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REVIEW ARTICLE

Systematic reviews and meta-analyses for more profitable strategies in peripheral artery disease

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In the peripheral arteries, a thrombus superimposed on atherosclerosis contributes to the progression of peripheral artery disease (PAD), producing intermittent claudication (IC), ischemic necrosis, and, potentially, loss of the limb. PAD with IC is often undiagnosed and, in turn, undertreated. The low percentage of diagnosis (~30%) in this setting of PAD is of particular concern because of the potential worsening of PAD (amputation) and the high risk of adverse vascular outcomes (vascular death, coronary artery disease, stroke). A Medline literature search of the highest-quality systematic reviews and meta-analyses of randomized controlled trials documents that, due to risk of bias, imprecision, and indirectness, the overall quality of the evidence concerning diagnostic tools and antithrombotic interventions in PAD is generally low. Areas of research emerge from the information collected. Appropriate treatments for PAD patients will only derive from ad-hoc studies. Innovative imaging techniques are needed to identify PAD subjects at the highest vascular risk. Whether IC unresponsive to physical exercise and smoking cessation identifies those with a heritable predisposition to more severe vascular events deserves to be addressed. Devising ways to improve prevention of vascular events in patients with PAD implies a co-ordinated approach in vascular medicine.

Key words: Absolute benefits, antithrombotic treatments, areas of research, diagnostic tools, harms, limitations, open issues, quality of the evidence

Key messages

- The overall quality of the evidence concerning diagnostic tools and antithrombotic interventions in PAD is low in most cases.
- New antithrombotic treatment is a major target to improve prevention of vascular events in patients with PAD.
- Innovative imaging techniques should be explored to identify PAD subjects at the highest vascular risk.

Introduction

Atherothrombosis (thrombus formation superimposed upon atherosclerosis) is an unpredictable, sudden disruption (rupture or erosion/fissure) of an atherosclerotic plaque, which leads to platelet activation and thrombus formation (1). Rupture/fissure of a plaque acts as a stimulus for atherothrombosis (2). From a clinical point of view, atherothrombosis is a progressive, generalized disorder with manifestations—either acute or chronic and often multiple in any single patient—affecting the coronary, cerebral, and peripheral circulation (3). In the case of a non-occlusive thrombus, ischemic symptoms are temporary and thrombosis can contribute to plaque growth through formation and resolution of subclinical platelet thrombi (thrombus formation is a dynamic process in which platelets aggregate but also spontaneously disaggregate, eventually leading to embolization of platelet aggregates from an evolving thrombus) (4). In the case of an occlusive thrombus, there will be an acute ischemic syndrome in the coronary, cerebral, or peripheral vascular territory depending on the localization of the atherosclerotic plaque, potentially leading to permanent tissue damage. Because of the generalized and progressive nature of atherothrombosis, symptoms of the disease in one vascular bed are highly predictive of the risk of further ischemic events elsewhere. Cardiovascular and cerebrovascular events and peripheral artery disease (PAD) are thus part of a continuum of disease with the common underlying pathophysiology of atherothrombosis (5).

In the peripheral arteries, a thrombus superimposed on atherosclerosis contributes to the progression of PAD, producing intermittent claudication (leg pain on walking that is relieved by rest), ischemic necrosis, and, potentially, loss of the limb. PAD affects about 8–10 million Americans, and every year it causes

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500,000 hospitalizations and 100,000 angiograms in the US (6). Significant coronary artery disease (in at least one coronary artery) has been documented in 60%–80% of patients with PAD, and hemodynamically significant carotid artery stenosis (by duplex ultrasound) has been found in 12%–25% (7). Accordingly, the annual overall major vascular event rate (acute myocardial infarction, ischemic stroke and vascular death) is ~5%–7% in PAD patients. The risk of AMI is increased by 20%–60%, whereas the risk of coronary death is increased 2–6-fold. PAD is associated with a 40% increase in the risk of stroke, and PAD severity is positively associated with the incidence of transient ischemic attacks (TIA) and stroke (6).

The clinical spectrum of PAD is widely variable: patients may either be asymptomatic or, because of an impaired equilibrium between oxygen demand and supply, have pain as a result of a minimal exercise (e.g. walking) (8). ACC/AHA recommendations for the diagnosis of PAD are reported in Table I. Most asymptomatic patients with PAD will be identified through ankle-brachial index (ABI) screening (9). The ABI is the ratio of the highest systolic blood pressure in the lower limb to that of the arm. The TASC-II (10) guidelines also indicate the ABI as an easy, reliable means for the evaluation of PAD severity (Table II). Resting ABI should be measured in both legs in all new patients with PAD of any severity to confirm the diagnosis and establish a baseline.

PAD (ABI <0.9) with intermittent claudication (IC) is often undiagnosed and, in turn, undertreated. In 5298 Italian patients at moderate vascular risk, with no overt vascular diseases nor diabetes mellitus (DM) (11), 0.02% had an ABI ≤ 0.4; 22.85% had an ABI ranging from 0.4 to 0.9; 23.9% had an ABI ranging from 0.91 to 0.99; 52.35% had an ABI ranging from 1.0 to 1.29; and 0.88% had an ABI ≥ 1.30. In 2027 Italian patients with non-valvular atrial fibrillation (AF), 21% had an ABI ≤ 0.9; 69% had an ABI ranging from 0.91 to 1.40; and ~10% had an ABI ≥ 1.40 (12). The low percentage of diagnosis (~30%) among those with an ABI <0.9 is of particular concern because of the high risk of adverse outcomes related to the worsening of PAD. Moreover, a low ABI (<0.90) is a predictor of AMI, stroke, and vascular mortality independently of established vascular risk factors (13–15). Among those with ABI <0.9, ~25% will experience worsening claudication necessitating surgical repair or amputation. During 5 years of follow-up (16), 10%–20% of patients with IC would be expected to experience non-fatal AMI or stroke. In addition, death from coronary artery disease, other vascular diseases, and non-cardiovascular causes would be expected in 30%. In a longer (10-y) follow-up (17), about 55% of PAD (ABI <0.9) patients died of cardiovascular disease, 10% of cerebrovascular disease, and 25% of non-vascular reasons. Less than 10% died of other vascular events (mostly, aortic aneurysms in the abdomen). In another follow-up (18), 10-y mortality was 61.8% in males with symptomatic PAD (ABI <0.9); in comparison, in males without PAD (ABI <0.9) mortality was 16.9%. Mortality rates in females were 33.3% and 11.6%, respectively. Less than 25% of patients with PAD (ABI <0.9) survived for 10 y, vascular mortality being the dominant cause of death in that setting. After correction for established risk factors, PAD was an independent predictor of death. In the latter report, the subjects were classified as normal (no evidence of PAD), asymptomatic (no claudication), symptomatic (with claudication), and as subjects with severe PAD (claudication + abnormal diagnostic tests). The risk of death was related to the severity of PAD and was as strong as that for cancer. The latter has emerged from 744 patients with PAD (19): in a 5-y follow-up, those with severe PAD (ABI <0.4) had 56% probability of surviving. Based on data collected in parallel (1986–1993), this figure was comparable with the 5-y survival curves (52%) in Caucasian patients with non-Hodgkin lymphomas.

These data set the stage for an extraordinary high morbidity and mortality in patients with PAD. As a matter of fact, over

Table II. TASC II guidelines for ABI interpretation.

ABI value	Interpretation
>0.9	Normal
<0.9	Atherosclerotic disease
0.4–0.9	PAD (IC)
<0.4	PAD (CLI)

Data from: J Vasc Surg. 2007;45(Suppl S):S5–67; modified.
ABI = ankle-brachial index; CLI = critical limb ischemia; IC = intermittent claudication; PAD = peripheral artery disease.

Table I. ACC/AHA 2013 recommendations for the diagnosis of PAD by non-invasive tools.

Diagnostic modality	Class of recommendation	Indications
Pulse volume recording	Class 2a; level B	To establish the initial PAD diagnosis, assess localization and severity, follow the status of lower-extremity revascularization procedures
Continuous-wave Doppler ultrasound	Class 1; level B	To provide an accurate assessment of PAD location and severity, to follow PAD progression, to provide quantitative follow-up after revascularization procedures
Treadmill exercise testing with and without ABI assessments and 6-min walk test[a]	Class 1; level B	To provide objective evidence of the magnitude of the functional limitation of claudication and to measure the response to therapy To differentiate arterial claudication from non-arterial claudication ('pseudoclaudication')[b] To determine functional capacity, assess non-vascular exercise limitations, and demonstrate the safety of exercise[c]

[a]Standardized exercise protocol (either fixed or graded) with a motorized treadmill should be used to ensure reproducibility of measurements of pain-free walking distance and maximal walking distance (level of evidence: B).
[b]Exercise treadmill tests with measurement of pre-exercise and post-exercise ABI values are recommended to this end.
[c]Exercise treadmill tests to be performed in individuals with claudication who are to undergo exercise training (lower extremity PAD rehabilitation). A 6-min walk test may be reasonable to provide an objective assessment of the functional limitation of claudication and response to therapy in elderly individuals or others not amenable to treadmill testing (Class IIb, level of evidence: B).

the last decades, while no currently available specific treatment for PAD is associated with a significant reduction in morbidity and mortality rates, screening programs for primary prevention of coronary artery disease and use of statins, ACE and platelet inhibitors, β-blockers, etc. have dramatically decreased the risk of major cardiovascular events (and of progression in arterial occlusion) in the PAD setting (20).

Critical limb ischemia (CLI; ABI < 0.4), is observed in 12% of the PAD population (21). In most cases, CLI is an advanced thrombotic complication of PAD, due to inadequate resting blood flow to the lower limbs, and marked by rest pain, ulceration, and eventually gangrene and loss of the limb (22). The limb typically has developed a collateral blood supply, and the final occlusion of the vessel often is not immediately limb threatening with slow progression of disease (23). CLI is seldom the result of an acute event (e.g. embolism, thrombosis, or trauma). Approximately 80% of emboli originate in the heart (e.g. left atrial appendage, left ventricular apex, cardiac valves) (24). In the remaining cases, they originate from the aorta or peripheral vessels or from the veins (with migration through patent foramen ovale and atrial septal defects). Patients with CLI are candidates for prompt revascularization. CLI increases mortality: in the first year after the diagnosis 25% of patients (45% with amputation) will die, and 30% of them will have amputations, whereas only 45% will survive with both legs. After 5 years more than 60% of patients have died (25).

Literature search method

In an attempt to identify potential reasons why PAD with IC is underdiagnosed and undertreated, the following questions have been raised: 1) Is the overall quality of the evidence concerning diagnostic tools for PAD as good as that for other atherothrombotic conditions? And 2) Is the overall quality of the evidence concerning antithrombotic interventions for PAD as good as that for other atherothrombotic conditions?

To estimate absolute benefits, harms, and limitations associated with a given treatment/diagnostic tool, a Medline literature search of the highest-quality published systematic reviews and meta-analyses of randomized controlled trials in the area was performed using the key words 'diagnostic tools AND PAD' and 'treatments AND PAD', and references of relevance were selected manually. Other references were either provided by the authors or obtained from the reference lists within the relevant selected articles. Databases were updated to August 2013.

Non-invasive and invasive tools for the diagnosis of PAD

Non-invasive imaging is mandatory to detect the anatomy, morphology (e.g. subclinical non-obstructive), and characteristics (e.g. instability) of the plaque in PAD.

By combining B-mode ultrasound and color Doppler ultrasound, duplex ultrasound (DUS) identifies the anatomical location and the degree of a stenosis. Peak systolic velocity (PSV) ratios (as determined within and beyond the obstruction and as compared with the adjacent upstream segment) are useful to estimate the rate of stenosis: a PSV ratio $>$ 2:1 argues for $>$ 50% stenosis, a PSV ratio $>$ 4:1 for a $>$ 75% stenosis, and a PSV ratio $>$ 7:1 for a $>$ 90% stenosis (26). DUS helps identify patients with the need for endoluminal revascularization (27,28) and is currently employed to follow-up venous grafts (29–36). The high sensitivity, specificity, diagnostic accuracy, and cost-effectiveness of DUS has been documented (37–39).

Magnetic resonance angiography (MRA) very carefully defines the borders of the arterial wall (40–42) and identifies the unstable fibrous cup of an atherosclerotic plaque (43). Moreover, by allowing the identification of size, composition (i.e. the lipid-enriched necrotic core, hemorrhages, calcifications, etc.), and ulcerative components, MRA contributes to the morphological characterization of a plaque (44–46). The morphological characterization of the plaque is improved by gadolinium contrast media that help differentiate the necrotic core from the surrounding fibrous tissue (47,48) and document neo-angiogenesis and the inflammatory burden (49,50). Meta-analysis and systematic reviews argue for the diagnostic accuracy of MRA in the PAD setting (51–53). However, these studies also claim that MRA tends to overestimate the degree of stenosis. This is mostly due to turbulence and metal clips that, by mimicking vessel occlusions, can cause artifacts. Likewise, some metal stents may obscure vascular flow and, in turn, cause artifacts (54).

Short acquisition time, very thin slices, high spatial resolution, and improved multi-detector computed tomography scanners enable scanning of the entire vascular tree in a limited period of time by computed tomography angiography (CTA), with a low amount of contrast medium employed and radiation burden (55). These recent technical developments have made CTA one of the most important imaging techniques in PAD. A recent meta-analysis (56) showed its high diagnostic accuracy in the PAD setting. The pooled sensitivity to detect a $>$ 50% stenosis or occlusion was 95% (92%–97%) and the pooled specificity 96% (93%–97%). CTA correctly identified occlusions in 94% of segments, the presence of $>$ 50% stenosis in 87% of segments, and absence of significant stenosis in 96% of segments. Nevertheless, similarly to MRA, CTA tends to overestimate the degree of stenosis (see above for details) (54).

In spite of the current availability of less invasive imaging techniques, catheter angiography (CA) with or without digital subtraction angiography (DSA) is the gold-standard first-line imaging investigation for patients with PAD and the reference method for guiding percutaneous peripheral interventional procedures (54). However, due to the need for contrast media (that may cause renal toxicity, arterial wall dissection, emboli, fistulae, pseudoaneurysms, and access site complications) and to its inherent limitations (no careful hemodynamic study of the stenotic segment nor of its length (overestimated) is possible), the clinical use of DSA is currently limited (57).

Indications, limitations, and contraindications of each imaging technique are reported in Tables III and IV.

Antithrombotic treatment in asymptomatic and symptomatic PAD

Pharmacology of major antithrombotic agents

Antiplatelet agents in PAD

Following atherosclerotic plaque disruption/endothelial cell detachment, circulating platelets, exposed to a highly thrombogenic environment, become activated (58). A series of soluble agonists (ADP, thromboxane A_2 ($T\times A_2$), serotonin (5-HT), and thrombin) recruit and activate additional platelets. Upon activation, glycoprotein (Gp) IIb/IIIa ($\alpha_{IIb\beta3}$ integrin) mediates platelet aggregation and spreading by means of fibrinogen bridges, which, once converted to fibrin, ultimately contribute to thrombus stabilization. This leads to the formation of platelet-rich thrombi that, occluding the arterial lumen and impairing blood-flow and oxygen supply, cause acute ischemia. The efficacy of aspirin lies in its ability irreversibly to inhibit platelet

Table III. Recommendations for different imaging techniques to be employed in the diagnosis of PAD and of CLI.

Imaging technique	Indications	PAD Class of recommendation	CLI Class of recommendation
DUS	Diagnosis of anatomic location and degree of stenosis	Class 1; level A	Class 1, level A
	Routine surveillance after femoral-popliteal or femoral-tibial-pedal bypass with a venous conduit[a]	Class 1; level A	Class 1; level A
	Selection of patients as candidates for endovascular intervention	Class 2a; level B	Class 2a; level B
	Selection of patients as candidates for surgical bypass and selection of the sites of surgical anastomosis	Class 2a; level B	Class 2a; level B
	Assessment of long-term patency of PTA	Class 2b; level B	Class 2b; level B
	Routine surveillance after femoral-popliteal bypass with a synthetic conduit	Class 2b; level B	Class 2b; level B
CV-DUS	Assessment of PAD location and severity, to follow-up PAD progression, and to provide quantitative follow-up after revascularization procedures	Class 1; level B	
CTA[e]	Anatomic location and presence of significant stenosis	Class 2b; level B	Class 2b; level B
	Substitute for MRA for patients with contraindications to MRA	Class 2b; level B	Class 2b; level B
MRA	Anatomic location and degree of stenosis of PAD	Class 1; level A	Class 1; level A
	Anatomical location with use of gadolinium enhancement	Class 1; level B	Class 1; level B
	Selection of patients as candidates for endovascular intervention	Class 1; level A	Class 1 ; level A
	Selection of patients as candidates for surgical bypass and selection of the sites of surgical anastomosis	Class 2b; level B	Class 2b; level B
	Post-revascularization (endovascular and surgical bypass) surveillance	Class 2b; level B	Class 2b; level B
CA, DSA[f]	Arterial anatomy[b]	Class 1; level B	Class 1; level B
	Complete anatomic assessment of the affected arterial territory, including imaging of the occlusive lesion, as well as arterial inflow and outflow in patients who may be treated with invasive therapeutic interventions (percutaneous or surgical)	Class 1; level B	Class 1; level B
	Digital subtraction angiography recommended for contrast angiographic studies (enhanced imaging capabilities compared with conventional un-subtracted contrast angiography)	Class 1; level A	Class 1 ; level B
	Complete vascular examination before performing CA[c]	Class 1; level C	Class 1; level A
	Selective/super-selective catheter placement during lower-extremity angiography to enhance imaging, reduce contrast dose, and improve sensitivity and specificity of the procedure	Class 1; level C	Class 1; level C
	To image the iliac, femoral, and tibial bifurcations in profile without vessel overlap	Class 1; level B	Class 1; level B
	To develop individualized diagnostic strategic plan, including assistance in selection of access sites, identification of significant lesions, and determination of the need for invasive evaluation[d]	Class 2a; level B	Class 2a; level B

Data from: J Am Coll Cardiol. 2013;6:1555–70, modified.
[a]Minimum surveillance intervals are approximately 3, 6, and 12 months, and then yearly after graft placement for PAD and for CLI.
[b]Recommended for evaluation of patients when revascularization is contemplated.
[c]To optimize decisions on the access site, and to minimize contrast dose and catheter manipulation.
[d]As other non-invasive imaging modalities including MRA, CTA, and color flow duplex imaging, to be used in advance of invasive imaging procedures.
[e]Patients with baseline renal insufficiency should receive hydration before undergoing CTA (Grade A, level 2b).
[f]A documented history of contrast reaction before the performance of contrast angiography implies that an appropriate pre-treatment should be administered before contrast is given (Class 1; level B). When conducting a diagnostic lower-extremity arteriogram in which the significance of an obstructive lesion is ambiguous, trans-stenotic pressure gradients and supplementary angulated views should be obtained (Class 1; level B); hydration is needed before undergoing contrast angiography in patients with baseline renal insufficiency (Class 1; level B); treatment with n-acetylcysteine in advance of contrast angiography is suggested for patients with baseline renal insufficiency (creatinine > 2.0 mg per dL) (Class 2a; level B); follow-up clinical evaluation, including a physical examination and measurement of renal function is recommended within 2 weeks after contrast angiography to detect potential delayed adverse effects, such as atheroembolism, deterioration in renal function, or access site injury (e.g. pseudoaneurysm or arteriovenous fistula) (Class 1; level C).
CV-DUS = continuous wave Doppler ultrasound; PTA = percutaneous trans-luminal angioplasty.

COX-1 (by acetylating a serine located near the active site of the enzyme) and, in turn, $T\times A_2$ formation (59). The transduction of the ADP signal involves its interaction with two platelet receptors belonging to the P_2 purinergic family, the Gαq-coupled receptor P_2Y_1 and the Gαi-coupled receptor P_2Y_{12} (60). The concomitant activation of both the Gαq and Gαi pathways by ADP is needed for platelet aggregation to occur. Signaling from the P_2Y_1 receptor causes platelet shape change and rapid transient aggregation, whereas the signaling from the P_2Y_{12} receptor facilitates sustained irreversible aggregation and stimulates surface expression of the pro-inflammatory P-selectin. In addition, the P_2Y_{12} receptor plays a critical role in the amplification of platelet aggregation induced by agents other than ADP, including 5-HT, $T\times A_2$, and thrombin. Together, these contribute to thrombus growth and stability. Two main classes of antiplatelet agents are licensed and widely used chronically in PAD: acetyl salicylic acid (aspirin) and P_2Y_{12} inhibitors (ticlopidine, clopidogrel, prasugrel, cangrelor, ticagrelor) (61).

Aspirin

Owing to its efficacy and favorable cost-effectiveness, aspirin is the mainstay treatment for all atherothrombotic conditions. A recent meta-analysis (60) has assessed the role of aspirin in primary (95,000 subjects at low cardiovascular risk) and secondary (17,000 patients at medium/high risk) vascular prevention. While in high-risk conditions the advantage of aspirin outweigh the inherent bleeding hazard, in primary prevention aspirin is associated with an absolute benefit of 0.06%/year, too exiguous when compared to the 0.03% increase in major bleedings.

Ticlopidine

Ticlopidine was the first agent of the thienopyridine class shown both to prevent the interaction of ADP with its platelet purinergic receptor and to cause inhibition of fibrinogen binding to the $\alpha_{IIb\beta3}$ integrin (62). In subjects with a history of cerebrovascular events, ticlopidine was superior to placebo and to aspirin in the reduction of stroke, AMI, or vascular death (63). In addition, the combination of ticlopidine with aspirin was successful in acute coronary

Table IV. Comparison of different imaging techniques for patients with PAD: additional data.[a]

Parameters	Comparisons (over)	Comments
General:		
Time employed	CTA > MRA or DSA > DUS	15 min for CTA, 30 min for MRA and DSA, > 40 min for DUS (both legs)
Operator expertise	DUS > MRA or DSA > CTA	Expert operators needed especially for DUS
Arteriographic map[b]	MRA = DSA = CTA = DUS	Immediately available with MRA or DSA; post-processing needed for CTA, expert operators for DUS
Availability	DUS or DSA > CTA or MRA	
Equipment cost	MRA or DSA > CTA > DUS	
Diagnostic accuracy:		
Plaque composition[c]	CTA > MRA > DSA > DUS	Plaques: lipid-enriched necrotic core, hemorrhages, calcifications, surrounding fibrous tissue, neo-angiogenesis best seen with CTA
Stent assessment	DUS > DSA > CTA > MRA	MRA: poor assessment in those with steel stents, fair in those with nitinol stents
Aortoiliac	CTA, MRA or DSA > DUS	
Femoropopliteal	MRA = DSA = CTA = DUS	
Tibial	DSA > MRA > DUS or CTA	
Limitations by vascular calcification	MRA > DSA > DUS or CTA	
Complications and risks:		
Contraindications[c]	DUS > MRA > CTA or DSA	DUS: none; MRA: claustrophobia, cerebrovascular clips, electronic implants (infusion or monitoring devices, pace-makers, neurostimulatory devices, cardioverters, defibrillators); DSA: severe renal impairment
Radiation exposure	DUS or MRA > CTA > DSA	CTA: 7.5–13.7 mSv
Contrast-enhanced nephropathy	DUS > MRA > CTA or DSA	
Nephrogenic systemic fibrosis avoidance	DUS, CTA, or DSA > MRA	
Allergic reaction	DUS > MRA > CTA or DSA	
Access site	DUS, CTA, or MRA > DSA	

[a]Data from: Eur J Vascular Endovasc Surg. 2011;42(S2):S13–S32; modified.
[b]With CTA, scanning of the entire vascular tree is achieved in a limited time, and the amount of contrast medium and radiation burden is low.
[c]Known allergy to contrast media for both MRA and DSA.

syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI) with stent implantation (64). Diarrhea, aplastic anemia, thrombotic thrombocytopenic purpura, and neutropenia are the main limitations for a widespread use of ticlopidine.

Clopidogrel

The thienopyridine prodrug clopidogrel irreversibly binds the P_2Y_{12} platelet receptor after a two-step activation by cytochrome P450 (CYP) liver isoenzymes. A variety of polymorphisms in the CYP2C19 gene (most often the CYP2C19*2), associated with a 20%–25% production of inactive metabolite, diminish the response to clopidogrel. Among subjects under treatment with clopidogrel for a previous vascular event, carriers of these polymorphisms have a 50% higher risk of cardiovascular death, AMI, or stroke (58). Among clopidogrel-treated patients, carriers of at least one allele associated with the loss of or a reduced function in the CYP2C19 gene had a higher than normal occurrence of fatal and non-fatal coronary thrombotic events, as well as of stent thrombosis (58). In the same study population, polymorphic alleles of a gene modulating clopidogrel absorption (ABCB1) have been associated with a higher rate of cardiovascular events at 1-year follow-up as compared to wild-type subjects.

Ticagrelor

Ticagrelor, an orally active cyclopentyl-triazolo-pyrimidine, binds to domains of the P_2Y_{12} receptor other than those recognized by ADP (the 1, 2, and 7 transmembrane domains, the extracellular loop 2, and the N-terminal domain), determining a potent and rapid non-persistent receptor conformational change. After the occupancy of P_2Y_{12}, ADP-catalyzed conversion of cAMP from ATP, dephosphorylation of phosphorylated VASP, and activation of phosphoinositide 3-kinase are blocked. The net result is a reduced exposure of fibrinogen-binding sites on the $\alpha_{IIb\beta3}$ integrin receptor and, in turn, the inhibition of platelet aggregation. Inhibition of ADP-mediated constriction of vascular smooth muscle and enhancement of adenosine-induced coronary blood-flow are also reported. After oral administration, ticagrelor is rapidly absorbed and does not require hepatic biotransformation to be pharmacologically active. However, ticagrelor is also metabolized to an equipotent, active metabolite (AR-C124910XX) by CYP_3A_4 enzymes. As both ticagrelor and AR-C124910XX are excreted by the intestinal route, no dose adjustment is needed in kidney failure. On the other hand, the concomitant use of CYP_3A_4 inhibitors/inducers as well as a significant liver dysfunction may be of concern for its use. After pharmacodynamic evaluations (65,66), a 90-mg twice-daily dose of ticagrelor has been chosen to optimize its efficacy, safety, and tolerability. A loading dose of 180–270 mg may minimize intersubject variability as to initial inhibition in platelet aggregation and may be appropriate in ticagrelor-naive patients with ACS or in preparation for PCI. In 174 subjects with a recent coronary artery disease receiving 75–100 mg/day aspirin (92 also under ticagrelor 180-mg load and 90 mg twice-daily maintenance dose, and 82 also under clopidogrel 600-mg load and 75 mg/d maintenance dose) the genotyping of the cytochrome P450 (CYP) 2C19 (*1,*2,*3,*4,*5,*6,*7,*8,*17) was performed. In addition, platelet function was measured (by aggregometry, VerifyNow P_2Y_{12} assay, and VASP assay at pre-dose, 8 hours post-loading, and during maintenance). There was no significant effect of the genotype on platelet function during aspirin therapy alone. On the other hand, irrespective of the 2C19 genotype, of the metabolizer status, and of the assays employed, subjects on ticagrelor showed a lower platelet reactivity than did those on clopidogrel ($P < 0.01$). This is consistent with a genotype-independent better pharmacodynamic effect of ticagrelor as compared to clopidogrel (67).

Cilostazol

Cilostazol, selectively targeting phosphodiesterase type 3 (PDE3) and, then, determining intracellular cAMP accumulation, inhibits platelet aggregation (68). In diabetic patients on standard dual antiplatelet therapy, adjunctive treatment with cilostazol enhances inhibition of platelet P_2Y_{12} signaling (69). A Cochrane review (70), in which two randomized studies on stroke prevention were summarized, documented that, compared with aspirin, cilostazol was associated with a significantly lower risk of vascular events (6.77% versus 9.39%; RR 0.72; 95% CI 0.57–0.91, composite outcome) and a lower risk of hemorrhagic stroke (0.53% versus 2.01%; RR 0.26; 95% CI 0.13–0.55). In terms of outcome of safety, cilostazol was associated with significantly fewer adverse events (8.22% versus 4.95%; RR 1.66; 95% CI 1.51–1.83) than aspirin. In the SILOAM phase IV study (ClinicalTrials.gov Identifier: NCT01261832), a triple antiplatelet therapy (cilostazol plus aspirin and clopidogrel) is compared (at 1 month and at 6 months) with the standard dual antiplatelet treatment (ASA and clopidogrel) in 951 ACS subjects (expected number) undergoing PCI and drug-eluting stent implantation. The primary efficacy end-point is the occurrence of major cardiovascular and cerebrovascular events (total death, non-fatal myocardial infarction, repeat revascularization, stroke). The end of the study is expected by July 2014.

Primary prevention of cardiovascular events in asymptomatic PAD (Table V)

On the basis of an individual participant data meta-analysis for primary and secondary prevention of coronary artery disease (60) and of data from a meta-analysis on cancer (71), aspirin is expected to reduce total mortality and to increase major bleedings (72). Since this is especially true in subjects taking more than one drug daily (most PAD patients), and since similar benefits are seen in patients with IC and those who had undergone peripheral vascular grafting or angioplasty, the use of aspirin over a prolonged time period should be encouraged on an individual basis. Regardless of this decision, intensive treatment for cardiovascular risk factor modifications (73) is mandatory for primary prevention of cardiovascular events in patients with PAD. Tobacco cessation should be encouraged, eventually by behavior modification or pharmacologic strategies (74). Cessation of tobacco use significantly reduces lower-extremity symptoms and progression of PAD, thus helping improve the maximal walking distance achieved by structured exercise programs (75). As in other patients with high cardiovascular risk, LDL cholesterol levels should be lowered to <70 mg/dL in PAD patients (76). A sub-analysis of 6748 patients with PAD in the Heart Protection Study showed significant reductions in total mortality, vascular mortality, coronary heart disease events, strokes, and non-coronary revascularization in those treated with simvastatin (77). There was no threshold cholesterol value below which statin therapy was not associated with benefit (78–80). Statins improve the pain-free walking distance (81) and reduce the progression of PAD, the overall cardiovascular risk, and the occurrence of complications needing invasive procedures (82). The goal for blood pressure control in PAD is $<140/90$ mmHg; in those with PAD and DM or with chronic kidney disease, it should be $<130/80$ mmHg (83). In a subgroup of 4046 patients with PAD, the Heart Outcomes Prevention Evaluation study showed that those randomly assigned to the angiotensin-converting enzyme inhibitor ramipril had a 22% reduction in risk, compared with the placebo group, that was independent of lowering of blood pressure (84). Because of the additional cardio-protective effects, the use of β-blockers is important in patients with coexisting coronary artery disease. Although no trials have been designed or powered to examine glycemic control, a tight plasma glucose control reduces PAD progression in diabetic patients with PAD (85–90) and improves the clinical outcome of percutaneous revascularization (91). To this end, the reduction of the A1c hemoglobin levels $<7\%$ should be associated with the control of all risk factors, proper foot care (e.g. cleansing of skin lesions), and appropriate footwear (92).

Secondary prevention of cardiovascular events in symptomatic PAD

Main findings from the meta-analysis of aspirin therapy for primary and secondary prevention of coronary artery disease (60) also show that, in a population at high risk for a serious vascular event (i.e. 8.2%/ year), the risk/benefit ratio between bleedings and prevention of total mortality, non-fatal MI, and non-fatal stroke is in favor of the prolonged use of aspirin. Clopidogrel, when administered alone in about 20,000 patients (all with a history of AMI, stroke, or PAD) in the randomized CAPRIE trial (Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events) (93), was only marginally superior to aspirin (relative risk reduction (RRR) 8.7; $P = 0.043$) in preventing non-fatal AMI and non-fatal extracranial bleeding with little or no effect on total mortality. This was the overall outcome in patients with a recent stroke and in patients with a recent AMI. However, when the chronic 'PAD subset' was analyzed alone (over 8000 patients), a 24% risk reduction in major adverse ischemic events was found. This was a pre-specified (pre-randomization) stratification, and the validity of such a conclusion in PAD patients led to the positive study outcome and FDA approval.

A significantly high efficacy of clopidogrel has also been shown when this drug was employed for the 'dual antiplatelet therapy'. The CURE (94) and the CREDO (95) studies established the superiority of clopidogrel in combination with aspirin versus aspirin alone in ACS and in ACS with PCI, respectively. In high vascular risk patients with atherothrombosis (manifested as a recent stroke, recent MI, or symptomatic PAD), a meta-analysis of 10 studies examining the effects of thienopyridines (clopidogrel and ticlopidine) versus aspirin achieved results similar to those of the CAPRIE trial (96). A reduction in non-fatal stroke and an increase in non-fatal extracranial bleeding with no effect on total mortality or non-fatal AMI was found in the long-term efficacy of clopidogrel + aspirin versus aspirin alone in the randomized Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial (97). A Cochrane systematic review that evaluated short- and long-term dual antiplatelet therapy in patients with established coronary artery disease reached similar conclusions (98). Finally, in a meta-analysis of three studies there was no effect on mortality, non-fatal AMI, or non-fatal stroke, and a significant raise in major bleeding events in patients receiving warfarin (PT-INR 2-3) + aspirin versus aspirin alone (73).

Cilostazol, pentoxifylline, and prostanoids are used to improve the quality of life in patients with symptomatic PAD and with claudication. Since claudication itself is responsive to smoking cessation and exercise therapy, drugs for improving the quality of life should be considered only in patients who have limitations after smoking cessation and exercise therapy. Two systematic reviews have shown that patients with symptomatic PAD receiving cilostazol are more likely to experience important benefits as to physical health sub-scale (but not to health-related quality of life) than those receiving placebo (99,100) or pentoxifylline (101). No difference in rates of AMI, stroke, or death was found in another review on 1374 participants randomized to cilostazol and 973 randomized to placebo (102). Nor has a significant effect of cilostazol on major or minor bleeding rates been detected in another systematic review (103).

Table V. Antithrombotic drugs for PAD: different strategies for different objectives.

Patients with	Drug	Over	Grade of recommendation	Objectives, comments
Asymptomatic PAD[a]	Aspirin[d]	No therapy	2B	In 60-year-old men, aspirin use would result in six fewer deaths (12 fewer to 0 fewer) per 1000 patients treated (16 and 22 major extracranial bleeding events per 1000 moderate- and high-risk patients treated) if taken over 10 years and an increase in major bleeding events
Symptomatic PAD[b]	Aspirin[d]	No therapy	1A	In a high-risk (8.2%/year) population for serious events, aspirin significantly reduces total mortality, and the recurrence of non-fatal MI and non-fatal stroke. The number of vascular events and total deaths prevented is greater than the number of resulting bleeding events (mostly, non-fatal extracranial bleeding events)
	Clopidogrel[e]	Aspirin	1A	
	Aspirin[d] + clopidogrel[e]	Aspirin or clopidogrel	2B	
	Aspirin[d] + warfarin	Aspirin	1B	The primary efficacy analysis of CAPRIE was conducted in 19,185 patients on an intent-to-treat basis. After a mean follow-up of 1.9 years, a total of 939 patients in the clopidogrel group and 1021 patients in the aspirin group experienced one of the following events: ischemic stroke, AMI, or vascular death. The relative risk reduction (RRR) with clopidogrel versus aspirin was 8.7% (clopidogrel only marginally superior to aspirin: RRR 8.7; $P <$ 0.043). As to the pre-specified RRR by qualifying entry criteria, the following was found: Stroke: Clopidogrel better vs Aspirin better, 7.3%; AMI: Aspirin better vs Clopidogrel better, −3.7%; PAD: Aspirin better vs Clopidogrel better, 23.8
				In the CHARISMA trial, the long-term (28-mo follow-up, mean) efficacy of clopidogrel+ aspirin was evaluated versus aspirin alone in 15,603 patients with established vascular disease, PAD, or multiple risk factors. Dual therapy was associated with a reduction in non-fatal stroke and an increase in non-fatal extracranial bleeding with no effect on total mortality or non-fatal AMI
				Warfarin (PT-INR 2-3)+ aspirin versus aspirin in patients with asymptomatic coronary artery disease has been tested in the setting of a recent ACS. Together with a significant increase in major extracranial non-fatal bleeding events (from 20 more to 112 more), there was no detectable effect on mortality (from 25 fewer to 66 more), and non-fatal AMI/non-fatal stroke (from 28 fewer to 32 more), in those receiving warfarin+ aspirin
Claudication unresponsive to physical exercise and smoking cessation[c]	Cilostazol (100 mg b.i.d.)[h]	Pentoxifylline or placebo	2C	In 1374 participants randomized to 100 mg b.i.d. cilostazol (475 patient-years exposure) and 973 randomized to placebo (357 patient-years exposure), no difference in rates of AMI (1.0% vs 0.8%), stroke (0.5% vs 0.5%), or death (0.6% vs 0.5%) was found. Nor was a significant effect of cilostazol detected on major or minor bleeding rates (in a systematic review in 2809 patients undergoing percutaneous coronary intervention in which aspirin+ clopidogrel was compared with aspirin+ clopidogrel+ cilostazol)
Chronic CLI/rest pain in patients who are not candidates for vascular interventions	E.v. Prostanoids[h]	Placebo	2C	Prostanoids improve rest pain and ulcer healing (77 and 136 patients per 1000 treated, respectively) but do not significantly prevent amputations (from 75 fewer to 12 more) or mortality (from 42 fewer to 90 more)
	S.c. Heparin (therapeutic doses)	No therapy	2C	There are no formal studies demonstrating improved outcomes with short-term anticoagulation treatment (therapeutic doses of heparin) in acute limb ischemia
	Surgery	Intra-arterial thrombolysis[g]	1B	
Acute CLI due to arterial emboli or thrombosis	Intra-arterial thrombolysis[g]	E.v. Streptokinase	2C	In 1180 patients. Intra-arterial thrombolysis has been compared with surgery for ALI. While there was no effect on amputation, limb salvage, or death, compared to surgery, thrombolysis was associated with a high risk of stroke (10 per 1000 treated) and major bleeding (16 per 1000 treated) at 30 days
Peripheral artery PTA with/without stenting[f,h]	Aspirin[d]	No therapy	1A	Compared with placebo, pooled data from 356 PTA patients without stent placement showed a reduction in reocclusion at 6 months in those taking aspirin+ dipyridamole (OR 0.69; 95% CI 0.44–1.10). Following PTA (pelvic or lower extremity), in 179 patients complicated by extensive dissection to i.v. unfractionated heparin vs subcutaneous nadroparin was administered for 1 week post-procedure (followed by 6 months of aspirin in each arm). Nadroparin was associated with a reduction in vessel restenosis/occlusion at 6 months (OR 0.35; 95% CI 0.19–0.65) but not in the amputation rate (OR 1.0; 95% CI 0.20–5.10). However, the overall quality of the evidence is low due to risk of bias, imprecision, and indirectness. Thus, aspirin or clopidogrel should be preferred as in symptomatic PAD. In patients undergoing PTA with stent placement, the practice of a loading dose of clopidogrel in addition to aspirin pre-procedure and then continuing dual antiplatelet therapy for 1–3 months post-PTA, particularly if a stent is placed in a small peripheral vessel, is based on the results from coronary artery stenting trials. However, dual antiplatelet therapy is associated with a high risk of major bleeding compared with single antiplatelet therapy. Thus, aspirin or clopidogrel alone should be preferred
	Clopidogrel[e]	No therapy	1A	
	Aspirin + dipyridamole	No therapy	1B	
Peripheral arterial bypass with/without stenting[f]	Aspirin[d] + clopidogrel[e]	No therapy	2C	
	Aspirin[d]	No therapy	1A	
	Clopidogrel[e]	No therapy	1A	

(*Continued*)

Table V. (Continued)

Patients with	Drug	Over	Grade of recommendation	Objectives, comments
				In 966 patients receiving post-infrainguinal (venous or prosthetic) bypass graft surgery (for refractory claudication and limb salvage), aspirin+ dipyridamole resulted in 22 fewer graft occlusions per 1000 patients (32 fewer to 12 fewer) treated for 12 months (placebo as a comparator). The relative effects of aspirin plus dipyridamole vs aspirin alone have not been evaluated (Cochrane Systematic Review) In one study of that Cochrane Systematic Review, compared with placebo, aspirin plus dipyridamole for 12 months was associated with a reduction in amputations rates (34 fewer amputations per 1000 patients treated (51 fewer to one more)) Pooled data from three studies of that review suggested that treatment with aspirin plus dipyridamole was associated with a possible reduction in non-fatal AMI but not in non-fatal stroke. However, aspirin plus dipyridamole was associated with an increase in bleeding (eight more major bleeding events per 1000 treated (one fewer to 30 more)). However, the overall quality of the evidence is low due to risk of bias, imprecision, and indirectness. Thus, aspirin or clopidogrel alone should be preferred
Below-knee bypass graft surgery with prosthetic grafts	Aspirin[d] + clopidogrel[e] for at least 1 year	Aspirin	2C	The CASPAR study randomized 851 patients undergoing unilateral below-knee bypass graft surgery for PAD to clopidogrel (75 mg/d) plus aspirin (75–100 mg/d) vs placebo plus aspirin. In the (pre-specified) subgroup of patients undergoing venous graft bypass ($n = 598$), there was no difference in the rates of amputation, major bleeding, or death between the two treatment arms. In the subgroup of patients undergoing prosthetic graft bypass ($n = 253$), there was a significant decrease in amputations in those on clopidogrel+ aspirin (24 per 1000 treated; 95% CI, 35 fewer to three fewer)). No difference was found in total mortality or major extracranial bleeding
	High-intensity oral anticoagulation (target PT-INR 3-4.5)	Or aspirin	2C	The BOA study randomized 2650 patients who had undergone infrainguinal bypass grafting to either high-intensity oral anticoagulation (target PT-INR 3-4.5) or aspirin. Together with a reduction in non-fatal AMI, there was no effect of oral anticoagulation versus aspirin on all-cause mortality, non-fatal stroke, or limb loss, while there was a significant increase in extracranial major bleeding events (17 more per 1000, from 6 more to 32 more) in the oral anticoagulation group

[a]Patients > 50 y of age. The overall quality of evidence is moderate (imprecision in the estimates).
[b]Similar to patients with PTA with/without stenting.
[c]Available results in this clinical setting exclude benefits/harm as to quality of life related to the use of pentoxifylline, heparins (including low-molecular-weight heparins) or prostanoids.
[d]Long-term aspirin: 75–100 mg/d. Limited evidence (Grade 2B) of aspirin+ clopidogrel or aspirin+ warfarin over aspirin alone.
[e]Long-term clopidogrel: 75 mg/d. To be avoided in association with aspirin or warfarin (also in patients undergoing stent application).
[f]Dual antiplatelet treatment to be avoided for the inherent bleeding risk. Other studies failed to demonstrate or exclude an effect of aspirin and dipyridamole vs warfarin in reocclusion at 6 months following PTA or an effect on 12-month reocclusion in patients taking ticlopidine compared with warfarin.
[g]Urokinase bolus or t-PA 100 mg bolus. Compared to surgery, thrombolysis has a significantly higher 30-d risk of bleeding and stroke. Initially, streptokinase was the most widely used agent, but because of safety concerns (e.g. allergic reactions), it has largely been replaced by urokinase and rt-PA.
[h]Long-term aspirin[d] or clopidogrel[e] to be added for prevention of vascular events.

In a meta-analysis (seven randomized studies) (104), 643 patients were analyzed as to the use of prostaglandin E_1 (PGE_1) in the treatment of advanced PAD. At the end of treatment, PGE_1 showed a significantly better response (ulcer healing and/or pain reduction) as compared to placebo (47.8% for PGE_1 versus 25.2% for placebo, $P = 0.0294$). After a 6-month follow-up, a slight although still significant difference in favor of PGE_1 was seen for the combined end-point 'major amputation or death' (22.6% for PGE_1 versus 36.2% for placebo, $P = 0.0150$). That the benefit of PGE_1 is apparent in the short term but decreases over time had been previously reported in a multicenter trial on 1560 patients with chronic critical leg ischemia (105). The response rate (ulcer healing and/or pain relief) of the pooled treatment groups was 60.2% for PGE_1, 25.2% for placebo, and 53.6% for iloprost, in that report. The adverse events rate of the pooled treatment groups showed a good tolerability for PGE_1 with a rate of 39.6% in comparison to 73.9% for iloprost and 15.4% for placebo. In a recent Cochrane systematic review on 13 studies (106), >75% of subjects with critical limb ischemia without chance of rescue or reconstructive intervention that received prostanoids experienced at least one drug-related adverse event (i.e. headache, nausea, vomiting, diarrhea, and facial flushing) in addition to improved rest for pain and ulcer healing.

By preventing clot propagation and further embolism, short-term anticoagulation treatment is routinely used to reduce the extent of ischemia in acute limb ischemia. There are no formal studies demonstrating improved outcomes with such strategy. To restore flow to the occluded artery, either surgery or catheter-directed intra-arterial thrombolysis is employed. There are no data to support reperfusion therapy over anticoagulation alone in this setting. In a meta-analysis (107) that has compared benefits and harms of intra-arterial thrombolysis versus surgery, only the risk of stroke and of major bleeding at 30 days was higher for thrombolysis as compared with surgery, no effect being found on amputation, death, or limb salvage.

However, we believe that caution is needed when commenting this conclusion. Among those analyzed, the only randomized comparative study which was designed and performed by investigators was the STILE trial (108). In patients with true acute limb ischemia (1–14 days) the study reported a significant benefit of catheter-directed thrombolysis in terms of reducing amputation and improving amputation-free survival up to 1 year. These results were not reproduced in commercially written and performed studies.

In the past, thrombolysis for acute limb ischemia was administered i.v.; this strategy has been now replaced by catheter-directed thrombolysis. In a Cochrane systematic review on the management of acute lower-limb ischemia (109), compared to thrombolysis by recombinant tissue-type plasminogen activator (rt-PA) or urokinase, i.v. streptokinase was associated with a high rate of amputation at 30 days (7/20 versus 1/20; RR 7.0; 95% CI 0.95–51.80) and no effect on limb salvage, major hemorrhage, or death.

Surgical revascularization in patients with CLI (Table VI)

When antiplatelet drugs and the control of DM, of dyslipidemia, of cigarette smoking, and of hypertension are not sufficient in the treatment of CLI, surgery (110) or percutaneous transluminal angioplasty (PTA) with or without stenting (111) are needed. The objective of revascularization is to establish adequate inflow to the distal vessels. Balloon devices are used to this end, either in the contralateral retrograde common femoral artery (CFA) access or in the ipsilateral anterograde CFA access. This intervention is aimed at establishing straight line flow in at least one tibial vessel, to supply the area of the foot with rest ischemia (typically, the forefoot) or with tissue loss. This treatment shows a very high immediate limb salvage rates (>90%), with <2% intervention-related mortality and <5% risk of complications. In the first 12–24 months, the limb salvage rates are above 80%, and, when the therapeutic goal is achieved, the patency of treated arteries leads to resolution of ischemic lesions. The efficacy of angioplasty has been confirmed by several studies (112,113). A recent meta-analysis has shown that the efficacy and safety of endovascular techniques are comparable to surgical interventions (114). By releasing anti-proliferative drugs such as paclitaxel, drug-eluting balloons efficiently maintain arterial patency after PTA and reduce the risk of restenosis (115–117). A possible side effect of this procedure is wall dissection and restenosis. The use of stents is thought to reduce such risk (118–120). How-

Table VI. TASC II classification of aortoiliac lesions.

Type A lesions	• Unilateral or bilateral stenosis of common iliac artery • Unilateral or bilateral single short (<3 cm) stenosis of external iliac artery
Type B lesions	• Short (<3 cm) stenosis of infrarenal aorta • Unilateral occlusion of common iliac artery • Single or multiple stenoses totaling 3–10 cm involving the external iliac artery not extending into the common femoral artery • Unilateral occlusion of the external iliac artery not involving the origins of the internal iliac or common femoral arteries
Type C lesions	• Bilateral occlusions of the common iliac arteries • Bilateral stenoses of the external iliac artery 3–10 cm long not extending into the common femoral artery • Unilateral stenosis of the external iliac artery extending into the common femoral artery • Unilateral occlusion of the external iliac artery involving the internal iliac and/or common femoral artery • Heavily calcified unilateral external iliac artery occlusion with or without involvement of the origins of internal iliac or common femoral artery
Type D lesions	• Infrarenal aortic occlusion • Diffuse disease involving the aorta and both iliac arteries requiring treatment • Diffuse multiple stenoses involving the unilateral common iliac artery, external iliac artery, and common femoral artery • Unilateral occlusion of both common iliac and external iliac artery • Bilateral occlusion of external iliac arteries • Iliac stenosis in patients with AAA requiring treatment and not amenable to endograft placement or other lesions requiring open aortic or iliac surgery

Data from: Vasa. 2011;40:359–67; modified.

ever, presently it is unclear whether PTA with stent placement is superior to PTA alone with respect to patient-important outcomes. Compared with PTA without routine stenting, PTA plus routine stenting for superficial femoropopliteal arterial disease was associated with a reduction in restenosis (RR 0.85; 95% CI 0.69–1.06) but with no effect on the need for target vessel revascularization (RR 0.98; 95% CI 0.78–1.23) (121). Among strategies regarding surgical revascularization and endovascular revascularization, great attention is currently paid to benefits of drug-eluting stents. In the prospective, multinational randomized controlled Zilver PTX trial, the 2-year safety and efficacy of a paclitaxel-coated drug-eluting stent (DES) was compared with PTA in patients with superficial femoral artery lesions. In patients who received the paclitaxel-coated DES, 2-year outcomes showed statistically significant differences in terms of event-free survival, primary patency, and clinical benefits (122).

The TASC-II classification of ischemic lesions is used to decide between PTA or surgical interventions—TASC A and B lesions being best treated with PTA, TASC C and D lesions being usually treated with surgical strategies. The prosthetic material used is dacron or ePTFE, autologous materials (e.g. femoral veins or cryoconserved allogenic veins or arteries) being used in cases with infections of the original graft (123,124). After 5 years, the primary patency rate of all surgical procedures is $>80\%$, significant differences being found when comparing claudicants with patients with CLI (125). Such rates of success progressively decrease in patients with local co-morbidities. In a retrospective review (126), there was a significant difference in primary patency after 36 months (better for surgery). However, it was severely diminished in patients with diabetes and distal PAD, and, compared with patients undergoing PTA, surgical patients needed more often additional interventions of reconstruction. Debulking procedures are taken into account in selected patients (i.e. those at a high risk of PTA-related complications) (127). They include the excimer laser (to perform photoablation of occlusive material), the Rotablator (for the treatment of calcified plaques), and new techniques such as the Silverhawk system (designed for eccentric and not severely calcified infrainguinal lesions), the Rochawk system (for calcified plaques), and the newer Jetstream system (with an aspiration device to perform simultaneous thrombectomy and atherectomy).

Antithrombotic treatments in patients undergoing revascularization procedures (Table V)

A Cochrane review (128) on patients undergoing lower-extremity PTA without stent placement reported a reduction in reocclusion in patients taking aspirin + dipyridamole compared with placebo. Another study randomized patients to i.v. unfractionated heparin versus subcutaneous nadroparin administered for 1 week post-procedure (129). Nadroparin was associated with a reduction in the rate of vessel restenosis/occlusion but not in amputation. However, the overall quality of the evidence in these studies is low. Similarly poor is the evidence from studies on antithrombotic treatments in patients undergoing PTA with stent placement.

In a Cochrane systematic review in patients receiving post-infrainguinal bypass graft surgery compared to placebo, aspirin + dipyridamole resulted in fewer graft occlusions (130). In one study of that systematic review, compared with placebo, aspirin + dipyridamole was associated with a reduction in amputations rates. Also in this case, the overall quality of the evidence is low. Thus, aspirin or clopidogrel are suggested as the treatment of choice in symptomatic PAD.

The Clopidogrel and Acetylsalicyclate Acid in Bypass Surgery for Peripheral Arterial Disease (CASPAR) study randomized patients undergoing unilateral below-knee bypass graft surgery for PAD to clopidogrel + aspirin versus placebo + aspirin (131). There was a significant decrease in amputations in patients treated with clopidogrel + aspirin, but only in the subgroup of patients undergoing prosthetic graft bypass. Finally, together with a reduction in non-fatal AMI and a significant increase in extracranial major bleedings, there was no advantage over aspirin of a high-intensity oral anticoagulation (target PT-INR 3-4.5) on all-cause mortality and non-fatal stroke in patients who had undergone infrainguinal bypass grafting (132).

Open issues and areas of research

Due to imprecision, indirectness, and risk of bias, the overall quality of the evidence summarized above is low in most cases, and open issues and areas of research emerge.

Because of the paucity of studies regarding type and duration of antithrombotic therapy, in patients undergoing PTA with stent placement, the rationale for the current practice (aspirin and loading dose of clopidogrel pre-procedure; dual antiplatelet therapy for 1–3 months thereafter, particularly if a stent is placed in a small peripheral vessel) is largely based on indirect evidence from data in patients undergoing coronary stenting trials (133). However, the risk of stent thrombosis is conceivably lower in stenting larger-caliber peripheral arteries than in smaller coronary arteries. Differences in stent types and differing outcomes should be also considered in PAD.

A meta-analysis (134) has shown that, compared with those showing an optimal response to the drug, patients with persistent platelet reactivity despite clopidogrel treatment (~30% of total) have a significantly higher risk of death and/or ischemic recurrence (58). The same risk has been reported for aspirin ('aspirin resistance') (135). The possibility has been documented that genetic variations in gut/liver enzymes that control biotransformation (and in turn the pharmacological activity) play a role in the low response to clopidogrel (136). After oral administration, ticagrelor is rapidly absorbed and does not require hepatic biotransformation to be pharmacologically active. Compared to clopidogrel, a 16% RRR in major adverse cardiovascular events following acute coronary syndrome, a 21% RRR in cardiovascular mortality, and a numerical 22% RRR in all-cause mortality has been documented in 18,000 NSTEMI or STEMI patients in the multicenter, randomized, double-blind, double-dummy phase III PLATO trial (ticagrelor 90 mg b.i.d. versus clopidogrel 75 mg/d) (137). In ~11,500 male and female patients (>50 years of age) with established PAD, the EUCLID (Examining Use of tiCagreLor In paD) study protocol (ClinicalTrials.gov Identifier: NCT01732822) is now comparing 90 mg b.i.d. oral ticagrelor with 75 mg/d oral clopidogrel and the corresponding placebo on the risk of cardiovascular death, AMI, ischemic stroke, and TIMI major (primary safety objective) and major or minor bleeding events. October 2015 is the estimated primary completion date for the EUCLID study protocol.

By preventing clot propagation and further embolism, short-term anticoagulation treatment with therapeutic doses of heparin is commonly used to reduce the extent of ischemic injury in the management of acute limb ischemia. No formal studies demonstrating improved outcomes with anticoagulation (nor side effects of heparin versus other anticoagulant agents) are available. Although effective, vitamin K antagonists have numerous limitations, which complicate their use. These limitations have prompted the introduction of new oral anticoagulants that overcome many of the problems associated with vitamin K antagonists. The new oral direct oral

anticoagulants (DOACs) fall into two main classes: direct thrombin inhibitors (factor IIa inhibitors, dabigatran etexilate) and direct FXa inhibitors (rivaroxaban, apixaban, edoxaban) (138). Although agents in the two classes have distinct mechanisms of action, targeting distinct enzymes in the coagulation pathway, all of the new drugs attenuate fibrin formation and have features in common that distinguish them from vitamin K antagonists, such as warfarin. These common features include a rapid onset of action, few drug–drug interactions, and a predictable anticoagulant response that enables fixed dosing for several indications and across a diverse range of patients with no need for routine coagulation monitoring. Major issues concerning the pharmacology including the efficacy/safety of DOACs in clinical trials on prevention and treatment of thromboembolism (in medical and surgical patients), as well as in AF have been recently reviewed (139). Moreover, in a 14-mo follow-up in the everyday practice, 3.5 gastrointestinal bleedings and 2.4 intracranial hemorrhages/100,000 days at risk occurred in new users of warfarin, compared to 1.6 gastrointestinal bleedings and 0.8 intracranial hemorrhages/100,000 days at risk among new users of the DOAC dabigatran (140). A randomized trial of DOACs versus low-molecular-weight heparin in ALI should be considered.

Claudication unresponsive to physical exercise and smoking cessation is present in a relevant group of patients with IC. Data argue for this phenotype as identifying those with a heritable predisposition to more severe vascular events (i.e. with unfavorable combination(s) of genes modulating lipid metabolism, arterial pressure, vascular function, inflammation, hemostasis, and/or leukocytes and endothelial cell function) (141–144). This issue deserves to be thoroughly addressed.

Reports call attention to the occurrence of PAD in patients with AF (145) or with chronic renal failure (CRF) (146), a higher than normal risk of ischemic events and mortality being documented in both these settings (147–149). The prevalence of PAD is higher in patients with DM than in the general population (150–152); a distal location with an involvement of the infrapopliteal vessels is more common in DM (153,154), and the severity and outcome of PAD is worse in DM and is strongly related to duration and severity of the metabolic disorder (155–157). In a meta-analysis of ~48,000 healthy men and women, an ABI <0.90 at baseline was associated with an approximate doubling of the 10-year mortality, cardiovascular mortality, and major coronary event rate after adjusting for the Framingham risk score (158). When evaluating patients for primary prevention with aspirin, it has been suggested (81) to use a risk stratification tool (e.g. the Framingham risk score) which provides estimates of low ($<10\%$), moderate (10%–20%), and high risk ($>20\%$) of cardiovascular events over 10 years, doubling the patient's risk score (from a low to moderate or a moderate to high category) when his/her ABI is <0.90. Whether this is the case is unknown so far, and deserves to be addressed.

In the ICAI (Ischemia Critica degli Arti Inferiori) trial (159), of 1560 patients enrolled, 298 died within 1 year, 187 were amputees at 6 months, and 746 continued to suffer from CLI. Prior major vascular events doubled the risk of dying within 1 year. Previous revascularization was associated with a lower mortality and a higher probability of amputation. Among cardiovascular risk factors, diabetes increased mortality and lowered the probability of recovery from CLI. Patients with tissue loss had a higher amputation rate and less probability of recovery. Ankle pressure was predictive of mortality and amputation only when it was not measurable. Compared to those in whom surgery was deemed unnecessary, patients requiring revascularization had better chances of recovering from CLI, but not of longer-term survival or limb salvage. Antiplatelet drugs caused resolution of CLI and decreased the amputation rate by about one-third, while the advantage of the test treatment with alprostadil-α-cyclodextrine was confined to CLI resolution only. Together, these data provide the rationale for defining stratification criteria for a severity score to estimate reliably the achievable benefit in routine practice and/or identify PAD subjects at the highest risk of amputation/vascular death.

By allowing the identification of size and ulcerative components and by differentiating the necrotic core from the surrounding fibrous tissue, neo-angiogenesis, and the inflammatory burden composition, MRA contributes to the morphological characterization of a plaque (see above). Whether and the extent to which early and more aggressive strategies in PAD patients at the highest risk of ischemic events should be based, at least in part, on non-invasive and invasive tools for the diagnosis of PAD is poorly understood.

Innovative treatments with growth factors or blood progenitor transfer (160) are under evaluation to reduce pain and the rate of amputation in patients who have severe PAD and do not respond to PTA or surgery (e.g. those with DM) (161). In addition to the obvious pathophysiological and therapeutic implications, information from these model systems should help clarify whether conditions (e.g. CLI) other than an acute coronary syndrome argue for a 'pan-vascular destabilization' status (162).

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