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Pre-operative Diagnosis of Silent Coronary Ischaemia May Reduce Post-operative Death and Myocardial Infarction and Improve Survival of Patients Undergoing Lower Extremity Surgical Revascularisation

Dainis Krievins [a,b,*], Edgars Zellans [a,b], Gustavs Latkovskis [a,b], Andrejs Erglis [a,b], Ligita Zvaigzne [b], Indulis Kumsars [a,b], Roberts Rumba [a,c], Peteris Stradins [a,c], Sanda Jegere [a,b], Christopher K. Zarins [d]

[a] Pauls Stradins Clinical University Hospital, Riga, Latvia
[b] University of Latvia, Riga, Latvia
[c] Riga Stradins University, Riga, Latvia
[d] HeartFlow, Redwood City, CA, USA

WHAT THIS PAPER ADDS

This study shows that pre-operative evaluation of patients undergoing lower extremity surgical revascularisation using coronary computed tomography derived fractional flow reserve can identify high risk patients with silent coronary ischaemia. This information can facilitate a multidisciplinary team approach to improve patient outcome. Increased focus on peri-operative cardiac care combined with selective post-operative coronary revascularisation of patients with silent ischaemia resulted in fewer cardiovascular deaths and myocardial infarctions, and improved one year survival compared with patients having standard pre-operative cardiac evaluation. If confirmed by future studies, this strategy may improve long term survival of patients with peripheral vascular disease.

Objective: Patients undergoing peripheral vascular surgery have increased risk of death and myocardial infarction (MI), which may be due to unsuspected (silent) coronary ischaemia. The aim was to determine whether pre-operative diagnosis of silent ischaemia using coronary computed tomography (CT) derived fractional flow reserve (FFR_{CT}) can facilitate multidisciplinary care to reduce post-operative death and MI, and improve survival.
Methods: This was a single centre prospective study with historic controls. Patients with no cardiac symptoms undergoing lower extremity surgical revascularisation with pre-operative coronary CTA-FFR_{CT} testing were compared with historic controls with standard pre-operative testing. Silent coronary ischaemia was defined as $FFR_{CT} \leq 0.80$ distal to coronary stenosis with $FFR_{CT} \leq 0.75$ indicating severe ischaemia. End points included cardiovascular (CV) death, MI, and all cause death through one year follow up.
Results: There were no statistically significant differences between CT angiography (CTA-FFR_{CT}) ($n = 135$) and control ($n = 135$) patients with regard to age (66 ± 8 years), sex, comorbidities, or surgery performed. Coronary CTA showed ≥ 50% stenosis in 70% of patients with left main stenosis in 7%. FFR_{CT} revealed silent coronary ischaemia in 68% of patients with severe ischaemia in 53%. The status of coronary ischaemia was unknown in the controls. At 30 days, CV death and MI in the CTA-FFR_{CT} group were not statistically significantly different from controls (0% *vs.* 3.7% [$p = .060$] and 0.7% *vs.* 5.2% [$p = .066$], respectively). Post-operative coronary revascularisation was performed in 54 patients to relieve silent ischaemia (percutaneous coronary intervention in 47, coronary artery bypass graft in seven). At one year, CTA-FFR_{CT} patients had fewer CV deaths (0.7% *vs.* 5.9%; $p = .036$) and MIs (2.2% *vs.* 8.1%; $p = .028$) and improved survival ($p = .018$) compared with controls.
Conclusion: Pre-operative diagnosis of silent coronary ischaemia in patients undergoing lower extremity revascularisation surgery can facilitate multidisciplinary patient care with selective post-operative coronary revascularisation. This strategy reduced post-operative death and MI and improved one year survival compared with standard care.

Keywords: Coronary CT derived fractional flow reserve, Long term survival, Peripheral artery disease, Post-operative mortality, Silent coronary ischaemia, Surgical revascularisation
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* Corresponding author. 13 Pilsonu street, Riga LV-1002, Latvia.
E-mail address: dainis.krievins@stradini.lv (Dainis Krievins).

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INTRODUCTION

Patients undergoing surgery for symptomatic peripheral arterial disease (PAD) are at high risk of death and myocardial infarction (MI) due to co-existing coronary artery disease (CAD). In hospital mortality for major vascular surgery is 3%,[1] and 30 day cardiovascular (CV) death and MI rates exceed 5%.[2] Mortality is particularly high for patients with critical limb threatening ischaemia (CLTI), with 20% mortality at six months and 50% at four years.[3,4] Patients, successfully revascularised, have reduced long term survival, with high mortality in those with post-operative myocardial ischaemia.[5] While it is well known that most vascular surgery patients have statistically significant CAD by pre-operative coronary angiography,[6] randomised trials have shown no survival benefit from pre-operative coronary revascularisation.[7] Accordingly, systematic pre-operative cardiac testing is not recommended, as testing usually does not lead to modification of management strategy.[8,9] The increased risk to patients with combined PAD and CAD is highlighted in the 2017 European Society of Cardiology (ESC)/European Society of Vascular Surgery (ESVS) guidelines, with a strong recommendation for multidisciplinary vascular team management of patients presenting with PAD.[9] At the same time, guidelines emphasise that cardiac testing is not indicated for patients presenting with PAD symptoms but no symptoms of CAD.[9] Thus, despite strong evidence that symptomatic PAD is a consistent and powerful independent predictor of peri-operative cardiac events and mortality, patients with no cardiac symptoms usually undergo surgery with no knowledge of the extent and functional significance of CAD,[10] leaving them at high risk of early and late cardiac events.

A new non-invasive cardiac diagnostic modality, coronary computed tomography (CT) derived fractional flow reserve (FFR_{CT}) can identify patients with haemodynamically statistically significant, ischaemia producing coronary stenosis. FFR_{CT} analysis uses anatomical data provided by standard coronary CT angiography (CTA) imaging and mathematical modelling of coronary blood flow to compute FFR values throughout the coronary tree.[11] Prospective clinical trials have shown good correlation between computed FFR_{CT} and invasively measured FFR with accurate identification of patients with ischaemia producing coronary stenosis.[12] The clinical usefulness of FFR_{CT} in patients presenting with symptoms of CAD is well documented,[13–16] and FFR_{CT} analysis has been used to evaluate $>$ 50 000 patients with suspected CAD in Europe, the USA, Canada, and Japan. The value of FFR_{CT} in patients with no cardiac symptoms who are at high risk of coronary events, such as those presenting with symptomatic PAD in need of revascularisation surgery, is unknown. Initial experience with CTA-FFR_{CT} in patients with CLTI showed a high prevalence of unsuspected (silent) ischaemia producing coronary stenosis,[17] and prompted the current investigation. The purpose of this study was to determine whether pre-operative diagnosis of silent coronary ischaemia using CTA and FFR_{CT} can facilitate multidisciplinary care to reduce post-operative cardiac events and improve survival of patients undergoing peripheral vascular surgery *vs.* the current standard of care.

MATERIALS AND METHODS

Study design

Two consecutive cohorts of patients with symptomatic lower extremity PAD and no cardiac symptoms who were admitted to the Pauls Stradins Clinical University Hospital, Riga, Latvia, for elective open surgical revascularisation were compared: (1) patients enrolled in a prospective, open label study of pre-operative cardiac evaluation using coronary CTA and FFR_{CT}; and (2) patients with standard pre-operative cardiac evaluation who met the inclusion/exclusion criteria of the prospective study and had open surgical revascularisation during earlier year serving as controls. CTA-FFR_{CT} evaluation was not available to any patients during the control period, whereas in the prospective study all patients who met the inclusion/exclusion criteria and signed informed consent underwent CTA-FFR_{CT} evaluation. The primary study end point was CV death at 30 days, six months, and one year. Secondary end points included all cause death, MI, and major adverse cardiovascular event (MACE) rate consisting of death, MI, or unplanned coronary revascularisation over a one year follow up. End points were adjudicated by an interdisciplinary end points committee in accordance with the Academic Research Consortium-2 consensus document.[18]

CTA-FFR_{CT} group

The prospective study was approved by the institutional ethics committee and initiated in October 2017. The patient population comprised patients with stable CLTI or limiting claudication who were admitted for lower extremity revascularisation and cleared for open surgery following standard pre-operative cardiac evaluation, including resting electrocardiography (ECG). Criteria for study inclusion were age $\geq$ 50 years, stable, symptomatic PAD needing revascularisation, and no cardiac history or symptoms of CAD. Exclusion criteria included ischaemic changes on pre-operative ECG, prior MI, coronary revascularisation or pacemaker, suspicion of acute coronary syndrome, severe dysrhythmia, chronic renal failure (creatinine $>$130 μmol/L), any active disease with life expectancy $<$ 1 year, inability to obtain coronary CTA, and contraindication to beta blocking agents or nitroglycerin. After signing an informed consent form, standard coronary CTA imaging was performed using a single source 64 row scanner with beta blockers for heart rate control and sublingual nitroglycerin for coronary vasodilation in accordance with guidelines.[19] CTA image datasets were sent via a secure web based interface to HeartFlow (Redwood City, CA, USA) for computational analysis of FFR_{CT}. Results were available within 24 hours for patient management decisions, guided by a multidisciplinary vascular team comprised of vascular surgery, anaesthetics, cardiology, and cardiac surgery. Follow up care was provided by the vascular team in collaboration with local medical providers for each patient.

Coronary calcium score was determined using the Agatston method.[20] Statistically significant coronary stenosis by CTA was defined as $\geq$ 50% stenosis. Lesion specific coronary ischaemia was defined as $FFR_{CT} \leq 0.80$ distal to $>$ 30% stenosis in a $>$ 2 mm diameter coronary artery. Severe lesion specific ischaemia was defined as $FFR_{CT} \leq 0.75$ distal to stenosis in a $>$ 2 mm diameter vessel.

Control group

The registry of all vascular surgery operations performed at the Pauls Stradins Clinical University Hospital during the year prior to initiation of the prospective study was reviewed to identify patients who had had elective open surgical revascularisation for CLTI or limiting claudication. All patients signed informed consent at the time of operation with planned follow up. The institutional ethics committee granted approval for review of medical records and gathering of follow up information. From September 2016 to September 2017, a total of 470 vascular surgery operations were performed of which 295 were elective, lower extremity surgical revascularisations. Of these, 160 patients did not meet the inclusion/exclusion criteria for the following reasons: prior cardiac history or documented cardiac symptoms ($n = 108$); severe dysrhythmia ($n = 32$); chronic renal failure ($n = 13$); and comorbid condition with life expectancy $<$ 1 year ($n = 7$). The selected control group of 135 patients met the inclusion/exclusion criteria of the prospective study and had undergone standard pre-operative cardiac evaluation consisting of history, physical examination, chest Xray, and resting ECG. No pre-operative cardiac stress testing was performed, and operations were carried out by the same experienced team of vascular surgeons, medical staff, and critical care team as in the prospective study with access to cardiology or specialty consultation as needed. Medical care and long term follow up were provided by the vascular surgery team in collaboration with each patient's local medical provider.

Statistical analysis

Continuous variables were tested for normal distribution with the Shapiro–Wilk test and were expressed as mean ± standard deviation if normally distributed and as median (interquartile range [IQR]) if non-normally distributed. Continuous variables were compared between the two groups using the Student's *t* test if normally distributed and the Mann–Whitney *U* test if non-normally distributed. Categorical variables were expressed as count (percentage) and were compared using chi square test or Fisher's exact test as appropriate. Kaplan–Meier survival curves were compared using the log rank test. Statistical analyses were performed using SPSS Statistics version 23.0 (IBM, Armonk, NY, USA) with significance defined as $p < .05$.

RESULTS

Study groups

The baseline characteristics of the two study groups are shown in Table 1. There were no statistically significant differences between the CTA-FFR_{CT} and control groups with respect to age, sex distribution, comorbidities, medications, or pre-operative ankle brachial index. The primary

Table 1. Baseline characteristics of patients undergoing lower extremity surgical revascularisation with pre-operative coronary computed tomography angiography (CTA) and computed tomography derived fractional flow reserve (FFR_{CT}) evaluation or standard pre-operative evaluation (control) for detecting silent coronary ischaemia

Patient characteristics	CTA-FFR_{CT} ($n = 135$)	Control ($n = 135$)	p^*
Mean age ± SD – years	65 ± 8	66 ± 8	.66
Males	106 (78.5)	109 (80.7)	.66
Comorbidities			
Hypertension	104 (77.0)	101 (74.8)	.70
Hyperlipidaemia	42 (31.1)	52 (38.5)	.17
Diabetes mellitus	15 (11.1)	23 (17.0)	.15
Smoking history	88 (65.2)	91 (67.4)	.70
Medications			
Antihypertensives	75 (55.5)	69 (51.1)	.55
Statins	51 (37.8)	53 (39.2)	.73
Insulin	15 (11.1)	23 (17.0)	.15
Antiplatelets/anticoagulants	80 (59.2)	71 (52.6)	.33
Primary indication for surgery			
CLTI	116 (85.9)	110 (81.5)	.32
Limiting claudication	19 (14.1)	25 (18.5)	.32
Median pre-operative ABI (IQR)[†]	0.62 (0.47–0.71)	0.67 (0.48–0.74)	.13
Operation performed			
Aorto-iliofemoral	52 (38.5)	53 (39.2)	.90
Femoropopliteal/tibial	78 (57.8)	82 (60.7)	.90

Data are presented as *n* (%) unless stated otherwise. SD = standard deviation; CLTI = chronic limb threatening ischaemia; ABI = ankle brachial index; IQR = interquartile range.

* *p* value of difference between groups.

[†] Data available for 124 patients in the FFR_{CT} group and 120 patients in the control group.

indication for revascularisation surgery was CLTI in 86% of FFR_{CT} patients and 82% of control patients. The surgical procedures in both groups were performed by the same team of vascular surgeons and cardiovascular anaesthetists with no changes in protocol. Neuraxial anaesthesia was used in 95% of patients in both groups with continuous blood pressure, ECG, oxygenation, and urine output monitoring. Approximately 40% of operations in each group were inflow procedures (aorto-iliofemoral) and 60% were outflow procedures (femoropopliteal/distal). There were no statistically significant differences between groups with regard to duration of operation, blood loss during surgery, or post-operative haemoglobin level.

CTA-FFR_{CT}

Calcium scoring in 135 patients revealed extensive coronary calcification (median Agatston score 905 [IQR 390—1 674], total range 0—4 810). Coronary stenosis $\geq$ 50% by CTA was present in 70% of patients with left main stenosis in 7%. FFR_{CT} analysis was performed in 126 patients (93%). In nine patients FFR_{CT} analysis could not be performed because of excessive cardiac motion or image misregistration; there were no exclusions due to excess coronary calcification. Lesion specific coronary ischaemia ($FFR_{CT} \leq 0.80$) was present in 86 patients (68.2%) with no coronary ischaemia in 40 patients (31.7%) (Fig. 1). Single vessel ischaemia was present in 38 of 126 patients (30.1%), with multivessel ischaemia in 48 patients (38.1%). Mean FFR_{CT} in patients with ischaemia was 0.70 $\pm$ 0.14 and severe ischaemia ($FFR_{CT} \leq 0.75$) was present in 72 of 135 patients (53.3%).

With knowledge of the results of FFR_{CT} analysis, planned revascularisation surgery was performed in 130 patients (96.3%) using cardiac anaesthesia, continuous intra-operative monitoring, post-operative intensive care, and optimal medical management. There were no post-operative deaths. One patient had a MI on day three after aortofemoral bypass and had successful emergency percutaneous coronary intervention (PCI) with uneventful one year outcome. This patient did not have pre-operative FFR_{CT} analysis owing to poor coronary CT image quality. Vascular surgery was postponed in five patients, four of whom had coronary ischaemia. One patient had PCI followed by lower extremity bypass three months later. One patient with CLTI and severe three vessel coronary ischaemia declined recommended CABG surgery and left the hospital. He subsequently had femoropopliteal bypass at another facility and is well at one year. Surgery was cancelled in two patients with ischaemic ulcers because of absent target vessels for distal bypass, and both had below knee amputation during follow up. One patient with claudication with no coronary ischaemia decided on medical treatment rather than surgery.

Post-hospital care

All patients remained free of chest pain symptoms and received optimal medical therapy, including statins, antiplatelet or anticoagulant agents, antihypertensives, and diabetes control as appropriate. On the basis of the results of pre-operative FFR_{CT} analysis, patients with significant silent coronary ischaemia were selected for post-operative coronary angiography one to three months after lower extremity revascularisation. Criteria for selection included evidence of left main stenosis or lesion specific ischaemia in a major coronary artery. Coronary angiography was performed in 75 patients with confirmation of significant coronary stenosis in each patient. Elective coronary revascularisation was performed in 54 patients (63% of patients with silent ischaemia) with PCI in 47 patients and CABG in seven patients. Representative patient examples are shown in Fig. 2. One patient suffered a procedure

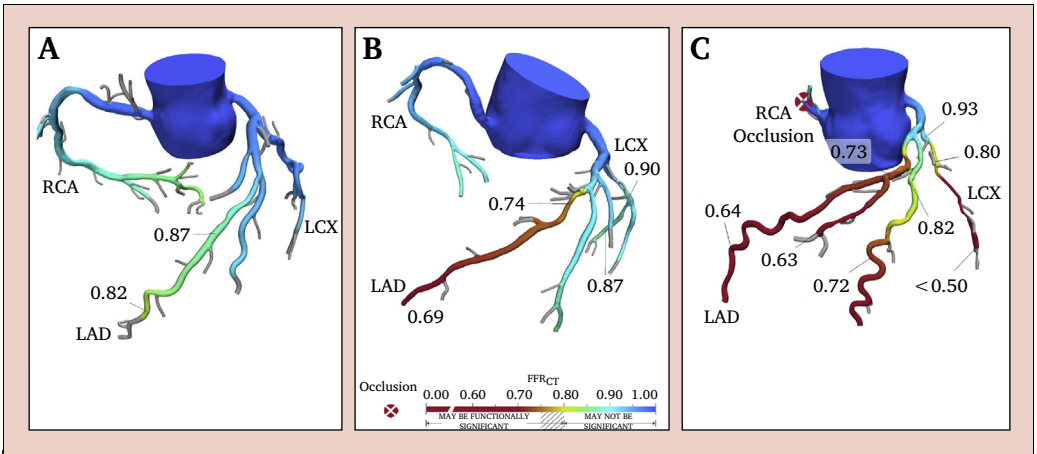

Figure 1. Silent coronary ischaemia in patients undergoing lower extremity revascularisation. Ischaemia producing coronary artery stenosis (computed tomography derived fractional flow reserve [FFR_{CT}] $\leq$ 0.80) was found in 86 of 126 patients (68.2%) in a spectrum of disease with representative examples of (A) no coronary ischaemia in 32%, as in a 67 year old woman with claudication; (B) single vessel coronary ischaemia in 30%, as in a 67 year old man with ischaemic rest pain; and (C) multivessel coronary ischaemia in 38% of patients, as in a 59 year old man with limiting claudication. RCA = right coronary artery; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery.

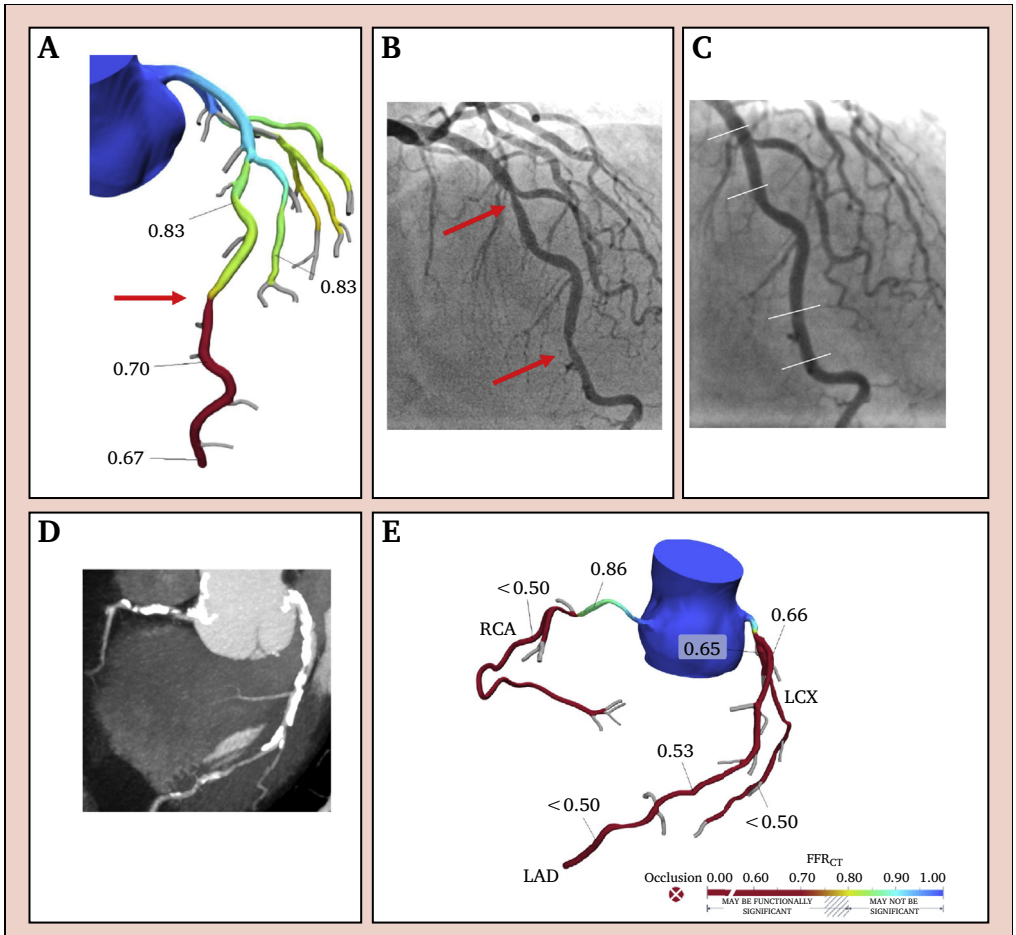

Figure 2. Coronary revascularisation after recovery from vascular surgery. Coronary revascularisation was performed in 63% of patients with silent ischaemia one to three months after lower extremity revascularisation. Percutaneous coronary intervention in 47 patients and coronary artery bypass grafting (CABG) in seven patients with representative examples: (A–C) 66 year old man with limiting claudication, hypertension, hyperlipidaemia, and smoking history. Computed tomography derived fractional flow reserve (FFR_{CT}) analysis (A) reveals silent ischaemia producing coronary stenosis within left anterior descending coronary artery (LAD) FFR_{CT} 0.70. Two months after aortofemoral bypass, coronary stents (C, between the white lines) were placed in tandem LAD lesions (B, red arrows). The patient was free of symptoms at one year. (D, E) Sixty-two year old man with ischaemic rest pain, hypertension, hyperlipidaemia, and smoking history. (D) Coronary computed tomography angiography reveals severely calcified coronary arteries with a calcium score of 2323 and (E) FFR_{CT} analysis documents severe left main and three vessel coronary ischaemia with $FFR_{CT} \leq 0.50$. One month after femoral endarterectomy and profundaplasty, CABG was performed. The patient had an uneventful recovery and was well at one year.

related MI during PCI of a severe left anterior descending lesion, which required coverage of the first diagonal branch. The patient experienced chest discomfort during the procedure and had post-procedure troponin elevation. Another patient with silent ischaemia declined recommended post-operative coronary angiography and had a spontaneous MI at six months, which was successfully treated by PCI.

Control

All 135 control patients had pre-operative clinical risk assessment with no evidence of ischaemia on resting ECG and underwent open lower extremity revascularisation surgery. The vascular surgical procedure was performed with cardiac anaesthesia, continuous intra-operative monitoring, post-operative intensive care, and medical management. All patients received guideline directed medical care and were discharged on optimal medical therapy, including statins, antiplatelet agents, antihypertensives, and diabetes control, as appropriate. During the 30 day post-operative period, seven patients (5.2%) had MIs, of which five were fatal (3.7%). Two patients with MI survived: one with medical treatment and one with urgent coronary revascularisation (PCI). During follow up there were four additional MIs, three of them fatal. No

patient had elective post-operative coronary revascularisation.

Study end points

The study end points are shown in Table 2. Primary end point analysis at 30 days revealed no cardiovascular deaths in the CTA-FFR$_{CT}$ group *vs.* five deaths due to MI in the control group ($p = .060$). At six months the CV death rate in the CTA-FFR$_{CT}$ group was zero *vs.* 4.4% in the control group ($p = .030$). At one year, the CV death rate in the CT-FFR$_{CT}$ group was 0.7% *vs.* 5.9% in the control group ($p = .036$). The one death in the CT-FFR$_{CT}$ group was due to a stroke at 11 months, whereas all eight deaths in the control group were due to MI.

Secondary end point analysis

At 30 days, the MI rate was 0.7% in the CTA-FFR$_{CT}$ group *vs.* 5.2% in the control group ($p = .066$). At one year, the MI rate was lower in the CTA-FFR$_{CT}$ group (2.2%) than in the control group (8.1%; $p = .028$). There were no statistically significant differences in MACE rates between the groups over the one year follow up. At one year, all cause death was lower in the CTA-FFR$_{CT}$ group (0.7%) *vs.* the control group (5.9%; $p = .036$).

Survival analysis

Over the one year follow up, in the CTA-FFR$_{CT}$ group there were no cardiac deaths and one death due to stroke at 11 months. In the control group, all eight deaths were due to MIs. Survival curves by Kaplan—Meier estimates are shown

Table 2. Patients outcomes at 30 days, six months, and one year after lower extremity surgical revascularisation with pre-operative coronary computed tomography angiography (CTA) and computed tomography derived fractional flow reserve (FFR$_{CT}$) evaluation or standard pre-operative evaluation (control) for detecting silent coronary ischaemia

Outcome	CTA-FFR$_{CT}$ ($n = 135$)	Control ($n = 135$)	p*
30 days			
CV death	0 (0)	5 (3.7)	.060
MI	1 (0.7)	7 (5.2)	.066
MACE	1 (0.7)	7 (5.2)	.066
All cause death	0 (0)	5 (3.7)	.060
Six months			
CV death	0 (0)	6 (4.4)	.030
MI	3 (2.2)	9 (6.7)	.076
MACE	3 (2.2)	9 (6.7)	.076
All cause death	0 (0)	6 (4.4)	.030
One year			
CV death	1 (0.7)†	8 (5.9)	.036
MI	3 (2.2)	11 (8.1)	.028
MACE	4 (3.0)	11 (8.1)	.063
All cause death	1 (0.7)	8 (5.9)	.036

Data are *n* (%). CV = cardiovascular; MI = myocardial infarction; MACE = major adverse cardiac event.
* p value of difference between groups.
† Death due to stroke.

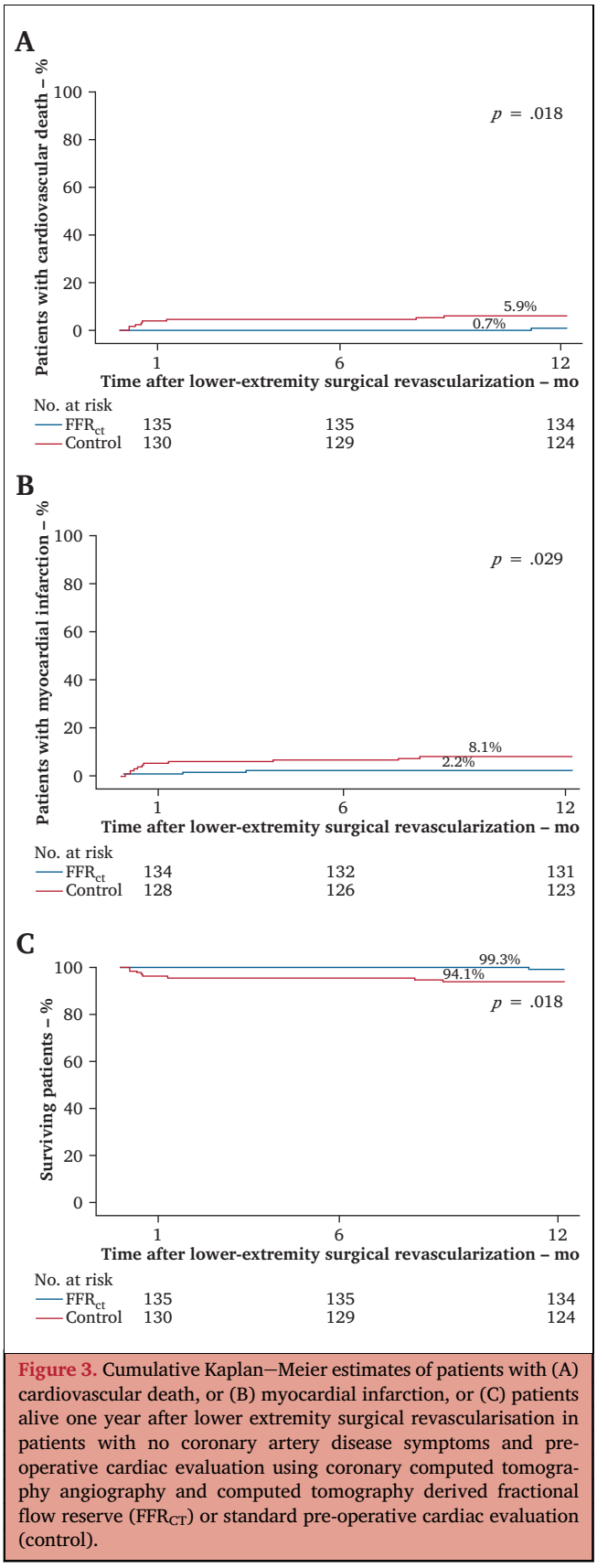

Figure 3. Cumulative Kaplan—Meier estimates of patients with (A) cardiovascular death, or (B) myocardial infarction, or (C) patients alive one year after lower extremity surgical revascularisation in patients with no coronary artery disease symptoms and pre-operative cardiac evaluation using coronary computed tomography angiography and computed tomography derived fractional flow reserve (FFR$_{CT}$) or standard pre-operative cardiac evaluation (control).

in Fig. 3. One year survival in the CTA-FFR_{CT} group was 99.3% *vs.* 94.1% in the control group ($p = .018$ [log rank test]).

DISCUSSION

This study demonstrates the potential value of pre-operative CTA-FFR_{CT} evaluation of patients with no coronary symptoms undergoing lower extremity revascularisation surgery. While it is well known that most patients with PAD have anatomical evidence of significant CAD by pre-operative coronary angiography,[6] this is the first study to document the functional significance of coronary lesions in patients undergoing peripheral vascular surgery using non-invasive FFR_{CT} analysis. Determining the haemodynamic significance of coronary lesions by invasive measurement of FFR during coronary angiography is now the standard of care for guiding coronary revascularisation.[21–25] The finding that 68% of patients in this study had lesion specific coronary ischaemia by FFR_{CT} was unexpected in view of the fact that patients had no CAD symptoms and were cleared for surgery, in accordance with the current standard of care. Perhaps more surprising was the extent and depth of ischaemia, with $>$ 50% of patients having $FFR_{CT} \leq 0.75$ and 38% having multivessel ischaemia. The mean FFR_{CT} value was 0.70 ± 0.14 in patients with silent ischaemia. Among medically treated patients with CAD with measured FFR, patients with a FFR $\leq$ 0.70 had the highest adverse cardiac event rates,[26] and the benefit of coronary revascularisation was greatest in patients with lower FFR values.[25]

Despite the severity of coronary ischaemia found in this study, vascular surgery was performed as scheduled in almost all patients, in accordance with guideline directed care.[2] This was driven by the primary clinical need, which was CLTI in 86% of patients. However, identification of high risk patients with silent coronary ischaemia resulted in more focused attention on peri-operative cardiac care, and early involvement of cardiology with selective post-operative coronary revascularisation. During the control period, guideline directed medical care was given to all patients, but cardiology was not involved in patient care unless there was a cardiac event such as MI or acute coronary syndrome. With the objective of improving long term survival, elective coronary revascularisation was performed in 63% of patients with silent ischaemia after recovery from vascular surgery. Through one year follow up, patient survival in the CTA-FFR_{CT} group was 99.3% with no cardiac related deaths and one death due to stroke at 11 months. By comparison, in the historic control group with no systematic pre-operative cardiac testing and no post-operative coronary revascularisation, one year patient survival was statistically significantly lower (94.1%), and all deaths were cardiac related. The new patient management strategy of systematic pre-operative CTA and FFR_{CT} testing to identify patients with coronary ischaemia, optimisation of peri-operative cardiac care, and selective coronary revascularisation after recovery from peripheral vascular surgery is shown in Fig. 4.

The high prevalence of CAD in patients with lower extremity PAD and the "invariably worse clinical outcomes" seen in patients with multisite artery disease are highlighted in the 2017 ESC/ESVS guidelines.[9] More recent ESVS position statements emphasise the importance of preventing atherosclerotic disease progression to avoid future cardiovascular events and call for extended surveillance of revascularised patients to document long term outcomes of specific vascular treatments.[27,28] However, little attention has been paid to the gap in evidence with regard to identifying patients with multisite artery disease and improving survival. This gap was identified in the 2017 ESC/ESVS guidelines, with a call for further investigation of "whether screening for other sites of atherosclerosis (e.g. CAD) in patients with PAD may improve their outcome".[9]

The current guideline recommendation that "systematic screening for asymptomatic disease is not indicated for any presentation of PAD as it would not consistently lead to modification of management strategy"[9] is largely based on the results of the Coronary Artery Revascularisation Prophylaxis (CARP) study, which found no difference in long term survival of vascular surgery patients randomised to pre-operative coronary revascularisation or no revascularisation.[7] It should be noted that the CARP study was performed $>$ 15 years ago using visual angiography to guide coronary revascularisation, before publication of strong evidence in favour of FFR guided revascularisation.[22,23] In a recent report of 18 000 patients in a real world setting, FFR guided revascularisation resulted in a 43% reduction in one year mortality *vs.* angioguided revascularisation.[29] Furthermore, the requirement for pre-vascular surgery coronary revascularisation in CARP delayed vascular surgery by almost two months, which may have obscured potential benefits of coronary revascularisation. In this study, the aim was to improve long term survival with FFR_{CT} guided coronary revascularisation *after* performing the limb salvage surgery rather than before. Finally, it should be noted that coronary angiography was used to screen patients for the CARP study with inclusion of those with $\geq$ 70% stenosis and exclusion of patients with $\geq$ 50% left main (LM) stenosis (4.6% of patients). Subsequent analysis revealed that coronary revascularisation statistically significantly improved the survival of LM patients at 2.5 years compared with those not revascularised ($p < .01$).[30] In the present study systematic pre-operative screening of vascular surgery patients identified LM stenosis in 7% of patients. This is similar to the 5%—7% LM stenosis rate found in patients with CAD screened by angiography or CTA prior to randomisation in large prospective, randomised CAD trials.[31]

The benefit of coronary revascularisation in patients with asymptomatic, haemodynamically significant CAD, as seen by invasively measured FFR, has been shown in a sub-analysis of the prospective, randomised FAME 2 (Fractional Flow Reserve *vs.* Angiography for Multivessel Evaluation 2) trial.[32] Of patients with angiographic coronary stenosis and a FFR $\leq$ .80 randomised to the medical treatment arm, 11% had no cardiac symptoms (had silent coronary ischaemia). During the five year follow up, asymptomatic coronary

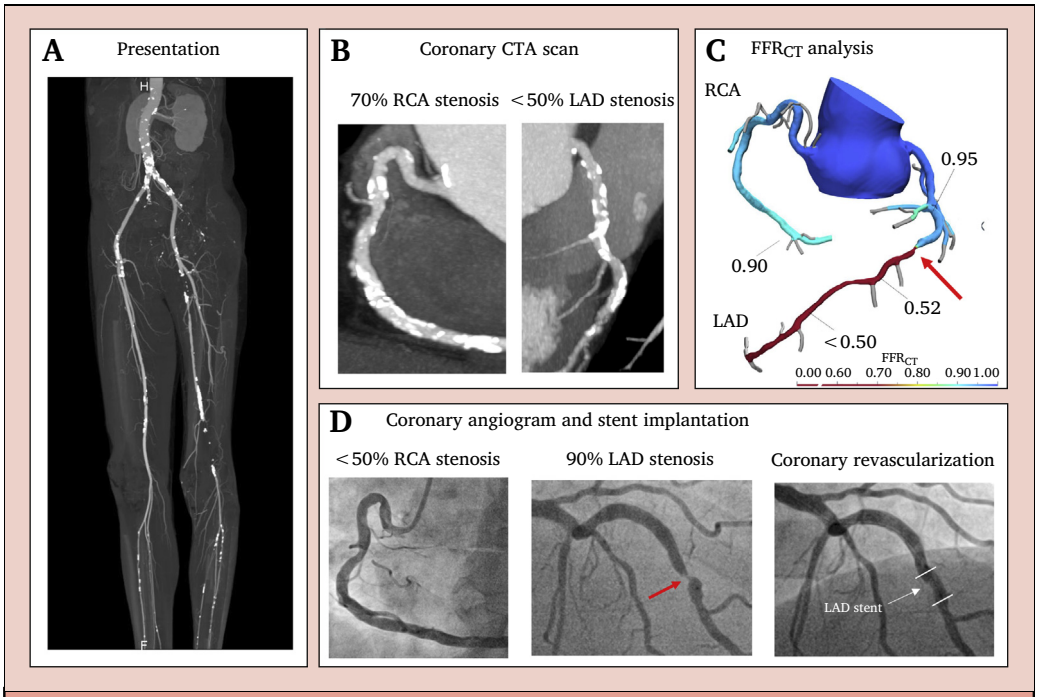

Figure 4. An example of a patient management strategy to diagnose silent coronary ischaemia in a patient undergoing lower extremity revascularisation. (A) Sixty-seven year old man with insulin dependent diabetes and limb threatening ischaemic left foot rest pain, with an ankle brachial index 0.45. There were no cardiac history or symptoms of coronary artery disease; electrocardiogram was normal. Peripheral computed tomography angiography (CTA) revealed multilevel occlusion of left femoral artery with reconstitution of the popliteal artery. (B) Pre-operative coronary CTA revealed severe coronary calcification (Agatston score 3 873) with 70% right coronary artery (RCA) stenosis and < 50% left anterior descending coronary artery (LAD) stenosis. (C) CT derived fractional flow reserve (FFR_{CT}) analysis showed no ischaemia in the RCA but severe ischaemia in the LAD (FFR_{CT} 0.52), with focal stenosis in the mid-LAD (arrow). (D) Using cardiac anaesthesia with optimal medical management, a femoropopliteal saphenous vein bypass was performed with complete relief of rest pain symptoms. One month later, coronary angiography confirmed the absence of RCA stenosis and 90% LAD stenosis (red arrow); placement of a coronary stent (white markings) relieved the LAD stenosis. The patient was asymptomatic and fully ambulatory one year later.

patients had a more than twofold higher risk of death or MI *vs.* symptomatic coronary patients (31% *vs.* 14%; $p = .002$), leading the authors to conclude that in patients with haemodynamically statistically stenosis, FFR guided revascularisation should be considered, even in the absence of symptoms.[32]

The benefit of systematic cardiac screening of patients undergoing carotid endarterectomy (CEA) with no clinical evidence of CAD using pre-operative coronary angiography has been shown in a recent prospective, randomised controlled trial. Pre-operative coronary revascularisation was performed in 31% of patients with a statistically significant reduction in post-CEA MI and improved six year survival compared with patients randomised to no pre-operative angiography.[33] As a result, the 2017 ESC/ESVS guidelines indicate that patients undergoing elective CEA may be considered for pre-operative CAD screening with coronary angiography (Class IIb, Level B).[9] It is now possible to evaluate patients with suspected CAD non-invasively using coronary CTA and FFR_{CT}.[14,16] Furthermore, CTA-FFR_{CT} has been shown to be equivalent to coronary angiography for planning coronary revascularisation.[34] In this study, the potential benefit of systematic pre-operative screening for CAD and selection of patients for revascularisation with a single non-invasive test in patients with lower extremity PAD was demonstrated. Through one year follow up, survival was improved *vs.* the current standard of care.

This study is limited by the fact that it is a single centre, non-randomised study with a non-concurrent control group and has the potential for selection bias. As the objective was to determine the value of a new cardiac diagnostic modality in improving the outcomes of high risk vascular surgery patients, the results of all patients evaluated with the new diagnostic test were compared with historic controls treated during a time period when the new diagnostic test was not available. This eliminated the potential of selection bias with regard to the method of pre-operative coronary testing. The patient groups were from two consecutive one year time periods and were cared for by the same group of physicians with no changes in treatment protocols. There were no statistically significant differences

in baseline patient characteristics and both groups were cleared to undergo vascular surgery in accordance with the current standard of care. However, the actionable information provided by FFR_{CT} analysis enabled multidisciplinary patient management decisions, which impacted on patient care in the FFR_{CT} group. In addition, there was a disparity between groups because planned vascular surgery was postponed or cancelled in five patients in CTA-FFR_{CT}, whereas all patients in the control group underwent revascularisation surgery. If these five patients are excluded from the analysis and 130 operated on CTA-FFR_{CT} patients are compared with 135 operated on control patients, the study end points remain unchanged, with statistically significantly fewer CV deaths and MIs, and improved survival in the CTA-FFR_{CT} group *vs.* the control group. It should be noted that the majority of adverse cardiac events in the control group occurred within 30 days of surgery, and coronary revascularisation in CTA-FFR_{CT} was performed one to three months after surgery. Thus, it is unknown whether the improved outcomes seen at one year are due to more focused peri-operative cardiac care or selective post-operative coronary revascularisation in patients with silent coronary ischaemia or a combination of the two. It seems reasonable to expect that the benefit of coronary revascularisation will become increasingly apparent with longer follow up, but this remains to be seen. The results of this single centre study are promising but are not generalisable and should be considered as hypothesis generating. Adequately powered, prospective, multicentre, controlled trials are needed to define the role of CTA-FFR_{CT} in the evaluation and treatment of patients with peripheral vascular disease.

CONCLUSION

Patients with no cardiac symptoms undergoing elective lower extremity surgical revascularisation have a high prevalence (68%) of unsuspected, silent coronary ischaemia, which may increase their risk of death and MI. Pre-operative testing using coronary CT derived fractional flow reserve can identify high risk patients with silent ischaemia and facilitate multidisciplinary patient care with increased focus on peri-operative cardiac care and selective post-operative coronary revascularisation. This resulted in fewer deaths and MIs and improved one year survival compared with historical controls with standard pre-operative cardiac evaluation. If confirmed by future studies, this strategy may improve the long term survival of patients with peripheral vascular disease.

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CONFLICT OF INTEREST

C.K.Z. has a financial interest in HeartFlow, Inc.

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