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Disparities between international guidelines (AHA/ESC/ESVS/ESVM/SVS) concerning - Lower extremity arterial disease: consensus of the French Society of Vascular Medicine (SFMV) and the French Society for Vascular and Endovascular Surgery (SCVE)

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*See appendix for conflict of interest declarations

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1. Introduction

Several international guidelines concerning lower extremity arterial disease (LEAD) have been published recently, in particular by the *American Heart Association* (AHA) (1), the *European Society of Cardiology/European Society for Vascular Surgery* (ESC/ESVS) (2), the *European Society for Vascular Medicine* (ESVM) (3) and the *Society for Vascular Surgery* (SVS) (4). These guidelines differ in some respects and certain issues are not addressed. In 2019, the ESC also published updated guidelines relating to dyslipidemias, as well as diabetes, pre-diabetes and cardiovascular (CV) diseases (5, 6). The objective of this project was to analyse the disparities between the different guidelines, as well as certain issues not covered, and develop proposals with regard to these points.

Achievement of consensus

The steering committee, comprising 12 vascular physicians and surgeons with expertise in LEAD, identified the disparities between the various international recommendations, as well as the issues not addressed, and drafted a set of proposals. The steering committee reviewed these proposals and suggested revisions during a plenary meeting.

The resulting text was submitted to a multiregional panel comprising 45 experts, vascular medicine physicians and vascular surgeons, for appraisal and grading of the proposals by vote according to the Delphi method. It should be emphasised that no member of the steering committee was involved in grading these proposals. This step was entrusted to the panel of experts, who received the text developed by the steering committee as well as a link enabling on-line responses and a vote on each of the proposals. The 45 experts were requested to indicate, for each proposal if they (1) strongly agreed, (2) tended to agree, (3) had no opinion, (4) tended to disagree, or (5) totally disagreed. A space was provided for comments on each proposal, constituting a source of possible explanations for the respondent's attribution of a particular grade. Consensus was considered to have been achieved if more than 80% of the responses corresponded to either "Agreement" (grades 1 and 2) or "Disagreement" (grades 4 and 5). It is important to note that the percentage consensus was calculated on the basis of all the responses submitted by the experts, including those stating "No opinion". If consensus was not achieved, a second vote was organised after clarification of the text and modification of the proposals if these were considered to be unclear. A total of 41 experts participated in this second round.

The votes were recorded progressively and the text was finalised at a plenary consensus meeting of experts by attribution of one the following four grades to each proposal:

- **Grade 1+**: strong positive recommendation: "we recommend doing or prescribing"
- **Grade 2+**: positive suggestion, "we suggest doing or prescribing"
- **Grade 1-**: strong negative recommendation, "we recommend not doing or prescribing"
- **Grade 2-**: negative suggestion, "we suggest not doing or prescribing"

On completion of this Delphi procedure, consensus had still not been achieved with regard to certain proposals. The steering committee for this project did not wish to take a stance on the proposals concerned and preferred to discuss these in the light of the reasons given by the experts for attributing a particular grade. The absence of consensus on certain issues clearly indicated that these are in abeyance and need to be further clarified.

2. Glossary of abbreviations and definitions

There is consensus on most of the definitions used in the various international recommendations (Table 1).

3. Classifications and stages

International recommendations use either the Leriche-Fontaine classification or the Rutherford classification. The working group wished to include further specifications in the classification of LEAD and, in clinical practice, prefers the classification proposed by the French College of Vascular Medicine Teachers (CEMV) and the French College of Vascular Surgery Teachers (CECV). This classification defines three stages of LEAD, characterised respectively by absence of symptoms, exercise-induced ischaemia and chronic limb ischaemia (CLI) at rest (also called chronic limb-threatening ischaemia by the ESC/ESVS) (Table 2) (7).

4. Clinical evaluation

The AHA, ESC-ESVS, ESVM and SVS guidelines are concordant with regard to the clinical evaluation of LEAD. The AHA specifies that the majority of patients present atypical symptoms or even no symptoms at all (1). The ESC-ESVS states that the sensitivity and reproducibility of the physical examination are low (2). A systematic physical examination is nevertheless obligatory. Asymmetry of brachial pressure is of prognostic value (8).

The proposals comprise:

- Assessment of CV risk factors, comorbidities, lifestyle habits, dietary patterns, and physical activity including walking,
- Reconstitution of symptom history, including pain characteristics, type of ischaemia (exercise-induced or permanent), and circumstances exacerbating or attenuating symptoms,
- Consideration of alternative diagnoses, notably pseudo-claudication of neurological, rheumatological or other origin,
- Measurement of systolic BP in both arms (abnormal if asymmetry ≥ 15-20 mmHg) (1, 2),
- Palpation of the pulses in all four limbs (characterised as absent, diminished, normal, or bounding) and auscultation of the carotid, subclavian, iliac, femoral and popliteal arteries (comparative examination),
- Examination of the feet and legs (noting absence of hair growth, dry skin, skin colour and temperature, persistent distal tissue loss, neuropathy, deformation of the feet, loss of muscle mass),
- Search for relevant family medical history: coronary, cerebrovascular or lower-limb artery disease, aortic aneurysm.

5. Diagnostic criteria for lower extremity artery disease

5.1. Resting ankle-brachial index

The resting systolic ankle-brachial index (ABI) corresponding to the ratio of ankle and arm systolic BP, was first proposed by Winsor in 1950 (9). A study reported sensitivities ranging from 68 to 84% and specificities ranging from 84 to 99% for the diagnosis of LEAD in patients suspected of having this disease (10). In 2012, the AHA issued recommendations for determining this index (10). These recommendations advise measuring systolic BP using a continuous-wave Doppler probe, after a 5- to 10-minute rest, in the following order: right brachial artery, right posterior tibial artery, right dorsalis pedis artery, left posterior tibial artery, left dorsalis pedis artery, left brachial artery and then once again the right brachial artery. The choice of this order is arbitrary and is above all of interest in the research context, its value in clinical practice being more controversial. The second measurement of BP in the right brachial artery is designed to offset a possible initial "white coat" effect. Based on these measurements, an index of resting systolic BP in the right and left lower limbs can be calculated on the basis of the highest BP measured in each leg divided by the highest pressure determined in the two arms.

Some publications have reported the possibility of using a Doppler probe in colour flow imaging or pulsed-wave mode to measure BP (11, 12). In another study, no difference was observed between arm BP values measured by an automatic BP monitor and those determined using a continuous-wave Doppler probe (13). To optimise efficacy in routine clinical practice, measurement of brachial BP using devices other than a continuous-wave Doppler probe (e.g. an automatic BP monitor or stethoscope) may therefore be proposed. The use of an automatic device for measuring BP in the arms may also be justified by the possibility of measuring post-exercise ABI which may be accomplished more rapidly and by a single operator using an automatic system (14). The use of automatic oscillometric devices to measure BP for ABI calculation has also been proposed, but is controversial (10, 15-17). The sensitivities and specificities achieved using oscillometric methods of measurement range from 67 to 97% and from 62 to 96% respectively (10, 15). Furthermore, these methods overestimate BP values when those

225 determined using a continuous-wave Doppler probe are low (10). The place of
226 oscillometric methods of BP measurement therefore remains to be determined.

227 All the guidelines insist on the importance of measuring ABI for the diagnosis of LEAD.
228 However, slight discordances were found concerning normal values. The SVS, AHA and
229 ESC-ESVS consider values ranging from 0.91 to 1.40 as normal (1, 10), whereas the
230 ESVM proposes a normal range of 0.90 to 1.30 (3).

231 The resting ABI nevertheless has certain limitations (10, 18), namely:
232 - overestimation in the context of arterial rigidity, as in diabetic patients or those with
233 renal insufficiency, as well as in elderly patients;
234 - low sensitivity in patients presenting minor lesions or lesions manifested only during
235 exercise.

236 For all these reasons, it seems more judicious to consider resting ABI as one diagnostic
237 method among others and not as the primary method of diagnosis. In diabetics, notably,
238 measurement of ABI may aid risk classification (Grade IIb according to the 2019 ESC
239 guidelines) (19). Normal values of resting ABI range from 0.91 to 1.40 inclusive. For
240 values exceeding 1.40, the term "non-compressible arteries" should be used in
241 preference to that of medial calcinosis which denotes a particular pathological process.
242 The AHA considers values between 0.91 and 0.99 inclusive as limit or borderline values
243 (20, 21). Values between 0.80 and 0.90 inclusive should prompt consideration of a
244 second measurement before conclusively diagnosing LEAD (20, 21). For asymptomatic
245 patients, the AHA, ESC-ESVS and SVS envisage screening for LEAD in patients presenting
246 risk factors such as age over 65 years, with no other CV risk factor, or age over 50 years
247 associated with other risk factors such as smoking, diabetes or dyslipidaemia. The ESVM
248 does not take any stance on screening (3). However, the VIVA study showed that
249 screening of a population of men aged from 65 to 74 years led to a reduction in LEAD-
250 related mortality, abdominal aortic aneurism (AAA) and hypertension (22). Screening
251 for LEAD therefore seems justifiable.

252

Section 5.1 - Suggestions and recommendations

1. **We suggest that resting ABI should be used as one means of diagnosis among others and not as the primary criterion for diagnosis (Grade 2+).**
2. **We recommend defining the normal values of resting ABI as 0.91 to 1.40 inclusive (Grade 1+).**
3. **We recommend diagnosing LEAD when the ABI is ≤ 0.90 (Grade 1+).**
4. **We recommend diagnosing incompressible arteries when the ABI is >1.40 (Grade 1+).**
5. **If a continuous-wave Doppler probe is not available for determination of the ABI, we suggest using a pulsed-wave Doppler probe to measure ankle BP (Grade 2+).**
6. **To determine the ABI, we suggest measurement of brachial BP using either an automatic BP monitor or a stethoscope if a continuous-wave Doppler probe is not available (Grade 2+).**
7. **Given the impact of LEAD on therapeutic strategy, we suggest screening for this disease by measuring ABI in patients aged over 50 years with another CV risk factor (Grade 2+).**
8. **In asymptomatic diabetic patients, we suggest screening for LEAD based on a distal haemodynamic criterion (ABI, TBI or Doppler waveform) (Grade 2+).**

Section 5.1 ISSUES IN ABEYANCE (full consensus not achieved during the DELPHI procedure)

1. **If a continuous-wave Doppler probe is not available, we suggest using Doppler colour flow imaging of the lower limbs to measure ankle BP.**
   Only 66% of the experts agreed with this proposal. The other experts justified their position on the grounds that the proposal was based on the results of a single study (12), and that the efficacy of this method depends too much on equipment calibration and is substantially reduced in the presence of calcifications.
2. **For measurement of the ABI in clinical practice, we suggest NOT TO necessarily respect the sequence of BP measurements in the four limbs recommended by the AHA.**
   This proposal obtained a consensus agreement of 76%. In the second round of voting, 12% of the experts still expressed no opinion.
3. **In view of the impact of LEAD on therapeutic strategy, we suggest screening for this disease based on ABI in patients aged over 65 years even in the absence of any other CV risk factor.**
   This proposal obtained a consensus agreement of 78%, three experts expressing no opinion. This absence of full consensus may be explained by the controversy with regard to screening asymptomatic patients as there is no consensus regarding their treatment. Detection of a decreased ABI in an asymptomatic patient may nevertheless result in a change in his/her class of CV risk and consequently lead to modifications in therapeutic strategy. Furthermore, it is conceivable that the suggested age limit of 65 years may have hindered acceptance of this proposal. Effectively, it could lead to numerous consultations in a context in which the therapeutic strategy is controversial. The AHA (2005) recommended screening for LEAD in patients aged over 70 years even in the absence of any other CV risk factor (23). The guidelines published by the ESC-ESVS (2) and the AHA (1) propose such screening from the age of 65 years onwards, whereas this is not recommended by the ESVM (3).

5.2. Post-exercise ankle-brachial index

The AHA, ESC-ESVS, ESVM and SVS guidelines all propose measurement of post-exercise ABI in patients with suspected LEAD presenting an ABI at rest > 0.90 (1-3, 10)

However, there is no consensus on how to measure post-exercise ABI. The following method may be proposed for this purpose. The ABI is determined 1 min after the cessation of exercise. The physician measures the ankle BP in the both legs, starting with the symptomatic leg, in the ankle artery used as the reference artery for measurement of the resting ABI (7, 14, 24). The position of this artery should be marked in pencil on the skin at the time of resting BP measurement to minimise difficulties in locating the artery after exercise. A second person should simultaneously measure the brachial systolic pressure to enable calculation of the post-exercise ABI (7). Ideally, the brachial BP should be measured using a Doppler probe, but for practical reasons, it may also be measured using an automatic BP monitor if the operator is alone (14). The AHA, ESC-ESVS and SVS propose the use of two threshold criteria to confirm the diagnosis of LEAD: either a fall in ABI after exercise >20% of the resting ABI or a fall in absolute ankle BP >30 mmHg whereas the ESVM proposes solely a fall in ABI post-exercise >20% (10, 25, 26). However, these criteria were validated without taking into account resting ABI values and using treadmill protocols now rarely used [1.5 mph (miles per hour, corresponding to 2.4 km/h) with a 7% slope (25), or 4 km/h with a 10% slope (26)]. Furthermore, it has been shown that these two criteria do not identify the same patients suffering from LEAD in 1 out of 5 cases (27).

A study in symptomatic patients subjected to exercise on a treadmill set at 3.2 km/h with a 10% slope showed that a decrease in ABI post-exercise ≥ 18.5% may be retained as a diagnostic criterion for ≥ 50% arterial stenosis in patients with a resting ABI > 0.91 experiencing exercise-related pain (14). On the basis of a retrospective study, it was proposed to adopt a post-exercise ABI < 0.90 as a criterion (28). However, the procedure used to measure post-exercise ABI in this study was not reported, several different imaging procedures were employed and the treadmill used was set at 2.4 km/h with a slope of 10% for a maximum duration of 5 min (28). The proposed post-exercise criteria therefore warrant confirmation. Exercise tests performed for diagnostic

purposes can be accomplished using treadmill speeds and slopes adapted to the patient, but the threshold values of ABI in these cases remain to be defined.

Section 5.2 - Suggestions and recommendations

1. **For patients presenting exercise-induced symptoms in the lower limbs, with a normal resting ABI at rest or a non-contributory Duplex UltraSound (DUS) at rest, we recommend measurement of post-exercise ABI as a basis for diagnosing LEAD (Grade 1+).**
2. **We recommend measuring post-exercise ABI not later than 1 min after the cessation of exercise (Grade 1+).**
3. **We suggest starting with the symptomatic leg when measuring post-exercise ABI (Grade 2+).**
4. **We suggest as the diagnostic criterion a decrease in ABI post-exercise ≥18.5% using a treadmill set at 3.2 km/h with a 10% slope (Grade 2+).**

5.3. Toe-brachial index

The AHA, ESC-ESVS, ESVM and SVS guidelines (1, 2, 4) also propose the toe-brachial index (TBI) as a criterion for diagnosing LEAD. Use of this index circumvents the problem of increased rigidity of large- and medium-calibre arteries (29). Before measuring toe pressure, it is important to check local skin temperature at the site of measurement (using an infra-red thermometer or laser probe) to ensure that this is not below 30°C (30), as a low skin temperature may lead to falsely low pressure measurements. These measurements may be accomplished using a laser Doppler probe or by plethysmography (31). Pressure is generally measured on the hallux, but the second or third toe may also be used (32). The sensitivity of the TBI ranges from 45 to 100% and its specificity from 17 to 100% (33). The pathological threshold is a matter of debate but the guidelines propose using a threshold of <0.70 (1, 34). AHA and ESC guidelines propose measurement of TBI when the resting ABI exceeds 1.40 (1, 2). The ESVM proposes measurement of TBI in any diabetic patient presenting a tissue lesion as well as in patients with a resting ABI >1.30 (3). The prevalence of pathological values of TBI in patients with resting ABI >0.90 varies in studies from 9 to 27% in populations comprising more than 100 patients (34). The TBI could nevertheless be measured

directly as the primary diagnostic criterion in diabetic patients, patients with renal insufficiency and very elderly patients, given the increased arterial wall rigidity in these populations.

Section 5.3 – Suggestions and recommendations

1. **We suggest that the diagnosis of LEAD may be based on toe pressure as a diagnostic criterion on a par with resting ABI (Grade 2+).**
2. **We recommend a threshold value of <0.70 to confirm the diagnosis of LEAD (Grade 1+).**
3. **For asymptomatic diabetic patients at intermediate CV risk, we suggest measuring the TBI (Grade 2+).**
4. **We recommend measuring toe pressure in diabetic patients (Grade 1+).**
5. **We recommend measuring toe pressure in patients with renal insufficiency (Grade 1+).**
6. **We suggest measuring the TBI in patients with diabetes if the resting ABI is normal (Grade 2+).**
7. **We suggest measuring the TBI in patients with renal insufficiency if the resting ABI is >0.90 (Grade 2+).**
8. **We suggest measuring the TBI at the second or third toe if the hallux is missing (Grade 2+).**
9. **When measuring the TBI, we suggest checking the skin temperature at the site of measurement (Grade 2+).**

5.4. Doppler waveform analysis

Doppler waveform analysis may enable both diagnosis of LEAD and location of the arterial lesions (35-37). A study in diabetic patients showed that the estimated prevalence of LEAD was higher if the patients were evaluated by Doppler waveform analysis (93%) rather than by measurement of the TBI (72%) or the resting ABI (57%) (38). In the San Diego study, LEAD was diagnosed in 104 patients out of 2343 (based on a resting ABI ≤ 0.90 or an abnormal Doppler waveform, defined by the absence of a negative component) (36). Among these 104 patients, a total of 69 legs showed both a pathological ABI and abnormal Doppler waveforms, 60 legs a pathological ABI alone and

33 legs an abnormal Doppler waveform alone (36). Another study conducted in 81 patients, over 60% of whom were at the stage of permanent ischaemia, showed that measurement of ABI and Doppler waveform analysis were complementary (39). One of the main difficulties in Doppler waveform analysis is that the description of these waveforms varies widely between different countries, including the United States, France and China (40-43). In a study in which 19 vascular medicine students were asked to describe Doppler waveforms, the mean number of different terms employed was 9±4. In contrast, when the descriptions were based on a classification system, the mean number of terms used fell to 2±1 (41). In 2017, the CEMV proposed to use of the simplified Saint-Bonnet classification as a consensus basis for describing these waveforms (Figure 1) (44, 45).

A French multicentre study revealed that more waveforms could be categorised using the Saint-Bonnet classification than with use of the classifications proposed by Cathignol and Descotes and by Spronk (manuscript submitted for publication). By analogy with the definition of an abnormal waveform used in the San Diego study (absence of a negative component and broadened) (36),the Saint-Bonnet waveforms B, CD, E or 0 with or without the presence of a continuous flow may be considered as pathological. In asymptomatic patients, the arterial Doppler waveforms should be recorded in addition to measuring the ABI or TBI. Exclusion of the diagnosis of resting LEAD is then based on a normal value of ABI or TBI as well as on either triphasic or biphasic Doppler waveform morphology (N or A according to the Saint-Bonnet classification).

Section 5.4 - Suggestions and recommendations

1. **For the diagnosis of LEAD, we recommend analysing Doppler waveform morphology in addition to measuring the ABI (Grade 1+).**
2. **For the diagnosis of LEAD, we recommend analysing Doppler waveform morphology as a diagnostic criterion on a par with ABI and TBI (Grade 1+).**
3. **We recommend using a classification system for categorising arterial Doppler waveforms (Grade 1+).**
4. **We suggest using the Saint-Bonnet classification for describing these waveforms (Grade 2+).**
5. **We suggest considering as pathological the waveforms C, D and E in the Saint-Bonnet classification with or without continuous flow (Grade 2+).**
6. **We suggest considering as pathological the waveform O (i.e. absence of a waveform) in the Saint-Bonnet classification (Grade 2+).**
7. **If the ABI or TBI is normal, we recommend additionally recording distal arterial Doppler waveforms, which should be Saint-Bonnet N or A, before excluding the diagnosis of resting LEAD (Grade 1+).**

Section 5.4 – ISSUES IN ABEYANCE (full consensus not achieved during the DELPHI procedure)

1. **We suggest considering as pathological the waveform B in the Saint-Bonnet classification with or without continuous flow. This proposal achieved a 78% consensus agreement.**

   Six experts had no opinion on this issue. As the Saint-Bonnet classification was published recently (in 2016) it is more than likely that all the panel participants were not familiar with it. This might explain the absence of full consensus.

5.5. Measurement of resting transcutaneous oxygen pressure

Measurement of resting transcutaneous oxygen pressure ($TcPO_2$) is a means of evaluating tissue viability and is proposed as a diagnostic criterion of chronic critical limb ischaemia (CLI) (46). However, this parameter must be measured under strictly controlled temperature conditions to avoid erroneous conclusion of ischaemia. $TcPO_2$ is affected by numerous factors, including inflammation, oedema, hypoxia and fever, which can result in misleading values. It is better to abstain from measuring this parameter if the conditions are unfavourable, for example, in the presence of a nearby infected wound.

A value of $TcPO_2$ at rest < 10 mmHg is an unfavourable prognostic factor (47). When performed at successive levels on an ischaemic limb, measurement of this parameter aids decision on the level of amputation (48). A value of $TcPO_2$ at rest >30 mmHg is a favourable indicator of wound healing (49, 50). AHA, ESC-ESVS, ESVM and SVS guidelines all advocate adopting a threshold value of <30 mmHg for the diagnosis of CLI (1-4, 51) (see section 10).

Section 5.5 - Suggestions and recommendations

1. **We recommend adopting a resting $TcPO_2$ value of <30 mmHg as a haemodynamic diagnostic criterion for CLI (Grade 1+).**

5.6. Exercise $TcPO_2$

Exercise $TcPO_2$ was suggested as a diagnostic criterion for LEAD in the 1980's (52, 53). However, the use of this parameter is not mentioned in any current guideline. In 2003, the DROP (*delta from resting oxygen pressure*) was proposed for the evaluation of proximal claudication using a treadmill with a slope of 10% set at a speed of 3.2 km/h (54). This technique was later also proposed for the exploration of distal claudication (55). Calculation of the DROP necessitates use of a dedicated software package (56). The Oxymonitor® software package, which can be downloaded on line, has been validated and may be used (https://imagemed.univ-rennes1.fr/en/oxymonitor/download.php (56). A threshold value of -15 mmHg is considered significant for the presence of arterial stenosis and has been observed in several populations (54, 57, 58). This evaluation seems to be indicated in particular when patients complain of proximal pain (in the buttocks, thighs and lumbar region) as in these contexts, the ABI may be falsely normal in 1 patient in 7 (59, 60). It also appears to be of value in patients with complicated pathological conditions (e.g. diabetes, narrowing of lumbar spinal canal) (58, 60). Its place in patient care is at present poorly defined. A recent study showed that its sensitivity and specificity in detecting arterial stenoses ≥50% are fairly similar to those of post-exercise ABI. (14). However, two other recent studies showed that post-exercise ABI and exercise $TcPO_2$ did not identify the same patients among those with suspected lower limb LEAD presenting a resting ABI > 0.90 (61-63). Exercise $TcPO_2$ is now rarely used as a diagnostic criterion owing to technical constraints, the time required for its evaluation and its cost. Its place in the decision tree for the diagnosis of LEAD remains to be defined.

Section 5.6 - Suggestions and recommendations

1. **In the event of difficulty in diagnosing or excluding LEAD, we suggest proposing the measurement of exercise $TcPO_2$ to patients with complicated pathological conditions (e.g. diabetes, narrowing of lumbar spinal canal) (Grade 2+).**

Section 5.6 – ISSUES IN ABEYANCE (full consensus not achieved during the DELPHI procedure)

1. **We suggest proposing exercise $TcPO_2$ when the patient manifests normal resting and post-exercise ABI values, but presents symptoms evoking exercise-induced ischaemia in areas vascularised by the internal iliac artery.** *This proposal was approved by 71% of the panel experts, six experts expressing no opinion. This absence of full consensus may be explained by the limited availability of this technique in France. In addition, for most practitioners, post-exercise ABI and exercise $TcPO_2$ are examinations identifying the same patients with LEAD. Three studies were published in 2020, after grading of the proposals by the panel of experts (61-63). All three studies showed that these tests do not in fact identify the same patients among those with suspected LEAD. Further studies are warranted to define more precisely the place of each test in the management of LEAD.*

5.7. Duplex ultrasound (DUS), computed tomography angiography (CTA), magnetic resonance angiography (MRA), catheter angiography

The indications for DUS examination differ between the AHA, SVS, ESC-ESVS and ESVM guidelines (1-4). The AHA and the SVS recommend the use of this examination solely in patients scheduled for revascularisation (1). In contrast, the ESC-ESVS and ESVM propose its use for confirmation of the arterial lesions whether or not an intervention is envisaged (2).

For patients at low or moderate CV risk (Table 3) (5) and for asymptomatic diabetic patients at moderate CV risk (patients with type 1 diabetes aged under 35 years, or those with type 2 diabetes under 50 years old, with an onset of diabetes < 10 years previously and with no other cardiovascular risk) (Table 4) (19), the ESC-ESVS proposes a search for plaques in the carotid and/or femoral arteries to define the CV risk more precisely (Grade IIa). The ESC-ESVS advises against measuring carotid intima-media thickness (19).

It is important to point out that certain risk factors for atherosclerotic disease are also risk factors for AAA. The prevalence of AAA is higher among persons suffering from LEAD (9%) than in the general population (64-66). DUS is effective in detecting aorto-iliac and femoropopliteal lesions (67).

The comparative proficiency of magnetic resonance angiography (MRA), computed tomography angiography (CTA) with injection of a contrast agent and duplex ultrasound (DUS) in detecting >50% stenoses of the lower limbs was evaluated in a systematic review. MRA showed the best diagnostic performance with a sensitivity of 95% (92-99.5%) and a specificity of 97% (64-99%). The sensitivity and specificity of CTA with injection of a contrast agent were respectively 91% (89-99%) and 91% (83-97%), those of DUS being 90% (74-94%) and 99% (96-100%) (68). However, both CTA and MRA are techniques necessitating the injection of a contrast agent that may be nephrotoxic and engender allergic reactions and thyroid dysfunction (CTA) or systemic nephrogenic fibrosis (MRA) (69).

Diagnostic catheter angiography is no longer indicated in the first instance, but remains indicated for the evaluation of infra-popliteal arterial disease in the context of planned endovascular revascularisation. The guidelines concur in advising against investigations involving imaging techniques such as CTA, MRA or catheter angiography in asymptomatic patients (1, 2).

The ESC-ESVS alone recommends exploration of the lower limb arteries in patients who are candidates for transcatheter aortic valve implantation (TAVI) or an intervention necessitating a risky arterial approach. Imaging of the aorta and the principal peripheral arteries by CTA is recommended prior to TAVI, notably to evaluate the aorta as a whole (2) (Grade I), see section 7.7.

Section 5.7 - Suggestions and recommendations

1. **We recommend performing a DUS examination to characterise the arterial lesions present in patients with LEAD (Grade 1+).**
2. **We recommend performing a DUS examination in patients with LEAD to detect the presence of an AAA (Grade 1+).**
3. **We recommend NOT TO propose invasive imaging examinations to patients presenting asymptomatic LEAD (if an AAA has been detected, the relevant specific recommendations should be followed) (Grade 1-).**
4. **In patients at moderate CV risk, we suggest searching for carotid and/or femoral atherosclerotic plaques by DUS to better evaluate the CV risk (Grade 2+).**
5. **In asymptomatic diabetic patients at moderate CV risk, we suggest searching for carotid and/or femoral atheroclerotic plaques by DUS to better evaluate the CV risk (Grade 2+).**

Section 5.7 – ISSUES IN ABEYANCE (full consensus not achieved during the DELPHI procedure)

1. **In contrast to the ESC-ESVS, we suggest NOT TO undertake a DUS search for carotid and/or femoral atherosclerotic plaques in patients at low CV risk.**

This proposal achieved a consensus agreement of 61%, three participants expressing no opinion. Some experts are in favour of such screening as it allows treatment to be started in patients with >50% stenosis of the internal carotid artery (2). The presence of atherosclerotic plaques in the carotid or femoral arteries could have an impact on evaluation of the subject's CV risk.

5.8. Methods of functional evaluation of maximum walking distance

Tests evaluating walking ability seem to be important both for precisely assessing the patient's functional impairment and for unmasking other potential causes of difficulty in walking (1, 23). A patient's walking capacity can be evaluated by the maximum walking distance (the maximum distance covered before the patient has to stop walking owing to the intolerable pain experienced) or the relative walking distance (the distance covered prior to pain onset) (23). Various methods for evaluating walking capacity have been proposed (declared walking distance, questionnaires, treadmill tests, the 6-minute walking test and measurement of distances covered in real life using a Global Positioning System (GPS) device). Walking distances reported by patients when questioned and those evaluated by a treadmill tests are only weakly correlated, coefficients ranging from 0.39 to 0.52 (70-72). In one study, patients overestimated their maximum walking distance to be 300 m (163-500), whereas treadmill test results showed a maximum distance of 184 m (144-246) (72). The correlation coefficients between maximum walking distances indicated by questionnaires, such as the *Walking Impairment Questionnaire* (WIQ), EACH-Q or the Welch questionnaire, and those determined by treadmill tests are around 0.40 to 0.68 (73-75). It is worth noting that the maximum walking distance in real life measured by a GPS device is at least twice that indicated by treadmill tests (72, 75). The AHA and ESC-ESVS guidelines concur in recommending objective evaluation of patients' functional impairment by a treadmill test, whereas the ESVM proposes this test principally in the case of atypical symptoms. The choice between a constant load test (Strandness: slope of 10%; speed of 3.2 km/h) and an incremental test (Gardner-Skinner test: speed of 3.2 km/h; slope of 0% at the start of the test, increased by 2% every two minutes) is left to the discretion of the operator (76). Evaluation of the maximum walking distance is recommended after treatment initiation (23). The reference test to be performed remains a matter of debate. Certain authors advocate the 6-minute test, on the grounds that this is more representative of patients' usual walking habits and also does not require any training in walking on a treadmill, whereas others are more in favour of the treadmill test (77-80). Finally, the walking test (whether treadmill or 6-minute) could enable diagnosis of masked LEAD (2).

598 All the various diagnostic strategies according to the clinical context are presented in
599 Figure 2.

600

Section 5.8 - Suggestions and recommendations

1. **For objective evaluation of the maximum walking distance of a patient with LEAD, we recommend using the treadmill test (either constant load or incremental) as the reference assessment (Grade 1+).**
2. **We suggest using the treadmill test (either constant load or incremental) to evaluate the response to treatment (Grade 2+).**

Section 5.8 – ISSUES IN ABEYANCE (full consensus not achieved during the DELPHI procedure)

1. **For objective evaluation of the maximum walking distance of a patient suffering from LEAD, we recommend using the 6-minute walk test as the reference assessment.**

This proposal achieved a consensus agreement of 70%, four participants (10 %) expressing no opinion. The debate as to which test is the best for objectively determining a patient's level of functional impairment is a recurrent issue as indicated in the literature (77, 78, 80), clinicians currently having three main choices: evaluation by a treadmill test, evaluation by the 6-minute walking test and ambulatory evaluation using a global positioning system (GPS) device. The treadmill test presents the drawback in France of being reimbursed by the national health insurance system only if an electrocardiogram is performed at the same time. The 6-minute walk test is reimbursable but requires the presence of adequate personnel as well as a corridor more than 20 m long, both conditions difficult to achieve in a general practice context. Finally, ambulatory evaluation is currently only feasible in a research context and is also not reimbursed.

6. Focus on the quantification of arterial stenoses using duplex ultrasound

Although existing guidelines describe the methodology of other functional investigations (pressure measurements), none of the guidelines compared specify the methodology and diagnostic criteria to be used for DUS examinations.

DUS examinations enable the echographic observation of parietal abnormalities as well as their haemodynamic repercussions. In colour mode, DUS detects haemodynamically relevant lesions in the form of turbulences and *aliasing* they induce; the degree of stenosis is quantified by pulsed-wave or continuous-wave DUS, by measuring peak systolic and end-diastolic velocities at the site of the lesion and calculating the ratio of these velocities to the corresponding velocities measured upstream of the lesion investigated (i.e. velocity at the site of the lesion divided by velocity proximal to the lesion). Thorough analysis of the Doppler signal, upstream and downstream of the lesions, enables evaluation of the haemodynamic repercussions distal to the stenoses and occlusions (45, 81, 82). In view of the widely varying descriptions of Doppler waveforms (40, 41), the CEMV proposes use of the Saint-Bonnet classification to define the haemodynamic repercussions (Figure 1, Section 5.4). With increasing severity of the arterial lesions, the initially triphasic waveform (normal; Saint-Bonnet N) changes, becoming biphasic (Saint-Bonnet A), with loss of diastolic flow reversal, and finally monophasic (Saint-Bonnet B, CD, E). The waveform sometimes becomes continuous owing to a delayed systolic upstroke.

Combined colour-mode and pulsed-wave DUS achieved a sensitivity and specificity in diagnosing LEAD of 88% and 95%, respectively, relative to catheter arteriography (83). The reliability of the DUS examination increases when the various criteria available are combined (peak systolic velocities, end-diastolic velocities, velocity ratios, and flow disturbances downstream of the lesions investigated).

6.1. Occlusions

Arterial occlusions are generally not difficult to diagnose as they result in an absence of blood flow (Doppler waveform Saint-Bonnet 0)

6.2. Arterial stenoses and their quantification

Quantification of the degree of stenosis is based on velocimetric criteria.

The velocities recorded under normal conditions are of the order of 1 m/s in the iliac arteries, subsequently decreasing to approximately 50 cm/s in the tibial arteries, but with substantial physiological variations (84). Stenoses in the lower limb arteries, as at other vascular sites, are manifested by blood flow accelerations. In view of the variability of the systolic velocities in the lower limb arteries, measurement of the velocity ratios (VR = ratio of the velocity at the site of stenosis/the velocity proximal to the stenosis) has proved to be more reliable than simply the peak systolic velocity (PSV) at the site of the stenosis (85). Several studies have investigated various criteria and have reported different thresholds of peak systolic velocity or velocity ratio (68, 85-87) (Table 5). Put simply, an arterial stenosis can be evaluated as 50 to 75% if the peak systolic velocity ratio (PSVR) is between 2 and 3, as 70 to 90 % if the PSVR is between 3.4 and 6, and as > 90% if this ratio is >6-7. It is also important to define the terms stenosis and plaque. The term stenosis should be reserved for lesions characterised by an acceleration of arterial blood flow, whereas the term plaque should be reserved for an arterial constriction that does not result in accelerated blood flow (88). An arterial constriction resulting in a PSVR ≤1 is therefore termed a plaque whereas a constriction leading to a PSVR exceeding 1 is termed a stenosis.

6.3. Evaluation of stenoses after bypass revascularisation

Stenoses located within bypass conduits or at anastomoses are similarly evaluated according to haemodynamic criteria. Absence of a stenosis in a prosthetic bypass graft does not exclude occurrence of a thrombosis, in contrast to its absence in an infrainguinal vein bypass graft (89). Specific criteria have been validated for this situation (Table 5), and a stenosis >70% is predictive of a bypass thrombosis.

6.4. Specific characteristics of multi-level stenoses

LEAD is often characterised by the presence of multiple stenoses at different levels. In this case, it is often neither possible nor useful to precisely quantify each lesion individually. In clinical practice, the cumulative effect of stenotic lesions is evaluated by surgical level (aortic, iliac, femoral bifurcation, above- and below-knee femoropopliteal and infrapopliteal), on the basis of changes in arterial waveforms. To describe these waveform changes, use of a dedicated classification system (Saint-Bonnet) is recommended.

Section 6 - Suggestions and recommendations

1. **We suggest that the term "plaque" should be reserved for an arterial constriction not giving rise to an acceleration of flow velocity (Grade 2+).**
2. **We suggest that the term "stenosis" should be used whenever an acceleration of flow velocity is detected (Grade 2+).**
3. **We suggest that a peak systolic velocity ratio (PSVR) <2 determined by DUS examination of lower-limb arteries should be considered as indicative of an arterial stenosis of less than 50% (Grade 2+).**
4. **We suggest that a PSVR between 2 and 3.4 determined by DUS examination of lower-limb arteries should be considered as indicative of an arterial stenosis of between 50% and 70-75% (Grade 2+).**
5. **We suggest that a PSVR between 3.4 and 6 determined by DUS examination of lower-limb arteries should be considered as indicative of an arterial stenosis of between 70% and 90% (Grade 2+).**
6. **We suggest that a PSVR above 6 determined by DUS examination of lower-limb arteries should be considered as indicative of an arterial stenosis of >90% (Grade 2+).**

7. Detection of asymptomatic multisite lesions in patients suffering from lower extremity artery disease

7.1. Atherosclerotic coronary artery disease

Even though atherosclerotic coronary artery disease (CAD) is frequently present in patients suffering from LEAD, the AHA does not recommend systematic screening for this condition, as the existence of LEAD already justifies best medical treatment and systematic screening for CAD has so far not been demonstrated to improve the clinical prognosis.

The ESC-ESVS regret the lack of data and favour a less categorical approach:

- As for all patients presenting LEAD, they recommend a search for clinical signs and symptoms of arterial lesions in other vascular beds, including CAD and to schedule any complementary heart examinations deemed necessary.
- Given the lack of data, they do not take a stance with regard to systematic screening for asymptomatic CAD.
- Candidates for revascularisation surgery are at high risk (>5%) of peri-operative *Major Adverse Cardiovascular Events* (MACE: cardiovascular death, myocardial ischaemia, stroke, coronary revascularisation, unstable angina). The ESC-ESVS consequently recommend systematic recording of a resting electrocardiogram (ECG) prior to surgery. For patients manifesting a change in functional capacity and with more than two risk factors such as a history of CAD, heart failure (HF), transient ischaemic attack (TIA) or stroke, chronic renal insufficiency or insulin-requiring diabetes, a cardiac stress test is recommended.
- Therapeutic management of patients with CAD should conform to ESC guidelines concerning non-cardiac surgery (95).
- The data obtained in the COMPASS trial might modify this screening strategy (96).

Section 7.1 - Suggestions and recommendations

1. **We recommend screening for CAD based on the patient's medical history and physical examination (Grade 1+).**
2. **We suggest seeking the advice of a cardiologist if CAD is suspected in patients with symptomatic LEAD irrespective of stage (Grade 2+).**
3. **We suggest seeking the advice of a cardiologist if CAD is suspected in patients with LEAD, even asymptomatic (Grade 2+).**
4. **We suggest seeking the advice of a cardiologist if CAD is suspected in patients with masked LEAD (Grade 2+).**
5. **Except in an emergency, we recommend seeking the advice of a cardiologist in addition to screening for CAD prior to revascularisation surgery (Grade 1+).**

7.2. Carotid artery stenosis

As in all cases of LEAD, the ESC-ESVS recommend a search for clinical signs and symptoms of arterial lesions in another vascular bed, including carotid stenosis. However, neither the ESC-ESVS nor the AHA recommend systematic screening for asymptomatic carotid stenosis in patients with LEAD.

According to the 2017 ESC-ESVS guidelines, 14 to 19% of patients suffering from LEAD have a >70% carotid stenosis (2). These lesions (carotid stenosis or even occlusion) may be asymptomatic, raising the question of whether systematic DUS screening should be envisaged.

As discussed in the previous section (5.1) concerning screening for CAD, the results of the COMPASS trial (96) could lead to changes in the recommendations for medical treatment of patients with multisite lesions.

Although this point is not explicitly addressed in the guidelines, we recommend annual measurement of BP in both arms to screen for any asymptomatic subclavian artery stenoses that could lead to underestimation of BP, or even myocardial infarction (MI) in the context of aorto-coronary bypass using a mammary artery.

Section 7.2 - Suggestions and recommendations

1. **We recommend screening for symptomatic carotid artery stenosis on the basis of the patient's medical history and physical examination (Grade 1+).**
2. **We recommend measurement of BP in both arms to detect any stenosis of the subclavian artery (associated with an increased CV risk and a risk of underestimating BP) (Grade 1+).**
3. **In the case of suspected carotid or subclavian stenosis, we suggest performing a DUS examination of the cervicocephalic arteries to optimize therapeutic management (Grade 2+).**
4. **If an asymptomatic carotid artery stenosis is detected, we recommend conforming to the guidelines concerning management of carotid artery stenoses (Grade 1+).**

7.3. Renal artery stenosis

Systematic screening for renal artery stenosis is not recommended other than in the presence of symptoms suggesting such a lesion (ESC-ESVS) or in the context of rapidly progressing renal insufficiency (ESVM).

Section 7.3 - Suggestions and recommendations

1. **In patients with LEAD, we suggest NOT TO systematically screen for renal artery stenosis (Grade 2-).**
2. **We suggest screening for renal artery stenosis in the case of flash pulmonary oedema (Grade 2+).**
3. **We suggest screening for renal artery stenosis in the context of rapidly progressing renal insufficiency (Grade 2+).**

7.4. Heart failure

The prevalence of heart failure (HF) is increased in the context of LEAD particularly in patients presenting CLI. HF may be asymptomatic or associated with few symptoms in sedentary patients. Detection of left ventricular (LV) systolic dysfunction is important,

as early therapeutic management in the form of optimised BP monitoring and prescription of an appropriate medication (e.g. angiotensin-converting enzyme (ACE) inhibitors, sartans, β-blockers, or sacubitril) reduces morbidity and mortality as well as the rate of hospitalisation (97). Left ventricular HF may also point to severe CAD which should be explored. In this case, β-blockers are recommended (97). In diabetics, the presence of left-ventricular HF will have an impact on the choice of oral antidiabetic agent (19, 97).

For all these reasons and despite the lack of specific data, the ESC-ESVS advise screening for HF based on the patient's medical history, physical examination and resting ECG. If HF is suspected, a transthoracic echocardiogram and/or a natriuretic peptide assay should be envisaged (particularly in the case of patient with poor echogenicity or diastolic dysfunction).

Section 7.4 - Suggestions and recommendations

1. **We suggest screening for HF on the basis of medical history, physical examination and resting ECG in patients presenting intermittent claudication (Grade 2+).**
2. **We recommend screening for HF in patients presenting CLI and/or having undergone revascularisation (Grade 1+).**
3. **We recommend seeking the advice of a cardiologist if HF is suspected (Grade 1+).**
4. **For patients with HF, we suggest seeking the advice of a cardiologist in the case of either symptomatic LEAD, irrespective of stage, or masked LEAD (Grade 2+).**
5. **For patients with HF, we suggest seeking the advice of a cardiologist in the case of asymptomatic LEAD, irrespective of stage (Grade 2+).**
6. **For patients with HF, we suggest seeking the advice of a cardiologist in the case of masked LEAD (Grade 2+).**

7.5. Atrial fibrillation

The risk of atrial fibrillation (AF) is increased in patients with LEAD (the *Cardiovascular Health Study* showing a hazard ratio [HR] of 1.52) (98), being estimated as around 10%

in these patients (REACH registry) (99). ABI remains a reliable criterion in the context of AF (100). An abnormal ABI is an independent risk factor for death and major bleeding in the context of anticoagulant treatment (101). Patients with LEAD associated with AF are often more elderly and present more comorbidities as well as more severe LEAD. They are at increased risk of MI, unstable angina, HF, renal insufficiency, stroke, infection, amputation and death.

If the CHA_2DS_2-VASc score is ≥2, the patient should receive anticoagulant treatment (ESC-IA) in the absence of any major contraindication. This score should also be calculated in other patients, as patients with vascular disease have a CHA_2DS_2-VASc score ≥ 1 (ESC-IIaB).

Section 7.5 - Suggestions and recommendations

1. **If the DUS examination gives grounds for suspecting AF, we recommend recording an ECG (Grade 1+).**
2. **If the DUS examination gives grounds for suspecting AF, we recommend urgently seeking the advice of a cardiologist to confirm the diagnosis of AF (Grade 1+).**
3. **We recommend seeking the advice of a cardiologist for patients with permanent or intermittent AF (Grade 1+).**
4. **For patients with AF, we recommend discussing the question of anticoagulation with a cardiologist without delay and initiating appropriate treatment as soon as possible (Grade 1+).**

7.6. Valvulopathy

The prevalence of aortic stenosis is increased in elderly individuals who are also at higher risk of LEAD. Furthermore, the symptoms of aortic stenosis (dyspnoea and/or exercise angina) may be masked in sedentary patients. In the majority of cases, the diagnosis of valve disease may be suspected on the basis of cardiac auscultation. The ESC/ESVS recommend investigating medical history and performing a thorough physical examination (2). If the diagnosis of valve disease is confirmed, the advice of a cardiologist should be sought.

If transcatheter aortic valve implantation (TAVI) or another structural cardiological intervention necessitating arterial access is scheduled, the ESC-ESVS recommend a CT-scan of the aorta as well as the iliac and femoral arteries prior to the intervention.

Section 7.6 - Suggestions and recommendations

1. **We recommend seeking the advice of a cardiologist if valvulopathy is suspected (Grade 1+).**

8. Screening for lower extremity artery disease in the context of cardiac disease

Only the ESC/ESVS guidelines specifically address this topic.

8.1. Atherosclerotic coronary disease

The ESC/ESVS guidelines recommend measuring the ABI in patients with CAD, as this is a non-invasive and inexpensive method for evaluating a patient's level of CV risk. Individuals suffering from LEAD in addition to CAD have a more unfavourable prognosis than those with CAD alone (99). The AMERICA trial (102) did not show that systematic screening for LEAD was of value, but this was a small study. Furthermore, as already mentioned in sections 7.1 and 7.2, the results of the COMPASS trial (96) could modify the therapeutic strategy implemented in patients at very high CV risk.

For coronarography, with or without stenting, the ESC/ESVS recommend favouring radial access, if possible, so as to limit the risk of complications at the puncture sites in patients with LEAD. If femoral access is necessary, the ESC/ESVS guidelines recommend examination of the common iliac and femoral arteries prior to the intervention (103).

If coronary artery bypass grafting (CABG) is envisaged in a patient suffering from LEAD, ESC/ESVS guidelines also recommend striving to preserve the saphenous veins.

Section 8.1 - Suggestions and recommendations

1. **In patients with CAD, we suggest measuring the ABI to better evaluate the patient's level of risk (Grade 2+).**
2. **If coronarography or coronary angioplasty is envisaged in a patient with LEAD, we suggest favouring radial access (Grade 2+).**
3. **If CABG is envisaged in a patient with LEAD, we suggest preserving the great saphenous veins (Grade 2+).**

8.2. Heart failure

LEAD is a risk factor for hospitalisation and death in patients with HF (104). For this reason, ESC-ESVS guidelines propose screening for LEAD in these patients.

With the aim of avoiding vascular complications, ESC-ESVS guidelines recommend performing a complete vascular examination prior to heart transplantation or implantation of a ventricular assist device (VAD).

Section 8.2 - Suggestions and recommendations

1. **In patients with HF, we suggest proposing screening for LEAD (masked LEAD) (Grade 2+).**
2. **We recommend a complete vascular examination prior to heart transplantation or implantation of a VAD (Grade 1+).**

8.3. Valvulopathy

The presence of LEAD is a risk factor in the context of aortic valve replacement (105) (*EuroSCORE interactive calculator* http://www.euroscore.org/calc.html) and is also a risk factor for complications associated with TAVI. For this reason, ESC-ESVS guidelines recommend a complete investigation of the aorta, as well as the iliac and femoral arteries, by CT-scan prior to TAVI or any other structural cardiological intervention necessitating arterial access.

Section 8.3 - Suggestions and recommendations

1. **We recommend investigation of vascular access prior to TAVI or any other intervention necessitating (or potentially necessitating) an arterial access carrying a risk of complications (Grade 1+).**

9. Medical treatment of lower extremity artery disease

9.1. Antiplatelet treatment

All the guidelines recommend treating symptomatic patients with an antiplatelet agent, aspirin or clopidogrel, (1, 106, 107), for secondary prevention of major CV events (class I). Whereas the AHA guidelines do not specifically mention clopidogrel, the ESC-ESVS and ESVM recommend use of this drug (grade IIb, B), based on the results of the CAPRIE trial (108). The meta-analysis published by Basili (109) reported a significant reduction in MACE (OR 0.839; 95% CI 0.729–0.965; p = 0.014) with antiplatelet agents, essentially thienopyridines (OR 0.779; 95% CI 0.639–0.950; p = 0.014), whereas an effect of aspirin was not demonstrated (OR 0.847; 95% CI 0.653–1.097; p = 0.084). The results of a second meta-analysis (110) were similar, showing a decrease in MACE with clopidogrel (RR 0.72, 95% CI 0.58-0.91, p = 0.004) but not with aspirin (RR 0.92, 95% CI 0.53-1.06, p = 0.25), the rates of major bleeding being the same (RR 1.01, 95% CI 0.71-1.46, p = 0.94 for clopidogrel, RR 1.14, 95% CI 0.87-1.50, p = 0.34 for aspirin). Outside the revascularisation context, no antiplatelet agent achieved a reduction in *Major Adverse Limb Events* (MALE), corresponding to ischaemia necessitating surgery in the form of major amputation.

For patients with asymptomatic LEAD, the ESVM makes no recommendation. In 2017, the ESC-ESVS, on the basis of two trials (1, 111, 112), advised against the systematic use of an antiplatelet agent (except in the case of another indication, e.g. CAD), whereas the AHA tentatively suggested a potential benefit. It is worth pointing out that the definition of asymptomatic LEAD differed between the trials, notably with regard to the threshold value and the methodology used to determine the ABI, offering a partial explanation for these contradictory positions.

The position of the ESC-ESVS was based on the unfavourable benefit-risk ratio of aspirin in asymptomatic patients in terms of CV risk *versus* bleeding. The recent ESC guidelines concerning diabetes (19) nevertheless authorise the prescription of aspirin for primary prophylaxis in diabetic patients at high or very high CV risk, in the absence of any contraindication (Grade IIb). Patients considered as being at high CV risk comprise those with at least a 10-year history of diabetes in association with another CV risk factor, but

without any target organ damage. Patients considered as being at very high CV risk comprise diabetics presenting a CV disease, target organ damage, a more than 20-year history of diabetes or at least three CV risk factors. Diabetics with asymptomatic LEAD are therefore considered as being at very high CV risk.

The ESC-ESVS differentiate asymptomatic LEAD and masked LEAD, but do not specify whether patients presenting the latter condition should be treated with an antiplatelet agent. Given the position of the AHA with regard to asymptomatic LEAD, it may be assumed that patients with masked LEAD should receive treatment with an antiplatelet agent.

According to a recent Cochrane review, the benefit-risk ratio of dual antiplatelet therapy (DAPT) is debatable, with the exception of certain specific cardiological contexts (such as acute coronary syndrome or coronary stenting) (113). Long-term DAPT is generally not recommended by the ESC-ESVS for patients with LEAD. In contrast, it is proposed by the AHA on the basis of the CHARISMA trial, even though the results of this trial were negative (114).

The AHA, ESC-ESVS and ESVM guidelines are all in favour of long-term DAPT after revascularisation involving a particular risk, notably after infrainguinal stenting (ESC-ESVS grade IIa C, ESVM grade IIa, B) (115), below-knee prosthetic bypass grafting (ESC-ESVS, grade IIb B) (116) or thrombectomy (ESVM grade IC).

In its updated recommendations concerning DAPT, the ESC recommends associating a proton pump inhibitor (PPI) to reduce the risk of gastrointestinal bleeding (113). Owing to the risk of drug-drug interactions with clopidogrel, the ESC advocates prescribing pantoprazole (117). The prescription of a PPI is also recommended in the context of co-prescription of an anticoagulant and an antiplatelet agent.

On the basis of the WAVE trial results (118), the AHA (IIIA) (119) and the ESVM advise against the use of a vitamin K antagonist (VKA) to reduce the risk of MACE in the context of LEAD (except when this is specifically indicated for a concurrent condition, such as AF, or in patients with a mechanical valve prosthesis, for example). Opinions diverge with respect to the use of VKA in the context of bypass surgery, notably when

964 infrapopliteal vein grafts are employed. The ESC-ESVS envisage this treatment if the
965 patient's risk of bleeding risk is not too high (grade IIb B) (120). The AHA (grade IIb)
966 and the ESVM (grade IIIb) advise against the use of VKA other than in the case of
967 precarious infrapopliteal bypass grafting involving a high risk of occlusion.

968 Based on the results of the COMPASS trial, the ESVM envisages the combined use of
969 rivaroxaban 2.5 mg twice a day (BID) and aspirin 100 mg/day (OD) for patients with
970 stable LEAD (grade B-IIa) (121).

971 The COMPASS trial included 7470 patients presenting either LEAD (n = 5551 patients
972 with a history of revascularisation or amputation, intermittent claudication, or an ABI
973 <0.90 in the context of concomitant CAD) or carotid artery disease (n = 1919 patients
974 with a history of carotid artery revascularisation or >50% stenosis). The patients were
975 randomised into three treatment groups (rivaroxaban 5 mg BID alone, aspirin 100 mg
976 OD alone, or rivaroxaban 2.5 mg BID + aspirin 100 mg OD) and followed up for a median
977 of 21 months. In total, 65% of the patients had CAD. Rivaroxaban combined with aspirin
978 significantly reduced the incidence of MACE compared to aspirin alone (5% *vs* 7%; HR
979 0.72, 95% CI 0.57 – 0.90, p = 0.0047), notably with regard to stroke (HR 0.54, 95% CI
980 0.33–0.87). Compared to aspirin alone, the combined treatment also significantly
981 reduced the incidence of MALE (ischaemia necessitating an intervention or major
982 amputation) as a whole (1% *vs* 2%; HR 0.54, 95% CI 0.35 – 0.84) and that of major
983 amputations in particular (HR 0.3, 95% CI 0.11 – 0.8). The rate of major bleeding was
984 higher in the group receiving rivaroxaban (2.5 mg BID) combined with aspirin *vs* aspirin
985 alone (2% *vs* 1%; HR 1.61, 95% CI 1.12 – 2.31). Major bleeding events comprised
986 principally gastrointestinal bleeding, notably among patients aged over 70 years. After
987 an initial MALE, the combination of rivaroxaban (2.5 mg BID) with aspirin decreased the
988 incidence of a second MALE by 43% compared to aspirin alone (HR 0.57, 95% CI 0.37 –
989 0.88) (122).

990 Stratification of the patients included in the COMPASS trial by CV risk enabled
991 identification of a high-risk population comprising patients with at least two vascular
992 beds affected, patients with heart failure or renal insufficiency (GFR < 60 mL/min), and
993 patients with diabetes. Although the combination of rivaroxaban (2.5 mg BID) with
994 aspirin was superior to aspirin alone, irrespective of the level of CV risk, the clinical

benefit achieved was substantially greater in the population at high CV risk. The absolute risk reduction was 6% in patients at high CV risk compared to 1.4% in those at low CV risk (123). A subgroup analysis of patients with diabetes (n=10,341) revealed that these patients also benefited from this therapeutic strategy. The rate of occurrence of the composite primary endpoint (CV death, MI, ischaemic stroke) was significantly decreased in patients receiving rivaroxaban (2.5 mg BID) combined with aspirin *vs* aspirin alone (HR 0.74, 95% CI [0.61-0.90]; p = 0.002). A significant increase in the risk of major bleeding with rivaroxaban plus aspirin compared to aspirin alone was observed at 3 years (HR 1.69, 95% CI [1.33-2.15]; p = 0.0006), but without a significant increase in the risk of intra-cranial or fatal bleeding (124).

The VOYAGER LEAD trial evaluated the effect of rivaroxaban 2.5 mg BID combined with aspirin 100 mg OD compared to aspirin alone (100 mg/day) in 6,564 patients having undergone lower-limb revascularisation (surgical or endovascular) within the past 10 days (125). This study demonstrated a reduction in occurrence of the primary endpoint (acute lower limb ischaemia, major amputation of vascular cause, myocardial infarction, ischaemic stroke, or CV death) at 3 years in the group receiving rivaroxaban combined with aspirin compared to aspirin alone (17.3% *vs* 19.9%; HR 0.85, 95% CI [0.76-0.96]; p = 0.009). A non-significant increase in major bleeding according to the TIMI classification was seen in the rivaroxaban + aspirin group compared to the group receiving aspirin alone (2.65% *vs* 1.87%; HR 1.43, 95% CI [0.97-2.10]; p = 0.07) (126). However, there was a significant increase in major bleeding according to the conventionally used ISTH classification (that employed in the COMPASS trial) in the group receiving rivaroxaban + aspirin *versus* aspirin alone (5.94% *vs* 4.06%; HR 1.42; 95% CI [1.10-1.84]; p = 0.007) (125).

In patients with AF presenting LEAD, antiplatelet agents should not be combined with anticoagulants, except in the case of recent stenting and/or specific indications (particularly cardiological) (127).

Section 9.1 - Suggestions and recommendations

1. **We recommend antiplatelet treatment in patients with symptomatic LEAD (Grade 1+).**
2. **We recommend NOT TO treat patients presenting asymptomatic LEAD with antiplatelet agents, unless they manifest other clinically relevant atherosclerotic lesions (affecting the coronary or carotid arteries, for example) or possibly, in the absence of any contraindication, if they are diabetic and at high CV risk (Grade 1-).**
3. **We recommend antiplatelet treatment for patients with masked LEAD as for those with symptomatic LEAD (Grade 1+).**
4. **We suggest DAPT for 1 month after infrainguinal stenting (Grade 2+).**
5. **We suggest DAPT for at least 6 months after below-knee bypass grafting using a prosthetic conduit (in the CASPAR trial DAPT was continued for 6 to 24 months) (Grade 2+).**
6. **We suggest NOT TO prolong DAPT (except in specific cardiological indications such as acute coronary syndrome or coronary stenting) (Grade 2-).**
7. **We recommend NOT TO combine VKA with aspirin to reduce MACE in patients with LEAD (unless there is a specific indication for VKA) (Grade 1-).**
8. **We suggest that treatment with aspirin combined with rivaroxaban (2.5 mg BID) should be initiated after discussion with a specialist in CV diseases (Grade 2+).**
9. **We recommend NOT TO combine antiplatelet and anticoagulant treatments in patients with AF, except in the case of specific indications (such as recent stenting or acute coronary syndrome) (Grade 1-).**

Section 9.1 – ISSUES IN ABEYANCE (full consensus not achieved during the DELPHI procedure)

1. **We suggest treatment with clopidogrel hydrogen sulphate rather than aspirin in patients with symptomatic LEAD.**

This proposal obtained a consensus agreement of 68%, three experts (7%) expressing

no opinion. One of these experts maintained that the level of evidence was low. Admittedly this suggestion is based on the results of a single trial (CAPRIE) (108). A meta-analysis nevertheless confirmed the decrease in CV adverse events with clopidogrel in contrast to aspirin (110). Furthermore, a systematic review of the literature published in 2009 showed that the effect of aspirin in patients suffering from LEAD was debatable (107).

2. **In the case of DAPT or combined antiplatelet and anticoagulant therapy, we recommend prescription of an IPP.**

This proposal achieved a consensus agreement of 73%, six participants (15%) expressing no opinion. A study in patients with CAD showed that co-administration of omeprazole with DAPT reduced the risk of gastrointestinal adverse events compared to a placebo without affecting the prevention of CV events (128). In view of the increased risk of bleeding with DAPT, this suggestion to additionally prescribe an IPP would seem to be justifiable (129). However, it is important to bear in mind that up to now no study of this type has been performed in patients with LEAD. A subgroup analysis of the COMPASS trial showed that the addition of pantoprazole to combined aspirin and rivaroxaban treatment did not diminish occurrence of the composite endpoint of gastroduodenal events (130) compared to the addition of a placebo (HR 0.88; 95% CI 0.67-1.15).

3. **In the context of clopidogrel treatment, we recommend choosing pantoprazole as the IPP.**

This proposal obtained a consensus agreement of 63%, 14 experts (34%) expressing no opinion. The level of evidence is low. The choice of pantoprazole is based on a review of the literature published between 1980 and 2009 including articles or reviews reporting interactions between IPP and clopidogrel hydrogen sulphate (117). Clopidogrel is metabolised by the cytochrome CYP2C19, as are IPP. However, the affinities of the various IPP differ (131). Omeprazole appears to be the IPP that interacts with clopidogrel to the greatest extent (117).

4. **For patients with at least two vascular beds affected, patients with heart failure, renal insufficiency (GFR < 60 mL/min) or diabetes and patients with a low risk of bleeding, we suggest dual therapy with rivaroxaban 2.5 mg BID and aspirin 100 mg OD in the case of symptomatic LEAD or after lower limb revascularisation. This suggestion does not take into consideration**

reimbursement issues or Transparency Commission opinions.

This proposal obtained a consensus agreement of 61%, six experts (15%) expressing no opinion. Several experts raised the issue that this therapeutic strategy combining rivaroxaban and aspirin is not reimbursed in France. However, it is recommended by several scientific societies aware of the results of the COMPASS trial (3). The results of the VOYAGER trial, published in March 2020 might also have modified the responses of the experts (125). Finally, the choice of the comparator, namely aspirin rather than clopidogrel is also considered controversial by certain experts (108).

9.2. Lipid-lowering agents

The guidelines issued by the AHA, the ESC-ESVS and the ESVM concur in recommending the use of a statin for all patients with LEAD (grade 1A), even those with asymptomatic disease, the different statins available varying in their intensity (Table 6) (132). The ESVM and the SVS set a target threshold for low density lipoprotein (LDL) cholesterol (LDLc) of <0.70 g/L (grade IC) or a decrease in LDLc >50% if the baseline level is between 0.70 and 1.35 g/L (3, 4, 19). In the event of intolerance or difficulty in achieving the target concentration of LDLc, the ESVM proposes the concomitant use of ezetimibe (grade IIa B). Based on the results of the FOURIER trial, the ESVM proposes the further addition of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (evolocumab) if treatment with a statin at the maximum tolerated dose plus ezetimibe proves ineffective.

The latest guidelines of the ESC and the European Atherosclerosis Society (EAS) concerning dyslipidaemias specify the indications for prescription of a PCSK9 inhibitor in patients with LEAD. For these patients, a lipid-lowering treatment comprising a statin at the maximum tolerated dose, ezetimibe and if necessary a PSCK9 inhibitor, is recommended to reduce the risk of an adverse event associated with the CV disease (5).

The ESC guidelines concerning dyslipidaemias establish four classes of CV risk (Table 3) (5). Besides the SCORE classification (http://www.heartscore.org), which evaluates the 10-year risk of fatal CV disease, the ESC also takes into account the duration of diabetes (type 1 or type 2), target organ damage, family history of hypercholesterolaemia, the presence of moderate or severe renal insufficiency), CV history in general, including the presence of atherosclerotic plaques in the carotid and/or femoral arteries and the coronary artery calcium (CAC) score established by CT-scan. The presence of atherosclerotic plaques in the carotid and/or femoral arteries increases the patient's level of CV risk. A patient with LEAD or >50% carotid artery stenosis is considered to be at very high CV risk (5). Initial treatment comprises respect of a healthy lifestyle and dietary regime, comprising no exposure to tobacco in any form, a diet low in saturated fats and rich in whole-grain cereals, fruits, vegetables and fish, regular moderate physical activity almost every day (3.5 to 7 h per week or 30-60 min/day), weight control (Body Mass Index [BMI] 20-25 kg/m^2, abdominal circumference <94 cm for men and <80 cm for women) and maintenance of systolic BP at <140 mmHg. In these patients at very high CV risk, the ESC recommends for primary or secondary prophylaxis, a reduction in LDLc level of at least 50% relative to baseline and an absolute LDLc level of < 0.55 g/L. Medical treatment constitutes in the first instance a statin at the maximum tolerated dose, possibly combined with ezetimibe and if necessary, based on the results of the FOURIER trial, a PCSK9 inhibitor (133).

In the FOURIER trial (134), 3642 patients with LEAD (including 2518 presenting intermittent claudication and an ABI <0.85, 2067 with a history of revascularisation and 126 with a history of amputation), having a LDLc level >0.7g/L and being treated with a statin, were randomised to receive either evolocumab (140 mg every 15 days or 420 mg per month) or a placebo and followed up for a median of 26 months (133). Half the patients (49.8%) suffered from CAD and 15% had previously experienced an ischaemic stroke. Compared to a placebo, evolocumab decreased the level of cholesterol (LDLc) by 59% (95% CI 57 – 61) achieving a median LDLc level of 0.3 g/L. Evolocumab also reduced the incidence of MACE (major adverse CV events, including CV death, myocardial infarct, stroke, coronary revascularisation and unstable angina) (HR 0.79, 95% CI 0.66 – 0.94, p = 0.0098). In the FOURIER trial population as a whole, the absolute risk reduction with evolocumab was greater in patients with LEAD (3.5% [95% CI 0.8 –

6.2]) than in those without LEAD (1.6% [95% CI 0.7 to 2.5]) (133). Overall, the incidence of MALE was reduced by 42% (HR 0.58, 95% CI 0.38 to 0.88).

The fibrates granted a marketing authorisation in France (AMM) up to now have not proved their efficacy in reducing morbidity and mortality (135). However, the REDUCE-IT trial which included 8179 patients (71% undergoing secondary prophylaxis) demonstrated the benefit of icosapent ethyl in reducing morbidity and mortality (HR 0.75; 95% CI 0.68 to 0.83; $p < 0.001$) in patients with hypertriglyceridaemia (136). Its effect on patients with hypertriglyceridaemia and LEAD was not specifically investigated.

Section 9.2 - Suggestions and recommendations

The presence of atherosclerotic plaques in the carotid and/or femoral arteries, particularly in the context of LEAD, constitutes a high or very high CV risk.

1. **For these patients, we recommend optimisation of lifestyle and dietary habits in terms of body weight, smoking, diet, physical exercise, etc. (Grade 1+).**
2. **For patients at very high CV risk, we recommend maintaining LDLc below 0.55 g/L or at least reducing the LDLc level by half compared to its baseline value (Grade 1+).**
3. **For these patients at very high CV risk, we recommend treatment with a statin in the first instance, adjusting the dose according to efficacy and tolerability (Grade 1+).**
4. **For patients at very high CV risk, we recommend the addition of ezetimibe to statin treatment if necessary (Grade 1+).**
5. **We suggest NOT TO use fibrates to reduce morbidity and mortality in patients with LEAD (Grade 2-).**

Section 9.2 – ISSUES IN ABEYANCE (full consensus not achieved during the DELPHI procedure)

1. **For patients at very high CV risk, insufficiently stabilised by combined treatment with a statin and ezetimibe, we suggest adding a PCSK9 inhibitor.** *This proposal obtained a consensus agreement of 78%, nine experts (22%) expressing no opinion. PCSK9 inhibitors were only recently granted reimbursement status for this indication in France (in August 2020) and that might have influenced the responses of the experts. This proposal was prompted by the results of the randomised FOURIER trial which demonstrated a substantial benefit of additionally treating patients with a PCSK9 inhibitor (133, 134).*
2. **For patients presenting hypertriglyceridaemia, we suggest using icosapent ethyl.**
   This proposal obtained a consensus agreement of 51%, 18 experts (44%) expressing no

opinion. The results of the REDUCE-IT trial (136) were published during the second round of proposal grading. This trial was conducted in patients with CV disease or diabetes but not specifically in those with LEAD.

9.3. Antihypertensive agents

The ESVM sets the BP threshold at 130/80 mmHg. For the ESC (2018), hypertension is defined by a BP ≥140/90 mmHg measured during a medical consultation and ≥130/80 mmHg measured by ambulatory BP monitoring (ABPM).

In 2017, the ESC-ESVS set the threshold BP values at 140/90 mmHg (grade IA) except in patients with diabetes (diastolic BP ≤ 85 mmHg). They recommended avoiding systolic BP values below 110-120 mmHg and warned against the risk of orthostatic hypotension in fragile and/or elderly individuals.

In 2018, the ESC guidelines concerning hypertension proposed stabilisation of systolic/diastolic BP values below 140/90 mmHg and if possible, at around 130/80 mmHg. For persons aged under 65 years, these guidelines recommended a systolic BP between 120 and 129 mmHg, whereas for those aged over 65 years, maintenance of systolic BP between 130 and 139 mmHg was recommended (137).

In 2019, in its guidelines concerning diabetes, the ESC lowered the BP threshold for diabetic patients (19), stating that the systolic BP should be maintained below 130 mmHg and, if possible, between 120 and 130 mmHg. However, it specified that in patients aged over 65 years, it should be stabilised at 130 to 139 mmHg. Diastolic BP should be maintained between 70 and 80 mmHg.

The ESC-ESVS, ESVM and AHA guidelines specifically recommend treatment with an ACE inhibitor or a sartan (ESC-ESVS grade IIa B, AHA grade IIa A). The ESC-ESVS guidelines nevertheless note that the choice of treatment should also consider any co-morbidities present. The ESC guidelines issued in 2018 (137) state that treatment should generally be initiated with a dual therapy at low dose, followed by progressive dose adjustment as necessary.

The ESC-ESVS and the SVS note that β-blockers are not contraindicated in patients with LEAD, but recommend caution in the case of patients presenting CLI (2, 4). The ESC recommends avoiding excessive lowering of BP in order to maintain a satisfactory distal pressure.

In contrast to the ESC, the AHA suggests treatment with ACE inhibitors or sartans, irrespective of BP levels, for all patients with symptomatic LEAD (Grade IIa A) (138, 139).

Section 9.3 - Suggestions and recommendations

1. **We recommend stabilising systolic BP between 120 and 140 mmHg and diastolic BP at 90 mmHg (85 mmHg in diabetic patients), while avoiding orthostatic hypotension in elderly and/or fragile patients with LEAD (Grade 1+).**
2. **We recommend starting treatment with an ACE inhibitor or sartan, often in combination with a diuretic or calcium entry blocker in hypertensive patients with LEAD (Grade 1+).**
3. **β-blockers are not contraindicated in patients with LEAD, but we suggest extreme caution in the case of patients with CLI (Grade 2+).**
4. **In patients with severe LEAD, we recommend avoiding excessive lowering of BP in order to maintain a sufficient distal pressure (Grade 1+).**
5. **We recommend adjusting antihypertensive treatment according to any co-morbidities present (Grade 1+).**
6. **We suggest treatment with an ACE inhibitor or a sartan for all patients presenting both hypertension and LEAD, in the absence of any contraindication (Grade 2+).**
7. **We suggest treatment with an ACE inhibitor or a sartan for all patients suffering from symptomatic LEAD, in the absence of any contraindication (Grade 2+).**

9.4. Other treatments

9.4.A. Diabetes control

The various guidelines concur in recommending strict equilibration of diabetes, especially in patients presenting critical ischaemia (1-4, 19).

The ESC recommends maintaining HbA1c below 7% to reduce microvascular complications. Target HbA1c levels should be individually tailored according to the duration of diabetes, comorbidities and the patient's age, while avoiding hypoglycaemic episodes. The ESC advises self-monitoring of blood glucose levels (19).

Several studies published up to now have demonstrated the benefit of certain antidiabetic drugs in patients with a history of CV disease or with a high or very high risk of adverse CV events. Glucagon peptide-1 (GLP-1) receptor agonists (evaluated in the LEADER, SUSTAIN-6, Harmony Outcomes, REWIND and PIONEER 6 trials) and sodium-glucose co-transporter-2 (SGLT2) inhibitors (assessed in the EMPA-REG OUTCOME, CANVAS, DECLARE_TIMI 58 and CREDENCE trials) are recommended in patients with type 2 diabetes at high or very high CV risk or with a history of CV disease. In these patients, the ESC recommends starting treatment with either a SGLT2 inhibitor or a GLP-1 receptor agonist alone, or in addition to metformin in the case of already ongoing metformin therapy. In "naive" patients, metformin may be added to the initial treatment with a SGLT2 inhibitor or a GLP-1 receptor agonist in the event of insufficient diabetes control. SGLT2 inhibitors are particularly recommended for patients at risk of CI. It should be borne in mind that these agents can be used only in patients with an adequate GFR (19).

Other classes of antidiabetic agents may be co-prescribed subsequently if necessary (19). Dipeptidyl peptidase 4 (DPP4) inhibitors are contraindicated in patients at risk of HF.

Randomised trials have shown an increase in the rate of lower-limb amputation in patients treated with SGLT2 inhibitors, particularly with canaglifozin (HR 2.32, 95% CI 1.37-3.91) (140), possibly owing to volume depletion. We therefore advise caution in patients at risk of dehydration or progression to severe forms of LEAD.

Section 9.4-A - Suggestions and recommendations

1. **We recommend maintaining HbA1c below 7% (Grade 1+).**
2. **We recommend adjusting target HbA1c values according to the duration of diabetes, comorbidities and age, while avoiding hypoglycaemic episodes (Grade 1+).**
3. **We suggest self-monitoring of blood glucose levels (Grade 2+).**
4. **For patients whose diabetes is insufficiently controlled by metformin treatment, we recommend adding either a SGLT2 inhibitor or a GLP-1 receptor agonist in the first instance (Grade 1+).**
5. **We recommend considering the patient's risk of dehydration or progression to severe forms of LEAD when prescribing SGLT2 inhibitors (Grade 1+).**

Section 9.4-A – ISSUES IN ABEYANCE (full consensus not achieved during the DELPHI procedure)

1. **For « naive » diabetic patients, we recommend initial treatment with a SGLT2 inhibitor or a GLP-1 receptor agonist alone (depending on the reimbursement conditions of the national health insurance system concerned).**
   This proposal obtained a consensus agreement of 61%, 13 experts (44%) expressing no opinion. These medicinal products were not reimbursed for this indication in France at the start of the Delphi procedure and this may have influenced the responses of the experts. In April 2020, dapagliflozin, a SGLT2 inhibitor, was granted reimbursement status. The ESC and the European Society for the Study of Diabetes (EASD) advocate this therapeutic strategy (19).
2. **For these « naive » diabetic patients, we recommend subsequent addition of metformin to the initial treatment if necessary.**
   This proposal obtained a consensus agreement of 73%, nine experts expressing no opinion. The different criteria for reimbursement of SGLT2 inhibitors and GLP1

receptor agonists may have influenced the responses of the experts. It is worth noting that both the ESC and the EASD advocate this therapeutic strategy (19).

9.4.B. Vaccination

The AHA alone mentions influenza vaccination. Observational studies have revealed a reduction in the rate of adverse CV events in patients with CV disease having been vaccinated against influenza (141). Two randomised studies including patients with CAD showed a benefit of influenza vaccination in preventing adverse CV events, notably ischaemic coronary events (142, 143). These clinical studies did not specifically include patients with LEAD, but CAD is present in the majority of such patients (141). Based on these data, annual influenza vaccination is recommended for patients suffering from LEAD.

Given the risk of chronic wounds, we also recommend maintaining valid vaccination against tetanus.

Section 9.4-B - Suggestions and recommendations

1. **We recommend influenza vaccination for patients with LEAD (Grade 1+).**
2. **We recommend systematically checking the validity of anti-tetanus vaccination, particularly in patients presenting wounds and/or CLI (Grade 1+).**

10. Supervised exercise therapy

10.1. In symptomatic patients

10.1.A. What is consensual

Supervised exercise training forms an integral part of treatment of all patients with LEAD at the stage of symptomatic exercise-induced ischaemia, having demonstrated short-, medium- and long-term efficacy (1). However, provision of advice on exercise training without implementation of a structured programme is ineffective. After exercise training, patients suffering from intermittent claudication could walk further without pain and their maximum walking distance evaluated by the *Strandness* test was also increased (144). In contrast, this training neither improved ABI (144) nor decreased mortality or amputation rate (144). A recent report published by INSERM nevertheless indicates a decrease in mortality among patients with LEAD as a result of physical activity (145). Exercise training has been the cornerstone of treatment for LEAD for over 40 years (4), in conjunction with smoking cessation, with the objective of improving functional status and quality of life and attenuating the symptoms of claudication (grade I A) (1).

In patients with intermittent claudication, supervised exercise training resulted in a 50 to 200% increase in walking distance maintained for over 2 years (144). Scientific societies concur in recommending exercise training, in the form of a structured programme supervised by a qualified health care professional, as the first-line treatment for patients suffering from claudication of arterial origin (grade I A (1, 2, 4) or grade I B (3)). Supervised exercise training in a specialised centre consists in walking exercises alternating with periods of recuperation in sessions lasting at least 30 min (3), 30-45 min (1) or 30-60 min (4), accomplished at least three times a week for at least 12 weeks [grade I A (1, 4) or grade I B (3)]. A self-directed, home-based structured exercise training programme accomplished under the direct guidance of a qualified healthcare professional and conforming to the programme implemented in a centre, may be envisaged if centre-based training is not possible [grade I B (4), grade IC (2), grade IIa A (1). Ideally, this self-directed, home-based structured exercise training programme should include behavioural modification techniques to enhance the walking capacity

and functional status of the claudicant patient [grade I B (4), grade I C (2) and grade IIa A (1)]. The 30-min self-directed structured exercise programme accomplished by the claudicant patient at home 3-5 times a week for 12 weeks, under the guidance of a healthcare professional, can be implemented either straightaway or following an initial supervised programme in a centre (30-60 min sessions, 3 times a week).

10.1.B. What is not consensual

10.1.B.1. Home-based exercise training after supervised exercise programme

In view of its long-term benefits, self-directed exercise training at home is recommended by the SVS after initial supervised training in a centre (grade IB) (4).

In contrast to the SVS guidelines, those issued by the AHA, ESC and ESVM do not mention the value of self-directed exercise training at home following initial supervised training in a centre (1-3).

10.1.B.2. Prerequisites for envisaging self-directed, home-based exercise training

The AHA/ACC guidelines specify that a self-directed structured programme of exercise training can be accomplished at home under certain conditions. It is essential to ensure that the patient understands the programme proposed (including the duration and frequency of the exercise sessions and the pain threshold to be respected) and also that he/she understands how to increase walking distance or the speed of walking (grade IIaA) (1).

In contrast, the ESC, ESVM and SVS guidelines do not mention any prerequisites for self-directed exercise training at home (2-4).

10.1.B.3. Pain threshold to be respected

A self-directed programme of exercise training, defining sub-maximal pain as the threshold for stopping the exercise and using an activity monitor to provide the patients

with the results attained and the progress made, can achieve outcomes in terms of the onset of claudication and the maximum walking time similar to those obtained with a supervised exercise training programme in a centre (grade IB) (4). Low-intensity physical exercises seem to be as effective as high-intensity exercises with regard to increasing walking distance on condition that the duration of exercise is prolonged in the case of a low-intensity programme (146).

The SVS alone envisages the possibility of proposing training programmes in which the patient is advised to avoid reaching the pain threshold while exercising. In the light of currently available evidence, this concept of reaching the pain threshold is controversial (147). Having to reach the pain threshold may be a factor limiting the patient's willingness to pursue the training programme. Several studies have even suggested a potentially detrimental effect of attaining the pain threshold (148). Furthermore, the results of studies investigating exercise training using a sub-maximal pain threshold seem to be comparable to those of studies involving attainment of the pain threshold (149-152).

10.1.B.4. Use of an activity monitor

Exercise training programmes may include the use of behavioural modification techniques, such as the intervention of a healthcare coach and use of an activity monitor (grade IIaA) (153). These new technologies might effectively palliate the insufficient numbers of exercise training centres and available healthcare professionals, besides diminishing the cost of the programmes.

10.1.B.5. Exercise training as a function of the location of LEAD

Exercise training is generally less effective in patients with aorto-iliac occlusion, high-grade popliteal stenosis or popliteal thrombosis (grade IC) (2). The CLEVER trial demonstrated the efficacy of exercise training in patients presenting iliac lesions with comparable functional walking test results in the exercise training group and the revascularisation group (154). In patients presenting stenosis of the common femoral artery (CFA) or lesions affecting both the deep femoral artery (DFA) and the superficial

femoral artery (SFA), revascularisation is indicated prior to the prescription of exercise training (155).

10.1.B.6. Exercise training *versus* revascularisation

Exercise training carries few risks in contrast to any revascularisation procedure (156). AHA/ACC guidelines recommend proposing a structured and supervised exercise training programme for patients suffering from claudication prior to any revascularisation (grade I BR) (1). Exercise training, whether in a centre or at home, is also recommended in the ESC and SVS guidelines as a complement to revascularisation for patients with claudication to increase their walking capacity (grade I B) (2, 4).

10.1.B.7. Alternatives to exercise training

For claudicant patients, alternatives to exercise training focused on walking (e.g. ergometric exercises of the upper and/or lower limbs, or cycling), involving variable durations and intensities of training, may be beneficial in terms of improving walking ability and functional status (grade IIa A) (1). These physical activities seem to be effective in increasing walking capacity (157-159).

Section 10.1 - Suggestions and recommendations

1. **We suggest, following a structured programme of supervised exercise training in a centre, pursuit of the programme in the form of self-directed, home-based exercise training (Grade 2+).**
2. **We suggest making sure that the patient has understood the principles of the exercise training programme (duration and frequency of the exercise sessions, pain threshold to be respected, impact of the speed of walking and the slope), as well as its value, before proposing a self-directed programme of exercise training at home (Grade 2+).**
3. **We suggest proposing a supervised exercise training programme not involving attainment of the pain threshold (Grade 2+).**
4. **We suggest proposing a self-directed, home-based exercise training programme not involving attainment of the pain threshold (Grade 2+).**

5. **We suggest using behavioural modification techniques to facilitate self-directed exercise training at home (Grade 2+).**
6. **We suggest using an activity monitor to facilitate self-directed structured exercise training (Grade 2+).**
7. **We suggest proposing in the first instance a structured exercise training programme in a centre, in the absence of any lesion in the femoral bifurcation with significant haemodynamic repercussions (Grade 2+).**
8. **We suggest NOT TO propose exercise training prior to revascularisation for patients presenting stenosis of the CFA or stenosis of the DFA associated with stenosis of the SFA (Grade 2-).**
9. **We suggest proposing exercise training either in a centre or at home, both before and after revascularisation, for patients presenting an iliac lesion, (Grade 2+).**
10. **If the patient has difficulty in accomplishing exercise training focused on walking, we suggest recourse to other physical activities (e.g. ergometric exercises of the upper and/or lower limbs, static lower-limb exercises, or cycling) to improve walking ability (Grade 2+).**

10.2. In asymptomatic patients

A structured programme of exercise training supervised by a qualified health care professional is indicated for all patients suffering from LEAD (160, 161), in conjunction with behavioural, lifestyle and dietary counselling.

Section 10.2 - Suggestions and recommendations

1. **We suggest proposing to asymptomatic patients a supervised or self-directed programme of exercise training in addition to behavioural, lifestyle and dietary counselling (Grade 2+).**

10.3. Contraindications to exercise training

The benefit-risk ratio of exercise training is favourable on condition that the absence of any contraindication to exercise, notably any cardiorespiratory contraindication, is checked beforehand. It is essential to ensure the absence of any formal contraindication to exercise training (serious CV or pulmonary disease, amputation, confinement to a wheelchair, or other limiting medical condition). Patients must be examined to ensure that they have a sufficient cardiopulmonary reserve to tolerate an exercise programme (162). According to the ESC guidelines, supervised exercise training is not dangerous and cardiac screening is not systematically indicated (see section 7) (163). However, exercise training is impossible in patients with CLI and there is currently no recommendation concerning exercise training after treatment of CLI. Exercise training should be accompanied by changes in behavioural, lifestyle and dietary habits and the use of appropriate footwear is essential for diabetic patients.

Section 10.3 - Suggestions and recommendations

1. **Before initiating an exercise training programme, we suggest consultation with a cardiologist to evaluate whether or not the patient should be screened for MI (Grade 2+).**
2. **As yet, no recommendation has been issued concerning exercise training for patients having undergone treatment for CLI. We nevertheless suggest prescription of a supervised structured programme of exercise training in a centre following effective treatment of CLI to improve the patient's physical capacities (Grade 2+).**

11. Revascularisation

11.1. Intermittent claudication

The authors of the various guidelines are unanimous in considering that the objective of revascularisation at the stage of claudication is not to protect against progression to CLI or the risk of amputation.

The AHA, ESC-ESVS, ESVM and SVS guidelines all agree in recommending revascularisation for patients suffering from claudication that is lifestyle-limiting (AHA), impacts everyday life activities (ESC and ESVM) or results in functional disability (SVS). The ESVM introduces the concept of quality of life impairment in its recommendations for interventional therapy. The ways in which disability should be evaluated are not clearly specified.

11.1.A. Definition of disability

Disability was initially defined solely on the basis of walking distance. Exercise training studies have employed several evaluation criteria including maximum or pain-free walking distances and quality-of-life scores (SF-36, EQ-5D) (ESC, AHA).

For the AHA, disability related to claudication and affecting lifestyle is defined more in terms of patient perception than on test performance and includes difficulties in performing everyday life, professional or recreational activities (AHA: grade IIa, A). The correlation between disability and the severity and haemodynamic repercussions of lesions is poor and varies from one patient to another (164, 165).

11.1.B. Duration of evaluation

The ESC and ESVS restrict the indications for revascularisation to patients who fail to respond favourably to exercise training within 3 months, the usual duration of exercise training programmes (155). Programmes extending for >26 weeks are more effective than shorter programmes (149).

The AHA considers that if claudication substantially affects the performance of everyday activities, revascularisation may be envisaged in addition to exercise training (1, 166, 167).

The ESVM suggests that if exercise training is impossible and the lesion is technically accessible, revascularisation may be proposed with the objective of improving quality of life (51).

11.1.C. Duration of revascularisation benefit

The long-term outcome of revascularisation depends on numerous factors, both local and general. In patients with claudication, a sustained benefit of revascularisation is essential to justify undertaking this procedure and the inherent risk involved must be low. The expected benefit is principally defined in terms of improvement in functional status and quality of life.

Both the location of the lesions and their characteristics contribute to determining the result of revascularisation, the long-term results of the procedure being better for aorto-iliac lesions than for infrainguinal lesions (1-4).

In view of these findings, certain authors consider that revascularisation should only be envisaged when the probability of a sustained benefit at 2 years is >50% (168). The SVS attributes a high grade to this recommendation. The evaluation of benefit is based on clinical efficacy. Patency of the revascularisation is considered as a prerequisite for sustained benefit (4).

11.1.D. Choice of the type of revascularisation

In the case of suprainguinal lesions, the long-term patency of extra-anatomical bypass grafts (axillofemoral, iliofemoral or femorofemoral) is of shorter duration than that achieved by direct bypass revascularisation (169). Open surgery is now reserved for patients in whom endovascular treatment is impossible or has failed (4).

Irrespective of the level of the arterial lesion, iliac or femoropopliteal, all authors recommend opting for an endovascular intervention in the first instance, particularly in

the case of femoropopliteal lesions less than 25 cm long (ESC, grade 1 C). The benefit seems to be clear for aorto-iliac lesions, but is more debatable for femoropopliteal lesions longer than 25 cm (level II recommendation) and is not documented for sural lesions (AHA, ESC, SVS) (1, 2, 4).

As regards the choice of bypass conduit, the data obtained in prospective, randomised trials favour vein grafts rather than prosthetic polytetrafluoroethylene (PTFE) grafts for both below-knee and above-knee bypasses (170, 171). The AHA recommends avoiding the use of prosthetic grafts for below-knee femoropopliteal bypass in patients suffering from claudication (1, 172-174). Vein grafts should be given preference for bypass interventions in this location (1-4).

Femoropopliteal lesions are frequent in patients manifesting claudication. If the deep femoral artery (DFA) is preserved, the likelihood of improvement through exercise therapy is high and, in most cases, revascularisation is unnecessary (2).

The management of ostial stenoses of the DFA in claudicant patients depends on the characteristics of the ipsilateral SFA. Hybrid procedures combine endarterectomy and endovascular treatment.

The SVS advises against endovascular revascularisation procedures for infrapopliteal lesions in claudicant patients (grade 1C), whereas for the authors of the AHA guidelines the value of these procedures remains unknown.

Section 11.1 - Suggestions and recommendations

1. **We suggest that disability should be evaluated on the basis of patient perceptions (Grade 2+).**
2. **We recommend evaluating disability on an appropriate quality of life scale (SF-36, EQ-5D) (Grade 1+).**
3. **We recommend pursuing best medical treatment for a minimum of 3 months before concluding lack of improvement in disability and resorting to revascularisation (Grade 1+).**
4. **For patients whose claudication has severe repercussions on their everyday activities, we suggest revascularisation without delay complemented by exercise therapy (Grade 2+).**
5. **For claudicant patients aged <50 years old, we suggest giving preference to medical treatment in the first instance (Grade 2+).**
6. **For claudicant patients with suprainguinal LEAD, we suggest NOT TO implement extra-anatomical bypass grafting in the first instance (Grade 2-).**
7. **For patients presenting a short femoropopliteal lesion, we recommend endovascular intervention in the first instance, after best medical treatment (Grade 1+).**
8. **For patients presenting ostial stenosis of the DFA associated with a short occlusion of the SFA, we suggest endovascular treatment of the SFA lesion in addition to endarterectomy (Grade 2+).**
9. **For patients with ostial stenosis of the DFA associated with a long occlusion of the SFA, we recommend endarterectomy of the DFA alone (Grade 1+).**
10. **For claudicant patients with isolated infrapopliteal lesions, we recommend NOT TO implement endovascular treatment (Grade 1-).**

Section 11.1 – ISSUES IN ABEYANCE (full consensus not achieved during the DELPHI procedure)

1. **If prior exercise therapy is impossible, we suggest envisaging suprapopliteal revascularisation without delay.**
   This proposal obtained a consensus agreement of 68%, three experts (7%) expressing no opinion. The experts made several comments on this proposal that might explain the absence of full consensus. The first comment concerned the term « without delay ». This expression effectively suggests an urgent need to treat claudicant patients, whereas in fact this is never the case. Other experts commented that if the patient was incapable of undertaking exercise therapy before revascularisation, he/she would not benefit from this type of treatment after the intervention.
2. **We recommend envisaging revascularisation only if the probability of a sustained positive outcome at 2 years is >50%.**
   This proposal obtained a consensus agreement of 78%, two experts (5%) expressing no opinion. According to the experts, several concepts in this proposal are difficult to interpret. Effectively, how can one evaluate the probability of maintaining a positive outcome? Furthermore, what is meant by a "positive outcome"?

11.2. Stenosis or occlusion of the internal iliac artery

The principal symptoms related to internal iliac artery (IIA) stenosis or occlusion are proximal claudication and erectile dysfunction (175, 176).

Proximal claudication can take several symptomatic forms, including the typical buttock or gluteal claudication, as well as pain in the hip or thigh, or exercise-induced lower back pain, hampering its recognition and its differentiation from other frequent conditions, such as hip osteoarthritis, sciatica, or lumbar spinal stenosis, constituting alternative diagnoses (177, 178).

The various potential causes of proximal pains in lower limbs are presented in Table 7 (58). The symptoms may be related to atherosclerotic lesions leading to stenosis or occlusion of the aorta, the common iliac arteries (CIA), the external iliac arteries (EIA) and/or the internal iliac arteries (IIA) (179, 180).

It is important to note that although these proximal symptoms decrease patient quality of life, no international guidelines address the management of this condition (1-4, 58).

One of the first problems encountered with regard to IIA stenosis is the difficulty in diagnosing this condition. The various complementary examinations generally used in the context of suspected LEAD, such as measurement of the ABI, DUS, CTA and MRA, enable documentation of proximal LEAD and characterisation of any lesions of the IIA, but may fail to prove the arterial origin of exercise-induced proximal symptoms, beyond clinical suspicion, in the case of isolated stenosis of an IIA (59, 181-184).

Studies have shown that one out of seven claudicant patients with a normal ABI nevertheless presents isolated proximal ischaemia (59). Furthermore, a normal penile pressure index (>0.60) does not exclude the presence of an IIA lesion (181). In this context, only tests such as exercise $TcPO_2$ (54, 185, 186), near infra-red spectroscopy (NIRS) during exercise (187-189) and thallium-201 muscular scintigraphy, revealing the existence of proximal exercise-induced ischaemia (190), can authenticate the arterial origin of certain, sometimes atypical, proximal symptoms. The results of a study comparing in the same population exercise $TcPO_2$ and NIRS suggest a superior diagnostic performance of exercise $TcPO_2$ (186).

Any patient presenting an IIA stenosis should be considered as a patient suffering from LEAD and should receive medical treatment accordingly (see section 9). Several authors have investigated the possibilities of revascularisation. For patients with isolated IIA stenosis, endovascular treatment is the most widely used procedure, as surgical revascularisation is more challenging technically and also carries a greater risk for the patient (191, 192).

No randomised trial has compared immediate stent placement to percutaneous transluminal angioplasty (PTA), or to surgery in the context of IIA stenosis, in contrast to stenosis of the CIA or EIA (193, 194). However, several studies have evaluated endovascular treatment (PTA alone or stenting) in small series of patients (191, 192). In nine patients presenting buttock claudication, PTA procedures alone or stenting involved no short-term risk and seven of the nine patients experienced pain relief after 1 month of follow-up) (192). In another study, including 21 patients followed up for a

mean of 14.7 ± 5.7 months, buttock claudication disappeared in all patients after endovascular treatment (PTA alone or stenting), leading to a significant increase in walking distance from 85 to 225 m (191). In a study conducted in 34 patients, endovascular treatment of IIA stenosis achieved a high rate of technical success (absence of any residual stenosis or a <30% stenosis post-intervention), with a low rate of complications (in 3/34 patients) (195). In this study, all patients obtained complete or partial relief of their symptoms. Several cases of symptomatic IIA stenosis treated successfully by endovascular procedures have also been published (196-199). Good results concerning the use of PTA to treat superior gluteal artery lesions have similarly been reported (200, 201). It has been suggested that in patients presenting CIA stenosis, reimplantation of the IIA in the context of aorto-iliac bypass grafting is worth considering (202). The same team performed another study in 40 patients, in whom direct revascularisation of the IAA was performed at the same time as aortofemoral or iliofemoral bypass grafting (203). In 23 out of the 27 patients with proximal claudication, this disappeared after revascularisation. The rate of IIA patency was 89% at 1 year and 72.5% at 5 years. It has also been shown that during endovascular aneurysm repair (EAR) it is advisable to preserve one of the IIA in order to limit proximal claudication and sexual disorders (204).

Section 11.2 - Suggestions and recommendations

1. **We suggest NOT TO exclude stenosis of the IIA in patients with proximal claudication with a normal ABI (>0.90) (Grade 2-).**
2. **We suggest performing a functional test in patients presenting atypical symptoms with suspected IIA stenosis (Grade 2+).**
3. **We suggest medical treatment for patients with symptomatic IIA stenosis as for patients with LEAD (Grade 2+).**
4. **We suggest PTA for symptomatic patients presenting typical proximal claudication and isolated IIA stenosis (Grade 2+).**
5. **We suggest PTA in symptomatic patients with documented proximal ischaemia presenting atypical proximal symptoms (Grade 2+).**
6. **We suggest PTA for patients presenting symptomatic IIA stenosis associated with other proximal arterial lesions if treatment of these lesions alone will not**

improve ipsilateral gluteal perfusion, and if the IIA is technically accessible during their treatment (Grade 2+).

7. **We suggest recanalisation for patients with symptomatic chronic IIA occlusion, in the context of a good quality distal IIA bed predicting an acceptable likelihood of technical success (Grade 2+).**
8. **We suggest NOT TO compromise the feasibility of using PTA to treat IIA stenosis by covering the ostium of this artery during stenting of the CIA or EIA (Grade 2-).**

Section 11.2 – ISSUES IN ABEYANCE (full consensus not achieved during the DELPHI procedure)

1. **We suggest NOT TO exclude the hypothesis of IIA stenosis in patients with a normal penile pressure index (>0.60).**
   This proposal obtained a consensus agreement of 76%, eight experts (20%) expressing no opinion. This absence of consensus may be explained by the insufficient availability of this type of test in France, as it requires considerable time to perform and necessitates the use of specific equipment (including a cuff capable of attaining the appropriate pressure, and a laser device). Furthermore, one expert pointed out that this proposal is based on the results of a single study (181). Although several other studies have been conducted, these were designed to define the threshold for concluding a vascular aetiology of impotence (205).
2. **We suggest leaving to the discretion of the operator the placement of a stent during revascularisation of an IIA stenosis.** *This proposal obtained a consensus agreement of 71%, seven experts (17%) expressing no opinion. Up to now, these two types of treatment for IIA stenosis have not been compared in any randomised trial. A 2015 Cochrane review comparing treatments for iliac artery lesions in general, emphasised the lack of publications on this subject (206).*

1696

12. Management of chronic limb ischaemia of the lower limbs

CLI is the most severe form of LEAD leading to a major deterioration in quality of life, associated with pain and in some cases tissue loss, a high rate of amputation and substantially increased mortality.

Its reported prevalence varies according to the source. Some authors consider that only 5 to 10% of patients with LEAD will progress to CLI within 5 years, the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC II) estimating a rate of 1 to 3% (35). In a meta-analysis of 35 studies published in 2016, the mean 5-year cumulative rate of progression of exercise-induced ischaemia to CLI was 21% (12-29%) (208). In this study, the rate of major amputations ranged from 4 to 27% and mortality at 1 year was very high, reaching 20% according to TASC II (35).

The management of these patients therefore involves high stakes, with regard to both local and general outcomes. A meta-analysis focusing on the 1-year outcome of the placebo groups of 11 randomised projects, confirmed the poor prognosis of patients with CLI in the absence of revascularisation. All-cause mortality at 1 year was 22% (95% CI 12-33%), as was the rate of major amputations (95% CI 2-42%), 35% of patients manifesting an aggravation of tissue loss (95% CI 10-62 %) (209).

12.1. Definition of chronic limb ischaemia

CLI denotes as chronic limb ischaemia. The ESC/ESVS have introduced the term “chronic limb-threatening ischaemia” (CLTI) without clearly defining this concept (51). In this work we have decided to keep to use the term CLI instead of CLI. This term encompasses two types of symptoms or signs:

- pain at rest in the forefoot lasting at least 15 days and not relieved by step II analgesics as defined by the WHO classification;
- tissue loss, typically affecting the forefoot. Tissue loss at other sites or related to other causes, but for which arterial disease is a contributary factor, may also be included (e.g. venous malleolus ulcers, foot ulcers, post-traumatic ulcers, bed sores).

It is relatively easy to document the presence of LEAD, but it is more difficult to confirm that this plays a role in the onset of a symptom at rest. Several definitions of CLI have been proposed (35, 210-214), differing with regard to the criteria included and therefore not comparable in terms of prognosis (215). Attempts to introduce different terms for this disease, such as permanent chronic lower-limb ischaemia (the term used by the French Haute Autorité de Santé [HAS]), or limb-threatening ischaemia (the term adopted by the ESC-ESVS) have not simplified the problem as they have not led to consensus on a haemodynamic definition. In contrast, the clinical picture does not pose a problem, being defined above.

The difficulty with regard to haemodynamic definitions results from the lack of available evidence. A study including 556 patients showed that an ankle pressure <70 mmHg was not found in 42% of the patients identified as having CLI by other methods, and that a low ankle pressure or a low ABI did not predict the risk of amputation at 1 year. In contrast, a systolic toe pressure <30 mmHg or a $TcPO_2$ <30 mmHg tripled the risk of major amputation at 1 year (216). These data confirm the poor reliability of ankle pressure in this population including many patients with diabetes and/or renal insufficiency (46). The ESVM recently advocated a strategy comprising the measurement of ankle pressure in a non-specialised facility as a preliminary test but defining toe pressure as the key parameter to be evaluated in any patient suspected of CLI but manifesting a normal or high ankle pressure. The diagnosis of CLI should be validated in a vascular medicine unit on the basis of toe pressure, ideally in combination with $TcPO_2$ (51).

12.2. Quantitative evaluation of chronic limb ischaemia

A quantitative haemodynamic evaluation of the ischaemia is essential to ensure that the observed clinical signs and symptoms at rest are related to LEAD and that the affected leg is effectively at high risk of amputation.

Given that ankle pressure is the most easily performed assessment in clinical practice, it may be used for the initial quantification of CLI by a non-specialist, based on a threshold value of systolic ankle pressure ≤50 mmHg (211).

Ankle systolic BP is a very imperfect parameter, notably in the context of diabetes or renal insufficiency. A pressure > 50 mmHg does not permit exclusion of CLI. If CLI is strongly suspected in a patient with an ankle systolic BP >50 mmHg, it is imperative to also measure toe pressure (51, 216).

Quantitative assessment of ischaemia is based on toe BP with a threshold of 30 mmHg (216). This parameter should be measured in all centres treating patients with CLI.

Measurement of $TcPO_2$ in the distal part of the foot provides information relevant to both quantification of ischaemia and assessment of its prognosis. The threshold value of $TcPO_2$ indicating CLI is a matter of debate. It was initially set at 10 mmHg (217), but then increased to 30 mmHg (TASC and subsequently TASC II) (35, 214). Analysis of the prospective cohort COPART suggested that the threshold of 30 mmHg should be retained (216). As the validity of this measurement is limited by certain causes of error, notably oedema, it is imperative to additionally measure toe pressure (see section 5.3) (35).

The evaluation of revascularisation options is based on a DUS examination coupled with CTA.

Catheter arteriography is not a purely diagnostic procedure in this context, but should invariably precede any treatment. If an endovascular intervention is planned, catheter arteriography should be performed as a simultaneously diagnostic and therapeutic procedure.

12.3. Prevention of tissue loss

Patients suffering from LEAD, just like diabetic patients, should be encouraged to examine their feet regularly and learn the rules for foot protection (218). In the AHA guidelines these recommendations concern non-diabetic (grade IIa C-EO) as well as diabetic patients (grade I C-LD), twice yearly medical examination of the feet also being recommended for the latter patients (grade IIa C-EO). The ESC-ESVS guidelines do not include any specific recommendation concerning this point.

In patients with LEAD, any foot infection should be immediately diagnosed and treated to avoid amputation (AHA recommendation, grade I-C) (219-221).

If a foot infection develops in a patient suffering from LEAD, a consultation with a specialised, multidisciplinary team, including a vascular expert, must be scheduled without delay. Several studies, mainly in diabetic patients, have demonstrated the value of multidisciplinary patient management in a specialised centre, resulting in a significant decrease in amputation rate (222-224).

In patients with confirmed CLI, revascularisation should be implemented whenever possible to limit tissue loss, diminish pain, promote healing, permit functional preservation of the affected limb and limit mortality (209).

The Wound, Ischaemia and foot Infection (WIfI) classification (219) should be used for diabetic patients presenting tissue loss to facilitate overall evaluation of the wound.

During the last decades, several classifications have been suggested, notably by Wagner (225) and by the University of Texas (226). More recently, the World Federation of Vascular Societies has proposed the WIfI classification (Table 8) (227). This classification has the advantage of taking several parameters into consideration and integrating these into a more global approach encompassing all forms of CLI. According to the ESC-ESVS, the WIfI classification should be used for all patients experiencing ischaemic pain at rest, with ischaemia confirmed by haemodynamic measurements, and for all patients manifesting diabetic foot, ulcers failing to heal or present for more than 15 days, or any gangrenous lesions.

The AHA has not issued a recommendation to employ this classification but emphasises its value and its validation in various populations (228-231), advocating its use in future trials to further extend its validation. In contrast, the ESC-ESVS specifically recommend use of this classification, particularly in the case of infection (grade I B/C).

It evaluates the risk of amputation and the expected benefit of revascularisation (219) and is based on the analysis of three items, integrating haemodynamic criteria:

- *Wound characteristics:* graded from 0 (no ulcer, simply pain when lying down) to 3 (deep and extensive ulcer with or without extensive gangrene)
- *Presence and severity of ischaemia:* quantified by measuring the ABI and/or ankle pressure and/or toe pressure and/or $TcPO_2$ graded from 0 to 3 (0: ABI ≥0.80 and/or ankle pressure >100 mmHg and/or toe pressure or $TcPO_2$ ≥60 mmHg) (3 : ABI <0.40 and/or ankle pressure < 50 mmHg and/or toe pressure or $TcPO_2$ <30 mmHg)
- *Presence and severity of foot infection:* graded from 0 (no sign or symptom of infection) to 3 (systemic inflammatory response syndrome [SIRS]).

These scores are then interpreted by means of two tables analysing the risk of amputation as well as the expected benefit of revascularisation (Figure 3). This analysis is also available on-line.

The overall risk of amputation increases with the total WIfI score: from 0% at a score of 0, to 8% (95% CI 3-21%) at a score of 1, 11% (95% CI 6-18%) at a score of 2 and 38% (95% CI 21-58%) at a score of 3 (based on data obtained in four studies altogether including 569 patients (232). It should be noted that this meta-analysis emphasises the poor methodological quality of the available data in view of their retrospective nature.

Over the last few years, the WIfI classification has been validated in various populations, both diabetic and non-diabetic (228) and several authors have reported a correlation between the WIfI score and the risk of major amputation or the time to healing (229, 231, 233). Nevertheless this correlation is not always found in patients with diabetic foot, owing to neuropathy or to the increased risk of infection in this population (234). Furthermore, even though this classification seems to be relatively robust, some points such as the definition of ischaemia or its impact on prognosis are debatable.

12.4. Revascularisation options

A multidisciplinary discussion of the revascularisation modalities should be conducted prior to any intervention in a patient presenting CLI (involving ulceration or pain). This discussion is obligatory before any decision to amputate, a rapid concerted decision being essential in this context.

1837 According to the AHA, a multidisciplinary evaluation of revascularisation options should
1838 be undertaken before any decision to amputate (grade 1 C-E0). A multidisciplinary
1839 approach substantially diminishes the rate of major amputation in diabetic patients
1840 (235), the creation of a multidisciplinary team diminishing the rate of major amputation
1841 by over 37% and increasing the rate of revascularisation by 44% (236). Endovascular
1842 procedures should be given preference for restoration of foot vascularisation in patients
1843 with CLI involving tissue loss (AHA: grade I B-R) (237, 238).

1844 Just as the WIfI classification defines the severity of CLI, the GLASS (Global Limb
1845 Anatomic Staging System) classification has been proposed to define the severity of
1846 arterial impairment (239) at both the popliteal and infrapopliteal levels. The Global
1847 Vascular Guidelines (GVG) writing group (227) proposed a four-level integrated
1848 approach including the WIfI classification, the anatomical complexity of the arterial
1849 lesions using the GLASS classification, patient risk factors and the PLAN (patient risk
1850 estimation, limb staging, anatomical pattern of disease) framework of clinical decision-
1851 making. PLAN constitutes an aid for patient management, including the criteria for
1852 deciding between an endovascular intervention and open surgery (227) (Figure 4).

Evaluation of lesion characteristics is essential for assessing the possibility of endovascular treatment (AHA: grade IIa B-R) (240, 241).

The choice between different types of endovascular revascularisation is based on the angiosome concept in the case of ulceration or gangrene. For the AHA (2), this forms the object of a grade IIb B-NR recommendation, based on two meta-analyses (242, 243).

Initially developed in the context of revascularisation surgery (244), the angiosome concept was first applied to revascularisation of patients with CLI in 2006 (245). Each angiosome is defined as a territory, extending from skin to bone and perfused by the same artery. Six distinct angiosomes have been identified in the ankle and foot (246) perfused by the three major arteries of the leg (the anterior and posterior tibial arteries and the fibular artery) (Figure 5).

Three meta-analyses (242, 243, 247) showed a greater efficacy of revascularisations based on the angiosome concept, in terms of healing and leg salvage, this benefit also being evident in diabetic patients (248).

For the ESC-ESVS, patients with CLI should benefit from a multidisciplinary approach with regard to pain control, CV risk and comorbidities (grade I-B). Furthermore, an interdisciplinary team is recommended for the management of tissue loss (grade I B-NR) (223, 236, 249, 250).

The ESC-ESVS integrates the value of a pluridisciplinary approach in the overall management of LEAD (grade I-C). The value of multidisciplinary and interdisciplinary teams is now recognised. The composition of these teams varies according to the region concerned and local practices and resources. The constitution of these teams was one of the initiatives proposed to avert the risk of amputation in diabetic patients, in whom the WHO and the International Diabetes Federation (IDF) considered that the majority of amputations could be avoided. Several studies have confirmed the major impact of such teams in decreasing the number of amputations (251), the reduction in amputation rate reaching 82% (222).

When bypass surgery is envisaged for patients with CLI, the bypass grafts connected to the popliteal artery or the major arteries of the leg should constitute segments of an autologous vein (171, 252). The various guidelines concur in recommending this practice (1, 2, 4).

If endovascular revascularisation is not feasible in patients with CLI involving tissue loss, bypass surgery should be performed whenever possible.

If endovascular revascularisation has failed and a venous graft is not available, bypass grafting on to the popliteal artery or the major arteries of the leg can be achieved using a prosthetic conduit (AHA: grade IIa B-NR) (253-255).

Patients presenting CLI should be treated by a multidisciplinary team coordinating its efforts to optimise wound healing. Patients with tissue loss may benefit from treatment in a centre specialised in wound healing.

12.5. Alternatives to revascularisation

Hyperbaric oxygen therapy

The efficacy of hyperbaric oxygen therapy (HOT) in patients with CLI has not been established (AHA: grade IIb C-LD) and the AHA considers that data are scarce apart from those derived from a few studies in diabetic patients (256). Further data have been published since the AHA issued its guidelines, but these seem to confirm the absence of any real benefit (257).

Although HOT provides numerous benefits mediated by various mechanisms (e.g. improved oxygen supply, angiogenic effects and anti-infective effects limiting the growth of anaerobic microorganisms), evidence of clinical efficacy remains insufficient. A review of 12 studies including 10 in diabetic patients, showed that despite improved healing at 6 weeks, no difference was evident in the longer term and no benefit was achieved in terms of amputation rate (258). The randomised, multicentre study DAMO$_2$CLES, including patients manifesting in total 120 cases of ischaemia-related diabetic foot, compared standard care (including revascularisation if necessary) to standard care plus HOT. Altogether 35% of patients in the HOT group did not complete

the planned treatment. At 12 months, there was no difference between the two groups in terms of wound healing, amputation or survival without amputation (257).

Medical treatment

In patients with CLI in whom revascularisation attempts have failed or are not feasible (patients for whom revascularisation is not an option), and amputation is not considered essential in the short term, medical treatment remains indicated. The ESC-ESVS guidelines do not include any specific recommendation concerning this point, but note that all patients presenting LEAD should receive the best medical treatment. The AHA guidelines contain no specific information on this issue.

Gene and cell therapy

No international guidelines recommend gene or cell therapy. The AHA guidelines do not mention this approach and for the ESC-ESVS, neither approach is indicated.

Intravenous prostanoids

In patients with CLI in whom revascularisation attempts have failed or are not feasible (patients for whom revascularisation is not an option), if amputation is not essential in the short term, intravenous prostanoids may be used subject to the general state of the patient.

The AHA considers that prostanoids are not indicated for patients with CLI (AHA: grade III B-R), based on the results of a meta-analysis of 20 studies including a total of 2724 patients. This meta-analysis detected no class effect on mortality or amputation rate, but the prostanoid iloprost specifically diminished amputation rate (259). A more recent analysis (260) including 33 studies (4477 patients) confirmed the absence of any benefit on CV mortality or amputation rate, but noted a benefit with regard to pain and wound healing. This analysis nevertheless emphasised the high incidence of adverse events and the questionable quality of several of the studies included. The ESC-ESVS and ESVM guidelines consider that prostanoids may confer a limited benefit, and that this treatment should be envisaged if no other therapeutic option is available (ESVM: grade IIa B). Nevertheless, prostanoid treatment does not constitute an alternative to

revascularisation (ESVM: grade III B). In June 2019, the Global Vascular Guidelines (GVG) reinforced this position, recommending that prostanoids should not be prescribed with the objective of limb salvage (grade1 C) (261), but should rather be reserved for "selected" patients experiencing pain with moderate tissue loss, for whom revascularisation is impossible (grade 2 B) (260).

Intermittent pneumatic compression (IPC)

For the AHA, intermittent pneumatic compression (IPC) may be envisaged, on the grounds of its arterial pump effect, to facilitate wound healing or to diminish pain (grade IIb N-R) (262).

The goal of IPC is to improve distal perfusion by increasing the arteriovenous gradient. The real benefit of this approach has not been adequately documented. In the absence of any randomised trial, available data are derived from case-control studies and retrospective analyses, presenting numerous methodological biases, forming the object of a recent review (262). Neither TASC II, nor the ESV refers to IPC for the management of CLI.

Section 12 - Suggestions and recommendations

1. **We recommend diagnosing CLI on the basis of symptoms at rest and haemodynamic evidence (Grade 1+).**
2. **We suggest that the quantification of CLI by a non-specialist should be based in the first instance on measurement of systolic ankle pressure with a threshold value of ≤50 mmHg (Grade 2+).**
3. **We recommend that the quantification of CLI should be based on toe pressure with a threshold of 30 mmHg (Grade 1+).**
4. **We recommend that toe pressure should be measured in all centres caring for patients with CLI (Grade 1+).**
5. **We suggest that resting $TcPO_2$ in the forefoot should be used to better define the prognosis of patients with critical ischaemia (Grade 2+).**
6. **We suggest that measurement of resting $TcPO_2$ should only be used in combination with measurement of toe pressure (Grade 2+).**

7. **We suggest setting a threshold of 30 mmHg for resting $TcPO_2$ to confirm the presence of CLI (Grade 2+).**
8. **We suggest including a DUS examination in the initial exploration of revascularisation options in patients with CLI (Grade 2+).**
9. **We suggest performing CTA (or MRA in patients with severe renal insufficiency) prior to treatment initiation (Grade 2+).**
10. **We suggest that catheter arteriography should be performed with a simultaneous diagnostic and therapeutic objective if an endovascular intervention is envisaged (Grade 2+).**
11. **We suggest an urgent specialised consultation with a team experienced in vascular medicine for patients with LEAD developing a foot infection (Grade 2+).**
12. **We recommend revascularisation whenever possible for patients with confirmed CLI in order to limit tissue loss, diminish pain, promote wound healing and enable functional limb salvage (Grade 1+).**
13. **We recommend using the WIfI classification for diabetic patients with tissue loss to facilitate overall wound evaluation (Grade 1+).**
14. **We recommend a multidisciplinary discussion of revascularisation options prior to any procedure in patients with CLI (Grade 1+).**
15. **We recommend giving preference to endovascular procedures to restore vascularisation of a foot with CLI (Grade 1+).**
16. **We recommend a coordinated multidisciplinary therapeutic approach for patients with CLI, if possible in a centre specialised in wound healing (Grade 1+).**
17. **If endovascular revascularisation is not feasible for a patient with CLI associated with tissue loss, we recommend bypass surgery whenever possible (Grade 1+)**
18. **When bypass surgery is performed in a patient with CLI, we suggest the use of an autologous vein segment as the bypass conduit for bypass grafting on to the popliteal artery or the leg arteries (Grade 2+).**
19. **If endovascular revascularisation has failed and no vein segment is available for bypass grafting, we suggest using a prosthetic conduit or an homologous vein for grafting on to the popliteal artery or the leg arteries (Grade 2+).**

20. We recommend medical treatment of patients with CLI in whom revascularisation attempts have failed or are not feasible (patients with no option of revascularisation), if amputation is not essential in the short term (Grade 1+).

21. We suggest the use of IV prostanoids for patients with CLI in whom revascularisation attempts have failed or are not feasible (patients with no option of revascularisation), if amputation is not essential in the short term and the general state of the patient permits such treatment (Grade 2+).

Section 12 – ISSUES IN ABEYANCE (full consensus not achieved during the DELPHI procedure)

1. **We suggest using the angiosome concept as the basis for selecting the type of revascularisation procedure for patients with ulceration or gangrene.**
   This proposal achieved a consensus agreement of 68 %, eight experts (20%) expressing no opinion. Three meta-analyses indicated a possible value of this angiosome-based type of revascularisation for patients with CLI (242, 243, 247). However, up to now, no randomised controlled trial has been performed.
2. **We suggest the use of intermittent pneumatic compression to facilitate wound healing and diminish pain.**
   This proposal achieved a consensus agreement of 44%, 13 experts (32%) expressing no opinion. The suggestion is based on the results of non-randomised studies as indicated in a systematic review published in 2015 (262). Furthermore, the equipment required for this type of treatment is not always readily available, or indeed available at all, in French vascular medicine centres.

13.Longitudinal follow-up

LEAD is a chronic disease, associated with an increase in CV and all-cause morbidity and mortality. The prognosis is greatly influenced by the quality of the medicinal treatment provided and the patient's CV risk factors, justifying regular specialised medical follow-up and long-term treatment (263-265). Medical treatment and therapeutic targets in the management of CV risk factors are detailed in Section 9. For patients with stable disease, we consider as justifiable an annual consultation to check their tolerance of the prescribed treatment and their adherence to this. The issue of smoking should be raised at each consultation, even if the patient has already given up smoking, as resumption of this habit is unfortunately not rare.

The different types of longitudinal follow-up advocated by the different scientific societies (in the absence of revascularisation or after this) are compared in Table 9.

13.1. In the absence of revascularisation

For patients receiving medical treatment for LEAD, the AHA advocates periodic check-ups by a health care professional experienced in vascular diseases, focused on the management of CV risk factors, lower-limb symptomatology and functional status (grade I), without specifying the frequency of these (1). The ESC-ESVS emphasise the increased morbidity and mortality in patients with LEAD and consequently the importance of managing CV risk factors, but without recommending a specific follow-up programme (2). The ESVM similarly gives no advice on this topic. Given the importance of monitoring the various CV risk factors, it seems important to see patients regularly in order to verify adequate control of these factors (3). These consultations can also provide an opportunity for patients to take advantage of any new therapies. A change in ABI >0.15 is considered clinically relevant (10).

Section 13.1 - Suggestions and recommendations

1. **For patients with LEAD who have not undergone revascularisation, we suggest an annual clinical check-up (Grade 2+).**
2. **For patients with LEAD who have not undergone revascularisation and show no change in their symptoms, we suggest measuring resting ABI (Grade 2+).**
3. **For patients with LEAD who have not undergone revascularisation and show no change in their symptoms, we suggest measuring TBI at rest if an increase in arterial rigidity is suspected (Grade 2+).**
4. **For patients with LEAD who have not undergone revascularisation and show changes in their symptoms, we recommend measuring resting ABI (Grade 1+).**
5. **For patients with LEAD who have not undergone revascularisation and show changes in their symptoms, we suggest measuring resting TBI if an increase in arterial rigidity is suspected (Grade 2+).**
6. **For patients with LEAD who have not undergone revascularisation and show changes in their symptoms, we suggest recording distal Doppler waveforms (Grade 2+).**
7. **For patients with LEAD who have not undergone revascularisation and show changes in their symptoms, we suggest performing a further DUS examination (Grade 2+).**

Section 13.1 – ISSUES IN ABEYANCE (full consensus not achieved during the DELPHI procedure)

1. **For patients with LEAD who have not undergone revascularisation and show no change in their symptoms, we suggest NOT TO perform a further DUS examination, but rather to ensure a follow-up including both clinical and laboratory assessments.**

This proposal obtained a consensus agreement of 68%, two experts (5%) expressing no opinion. This absence of full consensus may be explained by the fact that in France, vascular consultations are very poorly remunerated compared to a DUS examination. Furthermore certain experts pointed out that this examination allowed detection of an aneurysm and that patients with LEAD were at greater risk of developing an abdominal aortic aneurysm than the population as a whole (64-66).

13.2. After revascularisation

The patency of surgical or endovascular revascularisations may be compromised by local complications, precarious haemodynamic conditions or the progression of atherosclerotic disease. These complications are generally classified into three types: early complications (occurring less than 1 month after the intervention), medium-term complications (at 1-12 months) and late complications (at >12 months). In view of their high CV risk, revascularised patients require a follow-up comprising both clinical and laboratory assessments, with optimal control of risk factors and if possible, exercise training. Periodic verification of the surgical reconstruction aims to identify the factors favouring occlusion and if possible, to counteract these. It also enables detection of any new lesions. This monitoring is generally accomplished by DUS examination of the arteries and measurement of BP (267) in addition to questioning of the patient and physical examination.

Thromboses developing in venous bypass grafts during the 3 months post-surgery are often caused by technical problems. Medium-term complications are principally due to myointimal hyperplasia or valve fibrosis. These lesions are easily identifiable and can be corrected (266). Approximately 80% of the thromboses developing in venous bypass grafts occur during the year following the intervention.

The DUS examination should focus on the vascular bed above and below the revascularisation zone, the sites of anastomosis and then the entire bypass conduit. Its goal is to detect any anomalies that may necessitate a further intervention even in the absence of any symptom (as in the majority of cases), such as stenoses threatening the patency of a bypass graft or false aneurysms at the sites of anastomosis. Thromboses occurring in vein bypass grafts are often preceded by haemodynamic anomalies (268). A normal vein bypass graft exhibits a peak systolic velocity (PSV) >45 cm/s and a Doppler waveform of the high-resistance type (Saint-Bonnet N or A). A stenotic lesion manifesting an acceleration of PSV reaching 180 to 300 cm/s, with a peak systolic velocity ratio (PSVR) between 2 and 3.5, carries an increased risk of thrombosis (268). A PSV >300cm/s accompanied by a PSVR >3-3.5 and a fall in ABI >0.15 heralds imminent occlusion of the bypass graft (268) (Table 10). Despite the validation of these haemodynamic criteria, the benefit of DUS check-ups in terms of survival, patency of the revascularisation conduits, or amputation rate, remains uncertain (269, 270). Their benefit is still more debatable in the case of prosthetic bypass grafts, in which they do not invariably permit prediction of thrombosis (271). The combination of clinical and contextual criteria might increase the predictive capacity of DUS examinations (272). In view of the innocuity, ease of access and low cost of DUS examinations, added to the serious consequences of bypass graft occlusion, current international recommendations nevertheless advocate periodic DUS monitoring of infrainguinal revascularisations (1, 4, 273).

The AHA therefore recommends periodic clinical monitoring with calculation of the ABI after endovascular or surgical revascularisation (grade I) (1). Systematic DUS examination is proposed after infrainguinal revascularisation using vein bypass grafts (Grade IIa) and after endovascular revascularisation (grade IIa) (1). Although prosthetic bypass conduits are at greater risk of delayed thrombosis (40% at 5 years), the benefit of systematic DUS monitoring after prosthetic infrainguinal bypass grafting remains uncertain (274).

The 2017 ESC-ESVS guidelines did not address the question of follow-up procedures after lower-limb revascularisation, but this topic formed the object of a consensus document published by the ESC Working Group on Aorta and Peripheral Vascular Diseases and the ESVS in 2019 (266). After vein bypass grafting, ABI (or TBI) lacks sensitivity as the sole predictive criterion for graft stenosis or occlusion and should always be combined with DUS examination. The consensus document recommends an initial assessment within 4-6 weeks after the intervention, then at 3, 6 and 12 months, and subsequently once a year, at least during the first two years (Figure 6). Regular monitoring is particularly recommended if bypass grafting has been performed for CLI. In the case of reintervention prompted by graft stenosis or occlusion, the monitoring programme is started again from the beginning.

For patients with suspected stenosis of a venous bypass graft, the ESC-ESVS consensus document recommends catheter arteriography. Stenoses of vein bypass grafts exceeding 50% are treated by endovascular or surgical intervention, but few studies have compared the different endovascular techniques. Vein bypass graft occlusion can be treated by thrombolysis within 6 to 48 h after symptom onset. Renewed thrombosis is nevertheless frequent if the cause has not been corrected. Following post-thrombotic revascularisation of a vein bypass graft, anticoagulants (generally low-molecular-weight heparins [LMWH]) and antiplatelet agents (aspirin or clopidogrel) are frequently co-prescribed. Anticoagulation may be discontinued after 1 month or prolonged indefinitely, according to the benefit-risk ratio. In the case of prolongation, LMWH are replaced by VKA (2).

In patients experiencing thrombosis in a prosthetic bypass graft, thrombolysis (generally achieved by infusion of alteplase at 1 mg/h for 12 to 48 h) may be effective for up to 2 weeks. Following such a thrombosis, long-term anticoagulation by a VKA should be considered (2).

After endovascular revascularisation, the rate of restenosis or occlusion in the medium term ranges from 5% for the iliac arteries to over 50% for the infrapopliteal arteries. Unfortunately, little evidence is available concerning long-term follow-up after endovascular revascularisation. In contrast to surgical revascularisation, endovascular revascularisation is characterised by a relatively constant rate of re-stenosis/occlusion during the first 5 years and stent thrombosis is not invariably preceded by stenosis. However, re-stenoses with haemodynamic repercussions are often symptomatic. For this reason, the value of long-term DUS monitoring in these patients is controversial (266).

With regard to femoral artery stents, a PSV >190 cm/s with a PSVR ≥1.5 indicates a >50% stenosis, a PSV ≥200 cm/s with a PSVR >2, indicating a >70% stenosis (Table 10). The ESC-ESVS consensus document recommends clinical and laboratory monitoring (questioning of the patient, physical examination, laboratory tests) as well as calculation of the ABI or TBI, with or without additional measurement of $TcPO_2$. The initial check-up, including a DUS examination, should be scheduled within the first month following revascularisation. Subsequent check-ups (physical examination, laboratory tests and

ABI or TBI calculation) should be scheduled between 3 and 6 months following the intervention, then at 1 year, and afterwards annually in case of patient with claudication (Figure 7).

In patients who have undergone angioplasty for intermittent claudication, if the first post-operative DUS examination is normal, further examinations should be performed only in the event of symptom recurrence.

In the case of angioplasty for an imminent threat to limb conservation (chronic limb-threatening ischaemia [CLI]), a DUS examination is recommended at each consultation, at least during the first year after the intervention (or even during the first 2 years).

During the acute phase, stent thrombosis may be treated by aspiration and/or thrombolysis. Following stent thrombosis, the need for revascularisation should be re-evaluated on a case-by-case basis, preferably by a multidisciplinary team. Just as after surgery, monitoring after endovascular revascularisation should combine questioning of the patient, a physical examination, calculation of the ABI or TBI and a DUS examination. In the case of severe ischaemia, measurement of $TcPO_2$ may also be appropriate. If a further intervention is necessary owing to restenosis or occlusion within the stent, the ESC-ESVS consensus document favours an endovascular procedure, with or without restenting. If this fails, bypass grafting may be envisaged. In the event of restenosis after two endovascular revascularisations, the therapeutic strategy should be discussed by a multidisciplinary team. Following a renewed endovascular intervention, the ESC-ESVS expert consensus document recommends DAPT (aspirin plus clopidogrel) for a minimum of 3 months, to be prolonged as necessary according to the patient's risk of bleeding and the location of the stenosis.

The SVS bases its recommendations concerning patient follow-up after revascularisation by infrainguinal vein bypass grafting at the claudication stage (excluding CLI) on those of the TASC II consensus (35). It nevertheless emphasises that the majority of studies investigating the value of systematic DUS monitoring were conducted in patients having undergone revascularisation for CLI (4, 168). For patients at the claudication stage, presenting less severe lesions and in a better state generally, the monitoring strategy is not necessarily the same. After endovascular revascularisation for intermittent claudication, the relevance of any follow-up investigations other than clinical monitoring is not proven. In practice, following endovascular revascularisation, the SVS recommends monitoring based on questioning of the patient to identify any new symptoms, assessment of ongoing medicinal treatment, physical examination and BP measurements at rest and if appropriate, after exercise (Grade 2C) (4, 168). Monitoring of claudicant patients having undergone revascularisation by infrainguinal vein bypass grafting should additionally include periodic DUS examinations (Grade 2C). If this monitoring reveals a stenosis threatening the patency of the surgical reconstruction, notably a stenosis upstream of the bypass graft, or close to an anastomosis, this should be treated either surgically or by an endovascular intervention (Grade 1C). The ESVM does not address the issue of longitudinal follow-up after non-surgical revascularisation

(3), emphasising the importance of regular monitoring but without specifying a precise schedule.

Data concerning the frequency of monitoring are scarce. A detailed schedule was recently proposed by the SCV (275) including, for most revascularisations, an early initial DUS examination accompanied by BP measurements prior to patient discharge, these evaluations being repeated at 3 and 6 months and then annually (Table 11); the intervals between assessments should of course be adapted as necessary according to the onset of any new symptoms and the presumed fragility of the vascular reconstruction (266).

A report issued jointly by several American cardiovascular societies proposed the appropriate use of DUS examinations and ABI or TBI assessments according to the clinical context (276). These proposals are presented in Tables 11 and 12. It is important to note that this report focuses on the appropriate use of these examinations rather than on the optimisation of patient care in terms of medical treatment or the control of CV risk factors. If the results of the initial DUS examination were satisfactory or the ABI ≤0.90, but the patient subsequently reports the onset of new symptoms or worsening of previously existing symptoms, it is considered justifiable to perform another DUS examination and to measure the ABI again. Even though bypass grafting interventions and angioplasty or stenting do not give rise to the same complications, in the interest of simplicity, the report proposes a common follow-up schedule.

Section 13.2 - Suggestions and recommendations

1. **For revascularised patients, we recommend strict and regular monitoring of CV risk factors (Grade 1+).**
2. **For patients with LEAD revascularised by bypass grafting, we recommend performing a DUS examination to evaluate the proximal and distal anastomoses (Grade 1+).**
3. **For patients with LEAD revascularised by infrainguinal vein bypass grafting, we recommend performing a DUS examination to evaluate blood flow through the bypass conduit (Grade 1+).**
4. **For patients with LEAD revascularised by infrainguinal vein bypass grafting, we recommend performing a DUS examination to evaluate distal blood flows (Grade 1+).**
5. **For patients with LEAD revascularised by bypass grafting, we recommend measurement of the ABI (Grade 1+).**
6. **For patients presenting with LEAD revascularised by bypass grafting, we recommend measuring the TBI in the event of a suspected increase in arterial rigidity (Grade 1+).**
7. **For patients with LEAD revascularised by angioplasty and stent placement, we recommend performing a DUS examination to evaluate blood flows at the proximal and distal extremities of the stent (Grade 1+).**
8. **For patients with LEAD revascularised by angioplasty and stent placement, we recommend performing a DUS examination to evaluate blood flow within the stent (Grade 1+).**
9. **For patients with LEAD revascularised by angioplasty and stent placement, we recommend performing a DUS examination to evaluate distal blood flows (Grade 1+).**
10. **For patients with LEAD revascularised by angioplasty and stent placement, we recommend measurement of the ABI (Grade 1+).**
11. **For patients with LEAD revascularised by angioplasty and stent placement, we recommend measuring the TBI in the event of a suspected increase in arterial rigidity (Grade 1+).**

12. **For patients with LEAD revascularised by angioplasty and stent placement, or by bypass grafting, we recommend performing a DUS examination within the month following the intervention (Grade 1+).**
13. **For patients with LEAD revascularised by angioplasty and stent placement, or by bypass grafting, we recommend measuring the ABI within the month following the intervention (Grade 1+).**
14. **For patients with LEAD revascularised by angioplasty and stent placement, or by bypass grafting, we recommend measuring the TBI within a month post-intervention in the event of suspected increase in arterial rigidity (Grade 1+).**
15. **For patients with LEAD revascularised by vein bypass grafting, we DO NOT recommend monitoring by measuring the ABI or TBI without performing a DUS examination during the 2 years following the intervention (Grade 1-).**
16. **For patients with LEAD revascularised by vein bypass grafting, we recommend performing a DUS examination 6 months after the intervention (Grade 1+).**
17. **For patients with LEAD revascularised by vein bypass grafting, we recommend measuring the ABI or TBI 6 months after the intervention (Grade 1+).**
18. **For patients with LEAD revascularised by vein bypass grafting, we recommend a DUS examination 12 months after the intervention (Grade 1+).**
19. **For patients with LEAD revascularised by vein bypass grafting, we recommend measuring the ABI or TBI 12 months after the intervention (Grade 1+).**
20. **For patients with LEAD revascularised by vein bypass grafting, we recommend performing a DUS examination once a year, at least during the first 2 years following the intervention (Grade 1+).**
21. **For patients with LEAD revascularised by vein bypass grafting, we recommend measuring the ABI or TBI once a year (Grade 1+).**
22. **If thrombosis of a vein bypass graft necessitates recanalisation, we recommend correcting the cause (Grade 1+).**
23. **Following recanalisation after thrombosis of a vein bypass graft, we recommend treatment combining an anticoagulant (generally a LMWH) at curative dose and an antiplatelet agent (aspirin or clopidogrel) for at least 1 month in the absence of any contraindication (Grade 1+).**

24. **Following recanalisation after thrombosis of a vein bypass graft, we suggest treatment combining a VKA and an antiplatelet agent (aspirin or clopidogrel) if the benefit-risk ratio is favourable (to be re-evaluated annually) (Grade 2+).**
25. **For patients with LEAD revascularised by vein bypass grafting to relieve CLI, we recommend monitoring (Grade 1+).**
26. **In the event of a suspected >50% restenosis of a vein bypass graft, we recommend catheter arteriography (Grade 1+).**
27. **In the event of a >50% restenosis of a vein bypass graft, we recommend an endovascular (if possible) or surgical intervention (Grade 1+).**
28. **For patients having undergone recanalisation after thrombosis of an infrainguinal prosthetic bypass graft, we suggest long-term anticoagulation (Grade 2+).**
29. **For patients revascularised by femoral angioplasty and stent placement to relieve intermittent claudication whose initial check-up is normal, we recommend measuring the ABI or TBI 6 months after the intervention (Grade 1+).**
30. **For patients revascularised by femoral angioplasty and stent placement to relieve intermittent claudication whose initial check-up is normal, we recommend measuring the ABI or TBI 1 year after the intervention, then annually (Grade 1+).**
31. **For patients with LEAD revascularised by an endovascular procedure to treat CLI, we recommend a DUS assessment 6 months after the intervention (Grade 1+).**
32. **For patients with LEAD revascularised by an endovascular procedure to treat CLI, we recommend a DUS assessment 1 year after the intervention, then annually (for at least 2 years), in the absence of any change in symptoms (Grade 1+).**
33. **For patients with LEAD having undergone endovascular revascularisation to treat CLI, we recommend measuring the ABI or TBI 6 months after the intervention (Grade 1+).**
34. **For patients with LEAD having undergone endovascular revascularisation to treat CLI, we recommend measuring the ABI or TBI 1 year after the**

intervention, then annually, in the absence of any change in symptoms (Grade 1+).

35. **If reintervention is required owing to stent stenosis or occlusion, we recommend an endovascular procedure in the first instance (Grade 1+).**
36. **For patients having undergone endovascular re-intervention we recommend DAPT (aspirin plus clopidogrel) for at least 3 months (Grade 1+).**
37. **For patients having undergone endovascular re-intervention we suggest considering prolongation of DAPT (aspirin plus clopidogrel) according to the benefit-risk ratio (Grade 2+).**

Section 13.2 – ISSUES IN ABEYANCE (full consensus not achieved during the DELPHI procedure)

1. **For patients revascularised by femoral angioplasty and stent placement to treat intermittent claudication whose post-operative assessments are normal up to 1 year, we do not recommend DUS monitoring in the absence of any change in symptoms.**

This proposal obtained a 46% consensus agreement, three experts (7%) expressing no opinion and 19 (46%) expressing disagreement. Consequently, full consensus could not be achieved on this proposal. One of the concerns was that it would result in a loss of contact with the vascular medicine specialist and thereby lead to a reduced quality of follow-up.

14. Nutrition and lower extremity artery disease

The AHA and ESC-ESVS guidelines concur in recommending that patients suffering from LEAD should maintain a healthy diet, whereas those issued by the ESVM and SVS do not specifically address this issue (1-4). However, the SVS guidelines advise against the use of food supplements (4). Diet plays a major role in the development of CV diseases (277-279). In particular, the PREDIMED study showed that a healthy diet reduced the risk of LEAD (280). Another study, conducted in France and evaluating the nutrition of patients with LEAD on the basis of a 14-item questionnaire, revealed an unfavourable nutritional score, confirming the results of American trials (281-284). These findings indicate the importance of nutritional assessment of patients with LEAD.

As atherosclerotic disease is a chronic inflammatory condition, all foods containing nutrients with anti-inflammatory and antioxidant properties should be privileged (285). Patients suffering from LEAD are at high risk of CV events, such as MI and stroke. The Mediterranean diet has proved its value in CAD (286, 287) and it seems preferable to favour this diet rather than resorting to supplementation with individual nutrients (288). Diets as a whole involve complex interactions not achieved with individual supplements. It is worth noting that food supplements are often under-dosed (in omega-3 fatty acids, for example) and inadequately controlled. A study in patients with LEAD suffering from claudication revealed that 12 weeks after completing an exercise therapy programme, they still maintained an unhealthy diet (289). Regular reassessment of patients' food intake consequently seems to be essential.

Patients with LEAD requiring revascularisation (whether surgical or endovascular) have been shown to suffer from malnutrition (290, 291). Over half the patients studied, for the most part claudicant patients scheduled to undergo an endovascular procedure, manifested a state of malnutrition (291). In this population, malnutrition was associated with the occurrence of CV events and with lower limb amputation. Another study showed that among patients with CLI (n = 106), malnutrition was associated with an increased risk of death at 30 days (290). Furthermore, a high rate of malnutrition, ranging from 61 to 90%, has been reported among patients admitted to vascular surgery units (292-295). All these studies, although few, suggest the need for nutritional assessment of patients and correction of any state of malnutrition detected, prior to any

surgical intervention (296). Specific tools are required to evaluate such malnutrition (295, 297).

Section 14 - Suggestions and recommendations

1. **We recommend that patients with LEAD should undergo dietary assessment (Grade 1+).**
2. **We suggest that patients with LEAD should adopt a Mediterranean diet (Grade 2+).**
3. **We suggest regular dietary assessment of patients with LEAD (Grade 2+).**
4. **We suggest screening for malnutrition in patients with LEAD scheduled to undergo revascularisation (Grade 2+).**
5. **We suggest correcting any state of malnutrition in patients with LEAD scheduled to undergo revascularisation, if possible prior to this intervention (Grade 2+).**

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TABLE LEGENDS:

Table 1: Glossary

Table 2: The different clinical classifications used for LEAD (7)

Table 2legend: *CEMV: French College of Vascular Medicine Teachers.

Table 3: The four classes of CV risk (5)

Table 3 legend: GFR: glomerular filtration rate; LDLc: low density lipoprotein cholesterol; SCORE: systematic coronary risk estimation.

Table 4: Levels of CV risk in diabetic patients (19)

Table 4 legend: [a] Proteinuria, renal insufficiency defined by a GFR < 30 mL/min/1.73m^2, left ventricular hypertrophy or retinopathy. [b] Age, hypertension, dyslipidaemia, smoking, obesity.

Table 5: Validated criteria or the diagnosis of lower-limb arterial stenosis

Table 5 legend: PSV are expressed in cm/s.

Table 6: Intensities of currently available statins (132)

Table 6 legend: * Expected decrease in LDLc at the dose indicated in each intensity category. ** Although simvastatin 80 mg was evaluated in randomised controlled trials, initiation of simvastatin treatment at 80 mg or titration to 80 mg is not recommended by the FDA owing to the increased risk of myopathy, including rhabdomyolysis. *** Robust evidence from one randomised trial only: in the IDEAL study, the dose of atorvastatin was decreased if 80 mg was not tolerated

Table 7: Potential aetiologies of proximal exercise-induced pain

Table 7 legend: LEAD means Lower Extremity Artery Disease. Adapted from Hirsch et al. (23) and White C (207).

Table 8 : Score WIfI

Table 9 - Comparison of the types of follow-up recommended according to different international guidelines

Table 10: Duplex ultrasound criteria for restenosis after lower-limb revascularisation (2019 ESC-ESVS consensus) (268)

Table 10 legend: PSV: peak systolic velocity; PSVR: peak systolic velocity ratio.

Table 11: Follow-up after revascularisation, according to Zierler et al. (275).

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FIGURE LEGENDS

Figure 1: Saint-Bonnet classification of Doppler waveforms according to Mahé et al. (44)

Figure 2 – The different strategies for diagnosing LEAD

Figure 3: Interpretation of WIfI scores

Figure 3 legend: W: wound; fI: foot infection; VL: very low; L: low; M: moderate; H: high.

Figure 4: Strategy for evaluating patients with CLI (227)

Figure 4 legend: Please note that the term used in this original publication was CLTI (Chronic Limb Threatening Ischaemia). The authors of the present consensus decided to keep the original version and the term CLTI instead of CLI.

Figure 5: Ankle and foot angiosomes (246)

Figure 6: Monitoring schedule after lower-limb vein bypass grafting (ESC-ESVS consensus document) (266)

Figure 6 legend: ABI: ankle-brachial index; BP: BP; CLTI: chronic limb-threatening ischaemia (the term CLTI was kept in this figure because it corresponds to the original publication); DUS: duplex ultrasound; mo: month; TcPO2: transcutaneous oximetry; TP: toe pressure; WlfI: Wound, Ischaemia and foot Infection.

Figure 7: Monitoring schedule after stenting of a lower-limb artery (ESC-ESVS consensus document) (266)

Figure 7 legend: ABI: ankle-brachial index; BP: BP; CLTI: chronic limb-threatening ischaemia (the term CLTI was kept in this figure because it corresponds to the original publication; DUS: duplex ultrasound; mo: month; $TcPO_2$: transcutaneous oximetry; TP: toe pressure; WIfI: Wound, Ischaemia and foot Infection.

Table 1: Glossary

LEAD	Lower extremity artery disease.
Occult LEAD	Patients with occult LEAD are asymptomatic owing to the presence of certain comorbidities (e.g. respiratory insufficiency, heart failure, neuropathy)
ABI	Ankle-brachial index: calculated ratio between the systolic Blood Pressure (BP) measured at the ankle (in the anterior tibial or dorsalis pedis artery and the posterior tibial artery, retaining the higher value) and the brachial systolic BP (measured in both arms, retaining the higher value). The reference values are as follows: ≤ 0.90: LEAD 0.91-1.40: Normal > 1.40: Non-compressible arteries Values between 0.91 and 1.00, although within the normal range, are considered as indicative of borderline LEAD.
TBI	Toe-brachial index: calculated ratio between the systolic BP measured at the hallux and the brachial systolic BP (measured in both arms, retaining the higher value) Normal value ≥ 0.70.
Acute ischaemia	Acute, severe hypoperfusion (symptom onset < 2 weeks previously), characterised by pain, absence of pulse, pallor and cold skin. Neurological disorders, paraesthesia and paralysis are signs of serious disease.
Chronic limb ischaemia, also known as permanent chronic ischaemia (CLI)	Severe LEAD, manifested by permanent pain at rest or tissue loss during at least 15 days, confirmed by haemodynamic criteria.
Chronic limb-threatening ischaemia (CLTI) (ESC-ESVS)	Limb ischemia with threatened viability related to several factors (neurologic, infectious…). This term was proposed by the ESC and ESVS groups in the guidelines published in 2017.
Claudication	Pain, cramp or muscular fatigue of arterial origin, induced by exercise in active muscle group and relieved by rest (within a few minutes)
Maximum walking distance	Maximum walking distance in metres before the onset of severe pain precludes further walking.
Resting $TcPO_2$	Transcutaneous oxygen pressure measured at rest
Minor amputation	Distal amputation preserving the heel LEAD
Major amputation	Amputation involving loss of the heel LEAD
Endovascular treatment	Any endoluminal treatment, irrespective of the method used, as opposed to open surgery.

Table 2: The different clinical classifications used for LEAD (7)

Fontaine stage	**Clinical characteristics**	**Rutherford classification**	**Clinical characteristics**	**CEMV * classification**
I	Asymptomatic	0	Asymptomatic	Asymptomatic
IIa	Walking distance without pain > 200 m	1	Mild intermittent claudication	Exercise-induced ischaemia
		2	Moderate intermittent claudication	
IIb	Walking distance without pain < 200 m	3	Severe intermittent claudication	
III	Pain at rest	4	Pain at rest	Chronic limb Ischaemia at rest or chronic limb-threatening ischaemia
IV	Ulcer, necrosis, gangrene	5	Distal tissue loss	
		6	Tissue loss extending beyond the proximal metatarsal level	

**CEMV: French College of Vascular Medicine Teachers.*

Table 3: The four classes of CV risk (5)

Very high risk	Patients with any of the following risk factors: - atherosclerotic disease either clinically documented or confirmed by imaging. Documented atherosclerotic diseases include: history of acute coronary syndrome (ACS: myocardial infarction [MI] or unstable angina), stable angina, coronary revascularisation (percutaneous coronary intervention, coronary bypass surgery and other arterial revascularisation procedures), stroke or transient ischaemic attack, and LEAD. Atherosclerotic diseases confirmed by imaging include those known to be predictive of clinical events such as the presence of plaques revealed by coronary angiography or coronary computed tomography angiography (lesions in several coronary trunks with > 50% stenosis in two of the principal coronary arteries) or by carotid DUS. - diabetes involving target organ damage, or associated with at least three major risk factors, or early onset of type 1 diabetes (present for over 20 years). - severe renal insufficiency (GFR < 30 mL/min/1.73 m^2) - calculated SCORE (risk of fatal CV event at 10 years) ≥10%
High risk	Patients with: - a markedly elevated single risk factor, in particular total cholesterol > 8 mmol/L (> 310 mg/dL), LDLc > 4.9 mmol/L (> 190 mg/dL), or BP > 180 /110 mmHg - familial hypercholesterolaemia or other major risk factor. - diabetes without target organ damage, present for over 10 years or associated with another risk factor - moderate renal insufficiency (GFR between 30 and 59 mL/min/1.73m^2) - calculated SCORE (risk of fatal CV event at 10 years) ≥ 5% and < 10%
Moderate risk	- Young patients with diabetes (aged < 35 years for type 1 and < 50 years for type 2 diabetes) present for less than 10 years and not associated with any other risk factor. - SCORE ≥ (risk of fatal CV event at 10 years) ≥ 1% et < 5%
Low risk	- SCORE (risk of fatal CV event at 10 years) < 1%

GFR: glomerular filtration rate; LDLc: low density lipoprotein cholesterol; SCORE: systematic coronary risk estimation.

Table 4: Levels of CV risk in diabetic patients (19)

Very high risk	Patients with diabetes **AND** confirmed CV disease or with target organ damage[a] or with at least three major risk factors[b] or with early onset type 1 diabetes present for over 20 years.
High risk	Patients with diabetes present for 10 years or more, without target organ damage, associated with at least one other risk factor.
Moderate risk	Young patients (aged < 35 years for type 1 and < 50 years for type 2 diabetes) with diabetes present for less than 10 years, not associated with any other risk factor

[a] Proteinuria, renal insufficiency defined by a GFR < 30 mL/min/1.73m^2, left ventricular hypertrophy or retinopathy.

[b] Age, hypertension, dyslipidaemia, smoking, obesity.

Table 5: Validated criteria or the diagnosis of lower-limb arterial stenosis

Peak systolic velocities (PSV) and peak systolic velocity ratios (PSVR) according to the degree of stenosis (%) determined by catheter arteriography: Aorto-iliac stenoses								
	>50%	>50%	>70%	>70%	>75%	>75%	>80/90%	>80/90%
	PSV	PSVR	PSV	PSVR	PSV	PSVR	PSV	PSVR
De Smet et al (90)	>200	>2.8				>5		

Peak systolic velocities (PSV) and peak systolic velocity ratios (PSVR) according to the degree of stenosis (%) determined by catheter arteriography: femoropopliteal stenoses								
	>50%	>50%	>70%	>70%	>75%	>75%	>80/90%	>80/90%
	PSV	PSVR	PSV	PSVR	PSV	PSVR	PSV	PSVR
Hodgkiss-Harlow (91)	>200	>2			>300	>4		
Khan et al (92)	>150	>1.5	>200	>2				
Ranke et al (86)		>2.8						>7

Peak systolic velocities (PSV) and peak systolic velocity ratios (PSVR) according to the degree of stenosis (%) determined by catheter arteriography								
After revascularisation by infrainguinal vein bypass grafting								
	>50%	>50%	>70%	>70%	>75%	>75%	>80/90%	>80/90%
	PSV	PSVR	PSV	PSVR	PSV	PSVR	PSV	PSVR
Tinder et al (93)	>125	>1.5	>180	>2.5			>300	>4
After superficial femoral artery stenting								
Baril et al (94)	>190	>1.5					>275	>3.5

PSV are expressed in cm/s.

Table 6: Intensities of currently available statins (132)

	Low intensity	Moderate intensity	High intensity
Decrease in LDLc*	<30%	30-49%	≥ 50%
Statins	Simvastatin 10 mg	Atorvastatin 10 mg (20 mg) Rosuvastatin (5 mg) 10 mg Simvastatin 20–40 mg **	Atorvastatin (40 mg ***) 80 mg Rosuvastatin 20 mg (40 mg)
	Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg	Pravastatin 40 mg (80 mg) Lovastatin 40 mg (80 mg) Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 1 to 4 mg	…

* Expected decrease in LDLc at the dose indicated in each intensity category.

** Although simvastatin 80 mg was evaluated in randomised controlled trials, initiation of simvastatin treatment at 80 mg or titration to 80 mg is not recommended by the FDA owing to the increased risk of myopathy, including rhabdomyolysis.

*** Robust evidence from one randomised trial only: in the IDEAL study, the dose of atorvastatin was decreased if 80 mg was not tolerated

Table 7: Potential aetiologies of proximal exercise-induced pain

Aetiology	Location of the discomfort or pain	Characteristics	Exercise-induced symptoms	Effect of rest	Effect of body position	Other characteristics
LEAD (claudication)	Buttock, hip, lower back, thigh	Cramp, fatigue, weakness, pain	Yes	Resolves rapidly post-exercise	None	Presence of CV risk factors
Lumbar spinal stenosis	Buttock, hip, thigh	Cramp, fatigue, weakness, pain, tingling	Variable	Relieved by sitting or changing body position	Relieved by lumbar flexion (sitting or leaning forward)	History of lower back problems
Hip osteoarthritis	Buttock, hip, thigh	Pain	Variable	Absence of rapid relief (symptoms may persist at rest)	Improved in sitting position	Related to level of activity
Bone metastases	Bones	Pain	Variable	Absence of rapid relief (symptoms may persist at rest)	Avoidance of direct pressure on bones	History of cancer
Pelvic venous congestion	Groin, thigh	Tension	After walking	Decrease slowly	Relieved by a raised body position	History of venous thrombosis in the inferior vena cava or iliac arteries, presence of varicose veins

LEAD means Lower Extremity Artery Disease. Adapted from Hirsch *et al*. (23) and White C (207).

Table 8 : Score **WIfI**

Critère Score Description

	Score	Description		
W (Wound)	0	No ulcer (only pain when lying down)		
	1	Small, shallow ulcer on distal leg or foot without gangrene		
	2	Deeper ulcer, exposing bone, joint or tendon ± gangrenous changes limited to toes		
	3	Extensive deep ulcer ± extensive gangrene		
I (Ischemia)		ABI	Ankle pressure (mm Hg)	Toe pressure or $TcPO_2$
	0	≥ 0.80	> 100	> 60
	1	0,60 – 0.79	70 – 100	40 – 59
	2	0,40 – 0.59	50 – 70	30 – 39
	3	< 0.40	< 50	< 30
FI (Foot infection)	0	No sign or symptom of infection		
	1	Local infection involving only skin and subcutaneous tissue		
	2	Local infection involving deeper than subcutaneous tissue		
	3	Systemic inflammatory response syndrome		

1 Table 9 - Comparison of the types of follow-up recommended according to different international guidelines

	AHA	ESC -ESVS	SVS	ESVM
Longitudinal follow-up of patients treated medically	Periodical monitoring by a healthcare professional experienced in vascular diseases, focusing on management of vascular risk factors, lower limb symptomatology and functional status (grade I), frequency of monitoring not specified.	Management of CV risk factors.	Topic not addressed.	Topic not addressed.
Longitudinal follow-up after revascularisation	Periodic clinical monitoring combined with determination of ABI or TBI (Grade I). -After endovascular revascularisation: systematic DUS monitoring (Grade IIa). -After infrainguinal revascularisation by vein bypass grafting: systematic DUS monitoring (Grade IIa). -After infrainguinal prosthetic bypass grafting: benefit of systematic DUS monitoring uncertain.	**2016 guidelines:** Topic not addressed **2019 ESC-ESVS Consensus document** (266)**:** questioning of patient, physical examination -After endovascular revascularisation: for patients with CLI, DUS monitoring during the first month, then at 6 and 12 months if initial examination normal. For patients with intermittent claudication, DUS monitoring is required only during the first month, subsequent monitoring being adapted according to any change in symptoms. -After vein bypass grafting: DUS monitoring during the first 3 months, then at 6 and 12 months, and subsequently once a year.	-After endovascular revascularisation: monitoring based on questioning of the patient to identify any new symptoms, assessment of ongoing medicinal treatment, physical examination, BP measurements at rest and if appropriate, after exercise (Grade 2C). -After infrainguinal vein bypass grafting: periodic DUS monitoring (Grade 2C). -If a stenosis threatening the revascularisation is detected during this monitoring, this should be treated either surgically or by an endovascular intervention (Grade 1C).	-After a surgical or endovascular procedure, regular clinical monitoring is required in addition to measurements of ABI or TBI and a physical examination.

Table 10: Duplex ultrasound criteria for restenosis after lower-limb revascularisation (2019 ESC-ESVS consensus) (268)

Femoral vein bypass graft	**PSV (cm/s)**	**PSVR**	**Reference**
>50%	180-300	2-3.5	(93)
>70-80%	≥300	>3-3.5	(93)
Femoral stent	**PSV (cm/s)**	**PSVR**	**Reference**
>50%	≥190	≥1.5	(94)
>70%	≥200-250	>2	(94)
≥80%	≥275	>3.5	(94)

PSV: peak systolic velocity; PSVR: peak systolic velocity ratio

Table 11: Follow-up after revascularisation, according to Zierler et al. (275)

Type of revascularisation	Follow-up assessments	Monitoring schedule	Comments
Prosthetic aorto-bifemoral, iliofemoral, femorofemoral, or axillofemoral bypass grafting	Physical examination and ABI with or without associated vascular DUS examination	Post-operation prior to patient discharge, at 6 and 12 months, then annually (grade 1C)	To be adapted if any new clinical symptoms appear
Prosthetic infrainguinal revascularisation	Physical examination, ABI, with or without associated vascular DUS	Post-operation prior to patient discharge, at 6 and 12 months, then annually (grade 1B)	
Infrainguinal revascularisation by vein bypass grafting	Physical examination, DUS and ABI	Post-operation prior to patient discharge, at 3, 6 and 12 months, then at least once a year (grade 1B)	
Endovascular aorto-iliac revascularisation	Physical examination, DUS and ABI Physical examination, ABI, with or without associated DUS	Within the first postoperative month at 6 and 12 months, then annually (grade 1C)	
Post-revascularisation monitoring schedules according to The Society for Vascular Surgery practice guidelines on follow-up after vascular surgery arterial procedures (275).			

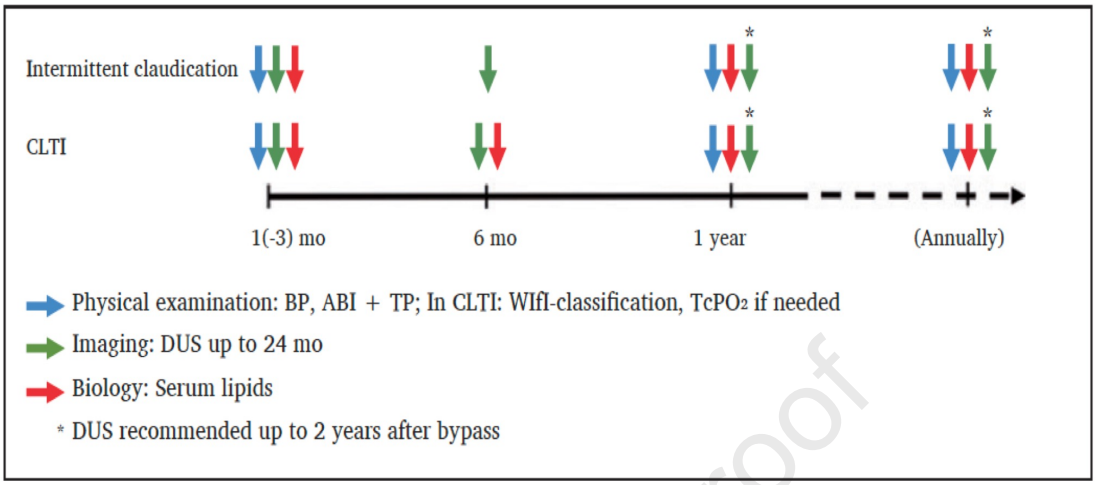
Table 12: Monitoring of patients with known LEAD and post-revascularisation follow-up (276)

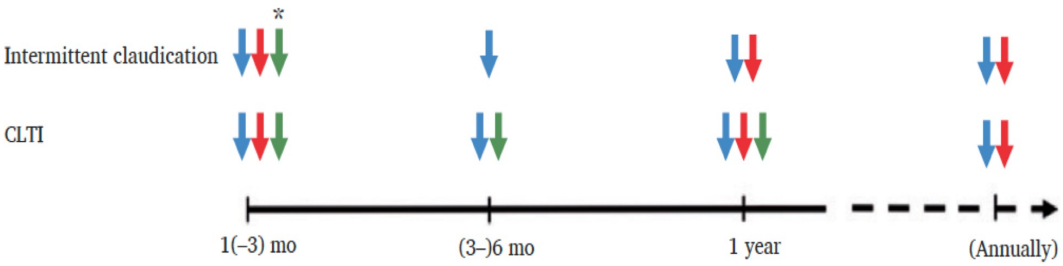
KNOWN LEAD			
Indication		Appropriate use scores (1 - 9)	
Worsening of symptoms or onset of new symptoms			
Normal baseline study		**A (7)**	
Abnormal baseline ABI ABI ≤ 0,90)		**A (8)**	
No change in symptoms (no revascularisation)			
Patient asymptomatic or stable after the baseline study, rate of monitoring during the first year	**At 3 to 5 mo.**	**At 6 to 8 mo.**	**At 9 to 12 mo.**
Baseline ABI normal (no stenosis)	**I (1)**	**I (1)**	**I (1)**
Mild or moderate LEAD (e.g. ABI > 0.4)	**I (2)**	**I (2)**	**U (4)**
Severe LEAD (e.g. ABI < 0.4)	**I (3)**	**U (5)**	**U (5)**
Patient asymptomatic or stable after the baseline study, rate of monitoring after the first year	**Every 6 mo.**	**Every 12 mo.**	**Every 24 mo. or more**
Normal baseline ABI (no stenosis)	**I (1)**	**I (1)**	**I (2)**
Mild or moderate LEAD (e.g. ABI > 0.4)	**I (2)**	**I (2)**	**U (4)**
Severe LEAD (e.g. ABI < 0.4)	**U (4)**	**U (4)**	**I (3)**
AFTER REVASCULARISATION			
Baseline monitoring (during the first month)		**A (8)**	
Worsening of symptoms or onset of new symptoms			
After revascularisation (angioplasty ± stent placement or bypass graft)		**A (9)**	
Patient asymptomatic or stable			
Patient asymptomatic or stable after the baseline study, rate of monitoring during the first year	**At 3 to 5 mo.**	**At 6 to 8 mo.**	**At 9 to 12 mo.**
After angioplasty ± stent placement	**I (2)**	**U (6)**	**U (6)**
After vein bypass graft	**U (6)**	**A (8)**	**U (6)**
After prosthetic bypass graft	**U (5)**	**A (7)**	**U (5)**
Patient asymptomatic or stable after the baseline study, rate of monitoring after the first year	**Every 6 mo.**	**Every 12 mo.**	**Every 24 mo. more**
After angioplasty ± stent placement	**I (3)**	**A (7)**	**U (5)**
After vein bypass graft	**U (5)**	**A (7)**	**U (5)**
After prosthetic bypass graft	**I (3)**	**A (7)**	**U (5)**

A = appropriate; I = inappropriate; U = uncertain; mo. = month

Risk of amputation																
	Ischaemia - 0				Ischaemia - 1				Ischaemia - 2				Ischaemia - 3			
W-0	VL	VL	L	M	VL	L	M	H	L	L	M	H	L	M	M	H
W-1	VL	VL	L	M	VL	L	M	H	L	M	H	H	M	M	H	H
W-2	L	L	M	H	M	M	H	H	M	H	H	H	H	H	H	H
W-3	M	M	H	H	H	H	H	H	H	H	H	H	H	H	H	H
	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3

Benefit of revascularisation																
	Ischaemia - 0				Ischaemia - 1				Ischaemia - 2				Ischaemia -3			
W-0	VL	VL	VL	VL	VL	L	L	M	L	L	M	M	M	H	H	H
W-1	VL	VL	VL	VL	L	M	M	M	M	H	H	H	H	H	H	H
W-2	VL	VL	VL	VL	M	M	H	H	H	H	H	H	H	H	H	H
W-3	VL	VL	VL	VL	M	M	M	H	H	H	H	H	H	H	H	H
	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3





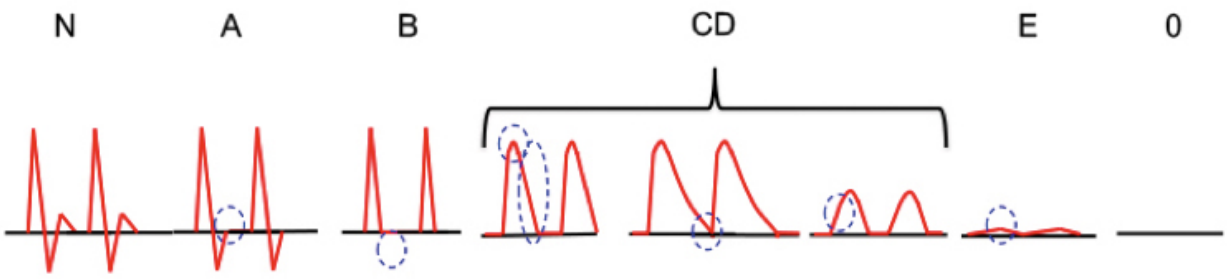
Physical examination: BP, ABI + TP; In CLTI: WIfI-classification, $TcPO_2$ if needed

Imaging: DUS up to 24 mo

Biology: Serum lipids

* DUS should be repeated after discharge only in case of symptom recurrence

Simplified Saint-Bonnet classification without continuous flow

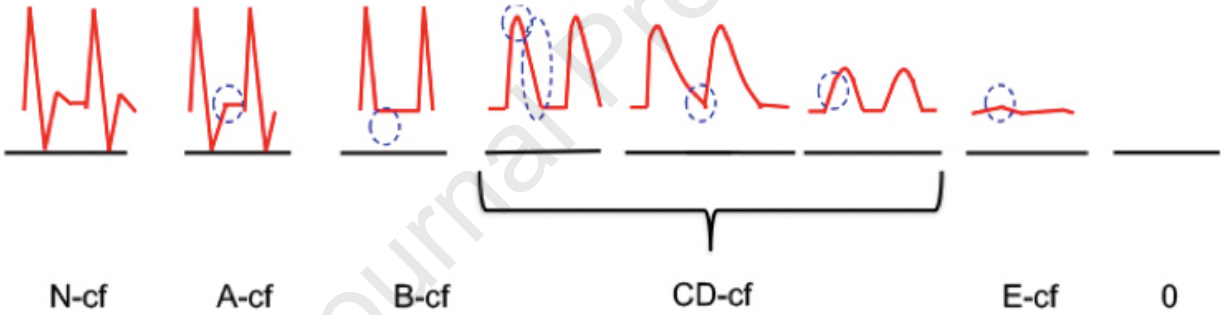


Degree of stenosis

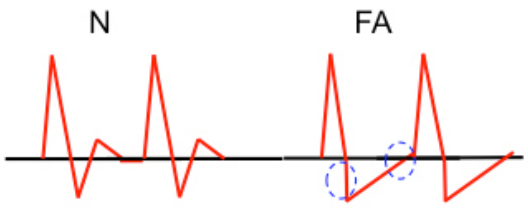
No stenosis

High degree of stenosis without collaterals

Simplified Saint-Bonnet classification with continuous flow

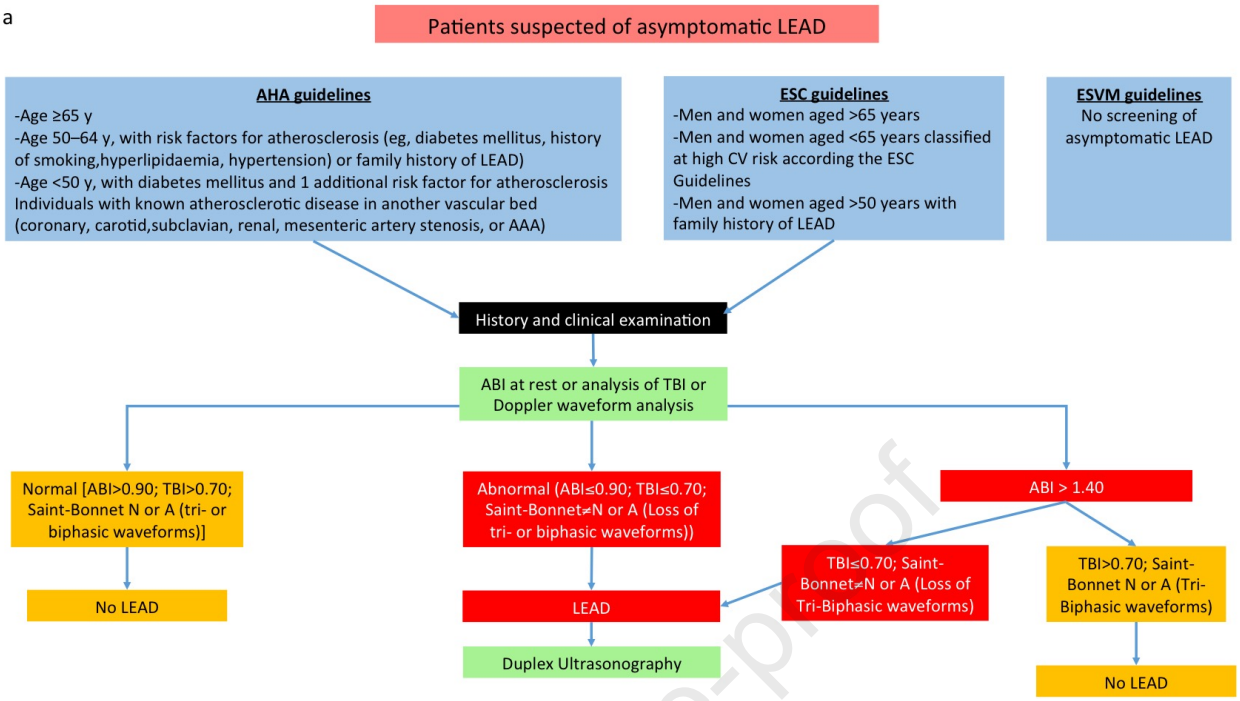


Simplified Saint-Bonnet classification FA: false aneurysm



In certain cases, the waveform morphology does not correspond to any of the above descriptions and should then be described as undefined (Saint Bonnet U)

a



b