incidence of adverse events throughout the length of the study. Likewise, the heterogeneous nature of CLTI results in a highly variable natural history. Patients with ischemic tissue loss have a major amputation rate at 1 year of up to 35% compared with <10% in patients with rest pain. In addition, the FDA recommends that AFS should be the primary efficacy end point in a phase 3 CLTI trial. This has resulted in studies with an expected enrollment requirement of at least 500 patients. The reason for these large numbers in a phase 3 trial is that biologic treatment of CLTI is a limb-sparing procedure. As such, it is not expected to significantly influence mortality, although mortality is a component of the primary end point. Consequently, because of the heterogeneous and frail nature of the population of CLTI patients, larger numbers of patients are needed to complete a clinical trial that can detect any potential efficacy on amputation at 1 year.

Selection of patients. Many trials have recruited individuals who are considered to have no option for revascularization. Unfortunately, there is no consistent definition of no-option CLI. Published studies referred to in this section have broadly included individuals who were considered poor candidates for surgical or endovascular revascularization. This was due to either technical factors (inadequate venous conduit; unfavorable anatomy, such as absence of a patent artery in the calf that is in continuity with the foot) or patient-related factors (poor operative risk, but pain or tissue loss was unlikely to require amputation within 4 weeks). In several studies, imaging was assessed by an independent vascular specialist.

The development of advanced endovascular techniques gives many patients who were previously considered to have no option for revascularization a new opportunity to be considered potentially suitable for endovascular intervention. Nonetheless, there are few data supporting many of these techniques. Novel methods to measure circulating stem or progenitor cells before therapy may prove helpful in serving as companion diagnostics to identify those individuals who may or may not respond to angiogenic therapy.[536]

Conclusions

There have been promising early safety and efficacy trial data for both gene and cellular therapies in patients with CLTI. Despite these early promising results, no phase 3 trials have shown this therapy to be effective. Still, current trial design has improved, and there are multiple phase 3 clinical trials that either are actively enrolling or are in early stages of development. These involve potentially disruptive technologies that, if proven effective, could dramatically alter how patients with CLTI are cared for in the future. Until further evidence is available, these therapies should be considered investigational.

	Recommendation	Grade	Level of evidence	Key references
8.1	Restrict use of therapeutic angiogenesis to CLTI patients who are enrolled in a registered clinical trial.	1 (Strong)	B (Moderate)	Abu Dabrh,[4] 2015 Peeters,[113] 2015

	Research priorities
8.1	Identify surrogate markers (biomarkers, imaging) that would assist in understanding the possible mechanisms of action of gene- and cell-based therapies in CLTI.
8.2	Determine whether gene- or cell-based therapies can serve as an adjunct to revascularization to improve clinical outcomes in subsets of CLTI patients.

9. THE ROLE OF MINOR AND MAJOR AMPUTATIONS

CLTI is associated with a reduced life expectancy, a significant curtailment in ambulation, and a high likelihood of limb loss. Preservation of a patient's ability to walk is an important aspect of care in CLTI, and vascular reconstruction is the most direct method for achieving functional limb salvage in these often critically ill patients. When properly applied, open surgical and endovascular techniques have proved useful and successful for the preservation of limb function. A successful limb salvage intervention is associated with low postprocedural morbidity and mortality, preservation or restoration of independent ambulation, improved quality of life for the patient, and lower cost to the health care system. Although most patients require a single procedure to accomplish this, many will need minor amputations to remove distal necrotic or infected tissue to achieve a completely healed and functional extremity. This is especially true of diabetics, who have a lifetime risk of foot ulceration of 25%, with 50% of ulcers becoming infected.[154] Treatment of these patients requires both in-line pulsatile flow to the foot and wound débridement or minor amputation.[537]

Minor amputations. Minor amputations of the foot include digital and ray amputation of the toe, transmetatarsal amputation of the forefoot, and Lisfranc and Chopart amputations of the midfoot. Each of these