Rational and design of the INtentional COronary revascularization versus conservative therapy in patients undergOing successful peripheRAl arTEry revascularization due to critical limb ischemia trial (INCORPORATE trial)

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Abstract Critical limb ischemia is associated with excessively high risk for cardiovascular events, including myocardial infarction and death. Additionally, in this patient population non-invasive evaluation of coronary artery disease is limited due to (1) inability of exercise testing, (2) frequent occurrence of balanced ischemia and (3) frequent occurrence of diffuse coronary calcification.

Intentional Coronary Revascularization Versus Conservative Therapy in Patients Undergoing Peripheral Artery Revascularization Due to Critical Limb Ischemia trial (INCORPORATE trial) is a multicentric international randomized open label clinical trial. Trial will recruit patients, who underwent successful peripheral artery revascularization due to critical limb ischemia and randomize 1:1 to conservative medical therapy versus an immediate invasive strategy to investigate and treat coronary artery disease. The objective is to evaluate whether intentional invasive strategy with ischemia targeted reasonably complete coronary revascularization is superior as compared to conventional primarily conservative approach in terms of spontaneous myocardial infarction and overall survival at 12 months follow-up. The trial is registered at clinicaltrials.gov (NCT03712644). (Am Heart J 2019;214:107-112.)

Critical limb ischemia, which is at the most severe extreme of the peripheral artery disease spectrum, is associated with an excessively high risk for cardiovascular events, including myocardial infarction and death. Mortality rates, as high as 20% within 6 months from diagnosis and exceeding up to 40% at 2 years have been reported for this population and dominated by cardiovascular and cerebrovascular events.[1-3] This high mortality rate exceeds those for every other form of occlusive cardiovascular disease, including symptomatic coronary artery disease and reflects the systemic atherosclerotic burden associated with critical limb ischemia. Besides the overall severity of the disease, another major burden for this population is the limited diagnostic access to coronary artery disease by any non-invasive methods due to (1) inability of exercise testing, (2) and frequent occurrence of balanced ischemia and (3) frequent occurrence of diffuse coronary calcification.

In general patients with peripheral artery disease present often with angiographically highly complex coronary disease, and therefore short- and long-term outcome after coronary revascularization remains far beyond the same of the overall population.[4,5] One can hypothesize that the unfavorable outcome might be partially originated in the pure angiographically guided revascularization strategies, due to the lack of proper

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functional information, leading to complex and multiple interventions without a clear ischemic target. As up to 39% of angiographically obstructive coronary lesions lack functional significance, no benefit should be expected from revascularizing non-ischemic myocardium. On the contrary outcome might be confounded by negative effects arising from unneeded interventions.[6] This might be also suggested by the findings of Lee et al., who has done coronary angiography in 252 consecutive patients underwent lower limb angioplasty in critical limb ischemia and has found *angiographically* significant coronary artery disease in 145 patients, but without any impact on clinical outcome at one-year follow-up. Note, functional relevance of detected coronary artery disease was not performed.[7] Based on large multicentric randomized clinical trials, such as COURAGE, DEFER, FAME and several observational studies,[8-23] the joint European Society of Cardiology and European Association for Cardiothoracic Surgery revascularization guidelines recommended (*Level I, evidence B*) that prognostic indications for revascularization should be restricted to stenoses causing ischemia and jeopardizing at least 10% of the left ventricular myocardium.[24]

When non-invasive tests are not available or inconclusive, then *invasive* measure in the catheterization laboratory is recommended by interrogating all the angiographically intermediate stenoses (in the range of 50% to 90% diameter stenosis) by pressure-derived fractional flow reserve (FFR).[24] Note, in patients with critical limb ischemia non-invasive ischemia tests are markedly limited due to the limited exercise capacity. However, these conditions do not limit the applicability of invasive ischemia assessment by FFR.[25]

Considering (1) the extreme high cardiovascular morbidity and mortality of patients even with successfully revascularized critical limb ischemia and (2) the limited diagnostic value of non-invasive tests in this population the *Intentional Coronary Revascularization* Versus *Conservative Therapy in Patients Undergoing Peripheral Artery Revascularization Due to Critical Limb Ischemia trial (INCORPORATE trial)* will be the first of its kind to evaluate in a randomized fashion whether intentional invasive strategy with ischemia targeted, reasonably complete coronary revascularization is superior as compared to a conservative approach in patients, who underwent successful peripheral artery revascularization due to critical limb ischemia.

Methods

Hypothesis

The objective of the INCORPORATE trial is to evaluate whether an intentional invasive strategy with ischemia targeted, reasonably complete coronary revascularization and optimal medical therapy is superior as compared to a primarily conservative approach and optimal medical therapy alone in terms of spontaneous myocardial infarct-free and overall survival in patients with severe peripheral artery disease and critical limb ischemia, underwent successful peripheral artery revascularization. Based on previous data[1-5] we hypothesize that an intentional invasive strategy with ischemia-guided reasonably complete revascularization will be associated with survival benefit over the conventional conservative approach.

Design

The INCORPORATE trial is designed to be non-blinded, open-label, prospective 1:1 randomized controlled multicentric trial that will be performed in up to 10 European centers, where close collaboration of invasive cardiology and invasive or surgical peripheral vascular specialists can be anticipated. Randomization process will be computer-based. Study flow-chart is depicted in Figure 1. The trial is registered at clinicaltrials.gov (NCT03712644).

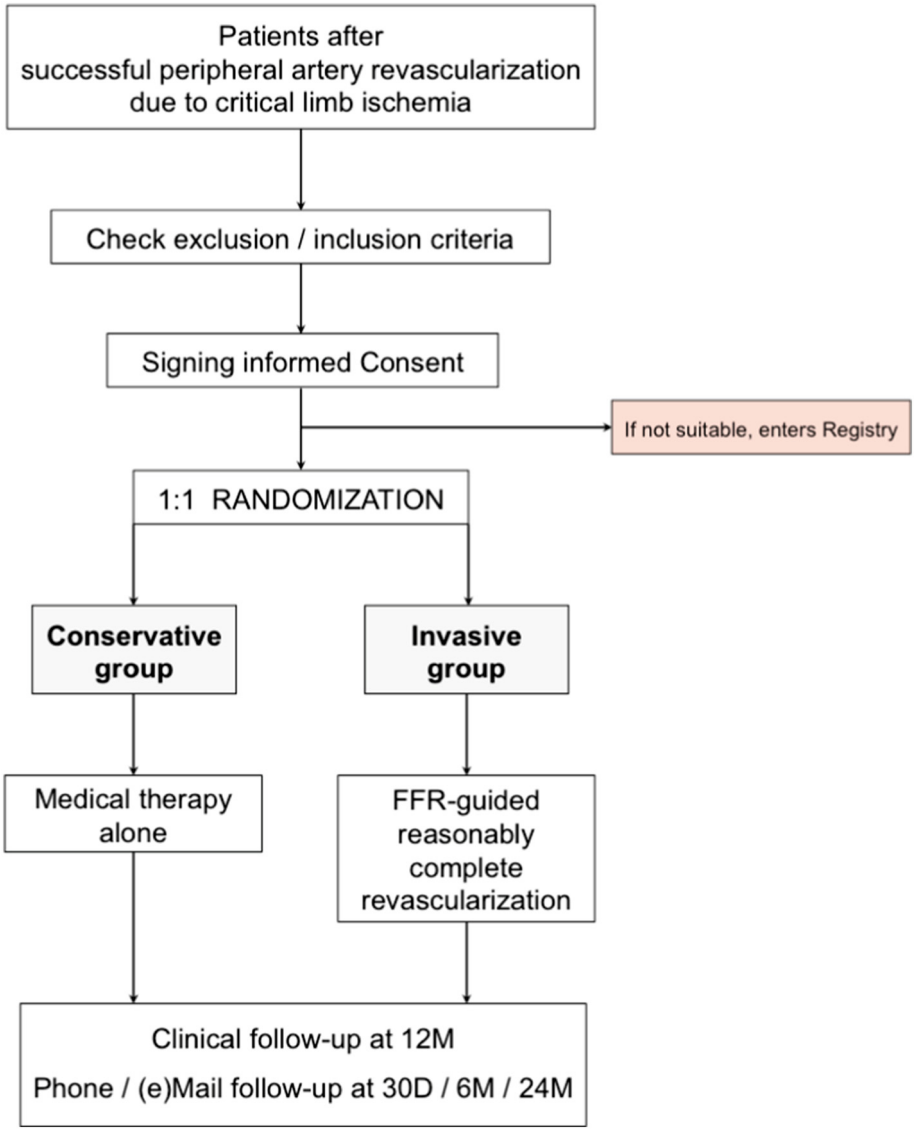
Patient population

Six hundred fifty patients, who underwent successful percutaneous or surgical peripheral revascularization due to critical limb ischemia (defined as Rutherford-Becker classification 4 or higher[26]) will be screened and enrolled if informed consent form is signed *and none of* the following exclusion criteria is met: (1) contraindication for dual antiplatelet therapy for at least 1 month; (2) contraindication for guideline-conform post-PCI antiplatelet/anticoagulation regime; (3) known heart failure with ejection fraction below 35%; (4) known significant valvular heart disease with indication for surgical or percutaneous repair; (5) any concomitant disease with a life expectancy less than 2 years; (6) severe renal dysfunction with glomerular filtration rate below 30 mL/min/1.73m^2, including patients on dialysis (7) ongoing sepsis; (8) coronary angiography with or without surgical or percutaneous coronary revascularization within 1 year; (9) CCS II-IV typical angina at the time of admission.

Patients, who cannot be enrolled for any reasons will enter a prospective registry.

Subjects will be 1:1 randomized to a *Conservative* versus *Invasive* group. In the reference group (*Conservative group*) patients will receive optimal medical therapy alone, as indicated after peripheral artery revascularization according to recent guidelines. Optimal medical therapy should include beta blocker, alone or in combination with a calcium-channel blocker or a long-acting nitrate; ACE-inhibitor or an angiotensin II–receptor blocker if the patient had unacceptable side effects with the ACE inhibitor; and statin alone or in combination with ezetimibe. Antiplatelet and anticoagulation regime is left for the discretion of the treating physician, according to the comorbidities (i.e. atrial fibrillation) and the indications at the performed peripheral

Figure 1



Flow chart of the INCORPORATE trial.

revascularization with- or without coronary revascularization. Patients will be followed, according to protocol. Any further cardiac investigation will be performed according to routine practice and exclusively in case of clinical suspicion of myocardial ischemia related symptoms.

In the study group (*Invasive group*) in addition to optimal medical therapy as outlined above, elective coronary angiography will be performed, escalated into FFR-guided reasonably complete coronary revascularization, as appropriate.[27] Coronary catheterization is preferably scheduled during the same hospitalization but definitely within 14 days after peripheral revascularization. However, in case of clinically relevant post-procedural increase of creatinine, coronary catheterization can be postponed until recovery to patients' baseline value, in order to minimize the risk of contrast-induced nephropathy. The same consideration is recommended in case of staged coronary revascularization.

Note, coronary angiography will be performed or denied according to the randomization group, regardless the presence or absence of any left ventricular regional wall motion abnormalities in the echocardiogram.

Peripheral revascularization

Peripheral revascularization will be performed according to current gold standard of care and up-to-date

clinical practices. The used technique (i.e. percutaneous versus surgical; stent vs. drug-eluting balloon vs. balloon only) is left for the operators' discretion. Definition of acute procedural success, as prerequisite of enrollment, is left for operators discretion, defined principally as sufficient anterograde flow and/or less than 30% residual stenosis by visual estimation.

Coronary catheterization and revascularization

Coronary catheterization should be performed preferably through radial access. Coronary catheterization will be performed *regardless* the presence or absence of any prior non-invasive proof of ischemia, therefore performance of any non-invasive tests prior coronary catheterization is not indicated. All lesions of 50–90% diameter stenosis by visual estimate in a major coronary artery of ≥2.5 mm vessel will be evaluated by FFR, as recommended[24] and intervened using standard percutaneous coronary intervention (PCI) techniques if FFR ≤0.80 or left for medical therapy if FFR >0.80, regardless angiographic appearance All lesions of ≥90% diameter stenosis in a major coronary artery of ≥2.5 mm vessel will be intervened using standard techniques with latest generation drug-eluting stents. This includes also efforts to recanalize chronic total occlusions (CTO) of large supplied viable myocardial territory (i.e. proximal or mid segment of major coronary arteries), however excessive and multiple revascularization attempts are discouraged. Note, CTO revascularization should be attempted only in case of any evidence of viability. Following the procedure dual antiplatelet therapy is indicated, according to current guideline recommendations.[24]

In case of complex or multiple vessel disease, complete revascularization can be achieved even during multiple staged procedures, still preferably during same hospitalization. In case of unsuitable anatomy for PCI such as severe and complex multivessel disease (i.e. multiple CTOs and/or high SYNTAX score) revascularization by coronary artery bypass surgery might be considered according to operator discretion. However, it is recommended that treatment with PCI should be performed whenever possible (i.e. left main stenoses, triple-vessel disease, etc.)

Fractional flow reserve measurement

FFR measurement will be performed as indicated.[27] Briefly, a pressure monitoring guide wire is advanced distal to the coronary artery stenosis. Maximal hyperemia is induced by administration of intracoronary isosorbide dinitrate (200 μg) and of intravenous (continuous infusion of 140 μg/kg/min) or intracoronary (bolus of 160–200 μg) adenosine. FFR is defined as the ratio of the simultaneously recorded mean arterial pressure distal to the stenosis and the mean aortic pressure at the tip of the guiding catheter during stable, steady state hyperemia.

FFR is considered to be *significant*, if equal to or lower than 0.80. Accordingly, in such case revascularization is indicated. FFR is considered to be non-significant, if higher than 0.80. Accordingly, in such cases revascularization is not indicated, regardless angiographic appearance. [24,27].

Follow-up

Clinical face-to-face follow-up will be performed at 1 year (12–1/+1 months). At the clinical follow-up-visit the quality of life status (based on EQ5D), adverse events according to protocol, hospitalization, medication intake and clinical status (based on Rutherford-Becker classification and on Canadian Cardiovascular Society Classification) will be evaluated. At 30 (−5/+10) days, at 6 (−1/+1) months and at 24 (−1/+2) months patients will be contacted via phone call *or* email *or* mail.

For patients in the registry only phone call follow-ups will be performed at 12- and 24 month.

Endpoints

The trial is powered to show superiority for the primary endpoint of composite of overall death and spontaneous myocardial infarction at one-year follow-up. Spontaneous myocardial infarction is defined as

Type I, Type II or Type IVb, according to third universal definition of myocardial infarction.[28]

Secondary endpoints are defined as follows: (1) Overall death at one- and two-years follow-up; (2) Spontaneous myocardial infarction at one- and two-years follow-up; (3) Composite of death and spontaneous myocardial infarction at two-years follow-up; (4) Composite of death, spontaneous myocardial infarction, any coronary revascularization and any stroke at one- and two-years follow-up; (5) Quality-of-life development over follow-ups (EQ5D); (6) Total days of hospitalization over one-year and two-years follow-ups; (7) Repeat revascularization of the target peripheral vessel at one- and two-years follow-up; (8) Limb salvage at one- and two-years follow-up defined as major amputation-free survival. Major amputation is defined as above ankle level, while minor amputation is defined as amputation at or below ankle level; (9) Clinical success after peripheral revascularization at 30 days, 6 months, one- and two-years follow-up, defined as an improvement of at least one clinical category in the Rutherford-Becker classification[26]; (10) Clinical success after coronary revascularization, defined as an improvement of at least one clinical category in the Canadian Cardiovascular Society Classification at 30 days, 6 months, one- and two-years follow-up.[29] For patients in the registry only overall survival, myocardial infarction and coronary revascularization will be sensored and

reported; (11) Development of renal failure, requiring dialysis up to 12 months.

An independent Clinical Event Committee is built by three cardiologists, who are otherwise not involved in the trial. Each clinical event will be adjudicated independently and blindly by two members of Committee. In case of disagreement the third member will be involved and joint agreement should be reached.

Statistics

Based on the limited data in the literature[1-5], we assumed an absolute difference of 10% in composite of spontaneous myocardial infarction and all-cause mortality at the end of the one-year follow-up, namely an event rate of 20% in the conservative group while an event rate of 10% in the invasive group. Therefore we calculated a sample size of 650 patients with alpha 5% and 90% power, expecting a cross-over of 5%.

A blinded interim analysis by steering committee is planned after the completion of 1-year follow-up in 50% of the planned sample size in order to verify (1) the assumed difference in mortality between the two groups; (2) the rate of patients lost to follow-up. Depending on the interim analysis, the steering committee will be responsible to continuation of recruitment (according to initially calculated or after readjusting the sample size analysis) or to stop the recruitment (in case of a too large recalculated sample size, i.e. more than 30% excess, as compared to initial calculation).

During the analysis continuous variables in the two groups will be compared by unpaired Student's t-test, Mann–Whitney test or ANOVA test, as appropriate. Categorical variables in the two groups will be compared with Fisher's exact or chi-square tests, as appropriate. Difference in event-free survival between the two groups will be evaluated by applying the Kaplan–Meier curves. Results will be adjusted by Cox-regression multivariate analysis where needed, as appropriate. A probability value of $P < .05$ is considered as statistically significant.

Data reporting

Central data management will be performed by principle investigators at the Medical University Graz. Data will be recorded at each site on a case report form, verified primarily by the local investigator. It is the investigators responsibility to ensure the accuracy, completeness and legibility of the data collection. Source documentation should indicate dates and details of routine examinations, treatment interventions and adverse events.

Ethics and funding

INCORPORATE is an investigator initiated trial, supported by Boston Scientific (Marlborough, Massachusetts, United States) with non-financial unrestricted support: COMET pressure-sensored guidewire for the functional assessment of patients in the invasive arm. Protocol is approved by the ethical committees of all collaborating centers.

Study status

First patient was enrolled on 4th July 2018. By the time of the submission of this manuscript in October 2018, 31 patients were recruited in two sites. Screening and initiation of up to 8 additional sites is in progress. Completion of enrollment is foreseen for end of 2022.

Summary

Patients with peripheral artery disease presenting with critical limb ischemia are exposed to extreme high one- and two-years mortality even despite successful peripheral revascularization, mainly dominated by cardiovascular death. It is important to emphasize that early diagnosis of coronary artery disease is hardly achievable in this population, on one hand, due to mainly lacking symptoms at markedly reduced daily exercise capacity by peripheral artery disease, on the other hand, due to limited diagnostic value of any non-invasive tests.

The INCORPORATE study is the first of its kind to compare the standard, primarily conservative approach with a proactive intentional invasive approach and functionally guided revascularization for the investigation and treatment of existing coronary artery disease in this high-risk population.

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