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Surgical revascularization for stable coronary syndrome: the ISCHEMIA trial versus a single-centre matched population—a real-world analysis of patients undergoing surgical revascularization

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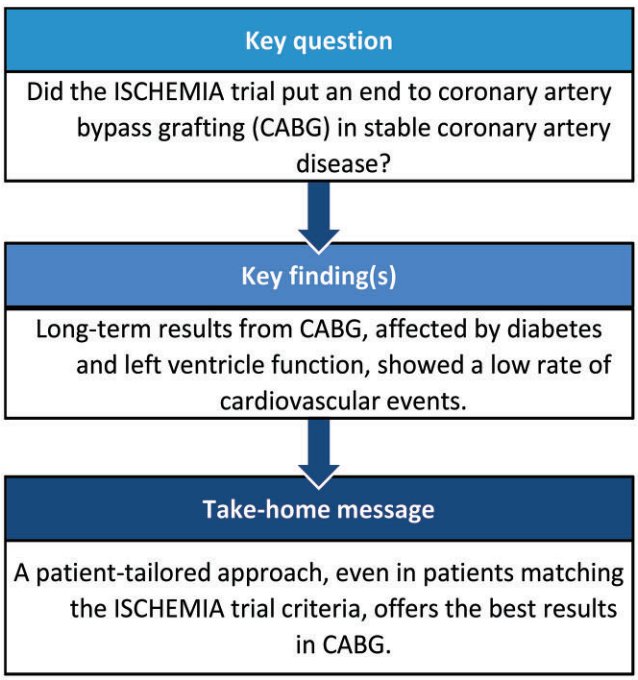

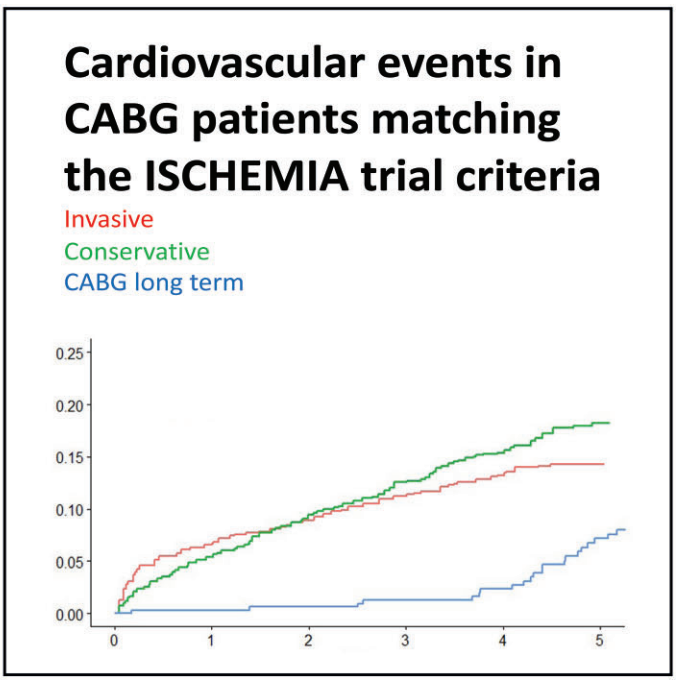

Abstract

OBJECTIVES: The aim of this study was to test if the current general practice of surgical revascularization is comparable to the setting of International Study of Comparative Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial and to evaluate the comparative risk of cardiovascular events or death after coronary artery bypass grafting.

METHODS: We selected patients undergoing surgical revascularization and matching ISCHEMIA inclusion criteria. Chronic coronary syndrome patients were included if diagnosis of myocardial ischaemia by functional testing and coronary artery disease at angiography were detected. The primary end point was a composite of cardiovascular death, myocardial infarction, rehospitalization for unstable angina,

heart failure and resuscitated cardiac arrest. Secondary end points were death by any cause, cardiovascular death, myocardial infarction and rehospitalization.

RESULTS: Among 353 patients, the primary outcome occurred in 62 (17.6%) patients. At 6 months, cumulative event-free survival was 97%, at 1 year 96%, at 5 years 89% and at 10 years 80%. Cumulative risk of the primary composite outcome at 5 years was 11%, 18% in the conservative arm of ISCHEMIA and 16% in the revascularization arm of ISCHEMIA ($P < 0.001$). Risk of myocardial infarction at 5 years was 7% in surgical patients and 12% and 10% in the conservative and invasive arms of the trial, respectively ($P < 0.001$).

CONCLUSIONS: Long-term results in surgical patients treated for chronic coronary syndromes showed that ISCHEMIA trial findings are not transferable in a 'real-world' scenario and have not changed previous medical practice. A patient-tailored approach, especially with diabetes and reduced left ventricle function, offers the best results in patients with stable coronary artery disease.

Keywords: Chronic coronary syndrome • Stable angina • ISCHEMIA trial • Coronary artery bypass grafting

ABBREVIATIONS

CABG	Coronary artery bypass graft
CAD	Coronary artery disease
EF	Ejection fraction
HR	Hazard ratios
ITA	Internal thoracic artery
ISCHEMIA	International Study of Comparative Effectiveness with Medical and Invasive Approaches
MI	Myocardial infarction
NYHA	New York Heart Association
OMT	Optimal medical therapy
PCI	Percutaneous coronary intervention
RC	Regression coefficients
SCD	Stable coronary disease

INTRODUCTION

The goals of myocardial revascularization in patients with chronic coronary syndromes are to improve survival and/or to improve symptoms. Several trials over the past 15 years have not shown that revascularization in such patients with coronary artery disease (CAD) prevents death or myocardial infarction (MI) compared to medical therapy [1–4]. However, major drawbacks of these trials have been the non-homogeneous selection of patients, with no need for ischaemia documentation at non-invasive testing, the variable presence of contemporary drug-eluting stents at percutaneous coronary intervention (PCI), the variable use of fractional-flow-reserve to guide revascularization, the use of arterial conduits and possibly bilateral internal thoracic artery (ITA) at coronary artery bypass graft (CABG) surgery and the variable use of currently best optimal medical therapy (OMT) [5].

In 2019, the results of the International Study of Comparative Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial showed no advantage of an initial revascularization strategy, mostly by PCI, over an initial conservative strategy in reducing the risk of cardiovascular events (or death) in patients with stable coronary disease (SCD), while initial revascularization was superior in relieving angina and improving quality of life compared to OMT alone [6].

We here aimed (i) to verify whether the current real-world general practice of surgical revascularization for stable CAD at our tertiary referral centre is comparable to the setting of the ISCHEMIA trial, (ii) to evaluate the comparative risk of cardiovascular events or death after surgical revascularization for SCD in our setting compared with that of the trial and (iii) to identify which patients, among that with stable ischaemic disease, have to be considered at risk of developing events in the long term.

METHODS

Ethics statement

All procedures complied with the Declaration of Helsinki, and the study received approval (No. 19268) by the local Ethics Committee (Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana). Informed consent was waived because of the retrospective nature of the study.

Study design

In this retrospective, observational, longitudinal study, we analysed data from patients with SCD treated with CABG. Between 2007 and 2015, 1520 consecutive patients underwent CABG at Pisa University Hospital. Among these, we selected patients matching the ISCHEMIA trial criteria. SCD patients were defined as those with a diagnosis of myocardial ischaemia by functional testing, and a diagnosis of CAD at coronary angiography. Like ISCHEMIA, exclusion criteria were history of a recent acute coronary syndrome (within 2 months) or PCI (within 1 year), the presence of left main coronary disease, ejection fraction (EF) <35%, heart failure NYHA (New York Heart Association) class 3 or 4 and chronic kidney disease (estimated glomerular filtration rate <30 ml/min or dialysis). Patients in which detection of ischaemia with functional testing was not available or unclear were also excluded.

Data collection and definitions

Clinical data were collected preoperatively, at discharge and at the last follow-up visit in a prospectively completed institutional database. The type of surgical revascularization, including the choice of grafts and off-pump surgery, was decided based on the patients' clinical condition and surgeons' preferences. Among postoperative complications, major cardiac events were defined as periprocedural MI, major arrhythmia or need for urgent PCI.

Cardiovascular death was defined as death due to heart failure, MI or sudden death. MI was defined according to the Third Universal Definition of Myocardial Infarction types 1, 2, 4b, 4c and 5 [7]. Patient follow-up was performed by telephone contact and direct visit when possible, or through information obtained by referring physicians.

Table 1: Preoperative and operative characteristics of the patients

Variable	Statistic (*N* = 353)
Age, years, median (IQR)	68.4 (62.1–73.8)
Male sex, *n* (%)	289 (81.9)
Race, *n* (%)	
White	353 (100)
Hypertension, *n* (%)	279 (79)
Diabetes, *n* (%)	126 (35.7)
Dislipidaemia, *n* (%)	239 (67.7)
Cigarette smoking, *n* (%)	157 (44.5)
Family history of CAD, *n* (%)	163 (46.2)
Previous cardiac operation, *n* (%)	0
Ejection fraction %, median (IQR)	55 (50–60)
History of atrial fibrillation or atrial flutter, *n* (%)	13 (3.7)
Previous stroke, *n* (%)	0
History of cerebrovascular disease, *n* (%)	23 (6.5)
History of peripheral artery disease, *n* (%)	45 (12.7)
Demonstration of ischaemia, *n* (%)	
Exercise electrocardiogram	22 (6.2)
Dobutamine stress echocardiography	98 (27.7)
Exercise stress echocardiography	87 (24.6)
Single photon emission computed tomography	120 (33.9)
Magnetic resonance imaging	26 (7.3)
EuroSCORE II, %, median (IQR)	1.93 (1.30–3.27)
Use of CPB, *n* (%)	269 (76.2)
Use of left ITA, *n* (%)	345 (97.7)
Use of right ITA, *n* (%)	73 (20.7)
Use of radial artery, *n* (%)	20 (5.7)
Use of saphenous vein, *n* (%)	275 (77.9)
Number of graft, *n* (%)	
1	20 (5.7)
2	41 (11.6)
3	80 (22.7)
4	116 (32.9)
5	73 (20.7)
6 or more	23 (6.5)

CAD: coronary artery disease; CPB: cardiopulmonary bypass; EuroSCORE II: European System for Cardiac Operative Risk Evaluation II; IQR: interquartile range; ITA: internal thoracic artery.

Statistical analysis

Categorical data were described by absolute and relative frequency, and continuous data by median and interquartile range. The primary end point was a composite of cardiovascular death, myocardial infarction or rehospitalization for unstable angina (independent from whether it led to a new PCI), heart failure and resuscitated cardiac arrest. Secondary end points were death by any cause, cardiovascular death, MI, rehospitalization for unstable angina, PCI and new CABG.

Multivariable survival analysis was performed by Cox regression models obtained by a stepwise method, using clinical characteristics, intraoperative data (use of arterial or vein grafts, off-pump or on-pump surgery), in-hospital complications and discharge medications as independent variables. The Bayesian Information Criterion has been considered as stopping rule criteria in the stepwise procedure; the Bayesian Information Criterion method automatically determines the threshold; it will be different for each variable, depending on the degrees of freedom and sample size [8]. Regression coefficients (RC) and hazard ratios (HR), with their related confidence interval, were calculated. Survival curves were obtained with the Kaplan–Meier method. Kaplan–Meier plots (cumulative event rates) were reported separated for PCI, CABG or a conservative strategy for the composite primary end point, as well as for death for any cause, cardiovascular death and MI. The conservative and invasive strategies raw data, as reported in Maron *et al.* [6], were reconstructed using the algorithm as per Guyot *et al.* [9]. The global log-rank test was reported on the plot. The *P*-values were adjusted within multiple outcomes and pairwise comparison by using the Benjamini–Hochberg's correction [10]. All analyses, descriptive and inferential, were performed using the SPSS v.26 software and R 3.4.2.

RESULTS

Early outcomes

After applying the exclusion and inclusion criteria, 353 patients were selected for the present analysis. The main demographic and clinical characteristics are listed in Table 1. The median age was 68 years (39–87 interquartile range), and 289 patients (82%) were men. Hypertension was present in 279 patients (79%), diabetes in 126 (36%) and history of cigarette smoking in 157 (44%). Family history of early cardiovascular disease was present in 163 patients (46%).

Reduced left ventricle function (between 35% and 45%) was present in 63 patients (18%), being due to previous MI (41 patients), atrial fibrillation (12 patients) and hypertensive cardiomyopathy (10 patients).

Demonstration of ischaemia was obtained by exercise electrocardiography in 22 (6%), while non-invasive imaging was used in the remaining, showing at least moderate ischaemia.

All patients underwent elective CABG surgery; 269 (76%) were operated with the use of cardiopulmonary bypass, and among these, 7 without aortic clamping; 84 patients (24%) underwent off-pump CABG. Enrolment in either group depended on surgeon's decision only.

Most patients (98%) received revascularization with the left ITA on the anterior descending coronary artery. The right ITA was used in 73 patients (21%), while the radial artery in 20 (6%), accounting for the 22% of patients receiving total arterial revascularization.

Only a small percentage of patients underwent revascularization of a single coronary artery (20 patients; 6%); most subjects (87% of the patients) received an extended revascularization, with 3 or more grafts.

Early mortality was 2.3% (8 patients). Two patients died because of major arrhythmia, 3 due to stroke, 3 for infective/respiratory cause.

Primary composite outcome

The primary outcome occurred in 62 (17.6%) patients.

At 6 months, the cumulative incidence of events was 3%, at 1 year 4%, at 5 years 11% and at 10 years 20%.

At stepwise multivariable analysis, diabetes [RC 1.034 and HR 2.813 (1.587–4.987)] and a major cardiac event during hospitalization, including periprocedural MI [RC 1.203 and HR 3.329 (0.954–11.613)], were risk factors for the composite outcome of cardiovascular death, MI and rehospitalization. Protective factors were the use of left ITA [RC -2.449 and HR 0.086 (0.031–0.238)] and the use of statins at discharge [RC -0.647 and HR 0.523 (0.305–0.898)] (Table 2).

Table 2: Multivariate analysis by step-wise model

End point and variables	RC	HR (95 % CI)	*P*-Value
Primary composite outcome			
Diabetes	1.034	2.813 (1.587–4.987)	<0.001
LIMA graft	-2.449	0.086 (0.031–0.238)	<0.001
In-hospital major cardiac events	1.203	3.329 (0.954–11.613)	0.059
Statins	-0.647	0.523 (0.305–0.898)	0.019
Death from any cause			
Age	0.139	1.150 (1.111–1.189)	<0.001
Chronic kidney disease stage 2–3	1.335	3.801 (1.596–9.049)	0.003
In-hospital major cardiac events	1.771	5.879 (2.605–13.266)	<0.001
Aspirin	-1.782	0.168 (0.052–0.549)	0.003
Cardiovascular death			
Diabetes	1.440	4.222 (1.398–12.746)	0.011
Cerebrovascular disease	1.576	4.835 (1.309–17.862)	0.018
Left ventricle ejection fraction	-0.112	0.894 (0.841–0.950)	<0.001
In-hospital major cardiac events	3.064	21.417 (4.604–99.618)	<0.001
Myocardial infarction			
Diabetes	1.214	3.367 (1.551–7.309)	0.002
LIMA graft	-2.915	0.054 (0.017–0.168)	<0.001
In-hospital major cardiac events	1.439	4.217 (1.091–16.304)	0.037
Statins	-0.811	0.444 (0.220–0.897)	0.024
Rehospitalization			
Diabetes	1.057	2.879 (1.529–5.421)	0.001
LIMA graft	-2.638	0.072 (0.024–0.215)	<0.001
Statins	-0.820	0.440 (0.242–0.802)	0.007

CI: confidence interval; HR: hazard ratio; LIMA: left internal mammary artery; RC: regression coefficients.

Secondary outcomes

Death by any cause occurred in 94 patients (27%). At 6 months, the cumulative event rate was 2%, at 1 year 3%, at 5 years 7% and at 10 years 15%.

After multivariable analysis, age [RC 0.139 and HR 1.150 (1.111–1.189)] and chronic kidney disease stage 2–3 (30 < estimated glomerular filtration rate < 90) [RC 1.335 and HR 3.801 (1.596–9.049)] were identified as risk factors for death by any cause; use of aspirin [RC -1.782 and HR 0.168 (0.052–0.549)] at follow-up was protective.

Cardiovascular death occurred in 19 (6%) patients. At 6 months, the cumulative incidence of cardiovascular death was 1%, at 1 year 1%, at 5 years 4% and at 10 years 7%.

Diabetes [RC 1.440 and HR 4.222 (1.398–12.746)] and cerebrovascular disease [RC 1.576 and HR 4.835 (1.309–17.862)] were identified as risk factors for cardiovascular death, and a high EF was protective [RC -0.112 and HR 0.894 (0.841–0.950)].

Freedom from MI was also tested: 37 (10%) patients experienced an MI during follow-up. The cumulative incidence of MI at 6 months was 2%, at 1 year 3%, at 5 years 7% and at 10 years 10%.

At multivariable analysis, diabetes was identified as a risk factor [RC 1.214 and HR 3.367 (1.551–7.309)], while use of left ITA [RC -2.915 and HR 0.054 (0.017–0.168)] and of statins [RC -0.811 and HR 0.444 (0.220–0.897)] was protective (Table 2).

Comparative evaluation of surgical revascularization versus ISCHEMIA trial results

The cumulative risks for the primary composite and the secondary outcomes of death by any cause, cardiovascular death and myocardial infarction were compared with both the OMT and the revascularization arms of the ISCHEMIA trial patients (Figure 1).

Cumulative risk of the primary composite outcome at 5 years was 11% in surgical patients, 18% in the OMT arm of ISCHEMIA and 16% in the revascularization arm of ISCHEMIA ($P < 0.001$).

The overall survival was similar in the tested populations, with a risk of death by any cause at 5 years of 7% in surgical patients, 8% in OMT arm of ISCHEMIA and 9% in the revascularization arm of ISCHEMIA ($P = 0.026$).

As to cardiovascular death, the surgical population had a 4% risk, while in the OMT arm of ISCHEMIA, it was 16% and in the revascularization arm of ISCHEMIA was 14% ($P < 0.001$).

Comparison of MI at 5 years between our patients and those of the ISCHEMIA trial found that 7% of our surgical patients experienced an MI vs 12% and 10% in the conservative and invasive arms of the trial, respectively ($P < 0.001$).

DISCUSSION

The main objective of our investigation was to examine survival and cardiovascular events in patients after CABG for stable CAD after selection of a population as similar as possible to that of ISCHEMIA and then to compare such results to those of the trial. To this purpose, we defined our primary outcome as a composite of the rate of death from cardiovascular causes, MI or hospitalization for unstable angina, heart failure or resuscitated cardiac arrest, as done in ISCHEMIA. In our study, we showed good results in long-term survival and cardiovascular events in patients treated by CABG for stable CAD, after demonstration of at least moderate ischaemic burden and epicardial coronary involvement, more often of 3 or more territories. The event rate registered in our series was lower than in the trial and mostly related to early morbidity and mortality of the CABG procedure. These results were similar in the comparison of the examined

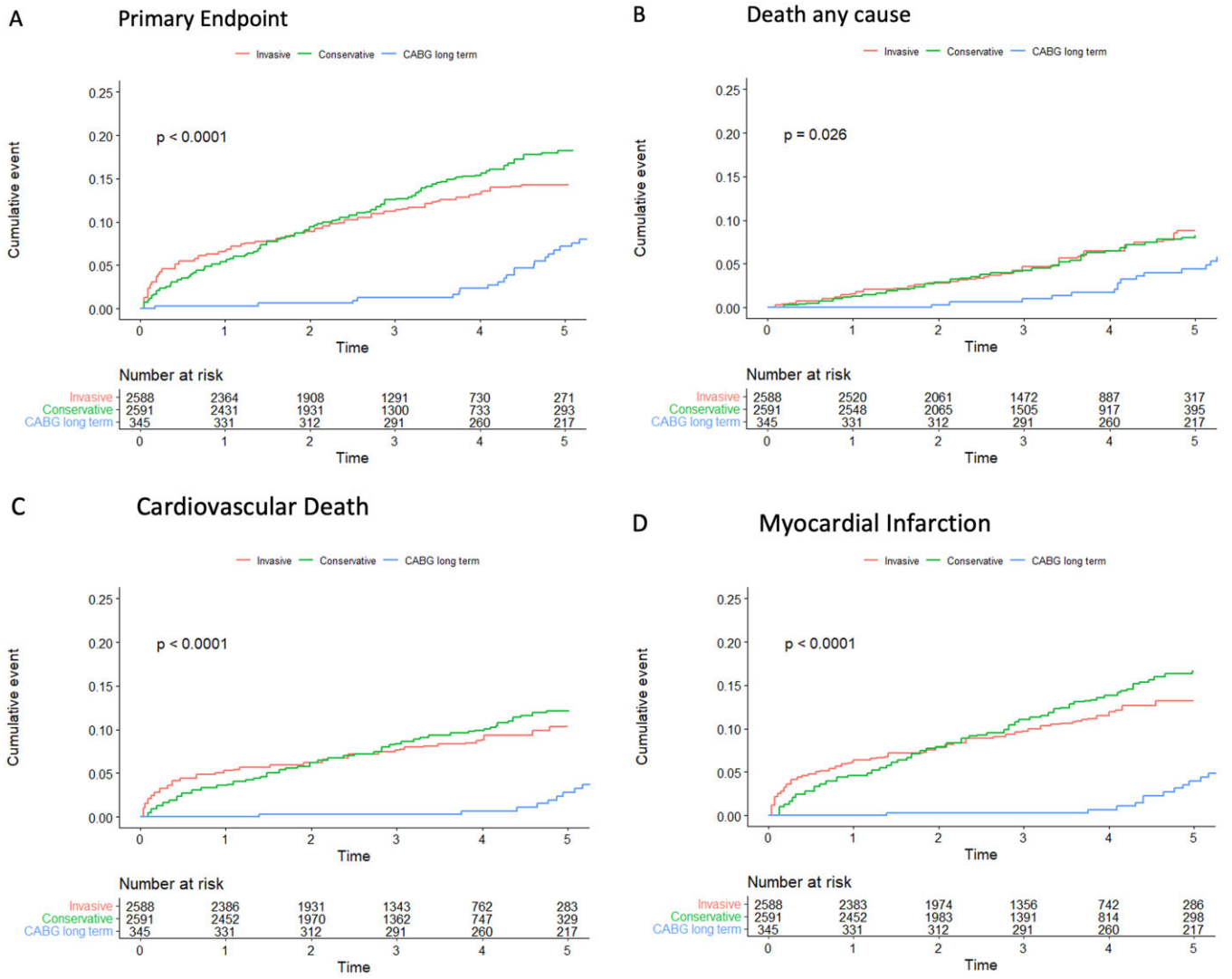

Figure 1: Kaplan–Meier plot (cumulative event rate) for invasive, conservative, and the coronary artery bypass graft strategy for primary end point (**A**), death from any cause (**B**), cardiovascular death (**C**) and myocardial infarction (**D**). The conservative and invasive strategy raw data have been reconstructed using Guyot *et al.* algorithm [9]. The global log-rank test has been reported on the plot, the pairwise comparison *P*-values have been reported in the tables by using the Benjamini–Hochberg correction for multiple comparisons [10].

secondary outcomes: while the rate of all-cause death in our series was close to that of ISCHEMIA, death from cardiovascular causes and MI echoed the results of our primary end point, resulting in better outcomes of our series compared to both arms of ISCHEMIA.

These results should not be interpreted as proving the inferiority of OMT alone as compared to surgical revascularization, for the evident limitations of this comparison needing to be acknowledged.

First, one-fifth of patients of ISCHEMIA randomized to the invasive strategy was not actually diagnosed as having obstructive CAD at angiography. Baseline coronary anatomy was investigated by CT, revealing <50% of patients having three-vessel disease. In our study, all patients under examination were deemed suitable for surgical treatment, while only 25% in the invasive arm of ISCHEMIA underwent CABG. Several studies in the past have shown that the benefit of revascularization arises if revascularization is complete [2], and this is easier to achieve with surgical revascularization than by PCI [11].

Second, one-fifth of patients of the OMT arm in ISCHEMIA crossed over to the other treatment arm. Indeed, surgical revascularization could offer greater protection from new MI since it protects the revascularized territory from subsequent events resulting from the rupture of a complex plaque upstream of the graft site [12, 13].

In 2019, the ISCHEMIA trial showed that, added to OMT, a strategy involving routine myocardial revascularization did not improve the prognosis of patients with moderate/severe ischaemia [6]. Nonetheless, beyond the strengths and limitations of the trial, ISCHEMIA results do not appear as having changed real-world clinical practice in the treatment of patients with SCD [14]. Recently, De Luca *et al.* found that, in a registry of 5070 consecutive patients enrolled for SCD, only 3.8% should have been enrolled in ISCHEMIA trial. Furthermore, these patients presented a very low annual risk of cardiovascular events as compared to other patients [15]. The results of ISCHEMIA should therefore be seen in the light of trial population not being representative of the real-world, also considering the great number of patients

excluded before enrolment [16]. Trial participants often have a healthier distribution than patients seen in clinical practice, translating into lower-than-expected event rates. For this reason, the primary end point of ISCHEMIA was changed to a five-component composite because of the lower-than-expected event rates [17].

We believe that differences in our population compared to that of ISCHEMIA are the main determinants of differences in outcomes. In addition, specific OMT was monitored in the ISCHEMIA trial, but not in our population. Our results confirm that adherence to OMT, at least statins and aspirin in our findings, should also be the key to a good long-term result, as recently demonstrated [18–20]. While statins showed a protective effect in preventing the examined primary outcome, MI and new hospitalization, the role of aspirin was herein more controversial, being protective 'only' from all cause death.

Another limitation of comparing surgical results to ISCHEMIA trial should be found in the heterogeneity of the invasive group that included surgical and percutaneous strategies of revascularization, while our study design included only CABG patients. Beyond the obvious limitation of comparing different study designs, we strongly believe that our report can add information to the literature by providing a real-world population that is selected for CABG after demonstration of ischaemia with functional testing and angiographic evidence of CAD. In fact, Miller *et al.* [21] demonstrated that early revascularization with either CABG or PCI after ischaemia detection was associated with reduced all-cause mortality, suggesting a 15% threshold of ischaemia as necessary to show reduction in death. Moreover, they stated that the choice of strategy of revascularization should be guided by the complexity of CAD and patient characteristics, but not by the burden of ischaemia, as also current guidelines do [22].

In our population, diabetes and reduced left ventricle function (between 35% and 45%) confirmed to be strong predictors of adverse cardiovascular events in the long term, underlining the need of particular attention when dealing stable ischaemic heart disease in patients with diabetes or reduced left ventricular function [23]. Analysis of the BARI-2D trial showed that in patients with type 2 diabetes and CAD, initial revascularization plus OMT did not offer advantage versus OMT alone; however, about 40% of OMT group was revascularized in the subsequent 5 years. That study did not include patients with extensive obstructive CAD and severe myocardial ischaemia [3].

Moreover, a secondary analysis of the ISCHEMIA trial showed that in patients with reduced EF, routine revascularization reduced the occurrence of the primary end point (17.2% vs 29.3%) in patients with a history of heart failure at baseline [24].

In 1990, Alderman *et al.* showed that after 10-year follow-up, there was no difference between surgical revascularization and initial medical therapy in survival and MI. At that time, however, both medical and surgical therapies were different [25].

In a recent meta-analysis of more contemporary trials, however, routine revascularization showed again no association with improved survival in patients with stable CAD over 4.5 years [26]. Indeed, the shortness of follow-up of these trials represents a great drawback because it is not predictable how the curves would behave in a longer period. In a median follow-up of 9 years, our results remained stable, thus evidencing the long-term benefit of surgical revascularization.

Limitations

Some limitations must be acknowledged. The retrospective design and small size of our patient population made comparison of the results challenging and reduced statistical power. Indeed, this is the consequence of a highly selected population of the examined trial. Early and late results, despite seeming somehow dated, should be read in the light of current practice made of patients undergoing surgical revascularization after demonstration of ischaemia and epicardial CAD. Finally, we cannot directly compare trial population to our patients, especially because some differences appear evident in cardiovascular risk factors and comorbidities, like previous stroke. Nonetheless, by selecting our population with the exclusion criteria of ISCHEMIA, we also aimed to demonstrate the low reproducibility of the results of the trial itself.

CONCLUSIONS

This study is the first investigation to compare the outcomes of surgical revascularization therapy to that of ISCHEMIA trial. Results of our study may be summarized as follows: (i) benefit with surgical revascularization in stable ischaemic heart disease appears related to the general practice of shared decision-making, demonstration of ischaemia and coronary anatomy and patient characteristics rather than surgical technique (on-pump/off-pump, arterial grafting); (ii) diabetes and reduced left ventricle function (between 35% and 45%) confirmed to be strong predictors of adverse cardiovascular events in the long-term of CABG; (iii) a patient-tailored approach, including surgical revascularization and OMT offers good results in patients with CCS; and (iv) ISCHEMIA trial findings are not transferable in a 'real-world' scenario and should be critically considered according to specific coronary anatomy and clinical conditions of patients.

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Data Availability Statement

All relevant data are within the manuscript and its supporting information files.

Author contributions

Andrea De Martino: Data curation; Investigation; Writing—original draft. **Federico Del Re:** Data curation; Methodology. **Dario Gregori:** Formal analysis. **Danila Azzolina:** Formal analysis. **Clemente Pascarella:** Data curation; Project administration. **Giosuè Falcetta:** Data curation; Investigation. **Giacomo Ravenni:** Investigation. **Michele Celiento:** Investigation. **Riccardo Morganti:** Formal analysis. **Andrea Colli:** Methodology; Supervision; Writing—review & editing.

Reviewer information

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