



Three-Year Survival of Critical Limb-Threatening Ischemia Patients With FFRCT-Guided Coronary Revascularization Following Lower-Extremity Revascularization

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Abstract

Objective. The study objective is to determine whether selective coronary revascularization following lower-extremity revascularization can improve long-term survival of patients with critical limb threatening ischemia (CLTI). **Methods.** This study compared CLTI patients with no cardiac history or symptoms who underwent limb-salvage surgery. Group I comprised 103 patients with preoperative coronary computed-tomography derived fractional flow reserve (FFR_{CT}) used to detect ischemia-producing coronary stenosis (FFR_{CT} ≤ 0.80) with selective postoperative coronary revascularization (the FFR_{CT}-guided group) and group II comprised 120 patients with standard preoperative evaluation and no postoperative coronary revascularization (the standard-care group). Both groups received guideline-directed medical therapy. Study endpoints were all-cause death, cardiovascular (CV) death, and myocardial infarction (MI) during 3-year follow-up. **Results.** Preoperative evaluation in the FFR_{CT}-guided group revealed unsuspected (silent) coronary ischemia in 2 of 3 patients (69%) with left main coronary ischemia in 8%. Elective coronary revascularization was performed in 47 patients (46%) 1-3 months following limb-salvage surgery. Standard-care patients had no coronary revascularization. During median follow-up of 36 months, the FFR_{CT}-guided group had fewer deaths (10.7% vs 27.5%; hazard ratio [HR], 0.32; 95% confidence interval [CI], 0.16-0.64; *P* < .01); fewer CV deaths (2.9% vs 17.5%; HR, 0.14; 95% CI, 0.04-0.48; *P* < .01); and fewer MIs (3.9% vs 22.5%; HR, 0.14; 95% CI, 0.05-0.40; *P* < .01) compared with the standard-care group. **Conclusions.** FFR_{CT} evaluation of CLTI patients with no coronary symptoms revealed a high prevalence of unsuspected (silent) coronary ischemia. Coronary revascularization of ischemia-producing coronary lesions following lower-extremity revascularization reduced CV deaths and MIs and improved 3-year survival (89%) compared with standard cardiac evaluation and care (73%).

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Patients with peripheral artery disease (PAD) are at high risk for adverse cardiac events and have poor long-term survival due to coexistent coronary artery disease (CAD).¹ The risk of death is particularly high for patients with critical limb threatening ischemia (CLTI), with 1-year mortality of 20% and 5-year mortality of 60%.^{2,3} This mortality rate is higher than for symptomatic CAD and most cancers.⁴ Moreover, this high mortality rate has remained unchanged over the past 30 years despite remarkable advances in medical treatment and interventional therapies.⁵

In the randomized BASIL (Bypass Versus Angioplasty in Severe Ischemia of the Leg) trial, which was conducted 20 years ago, all-cause mortality in both groups was 56% at 5 years.⁶ In a recent review of 168,553 Medicare beneficiaries revascularized with current endovascular techniques, the 5-year mortality rate was 55%.⁷ While it is well known that most PAD patients have significant CAD and that symptomatic PAD is a powerful independent predictor of cardiovascular death, guidelines do not recommend preoperative cardiac testing, particularly in

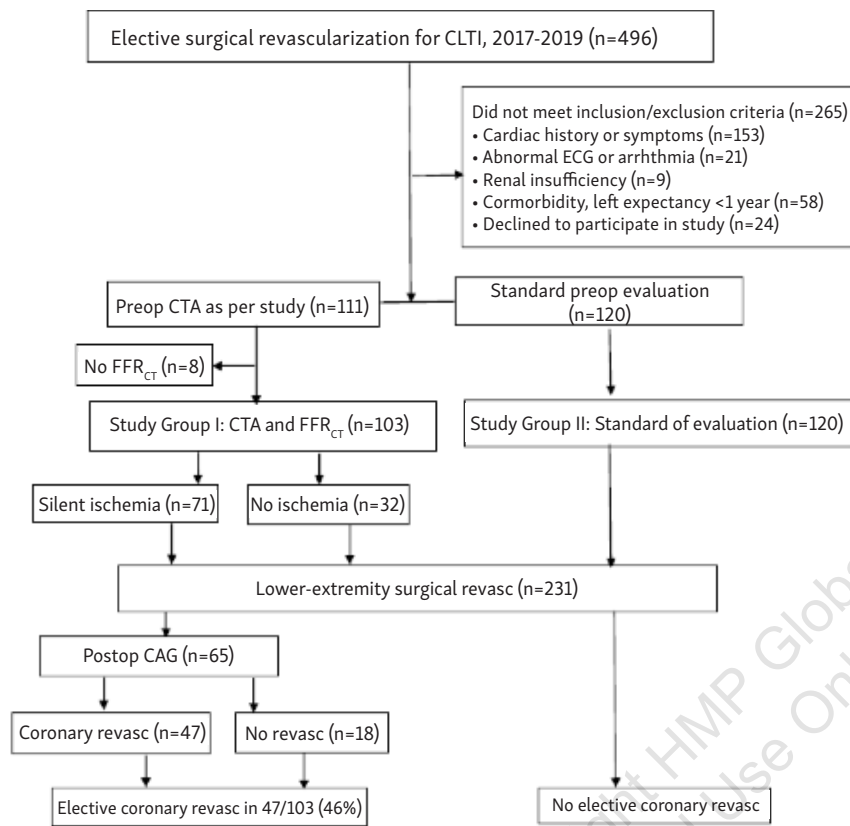


FIGURE 1. Flow diagram. CAG = coronary angiography; CTA = computed tomography angiography; FFR_{CT} = computed tomography derived fractional flow reserve; revasc = revascularization.

patients without cardiac symptoms, due to lack of evidence that coronary revascularization improves long-term outcome.⁸ Rather, efforts to improve the survival of PAD patients have been focused on optimizing medical treatment and aggressive risk factor control to limit the progression of systemic atherosclerosis.⁹ While medical therapy has reduced mortality in large CAD trials that include patients with PAD,¹⁰ there is no evidence that best medical therapy has improved the survival of PAD patients following lower-extremity revascularization.^{5,11-13}

The potential benefit of coronary revascularization to improve the survival of PAD patients was first brought to light by Hertzler et al in a landmark study of 1000 coronary angiograms in vascular surgery patients 4 decades ago.¹⁴ However, this strategy fell by the wayside due to lack of randomized trial evidence showing that coronary revascularization improved long-term survival of PAD patients.⁵ The most recent trial, the Coronary Artery Revascularization Prophylaxis (CARP) trial,¹⁵ was conducted 2 decades ago using angiography-guided coronary revascularization rather than the current standard of fractional flow reserve (FFR)-guided revascularization, which has been shown to reduce mortality.^{16,17} Furthermore, the requirement for preoperative coronary revascularization in CARP resulted in a 2-month delay of the vascular surgery procedure, which is not an option for most CLTI patients.

The alternative strategy of coronary revascularization after peripheral revascularization in order to improve long-term survival has not been evaluated in controlled clinical trials. This may be due to lack of a reliable non-invasive method for identifying PAD patients with hemodynamically significant coronary stenosis who may benefit from coronary revascularization.

A new non-invasive cardiac diagnostic test, coronary computed-tomography derived FFR (FFR_{CT}) provides a unified anatomic and functional assessment of CAD that can reliably identify ischemia-producing coronary lesions.¹⁸ FFR_{CT} accurately reflects invasively measured FFR and can help guide patient management and coronary revascularization decisions.^{19,20} In a single-center study of CLTI patients with no known CAD who were scheduled for lower-extremity revascularization, systematic preoperative FFR_{CT} evaluation revealed a high prevalence (69%) of unsuspected (silent) ischemia-producing coronary stenosis (FFR_{CT} ≤ 0.80).²¹ While this did not result in postponement of the revascularization procedure, it identified high-risk patients and facilitated multidisciplinary vascular team care, including selective coronary

revascularization of high-risk coronary lesions following recovery from lower-extremity revascularization.²² This resulted in improved 1- and 2-year survival of PAD patients compared with a control group receiving guideline-directed cardiac evaluation and care.^{22,23} The purpose of this study is to determine whether FFR_{CT}-guided coronary revascularization of CLTI patients with asymptomatic (silent) coronary ischemia after recovery from limb-salvage surgery can provide long-term survival benefit vs CLTI patients with no coronary symptoms receiving standard cardiac evaluation and care.

Methods

Study design. In this observational case-control study, we compared the 3-year outcomes of 2 groups of patients with CLTI and no cardiac history or symptoms who underwent elective lower-extremity revascularization surgery at Pauls Stradins Clinical University Hospital in Riga, Latvia from 2017-2019. Group I comprised 103 patients enrolled in a prospective open-label study of preoperative cardiac evaluation using coronary CTA and FFR_{CT} analysis to identify ischemia-producing coronary stenosis with selective postoperative coronary revascularization (the FFR_{CT}-guided group).¹⁸ Group II comprised 120 patients

TABLE 1. Patient characteristics.

Characteristics	FFR _{CT} -Guided (n = 103)	Standard Care (n = 120)	P-Value
Baseline characteristics			
Age (years)	66 ± 8	66 ± 7	.79
Male gender	81 (79%)	99 (83%)	.47
Hypertension	78 (76%)	80 (67%)	.14
Hyperlipidemia	29 (28%)	42 (35%)	.27
Diabetes mellitus	9 (9%)	22 (18%)	.04
Smoking history	60 (58%)	77 (64%)	.37
Postoperative medical therapy			
Statins	86 (83%)	98 (82%)	.94
Antiplatelets/anticoagulants	101 (98%)	119 (99%)	.45
Antihypertensives	62 (60%)	79 (66%)	.44
Insulin	11 (11%)	22 (18%)	.09

Data presented as mean ± standard deviation or count (%). FFR_{CT} = computed-tomography derived fractional flow reserve.

with standard preoperative cardiac evaluation and no elective postoperative coronary revascularization (the standard-care group). Patients in both groups had no history of myocardial infarction (MI), coronary angiography, or coronary revascularization, had no known cardiac disease, and had no cardiac symptoms. All patients were admitted to the hospital and were cleared for elective lower-extremity revascularization surgery in accordance with current guidelines.¹⁹ Following surgery, all patients received guideline-directed medical therapy. The study was approved by the institutional ethics committee and patients in both groups signed informed consent. Details of the inclusion and exclusion criteria with 1- and 2-year outcomes of all patients enrolled in the prospective study have been published.^{17,18} These reports included patients who did not have FFR_{CT} analysis due to poor coronary CTA image quality. The current study provides 3-year outcomes specific to CLTI patients who had FFR_{CT} analysis to help guide patient-management decisions compared with CLTI patients receiving standard guideline-directed care. A flow diagram of patients included in this study is shown in **Figure 1**.

Group I (FFR_{CT}-guided group). In addition to standard preoperative cardiac clearance, all patients in group I underwent protocol-driven coronary CT angiography (CTA) imaging prior to scheduled lower-extremity revascularization. CTA imaging was performed in accordance with Society of Cardiovascular Computed Tomography guidelines with sublingual nitroglycerin for coronary vasodilation and beta blockade for heart rate control.²⁴ CTA image datasets were sent to HeartFlow via secure web-based interface for computational analysis of FFR_{CT}. A color-coded map of FFR_{CT} values in each coronary artery along

with an interactive 3-dimensional model was returned within 24 hours for physician interpretation and clinical use to help guide patient-management decisions. A representative case is provided in **Figure 2**. *Lesion-specific coronary ischemia* was defined as FFR_{CT} ≤ 0.80 distal to coronary stenosis with *severe ischemia* defined as FFR_{CT} ≤ 0.75. Due to the pressing clinical need for lower-extremity revascularization in these CLTI patients, results of the FFR_{CT} analysis did not alter plans for limb-salvage surgery, which was performed as planned in all patients. However, FFR_{CT} analysis identified high-risk patients with significant lesion-specific coronary ischemia who were selected for elective coronary angiography 1-3 months after recovery from limb-salvage surgery (median, 61 days). Elective coronary revascularization was performed in accordance with the 2018 European Society of Cardiology/European Association for Cardiothoracic Surgery guidelines for myocardial revascularization, with consideration of patient preferences, comorbidities, and specifics of coronary anatomy.²⁵

Group II (standard-care group). Patients in group II underwent standard preoperative cardiac evaluation comprising clinical risk assessment, standard laboratory testing, chest x-ray, and resting electrocardiography, in accordance with current guidelines.⁸ No preoperative cardiac imaging or stress testing was performed since all patients were free of cardiac symptoms and had no clinical evidence of cardiac disease. Postoperatively, no patient had elective coronary angiography or coronary revascularization.

Study endpoints. The *primary endpoint* for this study was all-cause death (survival) during follow-up. *Secondary endpoints* included

TABLE 2. Deaths during 3-year follow-up.

Deaths During Follow-Up	FFR _{CT} -Guided (n = 103)	Standard Care (n = 120)
Total deaths	11 (10.7%)	33 (27.5%)
Cardiovascular deaths	3 (2.9%)	21 (17.5%)
Other deaths	8 (7.8%)	12 (10.0%)
Cancer	7 (6.8%)	12 (10.0%)
Trauma	1 (0.9%)	0 (0.0%)

Data presented as mean ± standard deviation or count (%).
FFR_{CT} = computed-tomography derived fractional flow reserve.

CV death and MI during follow-up. Endpoints were defined in accordance with the Academic Research Consortium-2 consensus document²⁶ and adjudicated by an interdisciplinary institutional endpoints committee.

Statistical analysis. Continuous variables were compared using Student’s t test if normally distributed and using Mann-Whitney U test if non-normally distributed. Categorical variables were compared using Chi-square test or Fisher’s exact test, as appropriate. Kaplan-Meier survival curves were compared using the log-rank test. A Cox proportional hazards model was used to determine the hazard ratio (HR) and 95% confidence interval (CI), adjusted for age, gender, diabetes mellitus, hyperlipidemia, hypertension, and smoking history. Statistical analyses were

performed using SPSS Statistics, version 23.0 (IBM) with significance defined as $P < .05$.

Results

Patient characteristics. Baseline characteristics of the 2 study groups are shown in **Table 1**. There were no significant differences between the FFR_{CT}-guided group and the standard-care group with regard to age, gender, hypertension, hyperlipidemia, or smoking history. However, the number of patients with diabetes mellitus was 2-fold higher in the standard-care group compared with the FFR_{CT} group (18% vs 9%, respectively; $P = .04$) (**Table 1**). All patients underwent open surgical revascularization with infrainguinal procedures (femoropopliteal-tibial) in >80% of patients in both groups. Postoperative guideline-directed medical therapy was similar in both groups regarding administration of statins, antiplatelet/anticoagulants, and antihypertensives.

Ischemia-producing coronary stenosis. In the FFR_{CT}-guided group, preoperative coronary CTA imaging revealed $\geq 50\%$ stenosis in ≥ 1 vessels in 70% of patients and FFR_{CT} analysis revealed unsuspected (silent) coronary ischemia in 71 patients (69%). Severe ischemia ($FFR_{CT} \leq 0.75$) was present in 58% of patients, with left main coronary ischemia in 8%. In the standard-care group, preoperative evaluation for coronary ischemia was limited to the demonstration of no ischemic changes on resting electrocardiography.

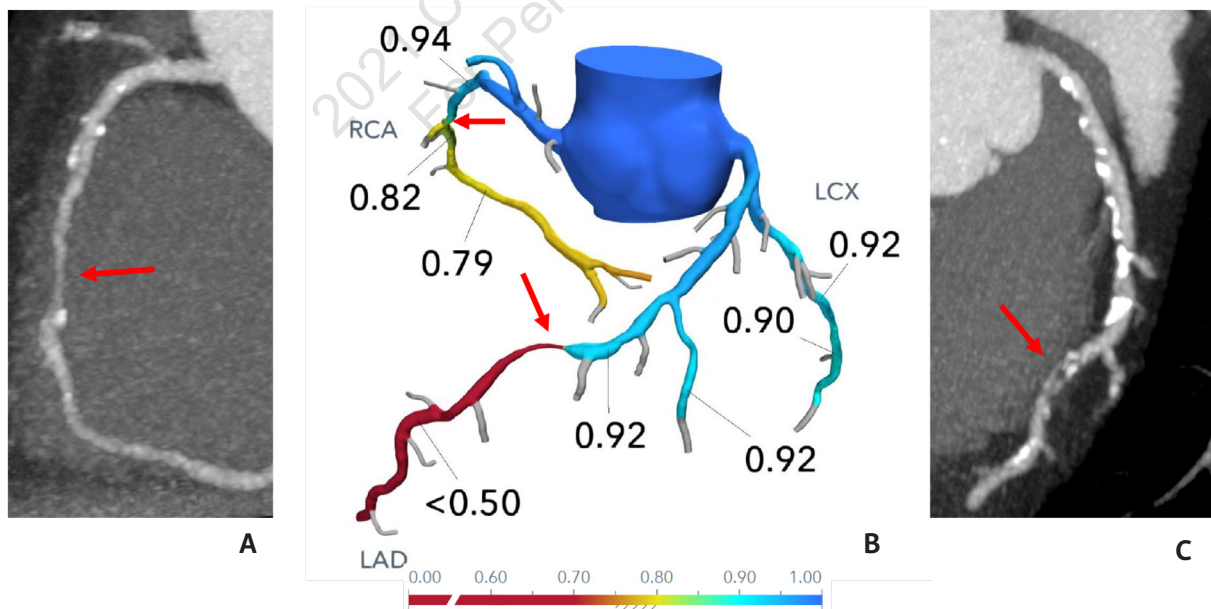


FIGURE 2. Preoperative cardiac evaluation of a 71-year-old man with ischemic rest pain of the foot and no known coronary disease. Coronary computed tomography angiography (CTA) demonstrates 30% right coronary artery (RCA) stenosis (A) and 60% left anterior descending (LAD) stenosis (C); Computed-tomography derived fraction flow reserve (FFR_{CT}) analysis (B) reveals moderate RCA ischemia (FFR_{CT} 0.79) and severe LAD ischemia ($FFR_{CT} < 0.50$). Lower-extremity bypass relieved the patient’s foot pain and 1 month later the ischemic coronary lesions (red arrows) were treated with percutaneous coronary intervention.

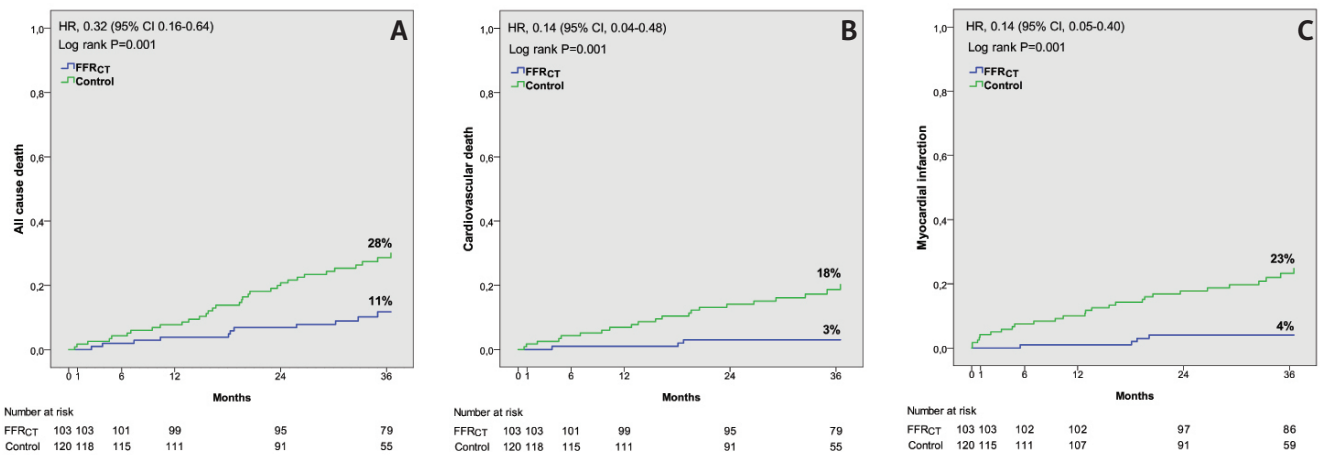


FIGURE 3. Kaplan-Meier curves: (A) all-cause death; (B) cardiovascular death; and (C) myocardial infarction. FFR_{CT} = computed-tomography derived fraction flow reserve.

Postoperative coronary revascularization. Of 71 patients with FFR_{CT} evidence of lesion-specific coronary ischemia, 65 were studied with coronary angiography 1-3 months after recovery from limb-salvage surgery (median, 61 days). Elective coronary revascularization was performed in 47 patients (46% of the FFR_{CT}-guided group) with percutaneous coronary intervention (PCI) in 42 patients and coronary artery bypass grafting (CABG) in 5 patients. In the standard-care group, the status of coronary ischemia was unknown, and no patient had elective postoperative coronary angiography or coronary revascularizations.

Patient follow-up. Median follow up was 36 months (interquartile range [IQR], 33-42 months) in the FFR_{CT}-guided group and 36 months (IQR, 27-43 months) in the standard-care group. There were 11 deaths (10.7%) in the FFR_{CT}-guided group and 33 deaths (27.5%) in the standard-care group. Most deaths (21 of 33; 64%) in the standard-care group were due to CV causes, whereas non-cardiovascular deaths (8 of 11; 73%) predominated in the FFR_{CT}-guided group (Table 2).

Endpoint analysis. Cumulative survival curves by Kaplan-Meier estimates are shown in Figure 3. At 3 years, the FFR_{CT}-guided group had fewer all-cause deaths compared with the standard-care group (10.7% vs 27.5%, respectively; HR, 0.32; 95% CI, 0.16-0.64; P<.01). The absolute risk reduction (ARR) for death was 17% with a relative risk reduction (RRR) of 61%. The risk of CV death was more than 5-fold lower in the FFR_{CT}-guided group compared with the standard-care group (2.9% vs 17.5%, respectively; HR, 0.14; 95% CI, 0.04-0.48; P<.01). ARR for CV death was 15%, with RRR of 95%. Similarly, there was more than a 5-fold reduction in MI in the FFR_{CT}-guided group compared with the standard-care group (3.9% vs 22.5%; HR, 0.14; 95% CI, 0.05-0.40; P<.01), with an ARR of 19% and RRR of 83%. Cumulative

3-year survival was 89.3% in the FFR_{CT}-guided group vs 72.5% in the standard-care group (P<.01) (Figure 4).

Discussion

This is the first study to report 3-year outcomes of a new strategy aimed at reducing the high mortality rate of CLTI patients following lower-extremity revascularization. This strategy is based on systematic preoperative evaluation using coronary CTA and FFR_{CT} to identify high-risk patients with asymptomatic (silent) coronary ischemia together with selective postoperative coronary revascularization in addition to optimal medical therapy. Compared with CLTI patients with no cardiac symptoms treated with optimal medical therapy alone, in accordance with current guidelines (no preoperative cardiac testing and no coronary revascularization),⁸ this new strategy resulted in a 68% reduction in the risk of death (11% vs 28%; P<.001) and an 86% reduction in the risk of myocardial infarction (4% vs 23%; P<.001) at 3 years. This represents a 17% ARR for death during 3 years of follow-up, which is greater than the previously reported 12% risk reduction seen at 2 years of follow-up (8% in the FFR_{CT} group vs 20% in the control group; P=.02).²³ As seen in Figure 4, the slope of the survival curves shows increasing divergence over time, suggesting that an improving long-term benefit may be expected from selective coronary revascularization of CLTI patients with silent coronary ischemia.

The improvement in 3-year survival was primarily due to a 5-fold reduction in CV deaths in the FFR_{CT}-guided group compared with the standard-care group (3% vs 18%, respectively; P<.01). Of all deaths in the standard-care group, 64% were due to CV causes, while only 27% of the deaths in the FFR_{CT}-guided group were CV related. The reduction in CV deaths was associated with elective coronary revascularization in 46% of patients in addition to best medical therapy following lower-extremity revascularization.

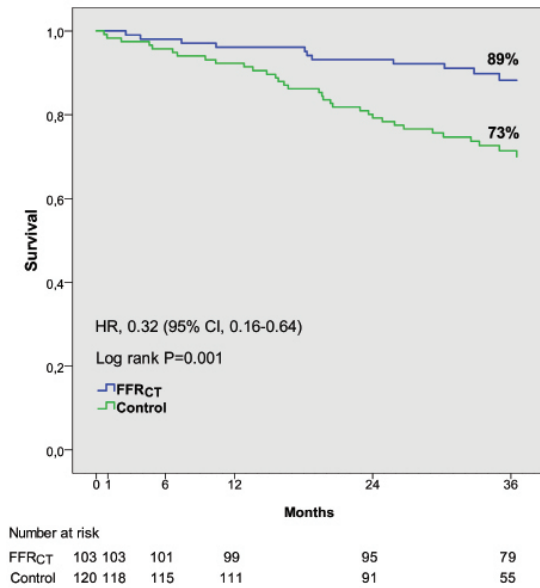


FIGURE 4. Survival curve. FFR_{CT} = computed-tomography derived fractional flow reserve.

In contrast, patients in the standard-care group had no elective coronary revascularization and were treated with best medical therapy alone in accordance with current guidelines.^{8,9}

Guideline-directed medical therapy in PAD patients is largely based on evidence derived from large randomized trials primarily focused on patients with symptomatic CAD who are often treated with coronary revascularization. In the FOURIER trial of 27,564 patients with CAD, PAD, or stroke randomized to best medical therapy plus PCSK9 inhibitor or placebo, 50% had prior MI, 63% had prior coronary revascularization, and only 13% had PAD alone.¹² Among the 3642 PAD patients, PCSK9 inhibition reduced the risk of major adverse limb events ($P < .001$) but did not reduce mortality.¹² In the COMPASS trial of 18,278 patients with chronic CAD or PAD randomized to rivaroxaban plus aspirin or aspirin alone, 90% of patients had CAD, 62% had prior MI, and only 27% had PAD.¹⁰ The combination of rivaroxaban plus aspirin reduced the risk of death in the entire study population (3.4% vs 4.1%; $P = .01$), but results specific for PAD patients were not reported.¹⁰ In the VOYAGER PAD trial, which was specifically focused on PAD patients who had undergone lower-extremity revascularization, 6564 patients were randomized to rivaroxaban or placebo, including 31% with symptomatic CAD and 11% with prior MI.¹³ While rivaroxaban was effective in reducing the composite endpoint of acute limb and cardiovascular events ($P < .01$), there was no reduction in CV or all-cause mortality.¹³ In a recent outcome analysis from our center, we compared a subset of VOYAGER PAD patients with no cardiac history or symptoms to a matched cohort of PAD patients enrolled in our prospective study of preoperative FFR_{CT} evaluation. We found that among PAD patients with no

known CAD, FFR_{CT}-guided coronary revascularization following lower-extremity revascularization was associated with a 70% lower mortality rate at 2.5 years compared with patients treated with best medical therapy in the VOYAGER PAD trial (5% vs 23%; $P < .01$).²⁷

The benefit of coronary revascularization seen in this study was not surprising, given the extent and depth of coronary ischemia that was present in the FFR_{CT}-guided group. More than 50% of patients had severe coronary ischemia with FFR_{CT} values below 0.75. It is known that low FFR values are associated with higher adverse event rates²⁸ and that patients with lower FFR values have greater benefit from coronary revascularization.²⁹ Moreover, 8% of patients had left main coronary ischemia, which is associated with sudden cardiac death. Thus, improvement in survival with coronary revascularization may be expected. However, it was surprising to find so many patients with life-threatening coronary ischemia in the FFR_{CT} group, since no patient had a cardiac history or coronary symptoms. Patients in the standard-care group also had no cardiac symptoms and were likely to have similar manifestations of coronary atherosclerosis; however, since no cardiac testing was done, the degree and extent of silent coronary ischemia was unknown.

The 3-year mortality rate of 28% in the standard-care group, although more than 2-fold higher than in the FFR_{CT}-guided group, compared favorably with recently reported 3-year mortality rates following lower-extremity revascularization. In a Swedish nationwide registry of 16,889 open and endovascular revascularizations for CLTI, the 3-year mortality rate was 41%.³⁰ A meta-analysis of 11 studies with 2213 patients with endovascular revascularization with or without paclitaxel-coated devices found that all-cause mortality at 3 years was 40%.³⁰ In the SWEDEPAD (Swedish Drug Elution Trial in Peripheral Arterial Disease) study of 2289 PAD patients randomized to endovascular treatment with paclitaxel-coated vs uncoated devices, all-cause mortality was 33% in CLTI patients at 2.5 years.³¹ The high mortality rates seen in PAD patients have been attributed to low use of guideline-directed medical therapy following revascularization.³⁵ In our study, patients in both groups received evidence-based medical therapy with statins in more than 80% of patients and antiplatelet/anticoagulants in more than 95% of patients. FFR_{CT}-guided coronary revascularization provided additional benefit over and above medical therapy and this is consistent with the findings of a recent meta-analysis of randomized trials comparing coronary revascularization plus medical therapy with medical therapy alone.³²

Study limitations. This study is limited by its observational nature and the potential for selection bias. Accrual of patients into each study group was unspecified and depended on the relative availability of operating room time for much-needed limb salvage surgery (5 days per week) and the limited availability of coronary CTA imaging for clinical research purposes (1 day per week). Although there was interest in enrolling all

eligible patients in the prospective FFR_{CT} study, this was not possible, largely due to CTA imaging constraints, resulting in a comparable number of eligible patients in the control arm of this study. Furthermore, removal of enrolled patients who underwent CTA imaging but did not have FFR_{CT} analysis due to CTA imaging artifacts and motion resulted in an imbalance in the study populations with a greater number of diabetic patients in the standard-care group, which may have contributed to the higher mortality in this group. Adjustment for this imbalance was made in the multivariate Cox proportional modeling, which in addition to diabetes, was adjusted for other baseline variables such as age, gender, hyperlipidemia, hypertension, and smoking history. While the 3-year results of this single-center study are promising, they are not generalizable and should be considered as hypothesis generating. Prospective, randomized trials are needed to further define the role of FFR_{CT}-guided coronary revascularization in patients with CLTI.

Conclusion

Preoperative FFR_{CT} evaluation of CLTI patients with no coronary symptoms revealed a high prevalence of unsuspected (silent) coronary ischemia. FFR_{CT}-guided coronary revascularization of ischemia-causing coronary lesions within 3 months following limb-salvage surgery resulted in increasing clinical benefit over time with fewer CV deaths and MIs and improved 3-year survival compared with CLTI patients receiving standard cardiac evaluation and care (89% vs 73%, respectively; $P < .001$).

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