to a recommendation *against* screening for asymptomatic carotid artery stenosis in general population.[2] In line with this, a recent analysis of an ongoing trial[3] comparing medical therapy alone vs. CEA vs. CAS in asymptomatic carotid stenosis looked for the clinical significance of progression of asymptomatic carotid stenosis. No statistically significant difference in annual stroke rates can be found between the progression- and non-progression groups, underlining the fact that the stenosis degree is not the sole factor of incident stroke. Further criteria are matter of active research, including ultrasound assessment of microembolic signals or cerebral blood flow reserve, identification of high-risk plaque through ultrasound, MRI or positron emission tomography, and the detection of asymptomatic brain damage.[3] Against the general trend showing safety in case of asymptomatic carotid stenosis treated with current standards of medical therapy, a recent series reported high rates of early ischaemic neurologic events after ultrasound diagnosis, especially in case of >90% stenosis, in favour of intervention.[4] This study suggests that there may be still some place for discussion regarding revascularization of asymptomatic carotid stenosis, mainly because there might be a subgroup of asymptomatic patients with a higher stroke risk, which must be identified by future research.

The preferred strategy to cure carotid stenosis (either asymptomatic or symptomatic) is also still debated. Carotid stenting has become increasingly popular as an alternative to CEA, with less invasiveness, more comfort for the patient and shorter recovery period. Long-term safety and clinical durability of CAS compared with CEA have been established by numerous randomized clinical trials (RCTs), although they differ regarding their reported peri-operative safety. In addition, significant differences in the requested operators' experience were present. A recent publication of the Carotid Stenting Trialists Collaboration highlighted the significant effect of operator's experience on outcome.[5] In 2014, the Cochrane Stroke Group updated their review and concluded that CAS was associated with a

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higher risk than CEA for death and any stroke within 30 days of treatment. This statement was supported by the results from a National Hospital Discharge Database.[6] Large registries have obtained data (only from expert centres of excellence) on equivalence, or the non-inferiority, of CAS over CEA.[7] The long-term (10 years) results of a single-centre study comparing CAS with CEA with equivalent risk of death (over 50%) and similar risk of ipsilateral stroke for both procedures has been recently reported.[8]

Based on the most updated literature, the 2014 AHA/ASA Guidelines[9] recommended CAS as an alternative to CEA for symptomatic patients at average or low risk for complications, quite similar to the ESC guidelines in 2011.[10] For patients >70 years, CEA may be associated with improved outcome compared with CAS. Importantly, the trials supporting these guidelines were mainly focused on mortality and stroke. The trial providing 10 years results reported higher long-term risk of myocardial infarction (MI) in case of symptomatic carotid stenosis, especially among patients who underwent CEA, in accordance with several earlier reports showing increased risk of peri-operative MI. It is plausible that the coronary risk should also be entered in the equation for selecting appropriate carotid revascularization modality, but this requires further studies.[8]

Renal arteries

The CORAL trial (*Table 1*), the largest ever performed to assess the benefits of angioplasty in case of renovascular disease put a definite full stop on the extended use of this technique to hypertension and/or limit renal failure.[16] A meta-analysis adding these new data to those of other six trials (a total of 2139 patients with atherosclerotic renal stenosis) confirmed the lack of improvement in any outcome.[18] At this point, even the analysis of subgroups (e.g. renal function class, hypertension severity, stenosis degree, intra-arterial pressure recovery, etc.) have not identified any benefit of renal angioplasty over medical treatment in any setting. Nonetheless, these data are related to atherosclerotic disease, and renal angioplasty should be discussed in case of fibromuscular dysplasia.

The even more disappointing data came from the multicentre randomized single-blind Simplicity-3 trial (*Table 1*), comparing renal denervation with a sham procedure, conducted to validate the prior promising results in favour of major benefits to control resistant hypertension (i.e. uncontrolled hypertension with systolic blood pressure ≥160 mmHg despite taking ≥3 anti-hypertensive drugs at maximally tolerated doses).[17] The lack of efficacy, both in office and ambulatory pressure change, halted the big momentum of ongoing (or planned) trials. New technology, pathophysiology insights, and a better selection of patients are potential keys for future success.

Lower-extremities artery disease

The Global Burden Disease estimated increased LEAD-related death between 1990 and 2010 (*Figure 1*).[19] In the USA, the incidence of CLI was estimated at 0.35% per year but one half of patients declared CLI without previous diagnosis of LEAD.[20]

Two studies identified elevated cardiac biomarkers as a tool for risk stratification in patients with LEAD, as they were tightly associated with worse prognosis. In patients undergoing endovascular revascularization, pre-procedural cardiac troponin-T (cTnT) levels >0.01 ng/mL were independently associated with 1-year all-cause mortality (HR = 8.1) and amputation (HR = 3.7).[21] In claudicants, high cTnT was associated with increased risk of 7-year all-cause and cardiovascular (CV) death.[22] The clinical relevance of the use of cTnT for risk stratification in LEAD needs further investigation.

The benefits of statins in preventing peripheral outcomes in LEAD patients (−18% at 4 years) were highlighted in the REACH registry.[23]

A recent meta-analysis confirmed the benefits of exercise training on walking distances.[24] Current research is focused on home-based exercise, with favourable effects in in terms of walking distance and vascular function.[25,26]

In the IRONIC trial (158 patients), quality of life improved in case of revascularization (vs. medical therapy) despite trivial amelioration of total walking distance, reopening the debate of revascularization in claudicants.[13]

Initial studies comparing drug-eluting balloons (DEBs) with percutaneous transluminal angioplasty (PTA) suggested that DEB may reduce restenosis and reintervention rates and improve wound healing/limb preservation in CLI patients. Two RCTs on DEB have been published in this setting in 2014.[11,12] The LEVANT-I trial randomized 101 Rutherford classes 2–5 femoro-popliteal lesions to Lutonix DEB or PTA, after stratification by intention to stent the lesion.[12] At 6 months, DEB yielded lower late lumen loss (LLL) (*Table 1*). The IN.PACT-DEEP randomized 358 patients with CLI 2 : 1 to DEB or PTA. Despite significantly longer lesions and deeper ulcers in the PTA arm, unexpectedly neither the clinically driven target lesion revascularization (TLR) nor the LLL were significantly better in the DEB arm at 1 year (*Table 1*).[11] While the study met its non-inferiority hypothesis regarding the primary safety endpoint, there was a trend towards increased major amputations (8.8 vs. 3.6%; $P = 0.080$) in the DEB arm. These results should be interpreted as device-specific and should not preclude further research, which should be systematically associated with standardized wound care.

Most recently, the IN.PACT SFA I trial was presented; 331 patients with femoro-popliteal lesions in Rutherford classes 2–4 were randomized 2 : 1 to DEB or PTA.[14] At 12 months, the DEB group showed better primary patency (*Table 1*), clinically driven TLR (2.4 vs. 20.6%), and MACE rate (6.3 vs. 24.3%) ($P < 0.001$ for all), setting DEB as a primary therapy for atherosclerotic lesions of the superficial femoral artery. This is the first trial showing superiority of DEB over PTA based on clinical endpoints. Balloon materials and coating technologies affect substantially the ability of DEB to deliver therapeutic paclitaxel regimens into the vessel wall. This, along with patients and lesions selection may explain the variability of results obtained, requiring therefore further trials to refine the best techniques and indications.

Abdominal aorta aneurysm

The ESC guidelines on the management of the whole aorta were published in 2014.[27] They emphasized on the opportunistic screening of abdominal aorta aneurysm (AAA) during echocardiography in men >65 years (Class IIa, Level B), based on a French nationwide study reporting a 5.4% prevalence, at the median cost of 1.7 min to screen AAA.[28] These guidelines emphasized on the high level of CV risk in these patients and the importance of prevention and

Table 1 Summary of major randomized trials or meta-analyses in peripheral intervention in 2014

Study	Aim	Type	Challenger	Reference	No. of participants: total (challenger/comparator)	Setting (indication)	Primary endpoint	Main objective achieved?
Carotid arteries								
Meta-analysis for the US Preventive Services Task Force[1]	To assess benefits of screening and treating CS (asymptomatic)	Meta-analysis	Screening + revasc. if needed	No screening	78 Reports/56 studies	Population	Stroke or TIA	No sufficient evidence
Lower-extremities arteries								
IN.PACT-DEEP[11]	To compare DEB vs. PTA for BTK lesions	Open	DEB	PTA	358 (239/119)	CLI	Efficacy: clinically driven TLR and LLL at 1 year; safety: composite of death, major amputation, and TLR	Efficacy No: TLR 9.2 vs. 13.1% ($P = 0.29$); LLL 0.61 ± 0.78 mm vs. 0.62 ± 0.78 mm ($P = 0.95$); safety yes: 17.7 vs. 15.8% ($P = 0.02$[a])
LEVANT-I[12]	Compare DEB vs. PTA in fem-pop lesions	Open	DEB ($\pm$ stenting)	PTA ($\pm$ stenting)	101 (49/52)	Rutherford classes 2–5 fem-pop lesions	Late lumen loss at 6 months	Yes: 58% lower LLL ($P = 0.016$)
IRONIC[13]	Benefits of revascularization on quality of life	Open	Revascularization (surgical or endovascular)	Non-supervised training advice	158 (79/79)	Unselected patients with claudication	Health-related quality of life after 1 year	Yes: improved quality of life ($P < 0.01$)
IN.PACT SFA I[14]	DEB vs. PTA for fem-pop lesions	Open	DEB	PTA	331 (220/111)	Rutherford classes 2–4 fem-pop lesions	Efficacy: primary patency at 1 year; safety: freedom MAE[b]	Efficacy yes: primary patency 82.2 vs. 52.4% ($P < 0.001$); safety yes: MAE[b] 6.3% vs. 24.3% ($P < 0.001$)
Abdominal aorta								
IMPROVE[15]	EVAR vs. open surgery in ruptured AAA	Open	EVAR	Open surgery	613 (316/297)	Patients referred for ruptured AAA	30-day mortality	No: 30-day death EVAR: 35.4 vs. 37.4% (surgery), $P = 0.62$
Renal arteries								
CORAL[16]	Benefits of renal artery stenting in renovascular HTN	Open	Renal artery stenting	Medical therapy	933 (459/472)	Renal artery stenosis with either HTN or CKD	Death, nonfatal MI, stroke, renal function, and hosp. for CHF.	No: HR = 0.94 ($P = 0.58$)
SIMPLICITY-3[17]	Benefits of renal denervation in resistant HTN	blinded	Denervation (+medical therapy)	Sham (+medical therapy)	535 (364/171)	Resistant HTN ($\geq$160 mmHg with $\geq$3 drugs)	6-months office SBP change	No: −2.39 mmHg difference ($P = 0.25$)

AAA, abdominal aorta aneurysm; CS, carotid artery stenosis; DEB, drug-eluting balloon; EVAR, endovascular aortic repair; Fem-pop, femoro-popliteal; HTN, hypertension; LLL, late lumen loss; PTA, percutaneous transluminal angioplasty; SBP, systolic blood pressure; TIA, transient ischaemic attack.

[a]For non-inferiority.

[b]Combining death, clinically driven TVR, major amputation, and thrombosis.

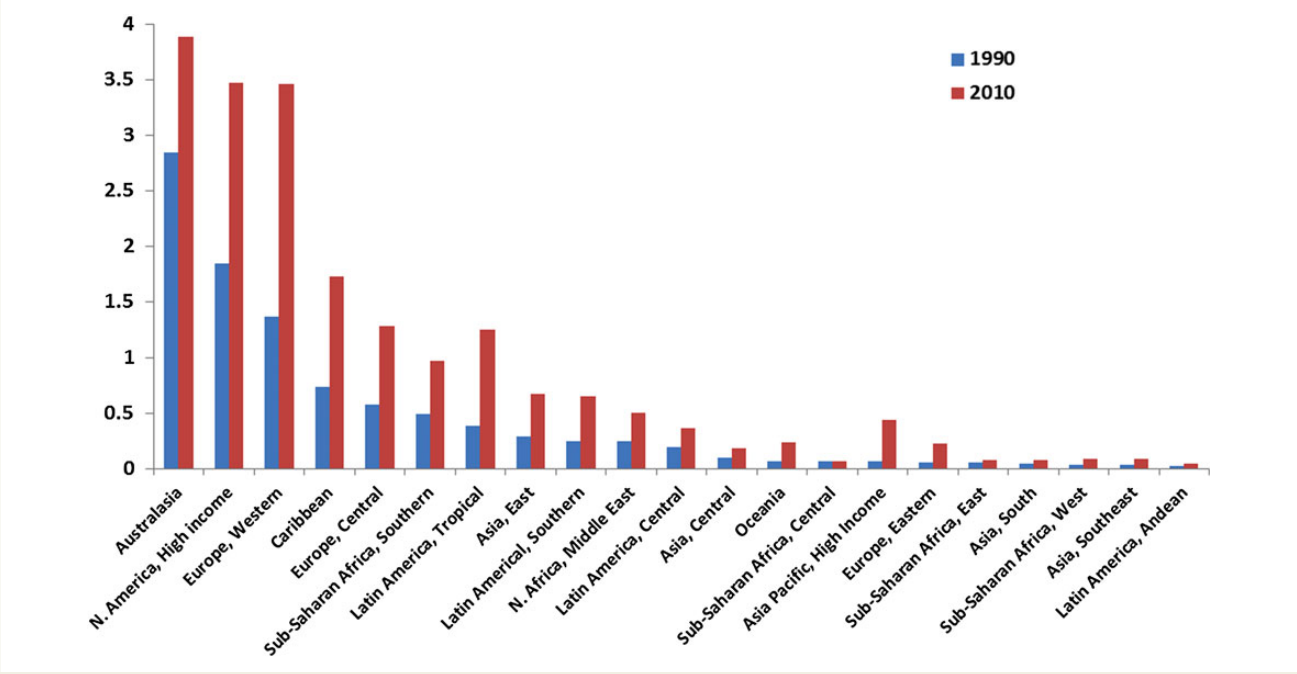

Figure 1 Mean death rates (per 100 000) related to lower-extremities artery disease in the 21 global regions, 1990 and 2010. The Global Burden Disease project. Adapted from Sampson *et al.*[19]

medical therapy beyond aortic interventions.[27] A *post hoc* analysis of a Dutch randomized trial comparing surgery vs. endovascular aortic repair (EVAR) for AAA showed a significant reduction of long-term total- (by 50%) and CV mortality (by 60%) in case of preoperative statins,[29] in line with data from a large national database (>20 000 interventions), which showed that >50% of these patients were regrettably not under statins.[30] In turn, anti-coagulation, often necessary for cardiac indications in patients undergoing EVAR, could increase the risk of endoleaks[31,32] and reintervention,[31] suggesting closer surveillance.

In most centres, patients with AAAs are usually treated endovascular (EVAR), if the anatomy is suitable. The ESC guidelines put at a same level of performance open surgery and endovascular therapy (EVAR).[27] Clinical evidence based on several RCTs indicates that EVAR is associated with superior peri-operative outcomes and similar long-term outcomes if compared with open surgery, although requiring more often re-intervention. Nevertheless, the mortality rates reported in these trials is lower than those in registries, outside the restrictions of RCTs.[33] Since these RCTs, stent-graft technology has been further developed by profile down-sizing, fixation, and sealing optimization, the use of low porosity fabrics, improved imaging techniques and better intervention planning. For these reasons, the ESC Guidelines recommended that the indication for EVAR be decided on an individual basis, according to anatomy, pathology, comorbidity, and anticipated durability.[27]

In the past few years, fenestrated and branched stent-graft systems have increasingly been used to treat anatomically challenging aneurysms. At the same time, chimney techniques have been used to extend landing zones for EVAR. The results of both techniques demonstrate that the procedure can be implemented with a high degree of success. On the other hand, there is concern about the major adverse events, including side-branch patency and endoleak.[34,35] Ongoing studies and technological refinement of stent grafts will hopefully continue to broaden the utilization of EVAR.

There is clinical equipoise between open surgical repair and EVAR for patients with a ruptured AAA (rAAA). A systematic review and meta-analysis and an RCT comparing treatment strategy showed that EVAR is not inferior to open repair in patients with an rAAA. This supports the use of EVAR in suitable patients and OR as a reasonable alternative.[15,36]

Vascular wall biomarkers

Peripheral vascular wall biomarkers show great potential in improving risk prediction beyond scores based on risk factors. An abnormal value of a biomarker would imply closer follow-up and earlier or even intensified preventive therapies. In a recent meta-analysis of 17 635 individual data, a 1 SD increase in carotid-femoral pulse wave velocity (cfPWV) increases CV events, CV mortality and total mortality by 30, 28, and 17%, respectively.[37] Most importantly, this arterial stiffness biomarker fulfils a stringent criterion for qualification as surrogate clinical endpoint: it improves overall 10-year risk classification for intermediate risk subjects by 13%.[37] In patients with erectile dysfunction, a prognostic marker of generalized arterial disease and CV events, cfPWV improves risk prediction and reclassifies 28% of patients to higher or lower risk category.[38] In contrast, cIMT showed a mediocre improvement (5.6%) in net reclassification index in intermediate risk patients with hypertension, currently tempering the expectations for this biomarker.[39] In an attempt to "map" arterial stiffness along the arterial tree, the Hoorn

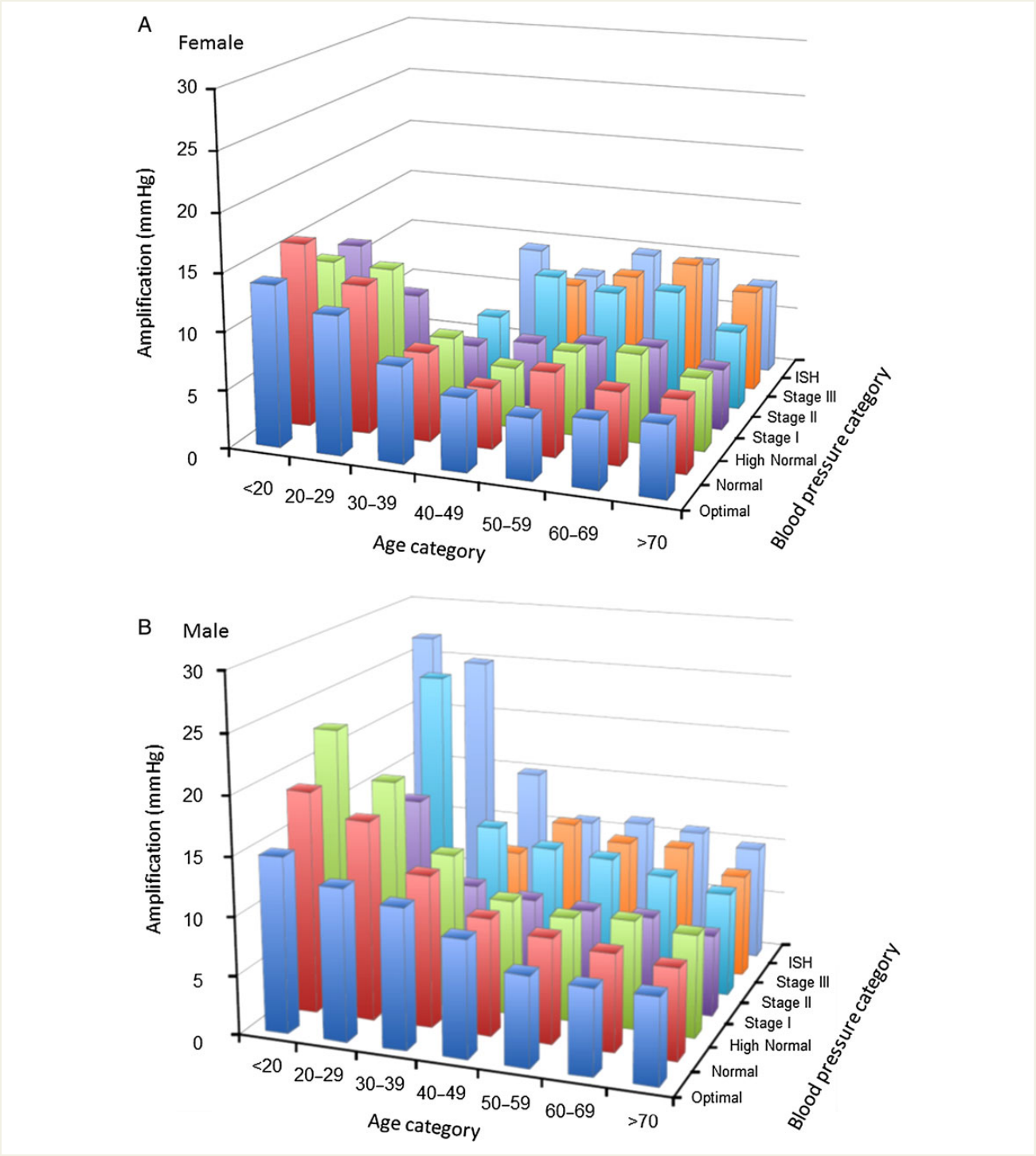

Figure 2 Tridimensional bar graphs representing amplification (peripheral—central systolic blood pressures represented by medians) according to sex (females up, males bottom), age, and blood pressure categories. Some categories are not represented because there were <50 observations.[41]

study[40] showed that local carotid and femoral arterial stiffness indices predicted, independently from each other and from cfPWV, all-cause mortality and CV events. Central (aortic, carotid) pressures are lower than peripheral (brachial) pressures and they may have a better predictive ability. Difference between central and peripheral pressures is higher in younger ages, in males, and with increasing levels of blood glucose, while smoking and dyslipidaemia decrease this difference.[41] In an important step towards clinical implementation, reference values for central pressures were determined in a general healthy population and according to CV risk factors (*Figure 2*).[41]

Venous thrombosis

In occasion of the first World Thrombosis Day (13 October 2014), an article by Raskob *et al.* showed that VT has a similar impact on CV mortality and morbidity as arterial thrombosis.[42] Across a wide range of low, middle, and high income countries, annual VT incidence ranges from 0.75 to 2.69 per 1000 individuals, up to 2–7 per 1000 among those aged >70, which represents a major global disease burden. Its prevention is therefore an important goal in CV prevention. The INSPIRE trial provides evidence of a 40% VT recurrence reduction under aspirin, suggesting a role for this drug in patients unfit for oral anti-coagulants (which remain the mainstream treatment).[43] Indeed, direct oral anti-coagulants are changing VT treatment paradigms showing a safer profile with similar efficacy as anti-vitamin K.[44] Likely, a growing number of VT patients will benefit from these drugs as their refinement is pursuing.

Identification of patients at low risk of VT recurrence after an initial episode is important to withheld unnecessary and potentially harmful anti-coagulation. The DULCIS study showed that persistently normal D-dimer tests allow safe anti-coagulation discontinuation in >50% of patients after a single VT episode (idiopathic or secondary to weak factors).[45] The Cancer-DACUS study[46] assessed the importance of residual VT, assessed by ultrasound, 6 months after low-molecular-weight heparin treatment in patients with cancer-associated DVT. Results showed that in the absence of residual VT, anti-coagulation discontinuation is safe while its continuation in case of residual VT, up to 1 year, does not appear to be beneficial. Early thrombolysis has been shown to increase vein patency and reduce the incidence of post thrombotic syndrome offering potential advantages for selected patients.[47] Further studies on long-term clinical outcomes, comparative procedures, and cost analysis of interventional procedures as well as risk stratification of patients with VT disease are necessary.

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