FEATURE ARTICLE

# Comprehensive Assessment of Current Management Strategies for Patients With Diabetes and Chronic Limb-Threatening Ischemia

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**Chronic limb-threatening ischemia (CLTI) is the most severe form of peripheral artery disease. It is estimated that 60% of all nontraumatic lower-extremity amputations performed annually in the United States are in patients with diabetes and CLTI. The consequences of this condition are extraordinary, with substantial patient morbidity and mortality and high socioeconomic costs. Strategies that optimize the success of arterial revascularization in this unique patient population can have a substantial public health impact and improve patient outcomes. This article provides an up-to-date comprehensive assessment of management strategies for patients afflicted by both diabetes and CLTI.**

More than 30 million Americans have diabetes and are presumably at higher risk of developing peripheral arterial disease (PAD) (1,2). Advanced PAD can manifest as chronic limb-threatening ischemia (CLTI), which is defined as limb pain at rest and/or the presence of ischemic ulceration or gangrene (3,4). CLTI affects ∼2 million Americans >40 years of age and is associated with higher risk of limb loss due to above-ankle (major) amputations (5–10). It is estimated that 60% of all nontraumatic lower-extremity amputations performed annually in the United States are in patients with diabetes and CLTI (11,12). These procedures are associated with substantial morbidity, considerable mortality, and high socioeconomic costs.

On a per-patient basis, the cost of treating CLTI in patients with diabetes is higher than the treatment of both coronary artery disease (CAD) and cerebrovascular disease (13–15). These increased costs are likely the result of higher rates of hospital admissions, procedures, and complications. CLTI and its significant financial burdens are anticipated to increase as the preva-lence of diabetes continues to increase globally from 450 million living with diabetes in 2017 to an estimated 700 million by 2045 (16).

Accordingly, strategies that optimize successful revascularization in patients with diabetes and CLTI can have a substantial public health impact and improve patient outcomes. Here, we review the medical and modern surgical management strategies for patients with diabetes and CLTI. We specifically reviewed studies with cohorts that were at least 50% patients with diabetes or CLTI, had subanalyses relevant for patients with diabetes or CLTI, and reported standard clinical outcomes relevant to patients with severe PAD.

## Medical Management

It is estimated that 50% of the mortality in patients with diabetes is caused by cardiovascular complications (17). Consequently, management of patients with diabetes and CLTI relies heavily on medical therapy to reduce cardiovascular morbidity and mortality. Here, we provide a brief overview of first-line and emerging medical therapies in patients with diabetes and CLTI.

Patients with poor glycemic control have lower rates of bypass patency after lower-extremity arterial bypass (18). Studies have shown that, in patients with diabetes

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and CLTI, A1C levels >6.8–8% are associated with major amputations (19,20). Similarly, adequate blood pressure management is essential for cardiovascular risk reduction in patients with diabetes and CLTI. A reduction in blood pressure to a mean of 128/75 mmHg was shown to significantly reduce cardiovascular events by almost 65% in patients with diabetes and PAD (21). A meta-analysis of 14 randomized controlled trials (RCTs) encompassing 18,686 patients with diabetes demonstrated that statins reduced all-cause and vascular mortality (22). It was deduced that there was a 21% reduction in major vascular events for every 1-mmol/L reduction of LDL cholesterol. A large observational study of 69,332 individuals with diabetes and PAD who received statin therapy found that this treatment reduced lower-extremity amputation and all-cause mortality rates (23). In another cohort study of 83,953 patients with diabetes in the Department of Veterans Affairs (VA) health care system, statin therapy was found to decrease the risk of major lower-extremity amputation (24).

Interestingly, the benefit of statins for limb salvage in patients with diabetes and CLTI is not well defined. A prospective multicenter German registry of 816 patients with CLTI (44–49% with diabetes) found that statin treatment lowered the hazard of death and improved the rate of amputation-free survival (AFS), but did not improve amputation rates when compared with no statin use (25). Another cohort registry of 2,067 patients with CLTI in New England (48% with diabetes) similarly found that statin use improved 5-year survival, but there was no difference in 1-year major amputation rates (26). However, a smaller cohort study of 380 patients with CLTI (61% with diabetes) found that statin treatment decreased the risks of both death and major amputation (27). The evidence for statin use in patients with CLTI and diabetes suggests that statins improve mortality but may not necessarily improve limb-related morbidity.

To compare the efficacy of statin intensity, a single-institution cohort study of 629 patients (53% with diabetes, 55% with CLTI) found that patients with CLTI on high-intensity statin therapy had significantly improved survival (47% lower hazard, $P = 0.004$) and reduced major adverse cardiovascular events (myocardial infarction [MI], cerebrovascular accident, or death) (42% lower hazard, $P = 0.02$) when compared with low- or moderate-intensity statin therapy (28). However, the study found no significant differences in AFS or major adverse limb events (MALE; defined as amputation or target lesion revascularization [TLR]).

Some studies showed that nonstatin lipid-lowering agents may demonstrate specific benefit in patients with diabetes. In the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) RCT, 9,795 patients with diabetes demonstrated a 1% absolute risk reduction in nonfatal MI and a 3.1% absolute reduction in coronary revascularization (29). Patients with diabetes who received fenofibrate were also significantly less likely to undergo below-ankle (minor) lower-extremity amputation, with a 0.5% absolute risk reduction over the 5-year study period (30). However, only 7% of participants in each arm had a history of peripheral vascular disease. In this context, the role of fenofibrate therapy in patients with diabetes and CLTI has yet to be determined.

Newer LDL cholesterol–lowering agents have yet to demonstrate clear benefit in patients with PAD. In the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) study, subgroup analysis of 3,642 patients with symptomatic PAD (43% with diabetes) found that PCSK9 inhibitor with background statin therapy lowered the absolute risk of composite cardiovascular death, MI, stroke, and MALE (defined as major amputation, urgent revascularization, or incidence of acute limb ischemia) by 4.1% when compared with statin therapy alone (31). However, when broken into components, there were no significant differences in all-cause death, MALE, or major amputation.

Several RCTs of bempedoic acid, a new oral agent that targets the LDL transport pathway upstream of statins, found that this drug lowered LDL cholesterol levels by 15–36% relative to placebo regardless of background statin therapy (32–37). Although the relative reduction in LDL cholesterol is comparable to that of ezetimibe, these trials were not designed to measure cardiovascular outcomes (38). An ongoing RCT comparing bempedoic acid with placebo in >14,000 participants, including patients with symptomatic PAD, is schedule to be completed in the near future (NCT02993406).

The American Heart Association recommends either aspirin or clopidogrel for patients with symptomatic PAD without increased risk of bleeding, regardless of their diabetes status (39). In a study of patients with intermittent claudication (76% with diabetes) randomized to receive aspirin, vitamins, both, or a placebo found that those who received any aspirin had a 7%

absolute risk reduction in major vascular events (MI, stroke, and pulmonary embolism) (40). A Swedish nationwide retrospective study evaluated dual antiplatelet therapy (DAPT) (aspirin and clopidogrel) in 1,941 patients with CLTI (44% with diabetes) (41). The study observed a lower rate of major amputation in patients who received endovascular stenting, patients with diabetes, and patients who received DAPT for ≥100 days. There was no difference in amputation risk for patients on DAPT who underwent angioplasty or for patients without diabetes. Alternative agents such as picotamide (a dual inhibitor of thromboxane $A_2$ synthase and the TX$A_2$ receptor) have demonstrated significantly reduced mortality in patients with diabetes and PAD when compared with aspirin alone (2.5% absolute risk reduction) (42). However, there was no difference in combined death and nonfatal vascular events (MI, stroke, and major amputation), suggesting reduction in mortality but not morbidity. Notably, 26% of the study participants in each arm discontinued their assigned medication, which reduced the power and increased the risk of confounding in this study.

Recently, two RCTs compared rivaroxaban to placebo with background aspirin therapy. The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial found that, when compared with aspirin alone, rivaroxaban with aspirin had a greater reduction in primary (cardiovascular death, MI, or stroke) and secondary (all-cause mortality or MALE) outcomes in patients with diabetes (43). Subgroup analysis of patients with PAD found that those randomized to combination therapy (rivaroxaban and aspirin) were less likely to experience MALE (1.1% absolute risk reduction) when compared with aspirin alone (44). Similarly, the VOYAGER-PAD (Vascular Outcomes Study of ASA [Acetylsalicylic Acid] Along With Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD [Peripheral Artery Disease]) trial found that, in patients with symptomatic PAD who underwent lower-extremity revascularization, rivaroxaban with aspirin reduced the rate of the primary end point (composite acute limb ischemia, major amputation, MI, ischemic stroke, or death from cardiovascular causes) by a 2.6% absolute difference at 3 years when compared with aspirin alone (45). Further analysis demonstrated that the primary end point findings were attributed to reduction in acute limb ischemia, whereas there was no difference in the rate of all-cause death.

In summary, studies continue to support optimization of blood glucose, blood pressure, and serum lipid levels in patients with diabetes and CLTI. Although lipid-lowering agents may not specifically improve limb outcomes, they continue to decrease overall cardiovascular morbidity and mortality. In patients with diabetes and CLTI who undergo revascularization, aspirin combination therapy with clopidogrel or direct oral anticoagulant may decrease the risk of MALE.

## Surgical Arterial Bypass

In addition to risk factor mitigation and medical optimization, management of CLTI in patients with diabetes often requires augmentation of arterial inflow to peripheral ischemic tissue. Suboptimal surgical revascularization in the setting of CLTI can lead to increased risk of ischemic wounds, gangrene, infection, and limb amputation in 50% of patients within 2 years (46). Patients with diabetes are at particularly high risk of ischemic complications because they often present with densely calcified atherosclerotic occlusive disease afflicting the infrageniculate tibial vessels of the lower leg (47,48). Thus, surgical management of patients with diabetes and CLTI is a truly important challenge in clinical practice.

Multiple studies have evaluated the efficacy of surgical lower-extremity arterial bypass in patients with diabetes and CLTI and found similar limb outcomes when compared with patients without diabetes (Table 1). A retrospective study of infrainguinal arterial reconstruction performed in 1,310 patients with CLTI (49% with diabetes) demonstrated that, despite patients with diabetes presenting at a younger age, with more comorbidities, and with more severe symptoms of ischemia, they have equivalent rates of AFS, overall survival, major amputation, and arterial bypass graft patency at the 5- and 10-year follow-up when compared with patients without diabetes (49). Similarly, a review of 211 patients with CLTI (45% with diabetes) demonstrated that, although patients with diabetes had a decreased rate of 1-year survival, they had nearly identical rates of limb salvage (freedom from any amputation) and arterial bypass graft patency when compared with patients without diabetes (50). A prospective audit of 265 infrainguinal bypass procedures in patients with CLTI (66% with diabetes) also observed no significant difference in graft failure, wound infection, or limb loss between patients with and without diabetes but observed significantly higher hospital mortality and lower 5-year survival rates among patients with diabetes (hospital mortality 8 vs. 1%, $P = 0.04$; 5-year survival 33 vs. 43%, $P = 0.03$) (51).

**TABLE 1** Infrainguinal Surgical Arterial Bypass

| Study | Study Type | *N* | With Diabetes, % | With CLTI, %* | With Diabetes, *n* | Without Diabetes, *n* | Major Outcomes | |
|---|---|---|---|---|---|---|---|---|
| Ballotta et al., 2014 (49) | Retrospective | 1,310 | 49 | 100 | 643 | 667 | AFS 5 y 45.5 vs. 51% ($P$ = 0.19) | OS 5 y 51 vs. 57% ($P$ = 0.41) |
| Wölfle et al., 2003 (50) | Retrospective | 211 | 45 | 100 | 94 | 117 | FF-amputation 1 y 85 vs. 83% ($P$ = 0.76) | Mortality 1 y 22 vs. 5% ($P$ <0.01) |
| AhChong et al., 2004 (51) | Prospective | 265 | 66 | 100 | 176 | 89 | FF-amputation 5 y 78 vs. 81% ($P$ = 0.79) | OS 5 y 33 vs. 43% ($P$ = 0.03) |
| Calle-Pascual et al., 2001 (52) | Prospective | 481 | 36 | – | 174 | 307 | FF-amputation 3 y Fem-pop 49.2 vs. 89.7% ($P$ <0.01) Fem-distal 73.5 vs. 95.2% ($P$ <0.01) | OS 3 y Fem-pop 97.2 vs. 90.3% ($P$ NR) Fem-distal 82.1 vs. 96.3% ($P$ <0.05) |
| Feinglass et al., 2001 (53) | Prospective | 4,288 | 40 | 63 | 1,711 | 2,577 | AFS 5 y for patients with diabetes RR 1.4 ($P$ <0.01) | AFS 5 y for patients with CLTI RR 1.2 ($P$ <0.01) |
| Singh et al., 2008 (54) | Prospective | 14,788 | 44 | – | 6,550 | 8,238 | Graft failure 30 d OR 0.72 (95% CI 0.58–0.89) | – |

*CLTI includes Rutherford classes 4–6 and Fontaine stages III–IV. d, day(s); Fem-distal, femoral to tibial, peroneal, or pedal bypass; Fem-pop, femoral to popliteal artery bypass; FF-amputation, freedom from amputation; m, months(s); NR, not reported; OS, overall survival; RR, relative risk; y, year(s).

In contrast, other studies have shown that patients with diabetes clearly demonstrate worse arterial graft patency and higher rates of limb loss compared with patients without diabetes (Table 1). A prospective study of 481 patients (36% with diabetes; no Rutherford class breakdown) demonstrated that femoral to distal arterial bypasses (to tibial or pedal arteries) were more often necessary in patients with diabetes and that, at 3 years, patients with diabetes were more likely to have lower rates of limb salvage and survival after femoral to distal arterial bypass (52). Similarly, a review of the VA National Surgical Quality Improvement Program (NSQIP) involving 105 VA hospitals demonstrated that, over a 4-year period, patients with diabetes were 1.5 times more likely to die or undergo subsequent limb amputation after arterial bypass procedures (53). Interestingly, a more recent VA NSQIP study involving 123 VA hospitals found that patients with diabetes had a 28% lower chance of early arterial graft failure compared with patients without diabetes (54).

Overall, these studies suggest that lower-extremity arterial bypasses in CLTI patients with or without diabetes may have comparable arterial graft patency and rates of amputation. However, patients with diabetes still experience lower overall survival. The factors contributing to this discrepancy in limb revascularization outcomes in patients with diabetes after arterial bypass are broad and may include differences in the types of outcome measures evaluated in each study, quality and caliber of conduits used, length of arterial bypass, markers of disease severity, and optimization of postoperative management (55–59). Furthermore, survival rates between patients with and without diabetes are particularly challenging to assess because of the competing risk of death associated with complications of diabetes. Thus, comparison of those who are alive at 5 and 10 years with a functional limb can be difficult. Accordingly, the Global Vascular Guidelines have instead recommended using MALE-free survival or AFS along with other objective (hemodynamic changes) or subjective (quality of life) clinical end points to augment outcome measures for patients with diabetes and CLTI enrolled in future clinical studies (3).

## Endovascular Therapy

### *Superficial Femoral Artery and Proximal Popliteal Artery Interventions*

Over the past two decades, there has been wide adoption of endovascular techniques for the treatment of CLTI. The minimally invasive nature of these interventions has dramatically altered the treatment landscape for individuals with CLTI, but recent results have questioned the durability of these interventions and their effectiveness in individuals with diabetes (Table 2).

The BASIL (Bypass Versus Angioplasty in Severe Ischemia of the Leg) trial was an intention-to-treat RCT that compared outcomes between patients undergoing percutaneous transluminal angioplasty (PTA) first and those undergoing bypass surgery first for treatment of patients with CLTI. In 452 patients (42% with diabetes), no significant difference was initially observed in AFS at 2 years, but among those who survived beyond 2 years, the group having arterial bypass first appeared to have improved AFS and overall survival rates (60,61). These data suggest that, although PTA was associated with lower 1-year hospitalization costs, it was less durable beyond 2 years. On the other hand, a retrospective review of 150 patients (73% with diabetes) observed that, at 1 and 3 years, AFS and overall survival rates were not significantly different between patients who received lower-extremity angioplasty first compared with those who underwent surgical bypass first (62). Further analysis suggested that PTA was still a reasonable first choice in high-risk individuals with CLTI (i.e., those >80 years of age or who have a history of CAD, congestive heart failure, or a nonambulatory limb).

Since these studies, peripheral endovascular treatment technology has significantly progressed, particularly for the treatment of superficial femoral artery (SFA)–proximal popliteal artery (PPA) obstructions. An example of this progress is the explosion in bare-metal stents (BMS) technologies and the U.S. Food and Drug Administration (FDA) approvals for SFA only (Zilver, Cook Medical), SFA with PPA (Everflex, Medtronic and Supera, Abbott), and SFA with full popliteal artery (LifeStent, Bard).

In 2007, a multidisciplinary vascular group (VIVA Physicians) proposed objective clinical end points for BMS (63). The group analyzed patient-level data from three industry-sponsored pre-market approval PTA trials and then compared these data with data from 11 RCTs from a literature review. They found that the aggregate vessel patency (defined as freedom from >50% stenosis based on duplex ultrasound) with PTA was 33% at 12 months. Thus, the study recommended that the objective end point for BMS should be set to at least twice that rate, or 66% 1-year patency, for future BMS studies. Notably, this study's analysis only included a small proportion of patients with CLTI, with

**TABLE 2** Interventions for SFA and PPA Lesions

| Study | *N* | With Diabetes, % | With CLTI, %* | Intervention, *n* (% With Diabetes) | Control, *n* (% With Diabetes) | Major Outcomes | |
|---|---|---|---|---|---|---|---|
| *RCTs* | | | | | | | |
| Bradbury et al., 2010 (61) | 452 | 42 | – | Bypass first, 228 (42) | PTA first, 224 (42) | AFS >2 y HR 0.85 (95% CI 0.50–1.07) | OS >2 y HR 0.61 (95% CI 0.50–0.75) |
| Saxon et al., 2008 (72) | 197 | 35 | 11 | PTA + stent-graft, 97 (37) | PTA, 100 (34) | †Patency 1 y 65 vs. 40% (*P* <0.05) | Mortality 1 y 1 vs. 2% (*P* NR) |
| Geraghty et al., 2013 (73) | 148 | 44 | – | Stent-graft, 72 (43) | BMS, 76 (45) | †Patency 3 y 24.2 vs. 25.9% (*P* = 0.39) | Mortality 3 y 12.5 v 3.9% (*P* NR) |
| McQuade et al., 2010 (74) | 86 | 40 | 28 | PTA + stent-graft, 40 (35) | Bypass, 46 (44) | Patency 4 y 59 vs. 58% (*P* = 0.8) | Mortality 4 y 18 vs. 16% (*P* NR) |
| Bosiers et al., 2015 (75) | 83 | 35 | 15 | Heparin-bonded stent-graft, 39 (33) | PTA, 44 (36) | †Patency 1 y 75 vs. 28% (*P* <0.01) | OS 1 y 91.9 vs. 95.3% (*P* = 0.38) |
| Lammer et al., 2013 (76), and Lammer et al., 2015 (77) | 141 | 35 | 8.5 | Heparin-bonded stent-graft, 72 (35) | BMS, 69 (36) | †Patency 1 y 71 vs. 55% (*P* = 0.11) Patency 2 y 69.3 vs. 40% (*P* <0.01) | Mortality 30 d none FF-TLR 2 y 79.4 vs. 73% (*P* = 0.37) |
| Schillinger et al., 2006 (64) | 104 | 38 | 12 | BMS, 51 (43) | PTA, 53 (32) | †Restenosis 6 m 24 vs. 4% (*P* = 0.05) 1 y 37 vs. 63% (*P* = 0.01) | Mortality 1 y 2 vs. 0% (*P* NR) |
| Laird et al., 2010 (67), and Laird et al., 2012 (68) | 206 | 38 | 0 | PTA + BMS, 134 (38) | PTA, 72 (39) | Patency 1 y 81.3 vs. 36.7% (*P* <0.01) OS 3 y 90 vs. 91.7% (*P* = 0.71) | *FF-TLR 1 y 87.3 vs. 45.2% (*P* <0.01) FF-TLR 3 y 75.5 vs. 41.8% (*P* <0.01) |
| *Prospective studies* | | | | | | | |
| Bosiers et al., 2011 (65) | 100 | 27 | 29 | BMS (200 mm), 100 (27) | – | †Patency 1 y 64.8% | Mortality 30 d 1% |
| Bosiers et al., 2009 (70) | 151 | 46 | 12.6 | BMS, 151 (46) | – | FF-restenosis 1 y 72.2% | Mortality 1 y 5.96% |
| Rocha-Singh et al., 2015 (71) | 287 | 43 | 4.9 | BMS, 287 (43) | – | †FF-restenosis 1 y 77.9%, 2 y 66.1%, 3 y 60% | Mortality 3 y 9.06% |

*Continued on p. 364 »*

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**TABLE 2** Interventions for SFA and PPA Lesions *(continued)*

| Study | *N* | With Diabetes, % | With CLTI, %* | Intervention, *n* (% With Diabetes) | Control, *n* (% With Diabetes) | Major Outcomes |
|---|---|---|---|---|---|---|
| *Retrospective studies* | | | | | | |
| Ohmine et al., 2015 (62) | 150 | 73 | 100 | Endovascular therapy first, 102 (77) | Bypass first, 48 (69) | AFS 1 y 71.7 vs. 79.5% (*P* NR) |
| | | | | | | OS 1 y 73.5 vs. 83.9% (*P* NR) |
| Rocha-Singh et al., 2007 (63) | 319 | 38 | <16 | PTA, 319 (38) | – | Patency 1 y 33% |
| | | | | | | Mortality 30 d 0.9% |
| Montero-Baker et al., 2016 (66) | 147 | 62 | 67 | BMS, 147 (62) | – | Patency 1 y 89.8% |
| | | | | | | Mortality 2 y 11.6% |
| Zeller et al., 2008 (69) | 110 | 43 | 1 | BMS, 110 (43) | – | †Restenosis 1 y 23.3% |
| | | | | | | Mortality 1 y 6.4% |

*CLTI includes Rutherford classes 4–6 and Fontaine stages III–IV. †Study primary end point. d, day(s); FF-restenosis, freedom from restenosis; FF-TLR, freedom from TLR; m, month(s); NR, not reported; OS, overall survival; y, year(s).

<16% of patient-level studies including patients with CLTI Rutherford class 4 or above, and a minority of patients (37%) with diabetes. Since then, the Global Vascular Guidelines have recommended additional objective end points such as hemodynamic changes (ankle and toe pressures) and subjective end points such as quality of life, in addition to clinical outcomes (AFS, MALE, or single end points), but have not defined or specified patency as an outcome measure (3).

The first RCT comparing BMS versus PTA alone found that, in 104 patients with SFA stenosis or occlusion (38% with diabetes), there was no significant difference in patency at 6 months (64) (Table 2). However, at 12 months, the BMS group had significantly higher patency when compared with PTA. Notably, this study excluded patients with CLTI who had evidence of tissue loss (Rutherford class 5–6), and only 12% of the participants had ischemic rest pain (Rutherford class 4).

After this study, several industry-sponsored trials evaluated BMS treatment of SFA obstructions, but only a minority of these studies adequately stratified outcomes relative to patients with diabetes and CLTI. A single-arm study of BMS (EverFlex, EV3/Medtronic) for long femoropopliteal arterial lesions (mean length 24 cm) in 100 patients (27% with diabetes, 29% with CLTI) observed no difference in primary patency at 12 months in patients with or without diabetes (65). Another single-arm study with a newer-generation biomimetic BMS (Supera, Abbott) observed that, in 147 patients (63% with diabetes, 67% with CLTI), the overall 12-month patency was almost 90% (66). However, although the study suggested higher rates of stent patency when compared with earlier first- and second-generation stent designs, there remains a lack of robust RCTs evaluating BMS outcomes in patients with diabetes and CLTI (67–71). Therefore, BMS patency and limb salvage outcomes between older- and newer-generation stents in patients with diabetes and CLTI remain unclear, and further assessment of these technologies is needed in this high-risk cohort.

Peripheral stent-graft technology using a nitinol stent covered with expanded polytetrafluoroethylene (PTFE) is another option for the treatment of femoropopliteal artery disease. In a pre-market RCT of 197 patients (35% with diabetes, 11% with CLTI), peripheral stent-grafts showed higher primary patency at 12 months compared with PTA alone (72) (Table 2). A corresponding RCT comparing stent-grafts with BMS in 148 patients (44% with diabetes, no breakdown of CLTI Rutherford class 1–5), all with long-segment obstructions in the femoropopliteal artery

(mean length 19 cm), observed no significant difference in 3-year primary patency (73). Similarly, another RCT comparing stent-grafts with open surgical bypass in 86 patients (40% with diabetes who were not separated by CLTI Rutherford class 1–6) found no significant difference in primary patency at 1 and 4 years between stent-graft and open bypass (74). Evidently, the open surgery group had more than twice the number of limbs classified as Rutherford class 4–6 (among entire study cohort) and 42% more patients with diabetes. This notable difference in distribution of patients with diabetes and CLTI between study arms raises concern for selection bias and overestimation of stent-graft patency. Overall, these studies suggest that stent-grafts have higher patency rates compared with PTA alone and similar patency when compared with BMS and surgical bypass. However, these stent-graft studies were not adequately powered to evaluate outcomes in patients with diabetes and CLTI and did not report outcomes for this specific patient cohort.

Studies have also evaluated the efficacy of heparin-bonded stent-grafts for patients with femoropopliteal artery occlusive disease (Table 2). The RELINE (Gore Viabahn Versus Plain Old Balloon Angioplasty for Superficial Femoral Artery In-Stent Restenosis) study evaluated heparin-bonded stent-grafts against PTA alone in 83 patients (35% with diabetes, 15% with CLTI Rutherford class 4–5) and observed higher 1-year primary patency in the heparin-bonded stent-graft cohort (75). The VIASTAR (Viabahn Endoprosthesis With Propaten Bioactive Surface Versus Bare Nitinol Stent in the Treatment of Long Lesions in Superficial Femoral Artery Occlusive Disease) trial compared a similar heparin-bonded stent-graft with BMS in 141 patients (35% with diabetes, 16% with CLTI) and found that there was no significant difference in primary patency at 1 year, but the heparin-bonded stent-graft group had a 29% relative higher primary patency at 2 years (76,77). However, the VIASTAR study showed no significant difference in primary end point of freedom from TLR at 1 year. Both RELINE and VIASTAR studies suggest superior 1- and 2-year patency with heparin-bonded stent-grafting but most patients treated in these trials did not have CLTI or diabetes. Thus, it remains to be determined whether heparin-bonded or PTFE stent-grafts improve outcomes in patients with diabetes and CLTI.

Despite the large number of studies evaluating endovascular therapy for PAD, only a minority of these studies have focused on patients with diabetes and CLTI, arguably the cohort with the highest risk of morbidity and mortality. Extrapolating current evidence to this high-risk cohort is challenging considering the small number of study participants with diabetes and CLTI who were recruited for these studies. This disparity supports the urgent need for more evidence-based research specifically exploring endovascular management techniques in patients with diabetes and CLTI.

## SFA Drug-Eluting Devices

In recent years, the use of peripheral arterial drug-eluting technology (drug-eluting stents [DES] and drug-coated balloons [DCB]) has become a matter of scrutiny and debate (78–83). These platforms were designed with the primary purpose of eluting a cytotoxic agent to the arterial intima and media to inhibit severe intimal hyperplasia in response to peripheral arterial stents or balloons (84–87).

The Zilver PTX study was among the first RCTs to evaluate the efficacy of paclitaxel DES in patients undergoing peripheral intervention for short segment (<8 cm) femoropopliteal artery occlusive disease (88,89) (Table 3). The study enrolled 474 patients (46% with diabetes, 8% with CLTI) and compared outcomes of paclitaxel DES with PTA ± secondary BMS. The study found that paclitaxel DES had higher primary patency compared with PTA alone at 1 year (83.1 vs. 32.8%, $P < 0.001$) and 5 years (66.4 vs. 43.4%, $P < 0.01$). When compared with a secondary BMS cohort who had failed the initial PTA-only treatment, the study also found higher primary patency in the paclitaxel DES group at 1 year (89.9 vs. 73%, $P < 0.01$) and 5 years (72.4 vs. 53%, $P = 0.03$). In addition, paclitaxel DES had superior 1-year event-free survival (defined as freedom from death, amputation, or reintervention) when compared with PTA (90.4 vs. 82.6%, $P = 0.004$), but at 5 years, all-cause mortality was significantly higher in the paclitaxel DES group (16.9 vs. 10.2%, $P = 0.03$) with no difference in 5-year thrombosis or occlusion rates between groups (90). The Zilver PTX study suggests a short-term clinical benefit in patients without CLTI and increased risk of long-term mortality with equivalent long-term patency when compared with PTA.

A single-arm study of 57 patients (35% with diabetes, 4% with CLTI) who were treated with the Eluvia paclitaxel DES reported a 2-year primary patency of 76.5% for patients with diabetes and a 3-year freedom from TLR of 82.5% (91). There was no difference in outcomes between patients with or without diabetes, with overall cohort primary patency at 83.5% and TLR at 85.3% over the same study period. Another study of 465 patients compared Zilver PTX system (42% with

**TABLE 3** Drug-Eluting Devices for SFA Lesions

| Study | *N* | With Diabetes, % | With CLTI, %* | Intervention, *n* (% With Diabetes) | Control, *n* (% With CLTI) | Major Outcomes | |
|---|---|---|---|---|---|---|---|
| *RCTs* | | | | | | | |
| Dake et al., 2011 (88), and Dake et al., 2016 (89,90) | 474 | 46 | 8 | Paclitaxel DES, 236 (49) | PTA, 238 (42) | †Patency 1 y 83.1 vs. 32.8% ($P$ <0.01)<br>Patency 5 y 66.4 vs. 43.4% ($P$ <0.01) | Mortality 1 y 3.8 vs. 1.7% ($P$ = 0.17)<br>Mortality 5 y 16.9 vs. 10.2 ($P$ = 0.03) |
| Gray et al., 2018 (92) | 465 | 42 | <10 | Eluvia DES, 309 (42) | Zilver DES, 156 (44) | †Patency 1 y 87 vs. 77.6% ($P$ <0.05) | Mortality 1 y 2.1 vs. 4% ($P$ = 0.23) |
| Rosenfield et al., 2015 (96) | 476 | 43 | 8 | Paclitaxel DCB, 316 (43) | PTA, 160 (42) | †Patency 1 y 65.2 vs. 52.6% ($P$ = 0.02) | Mortality 1 y 2.4 vs. 2.8% ($P$ = 0.82) |
| Tepe et al., 2015 (97), Laird et al., 2015 (98), Schneider et al., 2018 (99), and Laird et al., 2019 (100) | 331 | 43 | 5 | Paclitaxel DCB, 220 (40) | PTA, 111 (49) | †Patency 1 y 88.2 vs. 52.4% ($P$ <0.01)<br>Patency 2 y 78.9 vs. 50.1% ($P$ <0.01)<br>Patency 3 y 69.5 vs. 45.1% ($P$ <0.01)<br>TLR 5 y 25.5 vs. 34.7% ($P$ = 0.02) | –<br>Mortality 2 y 8.1 vs. 0.9% ($P$ <0.01)<br>Mortality 3 y 10.7 vs. 1.9% ($P$ <0.01)<br>Mortality 5 y 14.6 vs. 10.2% ($P$ = 0.2) |
| Tepe et al., 2020 (101) | 88 | 44 | 9 | Paclitaxel DCB, 47 (43) | PTA, 41 (46) | TLR 2 y 52 vs. 75% ($P$ = 0.1) | Mortality 6 m 8 vs. 9% ($P$ = 0.9) |
| *Randomized registry* | | | | | | | |
| Nordanstig et al., 2020 (109) | 2,289 | 45 | 65 | Paclitaxel devices, 1,149 (46) | Uncoated devices, 1,140 (45) | Mortality 2.5 y HR 1.06 (95% CI 0.92–1.22) | – |
| *Prospective studies* | | | | | | | |
| Müller-Hülsbeck et al., 2017 (91) | 57 | 35 | 4 | Eluvia DES, 57 (35) | – | Patency 2 y for patients with diabetes 76.5% | TLR 3 y for patients with diabetes 82.5% |
| Micari et al., 2012 (93), and Micari et al., 2013 (94) | 105 | 49 | 8 | Paclitaxel DCB, 105 (49) | – | †Patency 1 y 83.7%<br>Patency 2 y 72.4% | Mortality 1 y 2.2%<br>Mortality 2 y 2.2% |
| Scheinert et al., 2018 (95) | 157 | 41 | 17 | Paclitaxel DCB, 157 (41) | – | †Patency 1 y 91.1% | Mortality 1 y 4.5% |

*Continued on p. 367 »*

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**TABLE 3** Drug-Eluting Devices for SFA Lesions *(continued)*

| Study | *N* | With Diabetes, % | With CLTI, %* | Intervention, *n* (% With Diabetes) | Control, *n* (% With CLTI) | Major Outcomes | |
|---|---|---|---|---|---|---|---|
| Grotti et al., 2016 (102) | 86 | 100 | 70 | DCB, 44 (100) | PTA, 42 (100) | TLR 3 y 40 vs. 43% (*P* = 0.8) | Mortality 3 y 20 vs. 21% (*P* = 1.0) |
| *Retrospective studies* | | | | | | | |
| Bertges et al., 2020 (103)<br><br><br><br> | 2,976<br>1,196 | 61<br>53 | 34<br>50 | Paclitaxel DCB, 1,488 (61)<br>Paclitaxel DES, 598 (53) | PTA, 1,488 (61)<br>BMS, 598 (53) | Mortality 15 m<br>HR 0.84 (95% CI 0.66–1.06)<br>Mortality 15 m<br>HR 0.93 (95% CI 0.62–1.41) | –<br>– |
| Secemsky et al., 2019 (105) | 16,560 | 59 | 51 | Drug-coated devices, 5,989 (61) | Uncoated devices, 10,571 (58) | Mortality 1 y<br>HR 0.97 (95% CI 0.91–1.04) | – |
| Secemsky et al., 2019 (106) | 51,456 | 39 | 60 | DES, 4,105 (NR) | BMS, 4,7351 (NR) | Mortality 2 y 51.7 vs 50.1% (*P* = 0.16) | – |
| *Meta-analyses* | | | | | | | |
| Kastanos et al., 2018 (78) | 4,663 | 21–77 | 11 | Paclitaxel devices, 2,552 (44) | Uncoated devices, 2,006 (42) | Mortality 1 y<br>RR 1.08 (95% CI 0.72–1.61)<br>Mortality 2 y<br>RR 1.68 (95% CI 1.15–2.47) | Mortality 5 y<br>RR 1.93 (95% CI 1.27–2.93) |
| Schneider et al., 2019 (104) | 855 | 43 | 7 | Paclitaxel DCB, 712 (41) | PTA 143 (50) | TLR 5 y<br>HR 0.51 (95% CI 0.36–0.72)<br>Mortality 3 y<br>HR 3.76 (95% CI 1.22–11.55) | Mortality 5 y<br>HR 1.52 (95% CI 0.82–2.82) |
| Dinh et al., 2020 (107) | 1,450 | 30–95 | 94 | Paclitaxel devices, 866 (NR) | Uncoated devices, 584 (NR) | Mortality 1 y<br>RR 1.07 (95% CI 0.74–1.52) | Mortality 5 y<br>RR 0.91 (95% CI 0.75–1.10) |
| Rocha-Singh et al., 2020 (108) | 2,185 | 37–58 | 6 | Paclitaxel devices, 1,382 (NR) | Uncoated devices, 803 (NR) | – | Mortality 5 y<br>HR 1.38 (95% CI 1.06–1.80) |

*CLTI includes Rutherford classes 4–6 and Fontaine stages III–IV. †Study primary end point. m, month(s); NR, not reported; RR, relative risk; y, year(s).

diabetes, <10% with CLTI Rutherford class 4) with the Eluvia paclitaxel DES system (42% with diabetes, <5% with CLTI Rutherford class 4) and observed higher 1-year primary patency with the Eluvia paclitaxel DES (87 vs. 77.6%, $P < 0.05$) (92). These studies suggest that short-term primary patency of paclitaxel DES in patients with diabetes is comparable to that in patients without diabetes. However, longer-term data evaluating femoropopliteal patency between patients with and without diabetes remain underreported, and there is currently very limited evidence to extrapolate outcomes to patients with CLTI.

Similar challenges also apply to the interpretation of paclitaxel DCB data, for which the vast majority of trials evaluating efficacy of paclitaxel DCB include a minority of patients with diabetes, and participants with CLTI largely in Rutherford classes 2–3 (93–101) (Table 3). One study of 86 patients with diabetes comparing paclitaxel DCB (77% with CLTI) with PTA (67% with CLTI) found that there was no significant difference in TLR, major amputation, or all-cause death at 3 years (102). Another study of 331 patients (43% with diabetes, 5% with CLTI Rutherford class 4) stratified outcomes between paclitaxel DCB and standard PTA by presence of diabetes (98–100). The study observed that, at 5 years, freedom from TLR in patients with diabetes was equivalent between paclitaxel DCB and standard PTA (70.3 vs. 64.4%, $P = 0.24$). However, in the cohort without diabetes, 5-year freedom from TLR was superior in the paclitaxel DCB group (77.1 vs. 66.3%, $P = 0.046$). Further subgroup analysis of patients with CLTI Rutherford class 4 showed that paclitaxel DCB had superior freedom from TLR at 5 years when compared with standard PTA (68.2 vs. 16.7%, $P = 0.047$). Overall, no significant differences in 5-year major amputation or all-cause mortality were reported (15.8 paclitaxel DCB vs. 9.6% PTA, $P = 0.156$), but at 2 and 3 years, the paclitaxel DCB group had significantly higher all-cause mortality when compared with PTA (at 2 years, 8.1 vs. 0.9%, $P = 0.008$, and at 3 years, 10.7 vs. 1.9%, $P = 0.006$). The observed discrepancy could have been the result of the high rate of censoring (withdrawal), which was 16% in the paclitaxel DCB group and 12% in the PTA group over the years. Nonetheless, these studies provide a rare glimpse of potential equivalence in long-term patency between paclitaxel DCB and PTA in patients with diabetes and may suggest greater benefit of paclitaxel DCB in patients without diabetes. Patients with ischemic rest pain (Rutherford class 4) appear to respond to paclitaxel DCB in a manner similar to those with moderate to severe PAD (Rutherford class ≤3).

Although additional studies are needed to determine whether patients with diabetes and/or CLTI benefit from paclitaxel-eluting devices, recent studies on long-term mortality may instead pivot discussion to short-term benefit for patients with limited life expectancy such as patients with diabetes and end-stage CLTI. Katsanos et al. (78) in 2018 first reported an aggregate meta-analysis of 28 RCTs comparing paclitaxel-eluting devices with nonpaclitaxel devices for femoropopliteal artery and found that, in 4,663 patients (11% with CLTI), all-cause mortality at 2 and 5 years was significantly higher with paclitaxel-eluting devices compared with nonpaclitaxel devices (increased risk of 68% at 2 years and 93% at 5 years) (Table 3). The study further found that, on meta-regression, there was a significant positive association between paclitaxel dose over time and absolute risk of death. However, the study acknowledged heterogeneity in patient demographics (diabetes status differed between studies, ranging from 21 to 77%) that could not be examined because of a lack of patient-level data.

Several studies followed on the heels of the analysis by Katsanos et al. (Table 3). A retrospective, propensity-matched analysis of the Society for Vascular Surgery Vascular Quality Initiative database of 4,172 patients found no significant difference in 1-year mortality between paclitaxel DCB ($n = 1,488$) and PTA ($n = 1,488$) (overall 61% with diabetes, 34% with CLTI) or between paclitaxel DES ($n = 598$) and BMS ($n = 598$) (overall 53% with diabetes; 50% with CLTI) (103). Interestingly, when patients were classified into two overall cohorts (paclitaxel devices vs. nonpaclitaxel devices), the paclitaxel cohort had a lower 1-year mortality rate when compared with the nonpaclitaxel cohort (8.5 vs. 11.5%, $P = 0.03$). Subgroup analysis of patients with CLTI showed no difference in mortality between the paclitaxel and nonpaclitaxel cohorts, but in patients with CLTI Rutherford class ≤3, the paclitaxel cohort had a lower rate of mortality (1.6 vs. 4.4%, $P = 0.01$). Contrary to the meta-analysis by Katsanos et al., these data suggest a 1-year mortality benefit with paclitaxel devices, occurring mainly in patients without CLTI.

A meta-analysis of patient-level data from two single-arm studies and two RCTs (712 paclitaxel DCB with 41% diabetes and 143 PTA with 50% diabetes) found that paclitaxel DCB had a significantly higher 3-year mortality when compared with PTA (hazard ratio [HR]

3.76, 95% CI 1.22–11.55) (104). Beyond 3 years, there was no longer any significant difference in mortality between paclitaxel DCB and PTA, but this was largely because the analysis included only one study that had follow-up beyond 3 years. Notably, there were few patients with CLTI (7.7% in paclitaxel DCB and 5.6% in PTA), and there was a large ratio disparity between study arms (5:1 DCB to PTA).

Another study using Centers for Medicare & Medicaid Services (CMS) data compared drug-coated devices with uncoated devices in 16,560 patients (59% with diabetes, 51% with CLTI) who received treatment between 1 January and 31 December 2016 (105). After adjusting for patient and hospital characteristics, the study found that drug-coated devices were not associated with all-cause mortality at a median follow-up of 389 days. Subgroup analysis similarly found no significant mortality differences between patients with or without CLTI. A larger CMS study with 51,456 patients comparing paclitaxel DES with BMS (39% with diabetes, 60% with CLTI) found that, at a median follow-up of 2 years, there was no difference in mortality (106). Likewise, the study found no mortality difference in patients with or without CLTI. Although these large studies using real-world data suggest that drug-coated devices are not associated with short-term (1- to 2-year) mortality in patients with or without CLTI, they do not address the potential long-term mortality associated with paclitaxel devices.

Looking specifically at patients with CLTI, an aggregate meta-analysis of 11 RCTs with 1,450 patients (94% with CLTI) comparing infrainguinal (including infrapopliteal) paclitaxel-coated devices ($n = 866$) with uncoated devices ($n = 584$) found no significant difference in all-cause mortality at 1 year (10 RCTs), 2 years (three studies), 3 years (two studies), or 5 years (three studies) (107).

In contrast, a meta-analysis that was presented at the FDA panel meeting convened to review mortality data on paclitaxel devices used patient-level data from eight RCTs involving products of four of the five manufacturers of FDA-approved paclitaxel-coated devices. It found an absolute increase of 4.6% in all-cause mortality at a median follow-up of 4 years for paclitaxel devices (18.3%) when compared with nonpaclitaxel devices (13.7%) (HR 1.38, 95% CI 1.06–1.80) (108). The increased mortality risk associated with paclitaxel devices was consistent when analyzed with primary intention-to-treat, as-treated, and adjusted analyses. Subgroup analyses revealed that patients with or without diabetes and patients with or without CLTI had similarly increased risks of mortality. Notably, only 6% of the total 2,185 patients had CLTI, whereas diabetes status ranged from 37 to 58% among studies. Although it did not find correlation between drug dosage and mortality—leaving the mechanism of mortality unclear—this meta-analysis using individual participant data are the most comprehensive and robust to date and suggests that paclitaxel devices are associated with an increased absolute long-term mortality risk across patients with or without diabetes and/or CLTI.

Overall, current data show that, in studies in which <10% of patients have CLTI and <45% of patients have diabetes, treatment of SFA and PPA lesions with paclitaxel-coated devices provided increased patency up to 5 years. However, in the same cohort, there is an observed higher mortality beyond 3 years. Whether the increased risk of mortality is associated with paclitaxel-coated devices remains inconclusive. For patients with diabetes and CLTI, data remain relatively sparse. A recent unplanned interim analysis of a Swedish open-label, registry-based clinical trial involving 2,289 patients (45% with diabetes, 65% with CLTI) randomly assigned to paclitaxel-coated or uncoated devices showed no difference in the incidence of death during the first 4 years after implantation (109). However, the study included cohorts with femoropopliteal and infrapopliteal lesions, and no subgroup analyses were reported. Therefore, it remains unclear whether paclitaxel-coated devices for SFA and PPA lesions in patients with diabetes and CLTI definitively improve outcomes. While long-term safety data are being collected, the FDA currently recommends judicious use of paclitaxel-coated devices (81).

### *Infrapopliteal Revascularization*

Patients with diabetes and CLTI are more likely to present with infrapopliteal tibial artery stenosis and occlusions (110,111). In a retrospective study of 163 patients with CLTI (77.3% with diabetes), infrapopliteal revascularization with PTA demonstrated 1- and 2-year patency rates of 53 and 51%, respectively (112) (Table 4). Composite freedom from restenosis, reintervention, or major amputation was 39% at 1 year and 35% at 2 years. Outcomes were observed to be worse when stratified by TransAtlantic InterSociety Consensus (TASC) classification, which demonstrated that, although overall restenosis and reintervention rates were high (>60%) for infrapopliteal PTA, patients with TASC D (occlusion >2 cm long or diffusely diseased lesions) fared worse compared with other TASC classes.

**TABLE 4** Interventions for Infrapopliteal Lesions

| Study | *N* | With Diabetes, % | With CLTI, %* | Intervention, *n* (% With Diabetes) | Control, *n* (% With Diabetes) | Major Outcomes (%) | |
|---|---|---|---|---|---|---|---|
| *RCTs* | | | | | | | |
| Liistro et al., 2013 (118) | 132 | 100 | 100 | DCB, 65 (100) | PTA, 67 (100) | TLR 1 y 18 vs. 43% (*P* <0.01) | Mortality 1 y 7.7 vs. 4.5% (*P* = 0.4) |
| Zeller et al., 2014 (119) | 358 | 73 | 100 | Paclitaxel DCB, 239 (76) | PTA, 119 (69) | †TLR 1 y 9.2 vs. 13.1% (*P* = 0.29) | Mortality 1 y 10.1 vs. 8.1% (*P* = 0.55) |
| Zeller et al., 2015 (120) | 72 | 67 | 78 | DCB, 36 (61) | PTA, 36 (72) | TLR 1 y 34.9 vs. 30% (*P* = 0.8) | Mortality 1 y 9.4 vs. 6% (*P* = 0.58) |
| Mustapha et al., 2019 (121) | 442 | 70 | 90 | DCB, 287 (71) | PTA, 155 (68) | FF-amputation 6 m 98.9 vs. 98% (*P* = 0.25) | OS 6 m 96.8 vs. 96% (*P* = 0.7) |
| Schulte et al., 2015 (124) | 92 | 68 | 64 | BMS, 45 (71) | PTA, 47 (70) | Amputation 1 y 8.9 vs. 13.2% (*P* NR) | Mortality 1 y 7.4 vs. 2.1% (*P* NR) |
| Spreen et al., 2016 (127), and Spreen et al., 2017 (128) | 137 | 64 | 100 | Paclitaxel DES, 73 (60) | PTA BMS, 64 (67) | AFS 1 y 68.9 vs. 63.6% (*P* = 0.15)<br>MALE-FS 5 y 26.2 vs. 15.2% (*P* = 0.04) | Mortality 1 y 23.3 vs. 25.1% (*P* = 0.52)<br>AFS 5 y 31.8 vs. 20.4% (*P* = 0.04) |
| Rastan et al., 2011 (129), and Rastan et al., 2012 (130) | 161 | 54 | 47 | Sirolimus DES, 82 (57) | BMS, 79 (51) | FF-amputation 1 y 98.4 vs. 96.8% (*P* = 0.61)<br>Amputation 3 y 2.6 vs. 12.2% (*P* = 0.03) | Mortality 1 y 17.1 vs. 13.9% (*P* = 0.66)<br>Mortality 3 y 22.6 vs. 24% (*P* = 0.84) |
| Scheinert et al., 2012 (132) | 200 | 64 | – | Sirolimus DES, 99 (65) | PTA, 101 (64) | TLR 1 y 10 vs. 16.5% (*P* = 0.26) | Amputation 1 y 13.8 vs. 20% (*P* = 0.3) |
| Siablis et al., 2014 (133) | 50 | 70 | – | Paclitaxel DCB, 25 (76) | Paclitaxel DES, 25 (64) | TLR 6 m 13.6 vs. 7.7% (*P* = 0.65) | Mortality 6 m 8 vs. 12% (*P* NR) |
| *Prospective studies* | | | | | | | |
| Teichgräber et al., 2019 (117) | 164 | 80 | 96 | Paclitaxel DCB, 164 (80) | – | FF-TLR 1 y 90.6% | AFS 1 y 83.8% |
| Siablis et al., 2007 (131) | 58 | 76 | 100 | Sirolimus DES, 29 (76) | BMS, 29 (76) | Amputation 1 y 10.3 vs. 17.2% (*P* = 0.22) | Mortality 1 y 13.8 vs. 10.3% (*P* = 0.34) |

*Continued on p. 371 »*

« Continued from p. 370

**TABLE 4** Interventions for Infrapopliteal Lesions *(continued)*

| Study | *N* | With Diabetes, % | With CLTI, %* | Intervention, *n* (% With Diabetes) | Control, *n* (% With Diabetes) | Major Outcomes (%) | |
|---|---|---|---|---|---|---|---|
| *Retrospective studies* | | | | | | | |
| Giles et al., 2008 (112) | 163 | 77 | 100 | PTA, 163 (77) | – | TLR 2 y 39% | OS 3 y 53% |
| Schmidt et al., 2010 (115) | 58 | 90 | 100 | PTA, 58 (90) | – | TLR 3 m 50% | Mortality 15 m 10.5% |
| Schmidt et al., 2011 (116) | 104 | 71 | 82 | Paclitaxel DCB, 104 (71) | – | TLR 1 y 17.3% | Mortality 1 y 16.3% |
| Silingardi et al., 2015 (125) | 155 | 76 | 93 | PTA/stent, 155 (76) | – | Amputation 33 m 10.8% | Mortality 33 m 38.6% |
| Spiliopoulos et al., 2015 (126) | 214 | 100 | 100 | DES, 214 (100) | – | AFS 5 y 90.4% | OS 5 y 55.5% |
| *Meta-analyses* | | | | | | | |
| Mustapha et al., 2016 (113) | 6,769 | 75 | 97 | PTA, 6,769 (75) | – | Patency 1 y 69.9 vs. 55.9% ($P$ <0.05) for studies with <74 vs. ≥74% patients with diabetes | MALE 1 y 33.1% Mortality 1 y 15.1% |
| Cassese et al., 2016 (122) | 614 | 52–100 | 52–100 | Paclitaxel DCB, 378 (NR) | PTA + paclitaxel DES, 263 (NR) | TLR 1 y RR 0.71 (95% CI 0.47–1.09) | Mortality 1 y 11.4 vs. 10.6% ($P$ = 0.59) |
| Katsanos et al., 2020 (123) | 1,420 | 80 | 97 | Paclitaxel DCB, 844 (79) | PTA, 596 (80) | AFS 1 y OR 1.52 (95% CI 1.12–2.07) | Mortality 1 y OR 1.39 (95% CI 0.94–2.07) |

*CLTI includes Rutherford classes 4–6 and Fontaine stages III–IV. †Study primary end point. FF-amputation, freedom from amputation; m, month(s); NR, not reported; OS, overall survival; RR, relative risk; y, year(s).

A meta-analysis of 52 studies involving 6,769 patients (75% with diabetes, 97% with CLTI) who underwent infrapopliteal PTA found that 1-year patency was 63.1%, combined reintervention and major amputation was 33.1%, and all-cause mortality was 15.1% (113). Notably, there was significant heterogeneity among studies with varying definitions of patency and reintervention. Stratified analysis found that studies that included <74% patients with diabetes had higher 1-year patency compared with studies in which ≥74% of patients had diabetes (69.9 vs. 55.9%, $P < 0.05$). There were no significant differences in patency, reintervention, major amputation, or mortality in studies with <80% compared with ≥80% of patients with CLTI Rutherford class 5–6. These studies suggest that outcomes with PTA alone for infrapopliteal lesions remain suboptimal based on recommended objective performance goals for infrapopliteal endovascular treatment (114).

Current studies suggest an added advantage from treating infrapopliteal lesions in patients with diabetes and CLTI with paclitaxel DCB (Table 4). Two single-arm observational studies analyzed long infrapopliteal revascularization (mean length 17.3–18.4 cm) with either standard PTA ($n = 58$) or paclitaxel DCB ($n = 74$) in patients with CLTI (100 and 82%, respectively) and diabetes (90 and 71%, respectively) (115,116). At the 3-month follow-up, the PTA study had 31.2% restenosis, 37.6% reocclusion, and 50% reintervention, whereas the paclitaxel DCB study had 19.1% restenosis, 8.3% reocclusion at 3 months, and 17.3% TLR at 1 year. Notably, although restenosis and TLR were lower in the paclitaxel DCB study, 1-year mortality was higher (16.3%) compared with 15-month mortality in the PTA study (10.5%). A more recent single-arm, observational study involving nine centers and 164 patients with CLTI (80% with diabetes) found that paclitaxel DCB outcomes in patients with CLTI and diabetes have improved little in the past 10 years, with 1-year restenosis of 31.5%, TLR 9.4%, and AFS 83.5% (117).

Aside from observational studies, four RCTs also compared infrapopliteal revascularization with paclitaxel DCB versus standard PTA (Table 4). The DEBATE-BTK (Drug-Eluting Balloon in Peripheral Intervention for Below the Knee Angioplasty Evaluation) study randomized 132 patients with CLTI and diabetes at a 1:1 ratio to paclitaxel DCB or PTA and found that, at 1 year, the paclitaxel DCB group had lower restenosis (27 vs. 74%, $P < 0.001$) and lower TLR (18 vs. 43%, $P = 0.002$) compared with PTA (118). One amputation occurred in the PTA group at 1 year and none in the paclitaxel DCB group. In the IN.PACT DEEP (Randomized IN.PACT Amphirion Drug-Coated Balloon [DCB] vs. Standard Percutaneous Transluminal Angioplasty [PTA] for the Treatment of Below-the-Knee Critical Limb Ischemia [CLI]) study, 358 patients with CLTI (73% with diabetes) were randomized 2:1 to paclitaxel DCB or PTA (119). At 1 year, there was no difference in restenosis (41 vs. 35.5%, $P = 0.6$), reocclusion (11.5 vs. 16.5%, $P = 0.5$), or TLR (15.5 vs. 20.2%, $P = 0.27$). The study showed a trend toward higher composite all-cause mortality and amputations in the paclitaxel DCB group compared with PTA but this difference did not reach statistical significance (35.2 vs. 25.2%, $P = 0.064$). Further stratified analysis showed no difference in major amputation or mortality at 1 year in patients with Rutherford class 4–6. The BIOLUX P-II (BIOLUX P-II First-in-Man Study to Compare the Passeo-18 Lux DRB Against POBA in Infrapopliteal Arteries) study randomized 72 patients 1:1 to paclitaxel DCB or PTA (67% with diabetes, 78% with CLTI) and found that, at 1 year, there was no difference in restenosis (50.8 vs. 45.6%, $P = 0.9$), TLR (34.9 vs. 30%, $P = 0.8$), all amputations (23.7 vs. 25.7%, $P = 1.0$), or all-cause death (9.4 vs. 6%, $P = 0.6$) (120). The study found no difference in TLR or MALE (all-cause death, major amputations, or reintervention) between patients with or without CLTI at 1 year. Similarly, the Lutonix-BTK (Lutonix DCB Versus Standard Balloon Angioplasty for Treatment of Below-The-Knee [BTK] Arteries) trial randomized 442 patients (70% with diabetes, 90% with CLTI) 2:1 to paclitaxel DCB or PTA and found that paclitaxel DCB was noninferior to PTA at 30 days for MALE and perioperative death (121). At 6 months, there was no significant difference in major amputation or all-cause death.

Only one out of these four RCTs demonstrated that, in patients with diabetes and CLTI, paclitaxel DCB had superior short-term (1-year) patency, whereas three RCTs showed short-term patency equivalent to PTA. All four RCTs found no difference in amputation rates between paclitaxel DCB and PTA, and none had follow-up beyond 1 year. Notably, 12% of the total participants in the Lutonix-BTK study (28 paclitaxel DCB and 24 PTA) and 12.5% in the IN.PACT DEEP study (31 paclitaxel DCB and 14 PTA) withdrew, were lost to follow-up, or did not complete the study evaluations, which considerably decreased the overall power of these studies.

A meta-analysis of five trials (including three trials mentioned above: DEBATE-BTK, IN.PACT DEEP, and BIOLUX P-II) further showed equivalence between

paclitaxel DCB and PTA in patients with diabetes and CLTI (122) (Table 4). The study compared paclitaxel DCB ($n = 378$) to control (paclitaxel DES or PTA, $n = 263$), with varying proportions of patients with diabetes (52–100%) and CLTI (52–100%), and found that at 1 year, there was no difference in TLR (18.3 vs. 29.1%, $P = 0.12$), all amputations (13.3 vs. 14.9%, $P = 0.86$), or death (11.4 vs. 10.6%, $P = 0.59$) between paclitaxel DCB and PTA. A more recent meta-analysis comparing paclitaxel DCB with PTA in patients with CLTI undergoing infrapopliteal revascularization involved 1,420 patients (80% with diabetes, 97% with CLTI) in eight RCTs and found a significant reduction in 1-year TLR for patients treated with paclitaxel DCB compared with those who received PTA (11.8 vs. 25.6%, respectively; HR 0.53, 95% CI 0.35–0.81, $P = 0.004$) (123). However, despite this reduction in TLR, 1-year AFS was significantly lower in patients who received paclitaxel DCB than in those receiving PTA (86.3 vs. 90.6%; HR 1.52, 95% CI 1.12–2.07), whereas individual end points of major amputation and all-cause mortality did not reach statistical significance. The study also found a dose-response relationship with high-dose devices significantly lowering AFS (HR 1.62, 95% CI 1.16–2.27, $P = 0.005$), whereas there was no significant effect on AFS using single, low-dose devices. These studies suggest that infrapopliteal revascularization with paclitaxel DCB in patients with diabetes and CLTI remains equivocal compared with PTA. While short-term (≤1 year) restenosis and TLR may be lower compared with PTA, amputation and mortality rates appeared to be higher in patients receiving paclitaxel DCB.

Although in the United States there are currently no FDA-approved BMS for the treatment of infrapopliteal arterial occlusive disease, RCTs in Europe and Canada have evaluated the efficacy of this emerging technology. The EXPAND (Self Expanding Nitinol Stent Versus Percutaneous Transluminal Arterial Angioplasty [PTA] With Optional Bailout Stenting in Case of PTA Failure in Patients With Symptomatic Critical Limb Ischemia or Severe Intermittent Claudication) trial of 92 patients (68% with diabetes, 64% with CLTI) compared BMS to PTA for infrapopliteal revascularization and found that, at 1 year, there was no difference in TLR (23.4 vs. 22.4%, $P$ = NS), mortality (7.4 vs. 2.1%, $P$ = NS), or all amputations (8.9 vs. 13.2%, $P$ = NS) (124) (Table 4). Notably, the study was terminated early because of slow recruitment and fell short of having the prespecified 170 patients. Therefore, the hypothesis of noninferiority of BMS to PTA in infrapopliteal lesions could not be tested. Studies of stent technology in infrapopliteal lesions showed highly variable rates of restenosis, MALE, and mortality. A single-arm retrospective cohort study of 155 patients (76% with diabetes, 93% with CLTI) who received stents (84% BMS, 16% nonpaclitaxel DES) showed that restenosis occurred in 12% of patients at a mean of 10.3 months; 10.8% had a major amputation at a mean of 1 year; and all-cause mortality was 38.6% at a mean of 20 months (125). Another retrospective study involving 214 patients with CLTI and diabetes who received DES (either paclitaxel or sirolimus) found that 1-, 5-, and 10-year survival rates were 90.8, 55.5, and 36.2%, respectively, whereas AFS rates were 94.9, 90.4, and 90.4%, respectively (126).

Even with stent intervention, clinical outcomes for infrapopliteal revascularization in patients with diabetes and CLTI remain dismal, with 1-year AFS rates barely meeting the objective performance goals of 68%. The PADI (Percutaneous Transluminal Angioplasty Versus Drug Eluting Stents for Infrapopliteal Lesions) trial involving 137 patients with CLTI (64% with diabetes) investigated the performance of paclitaxel DES and PTA BMS in infrapopliteal lesions (127,128). There was no significant difference in patency at 6 months (48 vs. 35%, $P = 0.09$) or AFS at 1 year (68.9 vs. 63.6%, $P = 0.15$). Interestingly, at 5 years, the reported AFS (31.8 vs. 20.4%, $P = 0.04$) and MALE-free survival (26.2 vs. 15.2%, $P = 0.04$) were significantly lower in patients who received paclitaxel DES compared with those who received PTA BMS, although there were no significant differences in single end points (major amputation, MALE, or survival) between groups. Subgroup analysis of patients with and without diabetes or with and without tissue loss did not show a significant difference in 5-year AFS.

Besides paclitaxel DES, studies have also evaluated outcomes for sirolimus DES (Table 4). A study with 161 patients (54% with diabetes, 47% with CLTI) randomized to sirolimus DES or BMS found that 1-year primary patency was higher in the sirolimus DES group (80.6 vs. 55.6%, $P = 0.004$) (129). At mean follow-up of 1,005 days (2.7 years), event-free survival (composite events included TLR, all amputations, MI, and death) was also higher in the sirolimus DES group when compared with BMS regardless of CLTI or diabetes status (65.8 vs. 44.6%, $P = 0.02$) (130). Subgroup analysis found that patients with CLTI had lower rates of all amputations in the sirolimus DES group (5.3 vs. 22.6%, $P = 0.04$), but there was no difference in overall event-free survival when compared with BMS (57.9 vs. 32.3%, $P = 0.07$).

Another prospective study of 58 patients with CLTI (76% with diabetes) compared sirolimus DES with BMS and found that sirolimus DES had superior 1-year primary patency (odds ratio [OR] 10.4, 95% CI 3.4–31.6) and TLR (9.1 vs. 26.2%, $P = 0.02$) (131). There were no significant differences in 1-year mortality (13.8 vs. 10.3%, $P = 0.3$) or minor amputations (10.3 vs. 17.2%, $P = 0.2$). One amputation was observed in the sirolimus DES group at 1 year and none in the BMS group. Among patients with diabetes, the study found that sirolimus DES had higher 1-year primary patency (84.6 vs. 38.5%, $P = 0.008$) but no difference in TLR (7.7 vs. 30.7%, $P = 0.07$) when compared with BMS. These studies suggest that, in patients with CLTI and diabetes, DES may provide an advantage in patency when compared with BMS, but clinical benefits with respect to TLR, amputation, and mortality remain to be determined.

Similarly, studies comparing DES with PTA showed that, although short-term restenosis was superior with DES, there was no difference in clinically important outcomes such as reintervention, amputation, or mortality when compared with angioplasty (Table 4). The ACHILLES (Comparing Angioplasty and DES in the Treatment of Subjects With Ischemic Infrapopliteal Arterial Disease) trial randomized 200 patients (64% with diabetes) to sirolimus DES or PTA and found that 1-year restenosis was lower in the sirolimus DES group when compared with PTA (22.4 vs. 41.9%, $P = 0.02$) (132). Both groups had similar 1-year rates of reintervention (10 vs. 16.5%, $P = 0.2$), all amputation (13.8 vs. 20%, $P = 0.3$), and death (10.1 vs. 11.9%, $P = 0.8$). The IDEAS (Infrapopliteal Drug-Eluting Angioplasty Versus Stenting) trial randomized 50 patients (70% with diabetes, most with CLTI) to sirolimus-equivalent DES (sirolimus, zotarolimus, and everolimus) or paclitaxel DCB and found that the 6-month restenosis rate was lower in the DES group compared with paclitaxel DCB (28 vs. 57.9%, $P = 0.04$) (133). There were no significant differences in TLR, major amputation, or mortality at 6 months.

The Global Vascular Guidelines for CLTI suggest that endovascular treatment should, at a minimum, meet the proposed outcome performance goals until ongoing RCTs provide further guidance (3,114,134–136). However, current limited data so far suggest that endovascular revascularization for severe multivessel infrapopliteal disease in patients with diabetes and CLTI continues to be suboptimal. Therefore, PTA remains the most popular modality for endovascular treatment of infrapopliteal disease, as current evidence does not demonstrate any meaningful clinical benefit (e.g., lower rates of reintervention, amputation, and mortality) with the use of DCB or DES.

### *Atherectomy*

Modern practice peripheral arterial atherectomy devices aim to enhance arterial lumen recanalization, debulk plaque burden, microfracture calcified plaque, and prepare the arterial lumen for adjunct treatments with balloon angioplasty and stenting. To date, studies evaluating the use of atherectomy have demonstrated comparable outcomes between patients with and without diabetes (Table 5).

A retrospective study examined 204 atherectomy procedures (directional, orbital, and rotational), of which 65% were performed in patients with diabetes and 18% in patients with CLTI. It found that, at a mean follow-up of 1 year, there were no differences between patients with and without diabetes with regard to TLR (15.2 vs. 22.2%, $P = 0.2$), amputations (3.0 vs. 1.5%, $P =$ NS), or death (2.2 vs. 2.7%, $P =$ NS) (137). Similarly, a multicenter prospective registry (DEFINITIVE LE [Study of SilverHawk/TurboHawk in Lower Extremity Vessels]) comparing 598 patients with and without diabetes undergoing directional atherectomy (47% with diabetes; patients with CLTI were excluded) also found no significant difference in 1-year TLR (83.8 vs. 87.5%, $P = 0.2$) or primary patency (77 vs. 78%, $P = 0.9$) (138). However, at 1 year, hemodynamic (ankle-brachial index [ABI]) and subjective (EuroQol 5 Dimension [EQ-5D]) measures improved in both groups with and without diabetes when compared with baseline. A pooled analysis of 3,089 patients (60% with diabetes, 44% with CLTI) undergoing orbital atherectomy showed that rates of dissection, embolism, and thrombus were similar in patients with and without diabetes (139).

Data supporting the use of atherectomy in patients with diabetes and CLTI are limited. A retrospective study involving 76 patients (66% with diabetes, 82% with CLTI) compared directional atherectomy with PTA in the common femoral artery (140). Directional atherectomy had significantly higher primary patency than PTA over a 4-year follow-up (87.1 vs. 66.7%, $P = 0.04$). However, subgroup analysis of patients with diabetes showed no difference in primary patency between those treated with directional atherectomy and those undergoing PTA, suggesting no measurable outcome benefit in this subgroup.

**TABLE 5** Atherectomy Devices

| Study | *N* | With Diabetes, % | With CLTI, %* | Intervention, *n* (% With Diabetes) | Control *n* (% With Diabetes) | Major Outcomes | |
|---|---|---|---|---|---|---|---|
| *RCTs* | | | | | | | |
| Zeller et al., 2017 (144) | 102 | 31 | 2 | Directional atherectomy + paclitaxel DCB, 48 (27) | Paclitaxel DCB, 54 (35) | Patency 1 y 82.4 vs. 71.8% (*P* = 0.4) | MALE 1 y 89.3 vs. 90% (*P* = 0.9) |
| Gandini et al., 2013 (142) | 48 | 100 | 100 | Laser atherectomy + DCB, 24 (100) | DCB, 24 (100) | †Patency 1 y 66.7 vs. 37.5% (*P* <0.01) | Amputation 1 y 8 vs. 46% (*P* <0.01) |
| *Prospective studies* | | | | | | | |
| Garcia et al., 2015 (138) | 598 | 47 | 0 | Directional atherectomy in patients with diabetes, 280 (100) | Directional atherectomy in patients without diabetes, 318 (0) | Patency 1 y 77 vs. 77.9% (*P* = 0.9) | FF-TLR 1 y 83.8 vs. 87.5% (*P* = 0.19) |
| Lee et al., 2014 (139) | 3,089 | 60 | 44 | Orbital atherectomy in patients with diabetes, 1,842 (100) | Orbital atherectomy in patients without diabetes, 1,247 (0) | Dissection 11.4 vs. 10.8% (*P* = 0.68) | Perforation 0.5 vs. 1.1% (*P* = 0.03) |
| Mustapha et al., 2019 (141) | 1,189 | 61 | 58 | Rutherford 2–3 balloons, atherectomy, and/or stents, 500 (48) | Rutherford 4–5 balloons, atherectomy, and/or stents, 589 (69) Rutherford 6 balloons, atherectomy, and/or stents, 100 (79) | FF-MALE 1 y Rutherford 2–3 82.6 vs. Rutherford 4–5 73.2 vs. Rutherford 6 59.3% (all *P* <0.01) | – |
| *Retrospective studies* | | | | | | | |
| Guo et al., 2018 (140) | 76 | 66 | 82 | Directional atherectomy, 31 (65) | PTA, 45 (67) | Patency 4 y 87.1 vs. 66.7% (*P* = 0.04) | Amputation 4 y 3.2 vs. 4.4% (*P* NR) |
| Janas et al., 2020 (137) | 204 | 65 | 18 | Atherectomy in patients with diabetes, 132 (100) | Atherectomy in patients without diabetes, 72 (0) | TLR 1 y 15.2 vs. 22.2% (*P* = 0.2) | Amputation 1 y 3 vs. 1.5% (*P* NR) |
| Mallios et al., 2017 (143) | 300 | 63 | 66 | Laser atherectomy + PTA, 300 (63) | – | Amputation 2 y People with CLTI vs. those without CLTI OR 2.8 (95% CI 1.02–7.3) | Mortality 2 y People with CLTI vs. those without CLTI OR 2.9 (95% CI 1.07–7.7) |

*CLTI includes Rutherford classes 4–6 and Fontaine stages III–IV. †Study primary end point. FF-MALE, freedom from MALE (major amputation, target lesion revascularization, all-cause death); FF-TLR, freedom from TLR; NR, not reported; y, year(s).

Similarly, the recent multicenter observational LIBERTY 360 study of 1,189 patients (61% with diabetes, 58% with CLTI) evaluated a variety of peripheral endovascular devices (PTA, DCB, BMS, DES, stent-grafts, and atherectomy) (141). The study showed that 6-month and 1-year mortality, major amputation, and target vessel revascularization rates were all significantly higher in patients with CLTI than in those without CLTI regardless of endovascular device used. Multivariable analysis showed that 1-year major adverse events (mortality, major amputation, and target vessel revascularization) were significantly associated with wound severity, vessel occlusion, prior endovascular procedure, infrapopliteal lesions, CLTI status, and history of CAD. Notably, only 77% of patients without CLTI and 63% of those with CLTI completed 1-year follow-up, and mortality rates were 4.8% in those without and 9.2% in those with CLTI. Also of note, 11.8% of patients without CLTI and 16.9% of those with CLTI withdrew or were lost to follow-up.

On the other hand, laser atherectomy in combination with DCB may provide better patency in patients with diabetes and CLTI, but not when it is used in combination with PTA. This is in contrast to directional atherectomy, which has not been found to provide added benefit when used in combination with DCB (Table 5). A small RCT in Italy involving 48 patients with diabetes and CLTI refractory to prior stent placement in SFA compared laser atherectomy followed by DCB (LA + DCB) with DCB alone ($n = 24$ in each group) (142). At 1 year, primary patency (66.7 vs. 37.5%, $P = 0.01$), TLR (16.7 vs. 50%, $P = 0.01$), major amputation (8 vs. 46%, $P = 0.003$), and death (12 vs. 37%, $P = 0.04$) were superior in the LA + DCB group when compared with DCB alone. A single-arm retrospective study with 300 patients (64% with diabetes, 66% with CLTI) who underwent laser atherectomy followed by PTA (LA + PTA) found that, at a mean follow-up of 28 months, the overall cohort event rates for major amputation and death were 9%, respectively (143). Further analysis showed that patients with CLTI had higher odds of major amputation (OR 2.8, 95% CI 1.02–7.3) and death (OR 2.9, 95% CI 1.07–7.7) when compared with patients without CLTI. Similarly, patients with diabetes also had higher odds of major amputation (OR 5.8, 95% CI 1.4–24) when compared with patients without diabetes. Notably, 33% of patients also underwent stenting because of suboptimal angiographic findings during the atherectomy procedure, but stratified analysis of this subgroup was not reported.

An RCT investigated the efficacy of directional atherectomy followed by paclitaxel DCB (DA + DCB) compared with paclitaxel DCB alone in 102 patients (31% with diabetes, 2% with CLTI Rutherford class 4) (144). At 1 year, primary patency (82.4 vs. 71.8%, $P = 0.4$), freedom from major adverse events (major amputation, TLR, and all-cause mortality) (89.3 vs. 90%, $P = 0.9$), and functional outcomes (ABI and EQ-5D) were similar between DA + DCB and paclitaxel DCB alone. However, because of a lack of prespecified sample size calculations and adequate power, no significant conclusions were drawn about the noninferiority of DA + DCB.

Overall, these studies suggest that laser atherectomy used in combination with drug-coated devices (paclitaxel DCB) may provide longer patency in patients with diabetes and CLTI but not when used in combination with standard PTA. At this time, other types of atherectomy modalities (e.g., orbital and directional) have yet to show significant added clinical benefit in patients with diabetes and CLTI.

## Experimental Therapies

New therapies using stem cells or growth factors remain experimental and mostly confined to patients with no option for arterial revascularization. A handful of small studies demonstrate short-term clinical benefit, whereas most studies so far fail to show any sustained benefit in patients with diabetes and CLTI (Table 6).

A trial involving 21 patients with diabetes and CLTI (7 treatment, 14 control) showed that transplant of autologous mesenchymal stem cells from granulocyte-colony-stimulating factor (G-CSF)-mobilized peripheral blood mononuclear cells (PBMNC) resulted in significant improvement in ABI ($0.92 \pm 0.15$ vs. $0.65 \pm 0.25$, $P < 0.035$), ambulating without pain (86 vs. 29%, $P = 0.024$), and major amputations (0 vs. 50%, $P = 0.047$) at 3 months (145). No adverse events (infection or immunologic rejection) were observed in the transplant group.

Another study with 28 patients (14 treatment, 14 control) found similar results. At 3 months, the treatment group had significant improvement in ABI ($0.50 \pm 0.21$ vs. $0.63 \pm 0.25$, $P < 0.001$), ulcer healing (78 vs. 39%, $P = 0.02$), and amputations (0 vs. 21%, $P = 0.007$) (146). Interestingly, both treatment and control groups reported significant improvement in rest pain, suggesting a placebo effect. There were no side effects related to treatment, and the study did not report adverse events associated with treatment.

**TABLE 6** Experimental Therapies

| Study | *N* | With Diabetes, % | With CLTI, %* | Intervention, *n* (% With Diabetes) | Control *n* (% With Diabetes) | Major Outcomes (%) | |
|---|---|---|---|---|---|---|---|
| *RCTs* | | | | | | | |
| Mohammadzadeh et al., 2013 (145) | 21 | 100 | 100 | G-CSF + PBMNC, 7 (100) | G-CSF + PBS saline, 14 (100) | Improved walking ability 3 m 86 vs. 29% ($P$ = 0.03) | Amputation 3 m 0 vs. 50% ($P$ = 0.05) |
| Ozturk et al., 2012 (147) | 40 | 100 | 100 | G-CSF + PBMNC, 20 (100) | Standard care, 20 (100) | Pain score 3 m 8.2 to 5.6% ($P$ <0.01) vs. 8.5 to 7.7% ($P$ <0.01) | Amputation 3 m 15 vs. 25% ($P$ = 0.4) |
| Huang et al., 2005 (146) | 28 | 100 | 100 | G-CSF + PBMNC, 14 (100) | Prostaglandin E1, 14 (100) | Ulcer healing 3 m 77.8 vs. 38.9% ($P$ = 0.02) | Amputation 3 m 0 vs. 21% ($P$ <0.01) |
| Procházka et al., 2010 (148) | 96 | 94 | 100 | BMSC, 42 (88) | Standard care, 54 (98) | *Major amputation 4 m 21 vs. 44% ($P$ <0.05) | – |
| Lu et al., 2011 (149), Lu et al., 2019 (150) | 41 | 100 | 100 | BMMSC, 20 (100) BMMNC, 21 (100) | Normal saline, 41 (100) | BMMSC vs. control amputation 6 m 0 vs. 16% ($P$ = 0.02) AFS 3 y 37.5 vs. 27.1% ($P$ = 0.21) | BMMNC vs. control amputation 6 m 0 vs. 16% ($P$ = 0.02) AFS 3 y 30.9 vs. 27.1% ($P$ = 0.44) |
| Tateishi-Yuyama et al., 2002 (151) | 45 | 69 | 100 | Unilateral ischemia BMMNC vs. normal saline, 25 (72) Bilateral ischemia BMMNC vs. PBMNC, 20 (65) | – | BMMNC vs. saline pain-free walking difference 4 w: 3.4 minutes ($P$ <0.01) 24 w: 3.5 minutes ($P$ <0.01) BMMNC vs. PBMNC pain free walking difference 4 w: 1.2 minutes ($P$ <0.01) 24 w: 1.4 minutes ($P$ <0.01) | – |
| Perin et al., 2017 (152) | 78 | 39 | 0 | ALDHbr cells, 38 (37) | Cell-free serum albumin, 40 (40) | †Improved peak walking time 6 m 2.2 ± 3.9 vs. 1.2 ± 2.7 minutes ($P$ = 0.24) | Mortality 6 m None |
| Rajagopalan et al., 2003 (156) | 105 | 78 | 0 | $AdVEGF_{121}$, low dose 32 (25) high dose 40 (30) | Without vector, 33 (27) | †Improved peak walking time 3 m low dose 1.6 minutes high dose 1.5 minutes control 1.8 minutes | Mortality 293 d low dose 0 high dose 0 control 3 |

*Continued on p. 378 »*

« Continued from p. 377

**TABLE 6** Experimental Therapies *(continued)*

| Study | *N* | With Diabetes, % | With CLTI, %* | Intervention, *n* (% With Diabetes) | Control *n* (% With Diabetes) | Major Outcomes (%) | |
|---|---|---|---|---|---|---|---|
| Mäkinen et al., 2002 (157) | 54 | 54 | 26 | VEGF-ad, 18 (17)<br>VEGF-p/l, 17 (24) | Ringer's lactate, 19 (32) | Major amputation 3 m<br>VEGF-adv 5.6%<br>VEGF-p/l 0%<br>Ringer's lactate 0% | Mortality 2 y<br>VEGF-adv 5.6%<br>VEGF-p/l 5.9%<br>Ringer's lactate 5.3% |
| Kusumanto et al., 2006 (155) | 54 | 100 | 100 | $phVEGF_{165}$, 27 (100) | Normal saline, 27 (100) | Improved ulcers 100 d<br>33 vs. 0% (*P* = 0.01) | AFS 1 y<br>84 vs. 60% (*P* = NS) |
| Powell et al., 2008 (158) | 104 | 52 | 100 | HGF plasmid,<br>low dose 26 (56)<br>mid dose 25 (38)<br>high dose 27 (43) | Normal saline, 26 (71) | Total amputation 1 y<br>11% (*P* = NS) for all groups | Mortality 1 y<br>low dose 7.4%<br>mid dose 3.8%<br>high dose 7.4%<br>control 3.8% |
| Gu et al., 2019 (159) | 197 | 36 | 100 | $HGF_{723}$ and $HGF_{728}$,<br>low dose 48 (38)<br>mid dose 50 (34)<br>high dose 49 (35) | Normal saline, 50 (38) | Pain relief 6 m<br>low dose 49.9 vs. 6.4%<br>mid dose 56.3 vs. 6.4%<br>high dose 54.2 vs. 6.4%<br>(all *P* <0.05) | Ulcer healing 6 m<br>high dose 66.7 vs. 27.3% (*P* = 0.01)<br>all other groups (*P* = NS)<br>Total amputation 6 m<br>8% (*P* = NS) for all groups |
| Nikol et al., 2008 (160) | 107 | 44 | 100 | NV1FGF, 51 (37) | Normal saline, 56 (50) | †Complete healing of ≥1 ulcer 25 w<br>19.6 vs. 14.3% (*P* = 0.51) | Amputation 1 y<br>HR 0.50 (*P* = 0.01)<br>Mortality 1 y<br>HR 0.46 (*P* = 0.11) |
| Belch et al., 2011 (161) | 525 | 53 | 100 | NV1FGF, 266 (52) | Normal saline, 259 (54) | Major amputation 1 y<br>25 vs. 21% (*P* = 0.3) | Mortality 1 y<br>17 vs. 15% (*P* = 0.53) |
| Shishehbor et al., 2019 (162) | 109 | 79 | 100 | SDF-1,<br>8 mg 34 (76)<br>16 mg 36 (80) | Unspecified, 34 (82) | Complete wound healing 3 m<br>8 mg 26.5 vs. 26.5%<br>16 mg 25 vs. 26.5%<br>(all *P* = NS) | MALE 3 m<br>8 mg 20.6 vs. 8.8%<br>16 mg 8.3 vs. 8.8%<br>(all *P* = NS) |
| *Prospective studies* | | | | | | | |

*Continued on p. 379* »

« Continued from p. 378

**TABLE 6** Experimental Therapies *(continued)*

| Study | *N* | With Diabetes, % | With CLTI, %* | Intervention, *n* (% With Diabetes) | Control *n* (% With Diabetes) | Major Outcomes (%) |
|---|---|---|---|---|---|---|
| Baumgartner et al., 1998 (154) | 9 | 22 | 100 | phVEGF$_{165}$, 9 (22) | – | ABI 12 w 0.33–0.48% ($P$ = 0.02) FF-amputation 12 w 33.3% |
| *Retrospective studies* | | | | | | |
| Dubský et al., 2014 (153) | 84 | 100 | 100 | SCT, 31 (100) Repeat PTA, 30 (100) | Not eligible for repeat PTA, 23 (100) | Wound healing 12 m SCT 82.1% vs. PTA 57.7% ($P$ = 0.01) SCT 82.1% vs. control 19.1% ($P$ = 0.04) AFS 12 m SCT 74.2% vs. control 48% ($P$ = 0.02) PTA 70% vs. control 48% ($P$ <0.01) |

*CLTI includes Rutherford classes 4–6 and Fontaine stages III–IV. †Study primary end point. d, day(s); FF-amputation, freedom from amputation; m, month(s); NS, nonsignificant; PBS, phosphate-buffered saline; SCT, stem cell therapy consisting of either BMMNC or PBMNC; w, weeks; y, year(s).

A different study with 40 patients (20 treatment, 20 control) also examined the effectiveness of PBMNC (147). Similarly, at 3 months, the study found that, when compared with control, the treatment group had significant improvement in ABI (0.68 ± 0.24 vs. 0.87 ± 0.24, $P$ = 0.001), transcutaneous oximetry ($TcPo_2$) (33 ± 14 vs. 44 ± 10 mmHg, $P$ = 0.01), and ulcer healing (45 vs. 15%, $P$ = 0.031). However, both the treatment and control groups also reported statistically significant improvement in 6-minute walking distance, Fontaine score, and numeric pain score at 3 months. The study did not report adverse events, and there was no difference in amputation rates between groups (15 vs. 25%, $P$ = 0.4). These studies showed that autologous transplantation of PBMNC in patients with diabetes and CLTI improved short-term tissue perfusion, but it remains unclear whether this improvement translates to limb salvage and functional improvement.

Studies have also investigated the use of autologous bone marrow stem cells in patients with diabetes and CLTI (Table 6). One study recruited 96 patients with CLTI with foot ulcers (42 treatment, 54 control), of whom 88 and 98%, respectively, had diabetes (148). At 3 months, there was a significantly lower rate of amputation in the treatment group compared with the control group (21 vs. 44%, $P$ <0.05).

A two-arm study involving 41 patients with diabetes and bilateral CLTI compared bone marrow mesenchymal stem cells (BMMSC) with normal saline (control), and bone marrow–derived mononuclear cells (BMMNC) with normal saline (control) (149). At 6 months, both treatment arms reported significant improvement in rest pain, ABI, and $TcPo_2$, but those treated with BMMSC had significantly more improvement in ABI (0.17 ± 0.06 vs. 0.12 ± 0.06, $P$ = 0.02) and $TcPo_2$ (4.4 ± 7.6 vs. 16.4 ± 6.4, $P$ = 0.001) when compared with BMMNC. The number of healing ulcers (91 vs. 45%, $P$ = 0.02) was significantly higher with BMMSC, and healing also appeared earlier (at 4 vs. 12 weeks) with BMMSC than with BMMNC. Both treatment arms reported significantly lower amputation rates compared with control groups. However, at 3 years, there was no significant difference in AFS between treatment and control groups (150). Cox model analysis showed that BMMSC were associated with lower amputation rates (HR 0.21, 95% CI 0.05–0.95), whereas BMMNC were not (HR 0.41, 95% CI 0.13–1.28).

Another double-arm study with 45 patients with CLTI (69% with diabetes) compared BMMNC with normal

saline (control) and BMMNC with PBMNC (151). The study found that, at 4 weeks, ABI, $TcPo_2$, rest pain, and pain-free walking improved significantly with BMMNC compared with PBMNC or control. These improvements remained consistent through final follow-up at 24 weeks. These studies suggest that BMMSC and BMMNC could provide symptomatic and functional improvement in the short-term in patients with diabetes and CLTI who have no options for revascularization.

Other trials showed that stem cells may have no benefit in patients with diabetes (Table 6). One study with 78 patients (39% with diabetes; patients with CLTI were excluded) showed no statistically significant difference between patients treated with autologous bone marrow–derived aldehyde dehydrogenase bright cells (ALDHbr) and a placebo group with regard to peak walking time, collateral vessel count, peak hyperemic popliteal flow, capillary perfusion, and quality of life (152). No adverse safety outcomes were reported in either group.

A three-arm study compared stem cell therapy (PBMNC and BMMNC), standard PTA, and control (no stem cell therapy and no PTA) for patients with diabetes and CLTI (153). A total of 84 patients (31 receiving stem cell therapy, 30 receiving PTA, and 23 in the control group) with foot ulcers and CLTI showed that, at 1 year, both treatment groups had significantly improved $TcPo_2$ and AFS when compared with control. Wound healing based on University of Texas Diabetic Wound Classification was superior with stem cell therapy compared with PTA at the 3-, 6-, and 12-month follow-up. No adverse events were noted after stem cell therapy. This study suggests that stem cell therapy (PBMNC or BMMNC) could be a novel option for patients with diabetes and CLTI with no revascularization options. However, larger trials are required to confirm these results.

Other novel therapies that have been studied include peripheral administration of vascular endothelial growth factors (VEGFs) (Table 6). One study examined the effects of injecting naked plasmid DNA encoding the 165-amino-acid isoform of human VEGF ($phVEGF_{165}$) into the calf and/or distal thigh muscles of patients with CLTI (154). Of the 10 limbs treated (in nine individuals), ABI significantly improved from baseline to 12 weeks ($0.33 \pm 0.05$ to $0.48 \pm 0.03$, $P = 0.02$). Symptom and functional outcomes such as rest pain, graded treadmill exercise, pain-free walking time, and claudication-limited walking time also improved from baseline. The study reported transient lower-extremity edema, which occurred in six patients. Another study examined $phVEGF_{165}$ in 54 patients with diabetes and CLTI (155). At 100 days, there were no significant differences in amputation, ABI/toe-brachial index (TBI), or pain relief between the treatment ($n = 27$) and control ($n = 27$) groups. Skin ulcers improved significantly in the treatment group compared with the control group (0 vs. 26%, $P = 0.01$), and no adverse events were observed in either group.

Another study examined the safety and efficacy of intramuscular injections with recombinant adenovirus vector encoding the 121-amino-acid isoform of VEGF ($AdVEGF_{121}$) (156). A total of 105 patients (28% with diabetes; patients with CLTI were excluded) were recruited into a high-dose ($n = 40$), low-dose ($n = 32$), or placebo ($n = 33$) group. At 12 weeks, the primary end point of peak walking time did not differ among the three groups. Secondary end points such as ABI, claudication onset time, and quality of life were also similar at 12 and 26 weeks in all three groups. Intramuscular administration of $AdVEGF_{121}$ was associated with peripheral edema.

Instead of intramuscular injections, another study examined the effects of catheter-mediated VEGF therapy after PTA. The study recruited 54 patients (24% with diabetes, 26% with CLTI) for VEGF-adenovirus (VEGF-ad) treatment ($n = 18$), VEGF-plasmid/liposome (VEGF-p/l) treatment ($n = 17$), or a control group receiving Ringer's lactate ($n = 19$) (157). At 3 months, both treatment groups showed significantly increased vascularity in the entire limb distal to VEGF therapy (VEGF-ad, $P = 0.03$; VEGF-p/l, $P = 0.02$). However, there were no significant differences in objective or hemodynamic outcomes such as restenosis, major amputations, ulcer healing, resolution of rest pain, or ABI between treatment and control groups. As with stem cell therapies, studies of VEGF gene therapies have been small proof-of-concept trials. Although they show that VEGF gene therapy may provide short-term relief in patients with diabetes and CLTI, objective and subjective benefits beyond 3 months remain unclear.

Other trials have examined the effects of hepatocyte growth factor (HGF) in patients with CLTI (Table 6). A total of 104 patients with CLTI (52% with diabetes) were equally randomized into one of four groups: low-, middle-, and high-dose intramuscular injection of HGF plasmid or placebo (158). At 12 months, there was no difference in adverse events among groups. At 6 months, $TcPo_2$ was significantly improved in the high-dose group compared with all other groups (ANCOVA, $P = 0.0015$). However, there were no differences in ABI, TBI, pain relief, wound healing, or major amputations among groups at 6 months. Although this study

found that intramuscular injection of HGF plasmid was safe, there were no clinically significant benefits of HGF administration in patients with CLTI.

A more recent phase II trial evaluated 197 patients with CLTI (36% with diabetes) who received low-, middle-, or high-dose intramuscular injections of NL003, a plasmid designed to express two isoforms of $HGF_{723}$ and $HGF_{728}$ simultaneously (159). Patients were randomized equally into one of three treatment groups or placebo. The study found that low-, middle-, and high-dose treatment groups were significantly more likely than the placebo group to report complete pain relief at 6 months (48.94, 56.25, and 54.17 vs. 6.38%, respectively; $P < 0.05$). Additionally, >50% ulcer healing was significantly higher in the low-, middle-, and high-dose treatment groups compared with placebo (78.95, 65.22, and 77.78 vs. 40.91%, respectively; $P < 0.05$). Complete ulcer healing was significant only in the high-dose treatment group when compared with placebo (66.67 vs. 27.27%, $P = 0.01$). Interestingly, there were no differences in $TcPo_2$, ABI, or TBI among the groups. This study shows the potential benefit of HGF isoforms on ulcer healing and rest pain in patients with CLTI. However, because of the small proportion of study participants with diabetes, it remains unclear whether these benefits apply to patients with diabetes and CLTI.

In addition to stem cell, VEGF, and HGF therapies, studies have also examined the effects of fibroblast growth factor 1 (FGF-1) in patients with CLTI (Table 6). One study randomized 107 patients (44% with diabetes) to intramuscular injection of a novel plasmid-based gene therapy for FGF-1 (NV1FGF) ($n = 56$) or placebo ($n = 51$) (160). There were no differences in the primary end point (complete healing of at least one ulcer), $TcPo_2$, ABI, TBI, pain, or death between treatment and placebo groups at 25 weeks. However, rates of all amputation (HR 0.5, $P = 0.015$), major amputation (HR 0.37, $P = 0.015$), and combined major amputation and death (HR 0.44, $P < 0.01$) were significantly reduced in the treatment group compared with placebo. Although adverse events were high, they were similar in both groups. Notably, a large number of participants withdrew from the study because of adverse events or death (31% in treatment, 46% in placebo), thereby significantly reducing the power of the study.

A phase III trial also showed that NV1FGF had no significant benefit in patients with CLTI (161). A total of 525 patients (53% with diabetes) randomized to NV1FGF ($n = 259$) or placebo ($n = 266$) showed no differences in 1-year AFS (primary end point), major amputation, death, or adverse events between treatment and placebo groups. Notably, subgroup analysis in patients with diabetes showed no significant difference in AFS, and no patient was lost to follow-up in this study.

A more recent RCT investigated intramuscular injections of JVS-100, a nonviral gene therapy encoded for stromal cell–derived factor 1 (SDF-1) that activates angiogenesis and tissue reparative pathways (162). Of the 109 patients with CLTI enrolled, 79% of patients had diabetes. Patients were randomized equally into a low-dose, high-dose, or placebo arm. At 3 months, there were no differences in wound healing (primary end point), MALE, major amputation, or all amputations among groups.

## Conclusion

Overall, studies evaluating surgical, endovascular, and emerging treatment options for patients with diabetes and CLTI are plentiful. However, adequately powered, double-blind RCTs with low patient attrition and prespecified, clinically meaningful, and objective outcomes remain scarce. Furthermore, studies evaluating novel treatment options such as gene therapy in patients with diabetes and CLTI are limited. As the global prevalence of diabetes and CLTI continues to grow, a collective effort at improving study design and predetermined objective study outcomes should be a priority for evaluating the efficacy, safety, and effectiveness of therapies tailored to patients with diabetes and CLTI.

### DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

### AUTHOR CONTRIBUTIONS

S.T. wrote the manuscript, researched data, and reviewed/edited the manuscript. S.A and O.S. wrote the manuscript and researched data. N.H. and C.Y. researched data. C.F.S. and M.A.Z. wrote the manuscript and reviewed/edited the manuscript. S.T. and M.A.Z. are guarantors of this work and, as such, take responsibility for the integrity and accuracy of the article.

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