

Effects of Percutaneous Coronary Interventions in Silent Ischemia After Myocardial Infarction

The SWISSI II Randomized Controlled Trial

Paul Erne, MD

Andreas W. Schoenenberger, MD

Dieter Burckhardt, MD

Michel Zuber, MD

Wolfgang Kiowski, MD

Peter T. Buser, MD

Paul Dubach, MD

Therese J. Resink, PhD

Matthias Pfisterer, MD

SILENT ISCHEMIA HAS BEEN SHOWN to predict adverse prognosis in patients after myocardial infarction (MI),¹ coronary artery bypass graft surgery,² and percutaneous coronary intervention (PCI) with or without stenting.³⁻⁶ Despite these consistent findings, there are few prospective data unequivocally documenting a benefit of anti-ischemic therapy on prognosis in patients with silent ischemia.⁷ There is some indirect evidence of a better outcome after repeat PCI for silent restenosis.⁶ In patients with a recent MI, the Asymptomatic Cardiac Ischemia Pilot study documented a short-term benefit of anti-ischemic drug therapy and PCI in patients with silent and symptomatic ischemic episodes.⁸⁻¹¹

However, long-term outcome data in asymptomatic patients is lacking and it is not known whether PCI in addition to secondary preventive measures is superior to anti-ischemic drug therapy in these patients. Therefore,

Context The effect of a percutaneous coronary intervention (PCI) on the long-term prognosis of patients with silent ischemia after a myocardial infarction (MI) is not known.

Objective To determine whether PCI compared with drug therapy improves long-term outcome of asymptomatic patients with silent ischemia after an MI.

Design, Setting, and Participants Randomized, unblinded, controlled trial (Swiss Interventional Study on Silent Ischemia Type II [SWISSI II]) conducted from May 2, 1991, to February 25, 1997, at 3 public hospitals in Switzerland of 201 patients with a recent MI, silent myocardial ischemia verified by stress imaging, and 1- or 2-vessel coronary artery disease. Follow-up ended on May 23, 2006.

Interventions Percutaneous coronary intervention aimed at full revascularization (n=96) or intensive anti-ischemic drug therapy (n=105). All patients received 100 mg/d of aspirin and a statin.

Main Outcome Measures Survival free of major adverse cardiac events defined as cardiac death, nonfatal MI, and/or symptom-driven revascularization. Secondary measures included exercise-induced ischemia and resting left ventricular ejection fraction during follow-up.

Results During a mean (SD) follow-up of 10.2 (2.6) years, 27 major adverse cardiac events occurred in the PCI group and 67 events occurred in the anti-ischemic drug therapy group (adjusted hazard ratio, 0.33; 95% confidence interval, 0.20-0.55; $P<.001$), which corresponds to an absolute event reduction of 6.3% per year (95% confidence interval, 3.7%-8.9%; $P<.001$). Patients in the PCI group had lower rates of ischemia (11.6% vs 28.9% in patients in the drug therapy group at final follow-up; $P=.03$) despite fewer drugs. Left ventricular ejection fraction remained preserved in PCI patients (mean [SD] of 53.9% [9.9%] at baseline to 55.6% [8.1%] at final follow-up) and decreased significantly ($P<.001$) in drug therapy patients (mean [SD] of 59.7% [11.8%] at baseline to 48.8% [7.9%] at final follow-up).

Conclusion Among patients with recent MI, silent myocardial ischemia verified by stress imaging, and 1- or 2-vessel coronary artery disease, PCI compared with anti-ischemic drug therapy reduced the long-term risk of major cardiac events.

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Author Affiliations: Division of Cardiology, Kantonsspital Luzern, Luzern, Switzerland (Drs Erne and Zuber); Division of Geriatrics, Department of General Internal Medicine, University Hospital, Berne, Switzerland (Dr Schoenenberger); Division of Cardiology (Drs Burckhardt, Buser, and Pfisterer), Department of Research (Dr Resink), University Hospital, Basel, Switzerland; Department of Social and Preventive

Medicine, University of Berne, Berne, Switzerland (Dr Schoenenberger); Heart and Vascular Center Zürich, Klinik im Park, Zürich, Switzerland (Dr Kiowski); and Division of Cardiology, Rhätisches Kantonsspital, Switzerland (Dr Dubach).

Corresponding Author: Paul Erne, MD, Division of Cardiology, Kantonsspital Luzern, CH-6000 Luzern 16, Switzerland (Paul.Erne@ksl.ch).

the Swiss Interventional Study on Silent Ischemia Type II (SWISSI II) was started 15 years ago with the aim of comparing the effects of PCI with drug therapy. Each therapy group also received secondary preventive advice, aspirin, and statin therapy to determine long-term outcomes in patients with recent MI and an exercise test without symptoms but with silent myocardial ischemia verified by stress imaging.

METHODS

Participants and Setting

Three Swiss medical centers (Lucerne, Chur, and Basel) participated and screened eligible patients. Patients with a documented, first ST-segment elevation MI or non-ST-segment elevation MI within the preceding 3 months and no malignancy were eligible for enrollment. They had to fulfill the following inclusion criteria: undergo a maximal symptom-limited exercise test without chest pain; have significant ST depression as a sign of silent ischemia; silent ischemia had to be confirmed by stress imaging; and have 1- to 2-vessel coronary artery disease at coronary angiography suitable for PCI. Patients were then included into the long-term trial if they provided written informed consent.

The study protocol was approved by the institutional review boards (ethical committees) of the 3 participating institutions and was consistent with the principles of the Declaration of Helsinki. Written informed consent was obtained from all study participants.

Silent Ischemia Detection

All patients underwent a symptom-limited bicycle exercise test, starting at 50 W and increasing by 25 W every 2 minutes until exhaustion. Asymptomatic ischemia was defined as a 1 mm or larger horizontal or downward sloping ST shift in more than 1 of the 12 electrocardiographic leads measured 80 milliseconds after the J point. Patients with this finding were asked to undergo stress imaging (ie, stress myocardial perfusion scintigraphy, stress

echocardiography, or stress radionuclide angiography). These imaging tests were performed according to standard techniques and ischemia was diagnosed only in the presence of unequivocally reversible perfusion defects or new wall motion abnormalities, respectively. Silent ischemia was documented by stress myocardial perfusion scintigraphy in 98 patients, stress echocardiography in 91 patients, and stress radionuclide angiography in 12 patients.

Randomization and Interventions

Patients with verified silent ischemia underwent diagnostic coronary angiography. If they had 1- or 2-vessel coronary artery disease suitable for PCI, they were randomized to balloon angioplasty (PCI group; n=96) or medical management (intensive anti-ischemic drug therapy group; n=105). A computer-generated randomization was used. Individual assignments were placed in sealed envelopes that were distributed to the participating medical centers in sets of 36 envelopes.

Percutaneous coronary intervention (according to standard techniques but without stents during that period) was performed with the aim to attain full revascularization without residual coronary stenoses of more than 75%. Anti-ischemic drug therapy consisted of either 5 to 10 mg/d of bisoprolol, 5 to 10 mg/d of amlodipine, 4 to 12 mg of molsidomine twice daily, or combinations thereof, aiming to eliminate or maximally reduce silent ischemia during bicycle ergometry. The order of starting anti-ischemic drug therapy and the increase of drug dosages or a switch to combination therapy were left to the discretion of individuals' primary care physician and follow-up investigations. Angiotensin-converting enzyme inhibitors were recommended as an antihypertensive drug therapy. In addition, both patient groups received secondary preventive advice regarding weight control, eating habits, smoking cessation, daily exercise, and were treated with 100 mg/d of aspirin and a statin.

Follow-up and Outcomes

Follow-up was identical across treatment groups and participating hospitals. Patients were followed up in the outpatient clinics of the 3 participating hospitals after 3, 6, and 12 months and yearly thereafter up to the final follow-up after 10 years. Follow-up ended on May 23, 2006. Follow-up examinations included a bicycle exercise test and stress imaging (ie, stress myocardial perfusion scintigraphy, stress echocardiography, or stress radionuclide angiography) to document ischemic events or residual ischemia for further modification of anti-ischemic therapy or PCI. Patients without fatal events were further followed up until the last scheduled follow-up time. Patients lost to follow-up were censored with the last medical contact.

The primary end point of this study was survival free of major adverse cardiac events. Major adverse cardiac events were defined as cardiac death (ie, death not clearly due to a noncardiac reason), nonfatal (recurrent) MI, and/or symptom-driven revascularization (PCI or coronary artery bypass graft surgery). Myocardial infarction was diagnosed by presence of typical chest pain, ST-segment elevation on the electrocardiogram, and/or a typical increase and decrease of cardiac enzymes according to the definitions of the European Society of Cardiology.¹² Silent MI was diagnosed by presence of new Q waves on the resting electrocardiography documented by new distinct wall motion abnormalities on the resting echocardiogram with a decrease in left ventricular ejection fraction (LVEF) of 5% or more and/or a reduction in LVEF of more than 10% vs a previous echocardiography. Secondary end points included the individual components of the primary end point as well as noncardiac mortality, all-cause mortality, and angina not leading to revascularization. All end points were adjudicated by a committee blinded to the treatment groups and that consisted of 2 cardiologists (M.Z. and W.K.). In case of disagreement, a third cardiologist was consulted.

In addition, exercise-induced ischemia (significant ST-depression) and resting LVEF were recorded throughout follow-up as further outcome measures. To increase the validity of these additional findings, patients who experienced the primary end point were censored in this analysis at the time of the primary end point.

Sample Size and Statistical Analysis

Sample size for the trial was determined by the most demanding hypothesis to detect the effect of PCI on the primary end point based on the literature available in 1992. Sample size was calculated at 72 patients per group, using a significance level of .05, a power level of 80%, and an incidence of the primary end point of 30% in the drug therapy group and 10% in the PCI group after 2 years.

Data are expressed as percentages and mean (SD). Continuous variables were compared by use of the *t* test, assuming normal distributions or by the Mann-Whitney test for variables with nonnormal distributions. Dichotomous variables were compared by the χ^2 test or Fisher exact test when cell counts were less than 5. In all tests, *P* values of .05 were considered statistically significant. Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals for the comparison of event rates in the PCI and drug therapy groups after adjustment for age, sex, and other assignments that revealed possible influences on outcome in the univariate analysis (including weight, dyslipidemia, diabetes, number of diseased vessels, number of lesions >75%, lesions in left circumflex artery, LVEF, and left ventricular end diastolic pressure).¹³ Deviations from the proportional hazards assumption were tested by examining the global test of Schoenfeld residuals. The times to event were depicted with the Kaplan-Meier estimates of the survival function. Analyses of primary and secondary end points were performed according to

the intention-to-treat principle. Statistical analyses were conducted using Stata software version 8.2 (StataCorp, College Station, Tex).

RESULTS

Patient Selection, Baseline Findings, and Initial Therapy

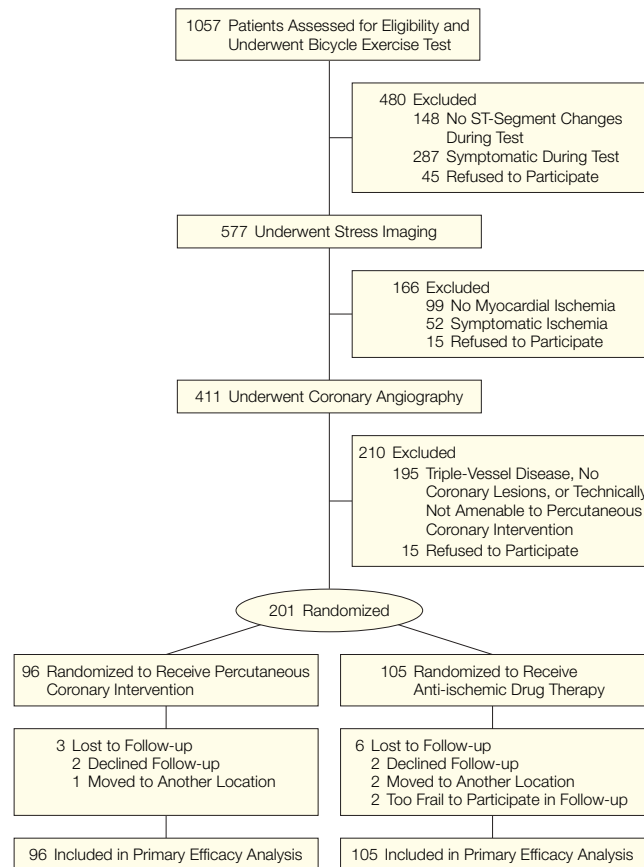
FIGURE 1 shows the patient selection and randomization. Of 1057 patients screened for enrollment, 201 patients (19.0%) fulfilled the inclusion criteria and were randomized between May 2, 1991, and February 25, 1997. Only 9 patients (4.5%) were lost to follow-up. Of these 9 patients, 4 withdrew consent, 3 moved away, and 2 were too frail to participate in follow-up. Follow-up was complete in the remaining 192 patients (95.5%) without missing data.

At baseline, the 2 treatment groups were well matched with regard to age, sex, risk factors for coronary artery dis-

ease, extent of ST depression during exercise, and coronary vessel involvement (TABLE 1). However, dyslipidemia was somewhat more prevalent in patients in the PCI group. In addition, resting LVEF (a prognostically important factor) was lower in patients in the PCI group. Baseline characteristics of study patients were not significantly different from those patients screened but not enrolled (data available from authors upon request).

Percutaneous coronary intervention was performed on a mean (SD) of 2 (1) lesions in the PCI group and complete revascularization was achieved in 91 patients (94.8%). In the drug therapy group, 95 patients (90.5%) initially received a β -blocker, 56 patients (53.3%) received a calcium channel blocker, and 66 patients (62.9%) received a long-acting nitrate. The anti-ischemic drug therapy was

Figure 1. Trial Profile



changed or increased according to exercise electrocardiographic findings during the first follow-up visit after 3 months and/or if symptoms occurred.

Main Outcome During Follow-up
 During a mean (SD) follow-up of 10.2 (2.6) years and a total observation time of 2067 person-years, at least 1

primary end point event occurred in 94 patients. Of these 94 patients, 67 (64%) were in the drug therapy group (7 cardiac deaths, 37 nonfatal recurrent MIs, and 23 symptom-driven revascularizations) and 27 (28%) were in the PCI group (1 cardiac death, 10 nonfatal recurrent MIs, and 16 symptom-driven revascularizations) (TABLE 2). Cardiac death, nonfatal MI, and symptom-driven revascularizations were all consistently more frequent in patients in the drug therapy group compared with patients in the PCI group. The same was true for angina not leading to revascularization whereas noncardiac deaths (n=3; one each due to cancer and infection and one not stated) were noted only in patients in the PCI group. FIGURE 2 shows the survival curves free of major adverse cardiac events for both treatment groups. Although the curves started to diverge from the beginning, the difference became statistically significant only after 2 years. After 10 years, there was an advantage in favor of patients in the PCI group with an incidence rate of major adverse cardiac events of 3.2% vs 9.5% for patients in the drug therapy group (P<.001). This corresponds to an absolute event reduction of 6.3%

Table 1. Baseline Characteristics

	No. (%) of Participants*		P Value
	PCI (n = 96)	Drug Therapy (n = 105)	
Age, mean (SD), y	54.4 (9.1)	56.2 (8.8)	.17
Female sex	11 (11.5)	14 (13.3)	.69
Height, mean (SD), cm	170.9 (6.9)	170.9 (7.4)	.97
Weight, mean (SD), kg	74.4 (10.8)	78.7 (14.8)	.02
Blood pressure, mean (SD), mm Hg			
Systolic	128.8 (21.8)	127.2 (21.0)	.60
Diastolic	76.3 (15.2)	77.6 (13.6)	.53
Risk factors for CAD			
Smoking	70 (72.9)	78 (74.3)	.83
Hypertension	43 (44.8)	47 (44.8)	.99
Dyslipidemia	72 (75.0)	61 (58.1)	.01
Diabetes	9 (9.4)	14 (13.3)	.38
Family history of CAD	43 (44.8)	42 (40.0)	.49
Bicycle ergometry			
Maximal workload, mean (SD), W	140.4 (31.2)	145.0 (33.2)	.22
ST-segment depression present	87 (90.6)	88 (83.8)	.15
Left ventricular ejection fraction, mean (SD), %	53.9 (9.9)	59.7 (11.8)	<.001
Left ventricular end diastolic pressure, mean (SD), mm Hg	14.5 (3.8)	13.3 (4.3)	.03
Coronary angiography			
No. of lesions >75%, mean (SD)	2.0 (1.0)	2.3 (1.3)	.08
Type of lesions			
Left anterior descending artery	57 (59.4)	64 (61.0)	.82
Left circumflex artery	32 (33.3)	46 (43.8)	.13
Right coronary artery	48 (50.0)	54 (51.4)	.84

Abbreviations: CAD, coronary artery disease; PCI, percutaneous coronary intervention.
 *Unless otherwise indicated.

Table 2. Event Outcomes

	Event Rates*		Hazard Ratio (95% CI)		P Value
	PCI (n = 96)	Drug Therapy (n = 105)	Hazard Ratio (95% CI)		
			Unadjusted	Adjusted†	
Primary end point‡					
Cardiac death, nonfatal recurrent MI, symptom-driven revascularization	27/841	67/703	0.35 (0.23-0.55)	0.33 (0.20-0.55)	<.001
Secondary end points§					
Cardiac death	3/1019	22/1048	0.14 (0.04-0.45)	0.19 (0.05-0.67)	.01
Nonfatal recurrent MI	11/938	40/856	0.26 (0.13-0.51)	0.31 (0.15-0.65)	.002
Symptom-driven revascularization	26/846	46/735	0.52 (0.32-0.84)	0.48 (0.28-0.82)	.008
Angina not leading to revascularization	11/973	32/948	0.33 (0.17-0.66)	0.37 (0.18-0.78)	.009
Death from noncardiac causes	3/1019	0/1048			
All-cause mortality	6/1019	22/1048	0.27 (0.11-0.68)	0.42 (0.16-1.11)	.08

Abbreviations: CI, confidence interval; MI, myocardial infarction; PCI, percutaneous coronary intervention.

*Presented as number of events/number of person-years of observation.

†Adjusted for age, sex, weight, diabetes, dyslipidemia, number of diseased vessels, number of lesions more than 75%, lesions in left circumflex artery, left ventricular ejection fraction, and left ventricular end diastolic pressure.

‡If a patient experienced more than 1 event of the primary end point, only the first event was counted.

§More than 1 type of event (initial and subsequent events) were allowed per patient.

per year (95% confidence interval, 3.7%-8.9%) in favor of patients in the PCI group ($P<.001$).

Secondary Outcome Measures

TABLE 3 summarizes the main secondary outcome measures of exercise-induced ischemia and resting LVEF as well as details on drug therapy and blood pressure control. Despite higher work loads achieved at each follow-up, patients in the PCI group had less prevalent and extensive ischemia on repeat exercise electrocardiograms and their resting LVEF remained preserved (mean [SD] of 53.9% [9.9%] at baseline to 55.6% [8.1%] at final follow-up in 69 patients), whereas LVEF decreased gradually and significantly ($P<.001$) in patients in the drug therapy group (mean [SD] of 59.7% [11.8%] at baseline to 48.8% [7.9%] at final follow-up in 35 patients). It may be noteworthy that these findings were obtained on patients who received extensive anti-ischemic drug therapy compared with patients in the PCI group, in whom only a minority took these drugs (Table 3).

COMMENT

This is the first, to our knowledge, long-term outcome study of an invasive therapy compared with an inten-

sive anti-ischemic drug therapy in asymptomatic patients with silent ischemia after a recent MI. We found a persistent benefit of PCI compared with optimized drug therapy. This benefit became apparent only after 2 years of observation, with survival curves continuously diverging up to the final follow-up after 10 years. The benefit of full revascularization by PCI compared with intensive anti-ischemic drug therapy was not restricted to hard events such as cardiac death or nonfatal MI only; benefits with respect to need for symptom-driven revascularization (including repeat PCI for symptomatic restenosis), other angina, as well as objective signs of ischemia

and long-term preservation of LVEF also emerged.

A number of retrospective^{1,14-16} and prospective¹⁷ studies have documented the prognostic impact of silent myocardial ischemia following MI. Several studies have documented the effect of medical drug therapy on angina or the total ischemic burden but objective cardiac events other than revascularization for aggravating angina were not significantly reduced.¹⁸⁻²¹ One small pilot study with a 1-year follow-up period showed that intensive medical therapy and PCI were comparable in suppressing ischemia in stable patients after MI, although it was not

Figure 2. Kaplan-Meier Survivor Function for Cardiac Death, Nonfatal Myocardial Infarction, and Symptom-Driven Revascularization

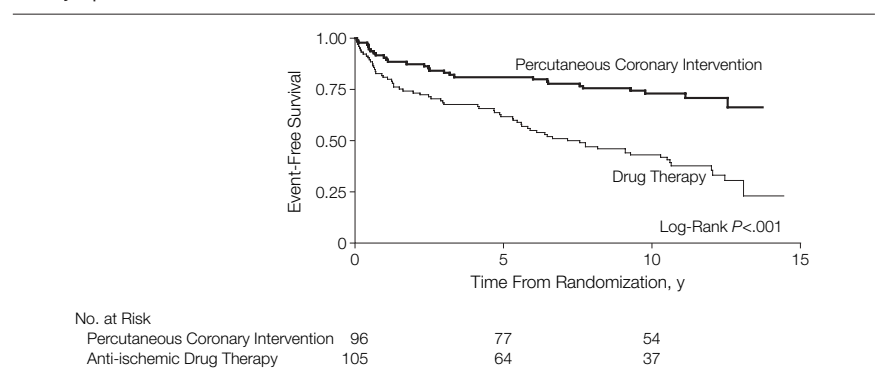


Table 3. Findings During Follow-up

	No. (%) of Participants at 4-Year Follow-up*			No. (%) of Participants at Final Follow-up*‡		
	PCI (n = 82)	Drug Therapy (n = 70)	P Value†	PCI (n = 69)	Drug Therapy (n = 38)	P Value†
Blood pressure, mean (SD), mm Hg						
Systolic	132.4 (17.8)	133.7 (16.5)	.54	127.0 (12.8)	127.0 (16.6)	.72
Diastolic	83.0 (10.3)	83.6 (8.6)	.88	79.7 (8.9)	81.2 (11.5)	.50
Drug therapy						
β-Blockers	40 (48.8)	60 (85.7)	<.001	27 (39.1)	32 (84.2)	<.001
Calcium antagonists	17 (20.7)	36 (51.4)	<.001	12 (17.4)	12 (31.6)	.09
Nitrates	10 (12.2)	33 (47.1)	<.001	3 (4.3)	17 (44.7)	<.001
Bicycle ergometry						
Maximal workload, mean (SD), W	168.6 (41.0)	147.7 (37.2)	.03	172.8 (45.2)	136.2 (38.3)	<.001
ST-segment depression present	14 (17.1)	37 (52.9)	<.001	8 (11.6)	11 (28.9)	.03
Left ventricular ejection fraction, mean (SD), %	54.4 (8.4)	50.6 (9.1)	.05	55.6 (8.1)	48.8 (7.9)	<.001

Abbreviation: PCI, percutaneous coronary intervention.

*Unless otherwise indicated.

†Calculated using generalized linear models.

‡Final follow-up occurred at 10 years.

stated whether ischemia was silent or not.²² The only previous study comparing the effect of an anti-ischemic drug therapy and revascularization therapy in patients with silent ischemia after MI was the Asymptomatic Cardiac Ischemia Pilot study.⁸⁻¹¹ However, patients could have asymptomatic ischemia in addition to symptomatic ischemic episodes in that study. After 2 years of follow-up, revascularization, particularly coronary artery bypass graft surgery, reduced the rates of death or nonfatal MI (to 4.7% compared with 12.1% in the angina-guided and 8.8% in the ischemia-guided medical therapy) and rates of death, MI, or cardiac hospitalizations (to 23.1% compared with 41.8% and 38.5% for the medical therapy groups, respectively; $P = .003$ between revascularization and medical treatments).

The present results of SWISSI II extend these findings to asymptomatic patients and a longer 10-year observation period. Patients in the present study were highly selected for absence of symptoms and documentation of silent ischemia. This makes them different from many of the patients previously reported on such as those in the Asymptomatic Cardiac Ischemia Pilot study who had silent ischemia along with symptomatic ischemia.⁸⁻¹¹ Thus, these findings reflect the standard of clinical practice in patients with significant post-MI silent ischemia, patients who are different from most who were enrolled in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial.²³

Recently, the Open Artery Trial (OAT) reported that a 4-year clinical benefit of opening an occluded infarct-related artery after MI did not exist.²⁴ In contrast to that study, SWISSI II included only patients with relevant ischemia and therefore viable myocardium. In fact, OAT patients with mild symptoms also benefited with regard to angina, as did SWISSI II patients. Taken together, these findings indicate a need for PCI after MI only in the

presence of symptomatic or silent ischemia but not without it. The findings favored angioplasty even though patients in the PCI group started with lower LVEFs and did not receive stents.

There are several aspects and potential limitations of the present investigation. First, the trial was not blinded. To limit the risk of bias, we used objective outcomes, and a committee blinded to the treatment groups adjudicated the end points and based its decisions on hospital case records by other physicians not involved in this study. Second, only a minority of patients were women. However, a first MI is less frequent in women than men who are younger than 60 years. The rate of 11% to 13% in this study was not much lower than the 15% noted in patients who were 6 years older in the COURAGE trial.²³ Third, the interventions in this study represent the state of the art from a decade ago. Newer developments in medical and interventional therapy such as high-dose statins and clopidogrel as well as the use of stents may have improved outcomes. Fourth, neither a particular drug nor a specific drug therapy was tested but rather an individualized anti-ischemic drug regimen with the aim to eliminate exercise-induced silent ST-depression as the proof of concept. Finally, despite formal power calculations, the sample size was relatively small.

CONCLUSIONS

Among patients with recent MI, silent myocardial ischemia verified by stress imaging, and 1- or 2-vessel coronary artery disease, PCI compared with anti-ischemic drug therapy reduced the long-term risk of major cardiac events. Our findings argue for an ischemic-targeted approach to PCI among asymptomatic survivors of MI.

Author Contributions: Drs Erne and Schoenenberger had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Erne, Burckhardt, Zuber, Buser, Dubach, Pfisterer.

Acquisition of data: Erne, Zuber, Buser, Dubach, Pfisterer.

Analysis and interpretation of data: Erne, Schoenenberger, Kiowski, Resink, Pfisterer.

Drafting of the manuscript: Erne, Schoenenberger, Resink, Pfisterer.

Critical revision of the manuscript for important intellectual content: Erne, Schoenenberger, Burckhardt, Zuber, Kiowski, Buser, Dubach, Resink, Pfisterer.

Statistical analysis: Erne, Schoenenberger, Kiowski.

Obtained funding: Erne.

Administrative, technical, or material support: Erne, Schoenenberger, Zuber, Dubach, Resink.

Study supervision: Erne, Burckhardt, Buser, Pfisterer.

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At first, we feel and believe that absolute truth is ours by right, but study will soon dispel these illusions bit by bit.

—Claude Bernard (1813-1878)