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Principal predictors of major adverse limb events in diabetic peripheral artery disease: A narrative review

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ABSTRACT

Background and aims: The increasing prevalence of diabetes mellitus is causing a massive growth of peripheral artery disease incidences, a disabling complication of diabetic atherosclerosis, which leads often to the amputation of the affected limb. Critical limb ischemia is the terminal disease stage, which requires a prompt intervention to relieve pain and save limbs. However, patients undergoing revascularization often suffer from cardiovascular, cerebrovascular and major adverse limb events with poor outcomes. Furthermore, the same procedure performed in apparently similar patients has various outcomes and lack of an outcome predictive support causes a high lower limb arterial revascularization rate with disastrous effects for patients. We collected the main risk factors of major adverse limb events in a more readable and immediate format of the topic, to propose an overview of parameters to manage effectively peripheral artery disease patients and to propose basics of a new predictive tool to prevent from disabling vascular complications of the disease.
Methods: Most recent and updated literature about the prevalence of major adverse limb events in peripheral artery disease was reviewed to identify possible main predictors.
Results: In this article, we summarized major risk factors of limb revascularization failure and disabling vascular complications collecting those parameters principally responsible for major adverse limb events, which provides physio-pathological explanation of their role in peripheral artery disease.
Conclusion: We evaluated and listed a panel of possible predictors of MALE (Major Adverse Limb Event) in order to contribute to the development of a predictive score, based on a summary of the main risk factors reported in scientific articles, which could improve the management of peripheral artery disease by preventing vascular accidents.

1. Introduction

The growing global prevalence of diabetes mellitus with nearly 500 million affected people [1,2] will make atherosclerosis and its complications the leading cause of death in the near future. The chronic subclinical inflammation underlying diabetic atherosclerosis along with the oxidative stress of advanced glycation end-product (AGEs) are the main promoter of macrovascular complications such as PAD [3–6]. The risk of developing cardio-cerebrovascular complications in patients with PAD is well known; however, these patients often suffer from disabling limb adverse events. Studies and knowledge on the causes of these complications are not as well-structured and organized as in the literature regarding major adverse cardiovascular events (MACE). Hence, this review is a comprehensive search of all relevant studies and a collection of available knowledge on possible predictors of MALE to provide a more organic, readable and immediate state of the art for future prospects. As a primary objective, this article provides a panel of parameters to identify new risk categories for adequate management of patients with PAD at risk of developing MALE. Moreover, as a secondary objective, this review introduces the basis for a predictive tool to locate our patients in risk categories

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and prevent the incidence of MALE in higher risk patients.

1.1. Diabetes mellitus: not only a matter of glucose

Diabetes mellitus is often described as a clinical syndrome characterized by hyperglycemia due to defective insulin secretion by pancreatic β-cells and reduced sensitivity of target tissues (muscle, liver and adipose tissue) to its action (insulin resistance) leading to the development of inappropriate hyperglycemia. The progression of oxidative stress due to an excess of reactive oxygen species (ROS) and the formation of AGEs induce harmful consequences to vessels leading to vascular complications [7]. Unlike type 1 diabetes mellitus which has a genetic and immune etiology [8], type 2 diabetes sees not-modifiable and acquired risk factors. The result of the coexistence of these factors causes the development of genetic and epigenetic changes, mitochondrial dysfunctions, intestinal dysbiosis and oxidative stress that lead to a metabolic memory characterized by reduced insulin production due to gradual loss of pancreatic beta cell function, and increased inflammatory response promoting insulin resistance [9]. Recently, a growing body of evidence is underlining the importance of obesity, nutritional habits, lifestyle and subclinical systemic inflammation as possible promoters of this disease and related complications. Unbalanced diets (excessive consumption of high-density calorie meals, refined sugars, animal proteins, saturated fats) and harmful behaviors (sedentary lifestyles and physical inactivity) are characterizing the lives of a substantial part of the population, involving all generations and increasing the incidence of diabetes mellitus, obesity, peripheral artery disease and metabolic syndrome [10–12]. Currently diabetes affects **almost** half a billion people with a worrying trend in the next future [2]. Additionally, globalization easily offers availability, attraction and addiction [13,14] to highly palatable, cheap and low quality junk food, with a preannounced epidemic of obesity [15] and a massive increase of type-2 diabetes mellitus **(T2DM) prevalence 1,16,17, with enormous impacts on economics.**

Individual inflammatory state has also been demonstrated to play an interesting role on glycemic control [18]. This enabled to further expand the function of adipose tissue as source of cytokines and related proinflammatory signaling pathways [19–25]. Moreover, new evidence is available on the close relationship between food and inflammation, and the effects of several dietary patterns (such as North America, the Northern Europe and the traditional Mediterranean diet) on systemic inflammation [26]. Interestingly, both insulin resistance (a preventable pre-diabetic condition) and type 1 diabetes mellitus (a condition characterized by hyperglycemia due to the immune-mediated destruction of pancreatic beta cells) trigger chronic inflammation, sustaining the metabolic dysfunction, insulin resistance, and promoting atherosclerosis [27]. Moreover, the early onset of hyperglycemia in type 1 DM determines a greater and lasting exposure to glycemic alterations, substantially increasing the risk of vascular complications [28]. Thus, hyperglycemia in DM is only an epiphenomenon of a fascinating relationship of factors already known, recently discovered and probably yet to be discovered.

1.2. Atherosclerosis: an old, but new protagonist

The exponential increase of T2DM is associated with a fast-growing incidence of atherosclerotic complications, which play a central role in global morbidity and mortality. The chronic exposure to high serum glucose levels determines a disruption of vascular homeostasis and endothelial dysfunction, inducing a subclinical inflammation, which precedes vessel injury [27]. Intracellular hyperglycemia stimulates the production of mitochondrial reactive oxygen species (ROS) along with the formation of AGEs, which enhance cytokine expression accelerating the diabetic atherosclerosis due to a chronic vascular inflammation [29]. Moreover, through the activation of ubiquitin molecular pathways, ROS induce insulin resistance perpetuating the entire process [27]. According to the World Health Organization, major vascular complications related to atherosclerosis will be the first cause of death in the next decades and scientific progress must contribute to prevent the otherwise inevitable dramatic effects on public health. Diabetic patients are often destined to suffer from complications of this atherosclerotic process **30–32 such as** peripheral artery disease (PAD), which is an increasing macrovascular disabling disease **3–5** associated to chronic vessel inflammation [33]. PAD is a relatively new pathological expression of the “old” atherosclerotic disease, which deserves proper research to identify efficient therapeutic solutions.

1.3. Peripheral artery disease: focus on an emerging disabling complication: MALE-

Peripheral artery disease is a main risk factor for cardio- and cerebrovascular death and a clinical expression of atherosclerosis [34,35]. In fact, diabetic PAD patients are directly exposed to a high risk of major adverse cardiovascular events (MACE)—defined as composite of acute myocardial infarction, stroke, transient ischemic attack and cardiovascular death [35,36]—. Unfortunately, an elevated percentage of PAD patients remains unaware of their disease because of their absence of symptoms [37]. The underestimation of PAD might be a direct result of a disconcerting low sensibility of clinicians towards this pathology [38] with disastrous effects on patients who, both asymptomatic and symptomatic, are exposed to an equally high risk of MACE [39,40].

Additionally, evidences underlined the presence of major adverse limb event (MALE)—defined as composite of acute limb ischemia, major vascular amputations, limb-threatening ischemia leading to urgent revascularization [36,41,42]—which is another pathological consequence of this disease involving the short-term management of diabetic PAD patients and affecting negatively patients’ quality of life [43] and public economy [44,45]. The ineffectiveness of currently available treatments often derives from the clinicians’ inadequate capability to recognize complications and from lacking predictive support, which could guide physicians to prevent MALE. However, the scientific resonance of MALE is not comparable to the amount of information on cardiovascular complications (defined as MACE) that are associated with PAD. This lower sensitivity of the scientific community on this topic leads to a current lack of systematic articles that can highlight the poor short and long-term results related to PAD when a MALE occurs, but above all, that can describe the main causes underlying the incidence by MALE. More studies are needed to understand and prevent this disabling, often fatal complication.

1.4. Arterial revascularization: a complete success?

Adequate life style promotion, principal modifiable risk factor correction and medical therapy optimization are the first fundamental therapeutic steps in PAD treatment [46–50]. However, in severe symptomatic cases or at the very late stage of the illness, named critic limb ischemia, revascularization results indispensable [48,51,52]. Peripheral artery revascularization is a therapeutic approach that gives relief from invalidating symptoms of claudication, improving patients’ quality of life [53], and it becomes a limb salvage treatment in patients affected by critical limb ischemia. In fact, available pharmacological and not pharmacological therapy (such as the injection of stem cells or colony-forming

endothelial cells of human cord blood) are not able to effectively manage invalidating symptoms of chronic threatening limb ischemia [54], in which impaired distal arterial blood flow provokes disabling tissue loss due to the necrosis and gangrene. In this setting, limb revascularization efficiently resolves ischemic pain and supports wound healing [55]. Balloon angioplasty is a safer revascularization technique compared to major vascular surgery. However, PAD patients, who underwent endovascular treatment often showed a high rate of MACE and MALE [51]. A retrospective observational study [55] demonstrated that 10% of PAD patients, who underwent limb revascularization, were within a year readmitted to the hospital for MALE [55]. Evidence suggests that the prognosis of patients with PAD strongly depends on the expression of traditional and non-traditional risk factors [51,56] (including previous revascularization treatments) and this manuscript is an attempt to provide a collection of these predictors in a unified work.

2. Review design, methods and results

We evaluated the recent evidence in the literature on the main risk factors of PAD and the possible correlation with the incidence of MALE. We conducted a literature review of key articles, narrative and systematic reviews, meta-analyzes, clinical studies of peripheral lower limb arterial disease, and major predictors of lower limb adverse events. We filtered the most relevant studies on PubMed and Google Scholar by using keywords and we selected 52 papers that served as a reference bibliography to list the main predictors of MALE in patients with PAD. We also collected the primary studies on the predictors of MALE in a summary table with corresponding bibliographic notes. After a careful review of the main scientific articles on the correlation between PAD risk factors and the incidence of MALE in order to identify the main predictors of adverse outcomes in the lower limbs, 52 articles and 13 main risk factors were selected. We have listed and divided all the predictors in 6 specific Macro Areas and reported all the corresponding bibliographic notes (Table 1). Age was supported by 3 articles and was included in the "Unmodifiable risk factors" Macro Area. Smoking was supported by 4 articles and was included in the "Modifiable Risk Factors" Macro Area. Diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, lower limb neuropathy, microangiopathy were supported by 5, 2, 12, 5, 4 and 2 articles respectively and were collected in the "disease and organic risk factors" Macro Area. Prior MACE, prior revascularization, pharmacological medications were supported by 2, 7 and 14 articles respectively and were collected in the "Individual background atherosclerosis" Macro Area. Serum cytokine levels were supported by 2 articles and were listed in the “serum cytokines” Macro Area. The ankle-arm index was supported by 3 articles and was listed in the "Diagnostic tools" Macro Area.

3. Predictors of MALE, why so important?

3.1. Age and MALE

Atherosclerosis is a chronic inflammatory process that slowly leads to an endothelial dysfunction, intramural thickening of the vessel subintima and vascular stenosis [27,29]. Atherosclerosis starts after birth and silently grows with us [57]. An older age means a longer exposure to inflammation along with age-related vascular remodeling due to dysfunctional endothelial progenitor cells [58]; therefore, age is an independent risk factor and cause of advanced atherosclerotic disease stage [36,59–62]. Consequently, age is a fundamental unmodifiable risk factor of PAD causing complications such as MALE [36,63]. Indeed, age seems to be a determining factor for MALE both in elderly patients due to the advanced deterioration of the arteries, and in younger individuals with significantly severe atherosclerosis-related comorbidities by demonstrating a more aggressive progression of atherosclerotic disease [64].

3.2. Diabetes mellitus and MALE

Diabetes mellitus (DM) is the main risk factor of PAD alongside smoking [33,34]. PAD patients, additionally affected by DM, suffer from a higher rate of MALE. A linear correlation between MALE incidence and glycemic control (determined by the HbA1c value) was demonstrated, suggesting that a strict pre-operative glycemic control provides a better surgical outcome [65]. In fact, diabetic PAD patients with HbA1c values > 10% before a surgical revascularization are increasingly affected by MALE compared to non-diabetics [66]; the poorer diabetes is controlled, the higher the incidence of MALE. However, preoperative normal values of HbA1c, result of well-controlled long-term glycaemia, has no significant effect on MALE treatment outcomes. This could be explained by the close interdependence between glycemic control and individual inflammatory status [18]. HbA1c is a not very sensitive marker of individuals' glycemic variability that has been observed to be a major obstacle to neoangiogenesis by preventing the formation of new collateral vessels due to impaired VEGF pathway [67,68]. Type 1 diabetes mellitus often involves long-term exposure to high blood glucose values with an increased risk of developing macrovascular complications leading to a high incidence of MALE and mortality [69]. The increased susceptibility of patients with diabetes type 1

Table 1
Predictors of MALE and corresponding references. List of the main predictors of MALE classified as Macro and Microarea, and references of the corresponding articles. MALE: Major Adverse Limb Event; LDL-c: Low-Density Lipoprotein cholesterol; Lp(a): Lipoprotein-a; MACE: Major Adverse Cardio/Cerebrovascular Event; IL-6: Interleukine-6; CRP: C Reactive Protein; TNF-a: Tumor Necrosis Factor-a; OPG: Osteoprotegerin; ABI: Ankle-Brachial Index.

Macro area	Micro area	References
Unmodifiable risk factors	Age	[36,63,64]
Modifiable risk factors	Smoking	[72,80–82]
Disease and organic risk factors	Diabetes mellitus	[55,65,66,69,74]
	Hypertension	[72,80]
	Dyslipidemia [LDL-c, Lp(a)]	[80,89–92,95,96,103,106–109]
	Chronic kidney disease	[55,72,81,138,139]
	Lower limb neuropathy	[147–150]
	Microangiopathy	[154,155]
Atherosclerosis individual background	Prior MACE	[56,163]
	Prior revascularization	[55,81,188–190,212,213]
	Pharmacological Medications	[41,83,84,89,90,92,93,178–183,187]
Serum cytokines	Serum levels cytokines (IL-6, CRP, TNF-a, OPG)	[36,231]
DIAGNOSTIC TOOL	ABI rest/post-exercise	[74,176,177]

mellitus with large glycemic changes and increased accumulation of end products of advanced glycation [70] and growth factors [28] in arterial vessel walls due to an inflammatory trigger increases the incidence of vascular adverse events [28,70]. To the best of our knowledge, little evidence is available on the role of glycemic variability on patient lower limb outcomes, with the need for new dedicated studies. Furthermore, although the duration of diabetes and therefore exposure to hyperglycemia has a significant importance on the progression of micro and macrovascular damage, its effect on the incidence of MALE is still controversial. Duration of diabetes is associated with an increased risk of foot ulcer complications [71], but has not shown a significant correlation with amputation or other adverse limb events [72,73].

DM is also a major cause of higher second-amputation rate in patients with previous amputation due to dysvascular conditions [74]. Additionally, 10% of patients who have undergone revascularization procedures, requires a hospitalization for MALE with diabetes mellitus such as one of the main MALE-related predictors [55]. The treatment of diabetes is a fundamental element for the correct management of the patient with diabetic PAD. Patients should frequently monitor blood glucose values and treat diabetes to keep glycated hemoglobin values below 7%. This therapeutic target is strongly recommended and allows to effectively reduce the risk of MALE [75].

3.3. Smoking and MALE

Smoking is a strong risk factor for atherosclerosis [76]. The association between smoking and PAD is stronger than for coronary artery disease [33,34,77], with a linear correlation between exposure to smoking and PAD development [78]. Although a high incidence persists in former smokers [79], smoking duration and point in time of quitting smoking (early vs. late in life) reduces PAD risk [76]. Smoking influences disease location with more proximal vascular lesions in smokers compared with non-smokers, and more distal critical stenosis in diabetic smokers compared with non-diabetic smokers. The duration of chronic exposure to smoking has a documented higher incidence of MALE [80], in particular if associated to diabetes [72], which confirms the fundamental role of non-medical interventions, such as mitigating risk factors, in PAD management [80]. Smoking is a predictive factor of amputation and post-amputations outcomes demonstrating the importance of quitting smoking habits in order to prevent disabling morbidity related to cigarettes [81]. Interestingly, living in distressed communities is significantly associated with smoking habit. Moreover, stressed individuals are more frequently affected by several comorbidities are more reluctant to follow non-medical interventions or assume pharmacological therapies and show a higher rate of MALE [82]. The intensity of smoking determines a cumulative risk of MALE in patients who underwent a revascularization procedure. Personal smoking behavior is a basic screening for PAD patients and a detailed description with a quantification of the individual smoking exposure allows a more precise prediction of post procedural outcomes rather than the approximate classification in “non-smoker, current smoker or former smoker” [82].

3.4. Hypertension and MALE

MALE incidence has a direct correlation with uncontrolled blood pressure [80] and an adequate pharmacological treatment (e.g., angiotensin converting enzyme inhibitors and angiotensin II receptor blockers) achieves increased limb salvage rates and better outcomes in high-risk PAD patients [83,84]. Furthermore, the presence of hypertension in PAD patients with diabetic foot ulcers increases the risk of amputation and re-amputation operations leading to disabling outcomes [72]. The target systemic blood pressure values recommended by the guidelines are below 130/80 mmHg since adequate blood pressure control has shown evident benefits on disease progression and reduces the incidence of complications. However, recent new evidence suggests an increased risk of MALE even in patients with systolic blood pressure below 120 mmHg with the need for further studies to identify the best therapeutic approach to manage the hypertension of our patients [85–87].

3.5. Lipid profile and MALE

“The lower, the better”, is a valid statement regarding serum cholesterol concentrations in PAD patients affected by dyslipidemia [88]. A growing body of evidence confirms the importance of achieving the therapeutic goal for low-density lipoprotein cholesterol since there is a consistent linear correlation between lowering serum LDL-c levels and prevention of limb adverse events [89]. Additionally, reduction of non-HDL cholesterol at very low levels results in a significant beneficial impact on prevention of MALE [80] together with greater tendency to survival, in parallel with a fairly certain safety for patients with PAD [90]. Pharmacological reduction of low-density lipoprotein-cholesterol (LDL-c) is beneficial for PAD outcomes [91], and high-intensity statins are a mainstay of this treatment with proven effect on MALE incidence [91,92]. Moreover, patients, taking statins for secondary prevention after revascularization, showed a longer patency rate of treated lesions [93]. Unfortunately, an efficient educational program for patients supporting clinicians to manage correctly PAD, is still an unmet aim [80,94]. In fact, sensitizing both clinicians and patients to introduce statins in therapy, could reduce MALE incidence [95]. However, the reduction of LDL-c would miss a residual cardiovascular risk [96] due to the discovery of another molecule that has recently attracted the interest of researchers. Lipoprotein a or Lp(a) is a complex polymorphic lipoprotein produced by the liver and it is structurally similar to LDL-c. In fact, this molecule has a strong association with PAD [97,98] and MACE [97,99–105]. Furthermore, Lp(a) is an independent risk factor of MALE [96,103,106–109] and showed a linear correlation between serum concentration and rate of vascular events [107]. Currently, there are a few therapeutic strategies to manage Lp(a)-related risk, such as apolipoprotein (a) targeted antisense therapy (RNA-targeted therapies) [100,110], the PCSK9 inhibitors already in use for the known cholesterol-lowering effect [110] and apheresis [103,110] which showed a significant effect of reducing MALE occurrence. New molecules (such as bempedoic acid [111–116], niacin [117–122] and carnitine [123–128]) with promising results in amelioration of lipid profile has been introduced but they are not yet backed by solid scientific support for routine use in clinical practice. In recent years there has been a greater understanding of the cardiovascular risk of patients with PAD with the strong recommendation to take a more aggressive approach to the treatment of dyslipidemia. Previous indications on target LDL cholesterol [129] have been revised and patients diagnosed with PAD have been included in the risk class defined as "very high" with therapeutic goal LDL cholesterol values < 55 mg/dL [88],[130-132].While triglycerides must be kept below 150 mg/dL, the role of triglycerides on cardiovascular risk in PAD [88] remains controversial.

3.6. Chronic kidney disease and MALE

Aging, diabetes mellitus and chronic kidney disease (CKD) are known factors of vascular calcification. Vascular calcification is the result of the intimal and tunica media vessel calcification leading to complete vascular calciphylaxis, which is associated with increased

morbidity and mortality. Several factors contribute to vascular calcification but new discoveries are needed to further understand this phenomenon. Bone morphogenetic proteins (BMPs) modulate bone production and their localization in vessels' tunica media could be associated to vascular smooth muscle cells (VSMCs) osteoblastic differentiation mineralizing the extracellular matrix [133]. CKD reduces serum fetuin A levels [134] that inhibits calcification of vessel walls bonding the circulating calcium and phosphate ions, promotes bone mineral accretion and, despite controversial opinions about its vascular beneficial role [135], appears to be a protective factors of cardiovascular disease [136]. Diabetes mellitus and CKD promotes exponentially vessels calciphylaxis [137]. In fact, the association of DM and CKD accelerates the medial arterial calcification in symptomatic PAD patients resulting in a high incidence of MALE [138] and urgent treatment, slowing down the progression of kidney disease to ameliorate PAD outcomes, is required. Chronic kidney disease is an independent risk factor for revascularization failure and amputation, from the early stage of pathological proteinuria to the end stage of renal failure requiring dialysis [55,72,81,139]. PAD patients affected by CKD, who underwent a limb endovascular revascularization (LER), are often re-hospitalized for MALE, which confirms the predictive role of CKD in PAD outcomes [140]. Thus, PAD patient management must include the prevention of kidney disease and a rigorous follow-up since it contributes to atherosclerotic progression. Furthermore, the presence of CKD is related to a more severe PAD disease (e.g., advanced Leriche-Fontaine and Rutherford classification scores) and it is an independent risk factor for MALE at any stage of kidney disease [141]. A new challenge is to identify the best revascularization strategy for end-stage renal disease PAD population where MALEs are responsible of poor outcomes [139]. People affected by end-stage renal disease often suffer from PAD with a high risk of MALE but their frailty strongly restricts therapeutic options [142].

3.7. Lower limb neuropathy and MALE

Diabetes is the main cause of neuropathy [143] and this disabling complication often has a silent onset that in a large percentage of patients leads to serious foot complications such as traumatic foot ulcers, infections, inability to walk and non-traumatic amputations. Hyperglycemia together with various molecular pathways involved in neuro-trophism and oxidative stress, contribute to the dramatic degeneration of peripheral nerves and related complications [144,145]. A common cause of hospitalization of patients with diabetic neuropathy is foot ulcer infection but unfortunately specific therapeutic approaches and effective prevention programs are not yet available [146]. Amputation is a common failure outcome in patients with diabetic neuropathy and arterial disease [147]. Local neuropathic impairment of vascular auto-regulation has been shown to be a strong predictor of MALE by promoting the incidence of neuro-ischemic ulcers [148]. Diabetic neuropathy affects patient survival and quality of life, as well, due to the high risk of hospitalizations and amputation rates [149]. Therefore, all diabetic patients should be regularly screened for early diagnosis of diabetic neuropathy in order to intervene on risk factors and slow the progression of the disease preventing the onset of MALE [150].

3.8. Microangiopathy and MALE

Capillary microangiopathy is a disease characterized by a progressive occlusion of the small terminal vessels that supply organs and tissues and supply nourishment to the walls of the great arteries, contributing to macrovascular pathology. Diabetic microangiopathy is often associated with the involvement of precapillary arterioles, further complicating the healing of neuroischemic foot ulcers [151]. Currently we do not have effective diagnostic techniques to be used in the clinical setting to characterize the degree of microangiopathy [152], but we know their role in progression of peripheral arterial disease together with macrovascular involvement [153]. In fact, a growing body of evidence has shown that microangiopathy and macrovascular disease simultaneously participate in the deterioration of the vessels and both contribute together with ischemic damage of the tissues of the lower limbs which increases the risk of amputation [154].

Microangiopathy impairs tissue perfusion and nutrition, deteriorates the complex interaction between thermoregulation, arterial blood flow, neurogenic control of the vascular system and endothelial function. Therefore, microvascular damage is a fundamental component that increases the risk of MALE as it establishes a profound structural change and irreversible dysfunction of the vascularity [155]. The reduction of glycated hemoglobin values by improving the control of diabetes is the most effective therapeutic approach for slow the progression of microangiopathic damage and the risk of MALE [156].

3.9. Prior stroke, myocardial infarction or limb amputation and MALE

PAD is a main disabling expression of atherosclerosis as well as a risk factor for other atherosclerotic manifestations such as stroke, transient ischemic attack and myocardial infarction [41,51,157,158]. Conversely, patients hit by prior cardiovascular and cerebrovascular events or prior limb amputation, have a higher incidence of PAD, which suggests that the involvement of multiple vascular sites determines a more aggressive and advanced atherosclerotic phenotype [159]. Moreover, prior cardio-cerebrovascular events and limb amputation in PAD patients are predictors of poor outcomes [160–162] and an independent factor of MALEs [56,163]. PAD patients deserve a comprehensive management of every single atherosclerotic complication, regardless of their location, to delay the progression of the disease and to reduce the incidence of MALEs.

3.10. Ankle-Brachial Index and MALE

The patient with subclinical PAD is a high-risk individual who requires timely diagnosis to intercept the disease before it can develop late-stage complications. Despite the limitations that emerge from the literature [164–166], ABI remains the first non-invasive tool in the diagnosis of PAD [46,166–168] with an additional prognostic value on the incidence of death and MACE [169–175]. In addition, as regards its prognostic value, a higher incidence of revascularization procedures and lower limb amputations [74] was found in patients with altered ABI values both at rest and after exercise. Furthermore, the trend towards higher all-cause mortality as well as a higher rate of cardiovascular events and poorer limb outcomes were also confirmed in presence of abnormal ABI [176,177].

3.11. Pharmacological therapy and MALE

PAD's best therapeutic strategies are still unknown and the urgency to discover new effective approaches is encouraging and stimulating new studies. However, the principal aim is a durable and effective improvement of modifiable risk factors [46–48]. Many therapeutic interventions, acquired from cardiovascular and cerebrovascular disease, have been applied to slow down PAD progression and to reduce the incidence of major adverse events. In

fact, antiplatelet therapy and statin therapy are the mainstay of PAD treatment. These drugs are effectively used for primary and secondary prevention; while, lowering-lipid therapy (such as statin use) along with antiplatelet therapy effectively reduce MALE risk [93,95,178–182]. Additionally, the further decrease of serum cholesterol, promoted by new PCSK9 inhibitors, determines a significant reduction of MALE with a reliable safety profile [89,90]. Although the best pharmacological approach has not been defined yet, studies suggest new interesting treatment combinations. Symptomatic PAD patients who required LER often suffer from a higher MALE rate [36], but the use of a dual antiplatelet therapy (DAPT) for ≥6 months after the procedure seems to be a safe, correlated with a low bleeding rate, and effective intervention to reduce MALE incidence [183]. Evidences about anticoagulants in PAD encouraged new studies proving a safe combination with antiplatelet therapy and a superior efficacy in comparison with mono-antiplatelet therapy alone [184]. Anticoagulation protects from the incidence of ischemic events in PAD even in high risk patients with multiple comorbidities [185]. The principal limit of antithrombotic therapy is bleeding. However, its incidence is relatively low and mostly affects patients with a more advanced atherosclerotic disease stage because of vessel frailty [186]. Moreover, treatment cessation due to bleeding is an independent risk factor of subsequent ischemic events [186]. Therefore, the significant reduction in the incidence of MALE in individuals taking a combination of antiplatelet and low-dose anticoagulant therapies supports this optimization of antithrombotic treatment in patients with a history of symptomatic CAD or PAD [41,187]. Interestingly, angiotensin converting enzyme inhibitors and angiotensin receptor blockers in PAD demonstrated longer amputation-free survival due to their anti-remodeling effect on arterial vessels [83,84]. Risk factor correction, symptom control, serum lipid lowering and antithrombotic therapy are the mainstays of PAD management and the new challenge is to adopt new evidence-based therapeutic approaches to reduce disease progression and MACE and MALE incidence [94].

3.12. Prior revascularization, procedure performer or adopted technique and MALE

Symptomatic PAD is an advanced stage of atherosclerotic disease requiring often a prompt intervention. In this case, revascularization is an effective therapeutic approach to restore adequate blood flow to ischemic tissues. Generally, revascularization is the most effective treatment with unmatched efficiency in terms of limb salvage, pain relief, wound healing and speed of results. In past, narrowing of arterial vessels and the presence of vascular stenosis were the main criteria for performing revascularization. Therefore, the restoration of the patency of the arterial vessels guided the therapeutic process towards an invasive treatment. However, the relatively recent awareness of a progression of PAD with a consistent risk of MALE [55,81,188–190] has led to the fundamental recommendation to prioritize the correction of risk factors, optimize pharmacological therapy and increase exercise tolerance through the introduction of supervised exercise programs. Revascularization at any stage of PAD is an independent risk factor of worse long-term limb salvage outcomes, therefore, the real clinical need for prompt revascularization should guide the physician to seek such treatment.

Although, preliminary studies demonstrated that an endovascular and an open revascularization are comparable [191–194], it remains still unclear, which technique is most effective and safe to reduce MALE [195], and which patient characteristics can be used to determine suitability of endovascular or open revascularization. Some individuals are more suited for an open surgical revascularization approach than an endovascular technique (and vice versa). Therefore, the next challenge is to identify the optimal revascularization strategy for each patient [196]. Additionally, the vascular anatomy, stenosis location [142], technique adoption and experience of the surgeon [166] are variables that should guide physicians towards the best revascularization approach. The gold standard for PAD revascularization is an open surgery that provides the best long-term results with lower MALE incidence. A longer vessel patency obtained with a surgical approach, correlates with a higher incidence of perioperative MACE [197,198] and this contributes to increased costs [142]. In particular, endovascular revascularization guarantees lower short-term adverse events, especially in PAD patients characterized by significant frailty related to comorbidities [198–201]. First, surgical suitability should be always evaluated [202,203] and endovascular revascularization should be offered as a second valid option in patients with high surgical risks or unfavorable vascular characteristics [204], although a higher incidence of MALE was observed. The most suitable surgical strategy should be determined considering personal characteristics and the individual surgical risks [205]. In fact, in frail patients, (e.g., in diabetic PAD), acceptable patency outcomes, cost effective results, shorter hospitalization time [191] and lower short-term adverse events suggest endovascular revascularization as the best approach [192,206]. Moreover, in some comorbid patients, endovascular revascularization resulted in lower MALE rates [207]. Since LER is increasingly applied, several studies compared techniques to identify which technique and correlated factors resulted in better outcomes, like for example reducing MALE incidence [208–211]. The performer experience seems to contribute fundamentally to patient outcomes after limb revascularization. An higher incidence of MALE was observed in procedures executed by non-cardiologists or non-revascularization specialist, suggesting that patients should be referred to high-volume revascularization centers [55]. Arterial limb revascularization is an effective symptomatic treatment, but whether it is always a worthy approach, is not clear yet. Therefore, prior revascularization is an independent risk factor for MALE [212,213] and determines an inflammatory burden, which could promote vascular inflammation and subsequent complications [214–216]. Currently, controversial opinions about the best revascularization approach exist and further studies are required to obtain stronger evidences [217] to provide guidelines, which could contribute to reduce significantly MALE incidence.

3.13. Serum cytokines and MALE

The prediction of MALE could be a fundamental strategy to prevent a treatment failure in diabetic PAD. The interest on predictive role of cytokines in PAD [218] to prevent vascular complications lead to expand further their function in vascular inflammation and degeneration [219], LDL cholesterol oxidation, endothelial cell dysfunction, regulation of calcium metabolism, modulation of foam cell activity and the influence on platelet adhesion [27,29,220–229]. However, only a few of these molecules have shown clinical importance for monitoring disease progression or as predictors of adverse outcomes [230].

Pre-procedural inflammatory status of PAD patients should be routinely assessed as elevated pre-procedural serum cytokine levels are associated with a significant increase in rate of MALE [231]. Indeed, the interaction between individual proinflammatory

status and the vulnerability of atherosclerotic plaques [232] could potentially explain the progression to harmful vascular complications.

The relevant interaction between cytokines and MALE is an interesting topic that requires further investigation in order to develop new therapeutic and preventive strategies for limb outcomes. A linear correlation between the increasing serum levels of these molecules and MALE rate was demonstrated [36]. Basal concentrations of serum high sensitivity C-Reactive Protein (hsCRP), C-Reactive Protein (CRP) [233,234], omentin-1 [235], High Mobility Group Box-1 [236], tumor necrosis factor-α (TNF-α) [237], interleukin-6 (IL-6) [227] and osteoprotegerin (OPG) [225,226,229,238] were measured in a population of diabetic PAD patients affected by a below-the-knee occlusive disease who were candidate to an angioplasty. MALE prediction was notably more precise and strongly enforced by the presence of higher serum levels of each cytokine [36]. Therefore, individual blood samples could predict suitability of diabetic patients for revascularization, support physicians to identify patients with higher risks of limb revascularization failure and their follow-up care to prevent MALE.

5. Discussion

PAD is certainly one of the most disabling complications of diabetes mellitus, although extensive guidelines have only recently been created for the correct management of patients at risk or affected by this disease. Unlike the more well-known cardiovascular adverse events of diabetes, the incidence of MALE is an underestimated complication that leads to disastrous clinical consequences. Unfortunately, patients come to the clinician when the disease is already in a very advanced stage, limiting therapeutic opportunities. The support of the current guidelines has made it possible to establish which are the priorities of the patient with PAD in terms of primary, secondary prevention and revascularization treatment [239–242]. All patients with diabetes should undergo regular outpatient check-ups with vascular ultrasound. Moreover, the ABI measurement remains a cost-effective preliminary tool recommended as a first screening approach [243,244].

Once patients with asymptomatic and symptomatic PAD (in its different stages of clinical presentation) have been identified, it is essential to understand the risk of cardiovascular consequences to which this population is exposed. In fact, this category of patients is considered to be at “very high risk” of developing MACE and MALE with the urgent need to set up an effective secondary prevention to face the otherwise inevitable and disastrous outcomes. Diabetes management has the therapeutic objective of maintaining glycated hemoglobin values below 7% for most patients and recently new drug classes (SGLT2 inhibitors [4,245–248] and Glucagon-Like Peptide-1 Receptor Agonists [249,250]) have shown an incredible contribution to the reduction of glycated hemoglobin values with additional beneficial effect on patients' risk of MALE and MACE [251].

The management of systemic arterial hypertension in PAD is still under study as the therapeutic range of blood pressure values is very narrow with risk of adverse events and mortality for blood pressure above 130/80 mmHg and systolic values below 120 mmHg [86].

The new therapeutic targets for the control of dyslipidemia represent a fundamental contribution for the improvement of clinical outcomes and the protection of the cardiovascular risk of patients with PAD. Indeed, the diagnosis of PAD, like CAD, is an intrinsic risk factor for the development of macrovascular complications. Therefore, PAD patients have been included in the highest risk category. Most “very high-risk” patients must reach LDL cholesterol values below 55 mg/dL demonstrating a consistent reduction in MACE and MALE occurrence [252]. A growing body of evidence confirms the safety of LDL cholesterol values even below 40 mg/dL in those with residual cardiovascular risk despite proper management of the other risk factors [131].

Finally, following scientific advances in CAD, it has been possible to improve the revascularization techniques of patients with threatening limb ischemia. The use of drug-coated balloon angioplasty and/or drug-eluting stents during revascularization procedures has led to enormous results in ensuring greater patency of the treated vessel and clinical benefits. The use of a double antiplatelet therapy for one month is also recommended after an endovascular revascularization procedure, although there is still a huge difference in knowledge from the cardiovascular world on this topic. However, the incredible results observed with the use of low-dose anticoagulants in CAD have already been confirmed in PAD which can therefore benefit from this additional therapeutic support to reduce the incidence of MALE and MACE. Currently, there are promising results on the treatment of the residual risk due to the systemic low-grade inflammation with the use of immunomodulatory therapies such as colchicine. In summary, the current European and American guidelines consider PAD among the main topics with growing scientific interest, epidemiological importance and therapeutic discoveries.

The growing prevalence of diabetes mellitus and its vascular disabling complications1 determined an increasing limb revascularization rate. Compared to the past, outpatient centers and hospitals offer increasingly revascularization and more patients are treated for chronic limb ischemia [55]. Not surprisingly, apparently similar patients who underwent the same revascularization procedure showed different results in terms of vessel patency, incidence of MALE and rate of cardio- and cerebrovascular events [36,55]. Follow-up programs after a revascularization often do not consider these individual differences hampering major adverse events prevention. Diabetic PAD patients are extremely frail, suffer from high complication rates and encounter prohibitive surgical risks; LER is suitable for diabetic PAD patients to achieve ischemic pain relief [192,206,207]. Unfortunately, a considerable part of patients who underwent LER is consequently affected by dramatic complications (e.g., MACE and MALE) determining the emerging doubt whether an invasive intervention is always worthy. In Fig. 1, all possible players of MALE pathogenesis are represented. Revascularization failure is responsible for disabling complications, additional costs and poor patient outcomes. We aimed at (Table 1) collecting all modifiable and unmodifiable risk factors related with PAD initiation and progression and, those related with increased MALE risk, to propose a set of main major adverse limb event and LER failure predictors to estimate the risk of MALE. Prompt identification of high-risk patients is critical to prevent disabling vascular complications through stricter follow-up programs, effective residual risk factor correction, anticipation of needed interventions. Furthermore, personalization of care is essential for this category of patients and very fragile individuals. Clinical practice is enriched by bed-side and predictive scores to guide physicians’ decisions like for example the CHA2DS2-VASc and HAS-BLED scores for atrial fibrillation, stroke [253] and bleeding risks [254]; the Padua, Geneva and Improve scores for thromboembolism risk assessment; or the ABCD2 score for stroke prediction after TIA [255]. However, the estimation of the incidence of MALE in PAD,

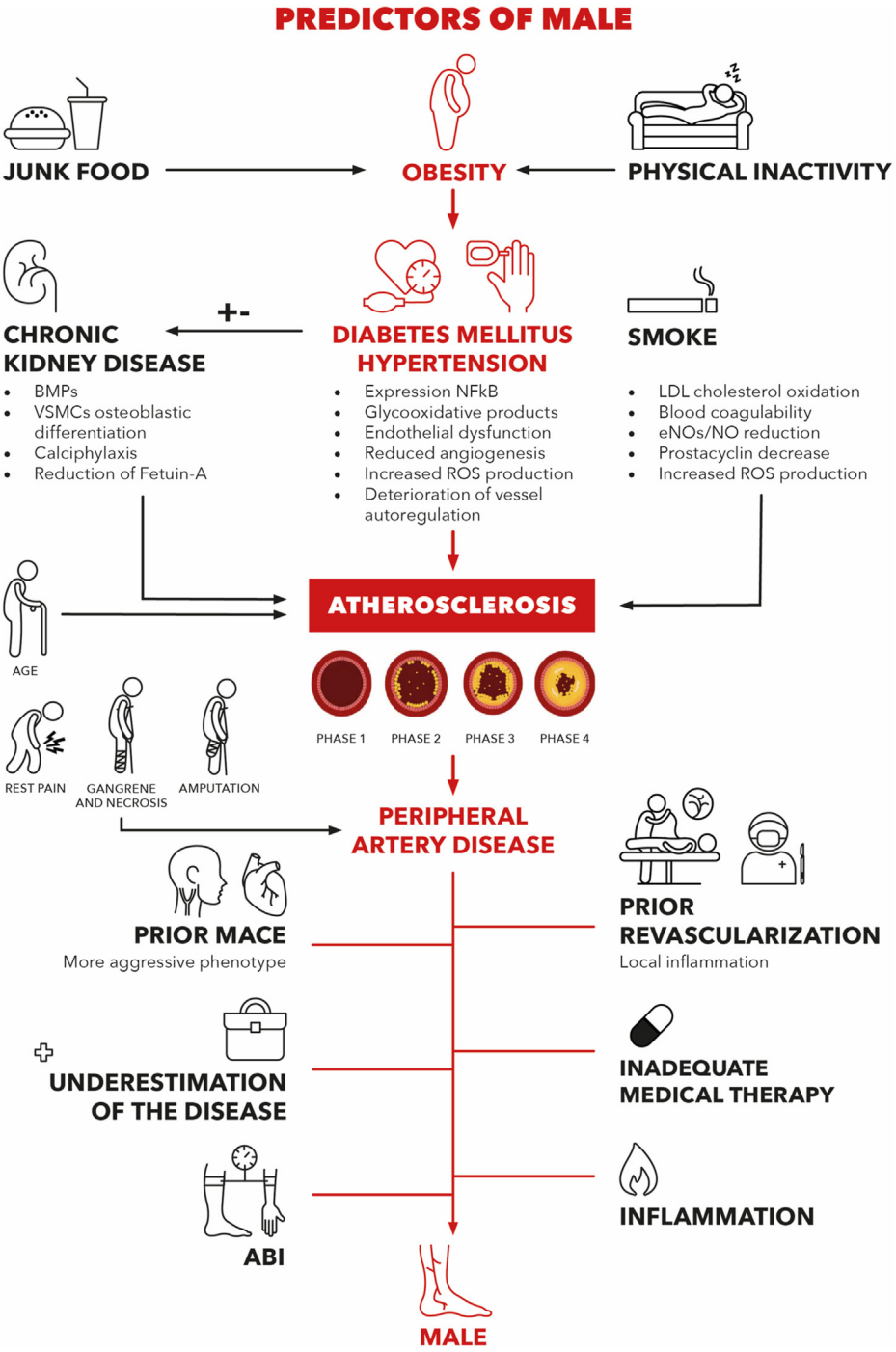

Fig. 1. Predictors of Male: Main risk factors promoting the atherosclerotic process underlying peripheral artery disease. All possible predictors of major adverse limb events. MALE: Major Adverse Limb Event; BMP's: Bone Morphogenetic Proteins; VSMCs: Vascular Smooth Muscle Cell; NFkB: Nuclear Factor Kappa-light-chain-enhancer of activated B cells; ROS: Reactive Oxygen Species; LDL: Low-Density Lipoprotein; eNOs: endothelial Nitric Oxide Synthase; MACE: Major Adverse Cardio/Cerebrovascular Event; ABI: Ankle-Brachial Index.

especially after a revascularization procedure, is still an unmet need, which we wish to contribute to understand. Although this is a critical aspect of peripheral artery disease, a greater scientific contribute is needed to improve the management of our patients. Our goal is to provide a useful and immediately available synopsis of the latest knowledge on the factors that increase the incidence of MALE in PAD, in order to facilitate the creation of a predictive score that can be applied in the clinical setting.

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Author contributions

All the authors contributed to the conception and design of the work, to the collection of data, to the implementation of the research, to the discussion of the results and to the drafting of the

manuscript with the final approval of the version to be published.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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