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Editorial

Misleading Points in Studies on Chronic Limb-Threatening Ischemia using Amputation-Free Survival as the Endpoint

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Abstract

Amputation-Free Survival (AFS) as a treatment endpoint does not independently assess the direct benefits of vascular intervention in Critical Limb-Threatening Ischemia (CLTI) and has many limitations. Whether in prospective or retrospective study, using AFS as a decisive criterion for evaluating the therapeutic effects is a logical leap and risks erroneous conclusions.

Editorial

Critical Limb-Threatening Ischemia (CLTI) is associated with a risk of lower limb amputation, diminished quality of life, and substantial mortality [1,2]. Arterial revascularization procedures in peripheral arterial occlusive disease have been evaluated with various endpoints. Anatomical endpoints include primary or secondary patency and restenosis. Clinical end points include survival, limb salvage, Amputation-Free Survival (AFS), and wound healing [3,4]. Acceptable limb salvage and AFS have been used to justify various treatments, especially in CLTI [5]. Although most large-scale studies of CLTI use AFS as a clinical endpoint [6-8], AFS is not effective in estimating treatment outcome [3]. Moreover, AFS is a composite end-point, and the logical uncertainty of composite end-point as an evidence in clinical trials has been discussed [9].

First, the clinical course of CLTI and risk of major amputation must be considered to estimate the actual therapeutic effects of the treatment modality. The 1-year AFS rates reported in two systematic reviews were 55% and 57% among patients with critical limb ischemia with no option for revascularization [10,11]. A recent study from Japan reported high limb salvage rate without arterial reconstruction in patients with critical limb ischemia [12]. It is evident that most (at least more than half) patients with ischemic tissue loss can avoid major amputation if appropriate conservative management is performed, despite the vessels being occluded following an invasive treatment [12-14].

Second, AFS specifically overestimates the clinical outcomes of vascular intervention in the short-term, while underestimating it in the longer-term. Avoidance of major amputation can occur as a natural course of CLTI (especially, in minor tissue loss without foot infection), not owing to the benefits of the revascularization procedure. This might act as the main driving factor for achieving high limb salvage rates, which would overestimate treatment outcome in the short-term when estimated using AFS. Contrarily, death from systemic atherosclerotic disease, which is not the target of peripheral revascularization, acts as the main driving factor for the decrease in patient survival and underestimates the treatment outcomes of the revascularization procedure in the long-term when estimated using AFS [14]. The survival of patients with CLTI is largely determined by their comorbidities [15-18]. It is noteworthy that most recent studies on endovascular treatment in CLTI deal with short-term outcomes.

Third, amputation can be a clinician-driven outcome. Except for overwhelming sepsis, the decision and timing of amputation is both physician and patient driven [19]. Only studies that are blinded for both the treating physician and the patient can eliminate bias of the timing and reason for amputation [19]. There are situations that require major amputation but patients or their family members refuse to comply. Similarly, despite the need for major amputation to avoid unnecessary treatment or to improve patients' quality of life, it may not be actively recommended by the clinicians. The decision of whether to perform major amputation depends on the opinions of both the patient and the doctor, with the clinician's opinion having an important influence. Thus, the number of major amputations that are not performed for various reasons in situations where they are indicated is unknown. Therefore, calculating the limb salvage rate based on whether a major amputation was actually performed or not can overestimate the treatment outcome.

Fourth, the efficacy outcome and safety outcome are different [5]. Recently, many studies have used AFS for the comparison of different treatments and to justify certain treatment modalities. However, there are some obvious logical errors. Comparable AFS does not mean equal therapeutic efficiency. Acceptable AFS means that certain treatment modalities fulfill the minimum safety criteria and are qualified to be compared with other standard treatment procedures in terms of efficacy. Evaluating the efficacy of treatment by defining the criteria as two simple combinations of all-cause mortality and major amputation has serious logical loopholes and can lead to misunderstanding, because most (at least more than half) event might be irrelevant to the therapeutic intervention. Measurement of treatment efficacy must include a Major Adverse Limb Event (MALE), re intervention, and stenosis at least [5].

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Fifth, limb salvage and patients' survival do not reflect all aspects of vascular treatment in CLTI. There are cases where it is impossible to define "success" or "failure" based on AFS. For example, a patient who died after a few months after treatment with complete wound healing or one who died a few months after treatment with unhealed wounds are captured as events in AFS analysis. However, the patient's mortality is not directly linked with percutaneous procedures performed on peripheral arteries. If a wound healed after percutaneous revascularization, the procedure itself would be considered clinically "successful" despite the death of the patient owing to other medical conditions. If a patient died with tolerable unhealed wounds after treatment, it would be difficult to consider it a "success" or "failure". If a patient survived for years without major amputation but was suffering from an unhealed or recurrent ulcer, this scenario is not captured as an event in AFS analysis. However, it is also difficult to classify this as a "success" because the benefits of treatment are unclear. In an initial wound with very low or low risk of major amputation according to the WIfI stage, the purpose of vascular intervention is definitely not to maintain AFS. To evaluate treatment outcome appropriately, we must consider other factors, such as wound healing, pain score, and quality of life.

AFS as a treatment endpoint does not independently assess the direct benefits of a certain intervention and has many limitations. Whether in prospective or retrospective study, using AFS as a decisive criterion for evaluating the therapeutic effects is a logical leap and risks erroneous conclusions. In particular, as the spectrum of the disease called CLTI is very diverse, and the risk of amputation according to the WIfI classification varies, it is necessary to evaluate the treatment effect, at least, considering the diversity of the amputation risk.

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