

Impact of coronary revascularization vs medical therapy on ischemia among stable patients with or suspected coronary artery disease undergoing serial myocardial perfusion scintigraphy

Francesco Nudi, MD,^{a,b,c} Natale Di Belardino, MD,^d Francesco Versaci, MD,^{e,f} Annamaria Pinto, MD,^a Enrica Procaccini, MD,^a Giandomenico Neri, MD,^a Maurizio Vetere, BSc,^a Giacomo Frati, MD, MSc,^{g,h} Mariangela Peruzzi, MD, PhD,^g Orazio Schillaci, MD,ⁱ Achille Gaspardone, MD, PhD,^j Fabrizio Tomai, MD,^k and Giuseppe Biondi-Zoccai, MD, MStat^{g,h}

^a Service of Nuclear Cardiology, Madonna della Fiducia Clinic, Rome, Italy

^b Ostia Radiologica, Rome, Italy

^c Etisan, Rome, Italy

^d Division of Cardiology, Anzio-Nettuno Hospital, Anzio, Italy

^e Department of Cardiovascular Disease, Ospedale A. Cardarelli, Campobasso, Italy

^f Department of Cardiovascular Disease, Ospedale F. Veneziale, Isernia, Italy

^g Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy

^h Department of AngioCardioNeurology, IRCCS Neuromed, Pozzilli, Italy

ⁱ Department of Nuclear Medicine, Tor Vergata University of Rome, Rome, Italy

^j Division of Cardiology, S. Eugenio Hospital, Rome, Italy

^k Division of Cardiology, European Hospital, Rome, Italy

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Background. Randomized trials have challenged the role of revascularization in stable coronary artery disease. We aimed to appraise the impact of revascularization on ischemia in patients undergoing serial myocardial perfusion scintigraphy (MPS).

Methods. We queried our institutional database for stable subjects undergoing serial MPS and appraised the impact of revascularization on changes in ischemia.

Results. A total of 3631 patients were included: 967 (27%) undergoing revascularization and 2664 (73%) receiving medical therapy only. Patients treated with revascularization had a significantly lower burden of myocardial ischemia at follow-up (odds ratio = 0.577 [95% confidence interval 0.483-0.689] vs medical therapy, $P < .001$). Among all those having moderate or severe ischemia at baseline, revascularization was associated with a follow-up prevalence of 80% for no, minimal, or mild ischemia and 20% for moderate or severe ischemia, vs 43% and 57% for medical therapy ($P < .001$). Even at multivariable analysis and propensity-adjusted, and propensity-matched analyses, revascularization was associated with a significantly lower prevalence of moderate or severe ischemia at follow-up (respectively $P < .001$, $P = .001$, and $P = .042$).

Conclusions. Revascularization appears superior to medical therapy in reducing ischemic

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Reprint requests: Giuseppe Biondi-Zoccai, MD, MStat, Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University

of Rome, Corso della Repubblica 79, 04100 Latina, Italy; gbiondi-zoccai@gmail.com, giuseppe.biondizoccai@uniroma1.it 1071-3581/\$34.00

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burden and normalizing myocardial perfusion among subjects with moderate or severe ischemia at baseline. (J Nucl Cardiol 2017;24:1690–98.)

Key Words: Cardiovascular disease • coronary artery bypass grafting • coronary artery disease • myocardial ischemia • maximal ischemia score • myocardial perfusion imaging • myocardial perfusion scintigraphy

Abbreviations

CAD	Coronary artery disease
EDVI	End-diastolic volume index
FFR	Fractional flow reserve
LVEF	Left ventricular ejection fraction
MIS	Maximal ischemia score
MPS	Myocardial perfusion scintigraphy
SPECT	Single photon emission computed tomography
VRI	Vessel-related ischemia

See related editorial, pp. 1699–1701

INTRODUCTION

The burden of cardiovascular diseases, including stroke and coronary artery disease (CAD), demands accuracy in selecting the most appropriate management strategy. Myocardial perfusion scintigraphy (MPS) has become a cornerstone in the choice of treatment for CAD.¹ Specifically, MPS has an established accuracy in defining myocardial ischemia and inform prognosis.¹⁻³ Recent trials comparing medical therapy vs coronary revascularization in stable CAD have questioned the rationale of routine revascularization.⁴⁻⁷ These trials relied, however, mainly on angiographic appraisal of CAD severity, which correlates imperfectly with ischemia, thus potentially leading to inclusion of patients with angiographically significant stenoses but no ischemia.⁶⁻⁹ As the benefits of revascularization in comparison to medical therapy in subjects with CAD might be stronger or limited to those with a certain amount of myocardial ischemia,^{2,10-12} we aimed to appraise in a large registry of stable CAD patients the impact of coronary revascularization vs medical therapy on ischemia as appraised by serial MPS.

METHODS

Design

This is a retrospective study stemming from our institutional research registry, which has been approved by the local ethics committee. All patients provided written informed consent.

Patients

Subjects undergoing two or more MPS for the diagnostic or prognostic work-up of CAD between 2004 and 2014 at our center were identified by retrospectively querying our institutional database, extracting data only for the initial two MPS in case of more than two tests. Additional exclusion criteria were age <18 years, recent (<6 months) or intercurrent unstable angina, prior or intercurrent myocardial infarction, left ventricular systolic dysfunction [defined as left ventricular ejection fraction (LVEF) <45%], or dilated cardiomyopathy [defined as left ventricular end-diastolic volume index (EDVI) >130 mL/m²]. The rationale for excluding patients with low LVEF or increased EDVI was that the benefits of revascularization in such setting have been already quite established. Conversely, inclusion of these patients might have led to results which could have been difficult to apply to stable patients without ischemic cardiomyopathy. The repeat MPS was performed for obvious stable clinical symptoms (e.g., persistence of stable angina), or routine monitoring of patients. Subjects were further stratified based on whether they had underwent coronary revascularization between baseline and repeat MPS, distinguishing also those receiving percutaneous vs surgical revascularization.

Stress and Imaging Protocol

Patients were exercised in a fasting state having discontinued long-acting nitrates, beta-blockers, and calcium-channel antagonists for at least 24 hours. Symptom-limited dynamic stress testing was performed on a bicycle ergometer according to a standard protocol. At peak exercise, a weight-adjusted dose (3.0-4.0 mCi) of ²⁰¹Tl or (10-15 mCi) of ^{99m}Tc-methoxy isobutyl isonitrile (^{99m}Tc-MIBI) was injected (with a 10-15 mCi dose for ^{99m}Tc-MIBI reinjection). Subjects unable to exercise underwent pharmacologic stress testing with dipyridamole. Post-stress and rest-gated single photon emission computed tomography (SPECT) was performed 3 minutes and 6-24 hours after radioisotope injection with the patient in the supine position to maximize redistribution. A dual-head gamma camera (Millennium MG or Millennium MyoSIGHT, GE Healthcare, Milan, Italy), equipped with a low-energy, general-purpose collimator, was used according to a standard protocol for data acquisition and elaboration.

The gated data were analyzed according to a 7-region segmentation method, which is in keeping with the anatomic distribution of the main coronary vessels: (1) apical, (2) antero-medio-distal, (3) antero-proximal, (4) septal, (5) postero-lateral, (6) lateral (which corresponds to the anatomic variability in coronary dominance), and (7) inferior (Figure 1S).³ Semiquantitative interpretation of stress/rest images

was then performed by consensus of 2 experienced observers, finally yielding a 5-tier maximal ischemia score (MIS, 0-no ischemia; 1-minimal ischemia; 2-mild ischemia; 3-moderate ischemia; 4-severe ischemia).³ In addition, the recently introduced vessel-related ischemia (VRI) classification system was applied based on the relative correspondence between coronary arteries and the 7-region model,¹³ distinguishing: VRI involving the left anterior descending (LAD) territory when regions (1), (2), (3), or (4) were ischemic; VRI involving the left circumflex (LCX) territory when regions (5) or (6) were ischemic; and VRI involving the right coronary artery (RCA) territory, when only region (7) or both regions (6) and (7) were ischemic. Accordingly, the variable combinations of VRI subtypes were used to define four separate groups of patients: single-VRI involving LAD, single-VRI not involving LAD, multi-VRI involving LAD, and multi-VRI not involving LAD. Finally, LVEF and EDVI were also computed with SPECT.

Notably, disagreements between readers were handled by open discussion leading to mutual consensus. Operators were not blinded to patient features, stress details, or prior MPS data, this being a pragmatic study stemming from our administrative database. We did not appraise disagreement rate in the present study, but as per our quality appraisal procedures, disagreements between two experienced readers for MIS range between 1% and 3%. Moreover, all MPS hereby included in the study were interpreted by the same team of two nuclear cardiologists, and for each repeat exam, the prior one was available in extenso and directly compared for clinical reporting purposes to the repeat one.

Statistical Analysis

Continuous variables are reported as mean \pm standard deviation, and categorical variables are reported as n (%). Bivariate analyses were performed distinguishing patients according to treatment strategy, using unpaired Student *t* test for continuous variables, Fisher exact test, and logistic regression (either binary or ordinal) for categorical variables. Adjusted analyses were based on three separate approaches: ordinal logistic regression analysis with multivariable adjustment, ordinal logistic regression with propensity score adjustment, and propensity score matching. Multivariable adjustment included in the model as covariates all those associated with revascularization with a $P < .05$ at bivariate analyses (Supplementary Material). Propensity scores were obtained with a nonparsimonious logistic model,¹⁴ with revascularization as dependent variable and several independent variables. One-to-one matching was performed with a 0.1 propensity score caliper, and subsequently multilevel generalized linear models and generalizing estimating equations were used for hypothesis testing (with identity link for continuous variables and logit link for dichotomous variables). Adjusted analyses provided odds ratios (ORs) with 95% confidence intervals and corresponding *P* values. Statistical significance was set at the 2-tailed 0.05 level. Computations were performed with Stata (StataCorp, College Station, TX, USA; Table 1S).

RESULTS

A total of 3631 patients undergoing serial MPS were included. The average interval between baseline and repeat MPS was 2.8 ± 1.9 years. Of these, 967 (27%) subjects underwent revascularization and 2664 (73%) medical therapy. The average interval between the baseline MPS and revascularization was 8.1 ± 14.5 months. Patients treated with coronary revascularization were often at higher risk than those treated medically (Table 1). Specifically, they were significantly older, more commonly diabetic, more frequently smokers, more commonly with hypercholesterolemia and hypertriglyceridemia, and had a higher prevalence of prior coronary revascularization ($P < .05$ for all). Conversely, medical therapy was more aggressive in patients subsequently undergoing revascularization.

Significant differences were evident in stress details of baseline MPS and repeat MPS (Table 2) in the revascularization and medical therapy groups, with coronary revascularization being associated with more marked improvements in several parameters in comparison to medical therapy, including chest pain, ST-segment deviation, workload, rate pressure product, LVEF, and EDVI (all $P < .05$), despite more adverse baseline stress features.

Focusing on the degree of myocardial ischemia at the baseline MPS, a total of 1762 (49%) patients exhibited no ischemia, 575 (16%) had evidence of minimal ischemia, 684 (19%) mild ischemia, 446 (12%) moderate ischemia, and 164 (5%) severe ischemia (Tables 3, 2S). These figures changed significantly at the repeat MPS, with a total of 28 (1%) having severe ischemia, 256 (7%) moderate, 756 (21%) mild, 886 (24%) minimal, and 1705 (47%) no ischemia at all.

Favorable results at the repeat MPS were found in all those who originally had only no, minimal, or mild myocardial ischemia at the baseline MPS, irrespective of their medical, percutaneous or surgical treatment (Figure 1; Tables 3S, 4S). Interestingly, in almost no patient without evidence of myocardial ischemia at baseline MPS was severe ischemia demonstrated at repeat MPS, irrespective of the treatment strategy (2/1762 [0.1%]), with similar comparative findings among subjects with minimal or mild ischemia at baseline MPS. Indeed, revascularization appeared associated with nonsignificant detrimental effects in those without baseline ischemia.

Conversely, among those with moderate or severe ischemia at baseline MPS, coronary revascularization appeared clearly superior to medical therapy in reducing or resolving altogether ischemia (with persistently moderate or severe ischemia in, respectively, 20% vs 57%). Similar findings were evident when focusing

Table 1. Baseline features according to management strategy

Feature	Total (N = 3631)	Medical therapy (N = 2664)	Coronary revascularization (N = 967)	<i>p</i>
Age (years)	64.0 ± 9.3	63.7 ± 9.3	65.0 ± 9.1	<.001
Male gender	1189 (32.8%)	997 (37.4%)	192 (19.9%)	<.001
Diabetes mellitus	1096 (30.2%)	737 (27.7%)	359 (37.1%)	<.001
Hypertension	2767 (76.2%)	2015 (75.6%)	752 (77.8%)	.186
Current or former smoking	2122 (58.5%)	1506 (56.5%)	616 (63.8%)	<.001
Hypercholesterolemia	2183 (60.2%)	1575 (59.2%)	608 (62.9%)	.042
Hypertriglyceridemia	642 (17.7%)	437 (16.4%)	205 (21.2%)	.001
Family history of coronary artery disease	1775 (48.9%)	1295 (48.6%)	480 (49.7%)	.573
Prior coronary revascularization	1243 (34.2%)	1014 (38.1%)	229 (23.7%)	<.001
Medical therapy after baseline MPS				
Anti-diabetic agent	1066 (29.4%)	725 (27.2%)	341 (35.3%)	<.001
Angiotensin-converting enzyme inhibitor	1244 (34.3%)	870 (32.7%)	374 (38.7%)	.001
Angiotensin-receptor blocker	1247 (34.3%)	945 (35.5%)	302 (31.2%)	.018
Antiplatelet agent	2833 (78.0%)	1930 (72.5%)	903 (93.4%)	<.001
Beta-blocker	1836 (50.6%)	1247 (46.8%)	589 (60.9%)	<.001
Calcium channel antagonist	1198 (33.0%)	886 (33.3%)	312 (32.3%)	.604
Nitrate	718 (19.8%)	483 (18.1%)	235 (24.3%)	<.001
Statin	2333 (64.3%)	1561 (58.6%)	772 (79.8%)	<.001

specifically on patients with severe ischemia at baseline (with persistently severe ischemia in 6% of patients undergoing revascularization vs 25% of subjects treated medically), or when comparing changes in the size of MIS classes over time (Figure 2).

Adjunct multivariable-adjusted, propensity score-adjusted, and propensity score-matched analyses confirmed that revascularization was associated with significantly less severe ischemia than medical therapy (Tables 4, 5S, 6S, 7S, 8S, 9S). Specifically, odds ratios were always in favor of revascularization, irrespective of the analytic approach (all *P* < .05). Conversely, comparison of surgical vs percutaneous revascularization showed that, taking into account baseline patient differences, the two revascularization strategies were associated with similarly favorable results on ischemia severity (all *p* > .05).

In addition, similar results in terms of magnitude and significance of effect were found when distinguishing patients with prior revascularization vs those without any prior revascularization, focusing only on subjects in optimal medical therapy, or excluding those without

baseline ischemia (Tables 10S, 11S, 12S). Finally, comparative analysis focusing on summed stress scores, summed difference scores, and VRI highlighted that, on top of the beneficial impact on ischemia severity, revascularization was also associated with less-extensive ischemia at repeat MPS than medical therapy (Tables 9S, 13S, 14S).

DISCUSSION

This study, building upon prior works on this topic,^{11,12,15-19} and providing a further appraisal of the impact of coronary revascularization on patients with scintigraphic evidence of myocardial ischemia, has several implications. First, coronary revascularization, either percutaneous or surgical, appears superior to medical therapy in ameliorating or resolving myocardial ischemia in patients with severely or moderately ischemic baseline MPS. Second, subjects without any evidence of myocardial ischemia at baseline MPS seem to have a more satisfactory outlook when managed conservatively.

Table 2. Stress details of baseline and repeat myocardial perfusion scintigraphy (MPS) according to management strategy

Feature	Total (N = 3631)	Medical therapy (N = 2664)	Coronary revascularization (N = 967)	P
Baseline MPS				
Type of stress				.003
Exercise	3186 (87.7%)	2312 (86.8%)	874 (90.4%)	
Pharmacologic stress	445 (12.3%)	352 (13.2%)	93 (9.6%)	
Anginal chest pain during stress	191 (5.3%)	39 (1.5%)	152 (15.7%)	<.001
ST-segment deviation ≥ 1.0 mm	673 (18.5%)	290 (10.9%)	383 (39.6%)	<.001
Workload (Watt)	98.1 \pm 41.2	98.3 \pm 42.1	97.7 \pm 38.7	.728
Rate pressure product (bpm mmHg)	26,061 \pm 3797	26,436 \pm 3768	25,132 \pm 3708	<.001
Left ventricular ejection fraction (%)	62.4 \pm 9.8	63.8 \pm 9.6	58.6 \pm 9.4	<.001
End-diastolic volume index (mm/m ²)	65.3 \pm 20.8	63.6 \pm 20.2	70.0 \pm 21.5	<.001
Time between baseline and repeat MPS (years)	2.8 \pm 1.9	3.1 \pm 1.9	2.0 \pm 1.8	<.001
Repeat MPS				
Type of stress				.127
Exercise	3040 (83.7%)	2215 (83.2%)	825 (85.3%)	
Pharmacologic stress	591 (16.3%)	449 (16.9%)	142 (14.7%)	
Anginal chest pain during stress	107 (3.0%)	58 (2.2%)	49 (5.1%)	<.001
ST-segment deviation ≥ 1.0 mm	568 (15.6%)	336 (12.6%)	232 (24.0%)	<.001
Workload (Watt)	99.8 \pm 41.9	99.1 \pm 42.7	101.8 \pm 39.6	.115
Rate pressure product (bpm mmHg)	26,081 \pm 3721	26,269 \pm 3706	25,614 \pm 3720	<.001
Left ventricular ejection fraction	65.3 \pm 10.1	65.9 \pm 10.2	63.5 \pm 9.8	<.001
End-diastolic volume index (mL/m ²)	59.9 \pm 21.1	58.9 \pm 21.0	62.6 \pm 21.4	<.001
Comparison between baseline and repeat MPS				
Improvement in chest pain	157 (4.3%)	30 (1.1%)	127 (13.1%)	<.001
Decrease in ST-segment deviation (mm)	0.5 \pm 0.5	0.5 \pm 0.5	0.6 \pm 0.5	.027
Increase in workload (Watt)	0.4 \pm 0.5	0.3 \pm 0.5	0.4 \pm 0.5	.006
Increase in rate pressure product (bpm mmHg)	-94 \pm 3921	-289 \pm 3942	390 \pm 3827	<.001
Increase in left ventricular ejection fraction (%)	0.6 \pm 0.5	0.6 \pm 0.5	0.7 \pm 0.5	<.001
Decrease in end-diastolic volume index (mm/m ²)	0.6 \pm 0.5	0.6 \pm 0.5	0.7 \pm 0.5	.020

Table 3. Comparison between maximal ischemia scores (MISs) at baseline and repeat myocardial perfusion scintigraphy (MPS) in patients receiving medical therapy (Med Rx) vs coronary revascularization (Revasc), after collapsing subjects with no, minimal, or mild ischemia into a single category and subjects with moderate or severe ischemia into another category only

Timing of MPS and MIS	Repeat MPS			
		No, minimal or mild ischemia (N = 3347)		Moderate or severe ischemia (N = 284)
Baseline MPS				
No, minimal or mild ischemia (N = 3021)	Med Rx	97.2% (2465/2537)	Med Rx	2.8% (72/2537)
	Revasc	91.1% (441/484)	Revasc	8.9% (43/484)
Moderate or severe ischemia (N = 610)	Med Rx	43.3% (55/127)	Med Rx	56.7% (72/127)
	Revasc	79.9% (386/483)	Revasc	20.1% (97/483)

P < .001 at binary logistic regression

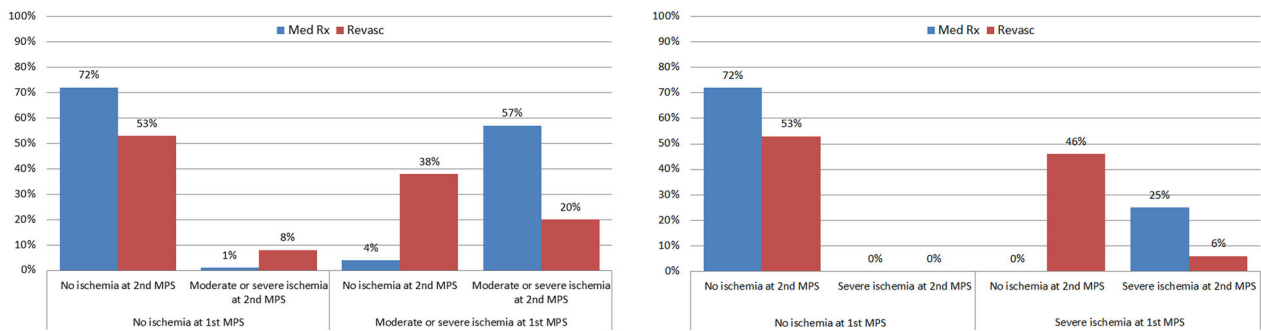


Figure 1. Degree of myocardial ischemia at repeat myocardial perfusion scintigraphy (MPS), distinguishing those undergoing medical therapy (Med Rx) vs coronary revascularization (Revasc), in patients who had evidence of no vs moderate or severe myocardial ischemia at baseline MPS (*left panel*), and in patients who had evidence of no vs severe myocardial ischemia at baseline MPS (*right panel*).

Myocardial perfusion scintigraphy is a cornerstone in the work-up of patients with CAD.^{1,10,15,16,20} In several prior registries, revascularization appeared beneficial, especially in subjects with more extensive ischemia.^{10,17} Nonetheless, recent trials appraising the prognostic benefit of revascularization vs optimal medical therapy have not systematically exploited the results of MPS or similar imaging modalities as an entry criterion.^{4,5} Conversely, the FAME trials confirmed the lack of correlation between anatomic and functional data, and also the importance of the presence of myocardial ischemia in selecting patients most likely to benefit from revascularization.^{6,7,21}

Despite the heterogeneity in patient selection typical of randomized trials, sub-analyses exploiting MPS from these studies have shed important insights on the role of revascularization vs medical therapy in stable CAD. Specifically, Shaw et al performed serial MPS in 314 patients randomized to revascularization vs

medical therapy, finding that a $\geq 5\%$ decrease in myocardial ischemia was achieved in 33% of those undergoing PCI vs 19% treated medically.¹¹ Notably, if the analysis was limited to only those with moderate or severe baseline ischemia, PCI reduced myocardial ischemia (using a $\geq 5\%$ cut-off) in 78% of subjects treated with revascularization vs 52% for medical therapy.¹¹ The BARI 2D trial has not reported similar data on paired MPS, but did report on 1505 patients undergoing follow-up MPS.¹² In this patient sample, 59% of subjects undergoing revascularization had no evidence of myocardial ischemia in comparison to 49% of those undergoing medical therapy only. Of note, in these trials as well as in a similar observational study stemming from the Duke Database, persistent ischemia at follow-up MPS was an independent prognostic factor.¹⁸

Our current results suggest a mechanistically different effect of revascularization vs medical therapy on

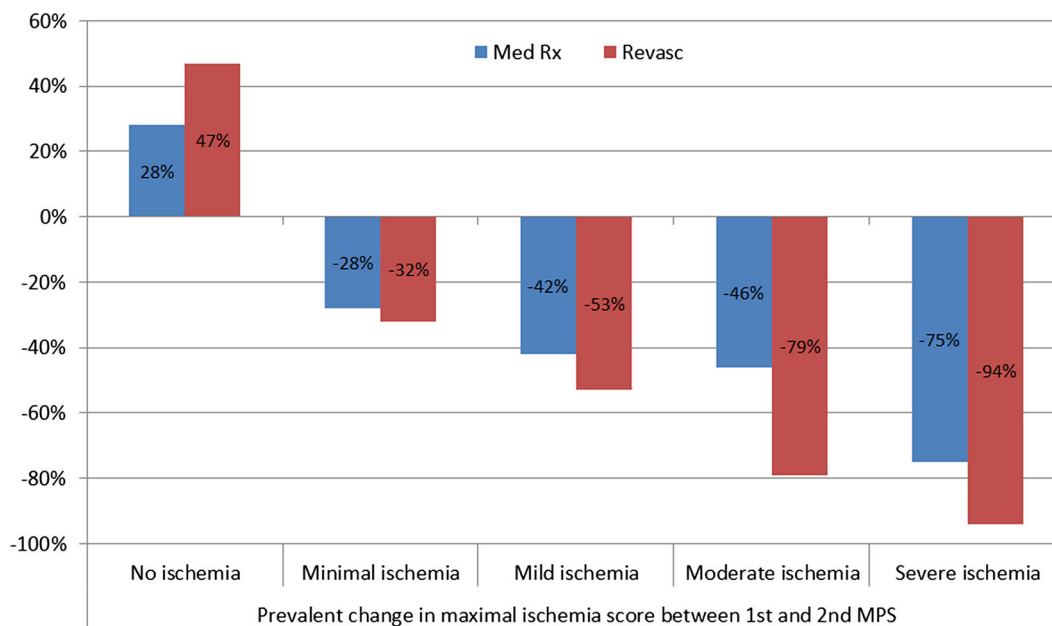


Figure 2. Prevalent changes in maximal ischemia scores (MISs) between baseline and repeat myocardial perfusion scintigraphy (MPS) comparing medical therapy (Med Rx) vs coronary revascularization (Revasc). Negative values indicate an overall decrease (i.e., improvement) in MIS, and positive values an overall increase (i.e., worsening) in MIS.

Table 4. Multivariable analysis appraising the independent prognostic role of revascularization vs medical therapy on the severity of ischemia at repeat myocardial perfusion scintigraphy (MPS), expressed as maximal ischemia score (MIS)

Analysis	Odds ratio for unit change in MIS		
	Point estimate	95% confidence interval	P value
Revascularization vs medical therapy			
Multivariable-adjusted analysis*	0.631	0.509-0.783	<.001
Propensity score-adjusted analysis†	0.687	0.550-0.856	.001
Propensity score-matched analysis‡	0.757	0.578-0.990	.042
Percutaneous revascularization vs medical therapy			
Multivariable-adjusted analysis*	0.616	0.492-0.771	<.001
Propensity score-adjusted analysis†	0.673	0.534-0.848	.001
Propensity score-matched analysis‡	0.650	0.491-0.862	.003
Surgical revascularization vs medical therapy			
Multivariable-adjusted analysis*	0.257	0.168-0.394	<.001
Propensity score-adjusted analysis†	0.475	0.283-0.798	.005
Propensity score-matched analysis‡	0.419	0.215-0.815	.010
Surgical vs percutaneous revascularization			
Multivariable-adjusted analysis*	0.862	0.603-1.232	.415
Propensity score-adjusted analysis†	0.905	0.631-1.299	.589
Propensity score-matched analysis‡	0.815	0.510-1.302	.392

* Ordinal logistic regression model with multivariable adjustment

† Ordinal logistic regression model adjusting for propensity score

‡ Multilevel mixed-effects generalized linear model after propensity matching

ischemia at follow-up in general, and on improvements in ischemia in particular. Specifically, revascularization appeared superior to medical therapy in reducing ischemia among those with moderate or severe ischemia at baseline. Moreover, revascularization appeared better than medical therapy in normalizing altogether myocardial perfusion among those with baseline ischemia. Conversely, there was no apparent benefit of revascularization (percutaneous or surgical) on follow-up ischemia among patients without ischemia at baseline, or among subjects with only minimal or mild baseline ischemia. Indeed, revascularization tended to be even detrimental in such patients.

The suboptimal therapy received by many patients having evidence of myocardial ischemia in our registry, while disappointing, is in keeping with real-world data on unselected patients with CAD. While optimal therapy as previously described was relatively more common among subjects undergoing revascularization, multivariable analysis accounting for the potential confounding effects of specific drug agents showed that the beneficial impact of revascularization on myocardial ischemia was independent from such potential moderators. Another key feature of our work is that we excluded pre hoc patients with abnormal LVEF or EDVI, thus limiting their confounding effects.²²

This work has several limitations, which mainly have to do with the observational and retrospective design. Extensive analyses, including propensity score adjustment and matching, should have reduced, though, the risk of selection bias. In addition, the decision to perform repeat MPS was based on clinical criteria, and thus there is an inherent and strong selection bias in performing a repeat MPS, especially after a normal or near-normal baseline MPS. Yet, the nonrandomized design may give indirect advantages to the medical therapy group, as this approach is commonplace in patients at lower risk, or even without CAD, leading to an underestimation of adverse events in the medical therapy group. A formal evaluation of the prognostic impact of changes in MIS after baseline MPS was beyond our scope, but recent evidence supporting the prognostic importance of changes in myocardial ischemia (and thus possibly in severity as well) are available elsewhere.^{11,12,19} Finally, the withdrawal of anti-anginal medications before MPS may have led to an overestimation of ischemic burden, favoring those undergoing revascularization.

NEW KNOWLEDGE GAINED

Myocardial perfusion scintigraphy (MPS) represents a valid means to appraise the comparative impact of medical therapy vs coronary revascularization in

patients with coronary artery disease. In our large retrospective cohort of patients undergoing serial MPS, revascularization appeared superior to medical therapy in reducing ischemic burden among those with moderate or severe ischemia at baseline, and even more so in normalizing myocardial perfusion.

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Disclosure

Dr Biondi-Zoccai has served as advisory board member for Abbott Vascular and Bayer, has consulted for Direct Flow Medical, and Novartis, and has lectured for Abbott Vascular, Astra Zeneca, Bayer, Medscape, and St. Jude Medical.

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