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Five-Year Follow-Up of the Argentine Randomized Trial of Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple Vessel Disease (ERACI II)

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OBJECTIVES The purpose of the present study is to report the five-year follow-up results of the ERACI II trial.

BACKGROUND Immediate and one-year follow-up results of the ERACI II study showed a prognosis advantage of percutaneous coronary intervention (PCI) with stents over coronary artery bypass grafting (CABG).

METHODS A total of 450 patients were randomly assigned to undergo either PCI (n = 225); or CABG (n = 225). Only patients with multi-vessel disease were enrolled. Clinical follow-up during five years was obtained in 92% of the total population after hospital discharge. The primary end point of the study was to compare freedom from major adverse cardiovascular events (MACE) at 30 days, 1 year, 3 years, and 5 years of follow-up.

RESULTS At five years of follow-up, patients initially treated with PCI had similar survival and freedom from non-fatal acute myocardial infarction than those initially treated with CABG (92.8% vs. 88.4% and 97.3% vs. 94% respectively, p = 0.16). Freedom from repeat revascularization procedures (PCI/CABG) was significantly lower with PCI compared with CABG (71.5% vs. 92.4%, p = 0.0002). Freedom from MACE was also significantly lower with PCI compared with CABG (65.3% vs. 76.4%; p = 0.013). At five years similar numbers of patients randomized to each revascularization procedure were asymptomatic or with class I angina.

CONCLUSIONS At five years of follow-up, in the ERACI II study, there were no survival benefits from any revascularization procedure; however patients initially treated with CABG had better freedom from repeat revascularization procedures and from MACE. (J Am Coll Cardiol 2005;46: 582–8) © 2005 by the American College of Cardiology Foundation

Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) are commonly used procedures to treat patients with multiple coronary artery disease (CAD) requiring myocardial revascularization. In the past, several randomized comparisons between bypass surgery and coronary angioplasty were performed (1–9).

See page 589

These studies, performed in the pre-stent era, showed no significant differences in mortality and non-fatal myocardial infarction (MI) between patients treated with surgery versus PCI. Surgery had an advantage only in treated diabetic patients (7). More recently, in the stent era, new randomized comparison between percutaneous intervention and bypass surgery has been done, and three multicenter clinical trials have reported their short- and mid-term outcome (10–13). Thirty-day and one-year major adverse cardiovascular events (MACE), including death, MI, stroke, and repeat revascularization procedures with both techniques were recently published.

The 30-day and 1-year outcome of the first randomized comparison between percutaneous interventions in the bare-metal stent era and coronary bypass surgery in patients with multiple-vessel disease was published in this journal by the ERACI II investigators (11). The one-year follow-up data of the four randomized trials of PCI using bare metal stents versus CABG (Stent or Surgery trial, Artery Revascularization Therapies Study [ARTS], ERACI II, and Medicine, Angioplasty, or Surgery Study [MASS] II) showed similar incidence in the combined death, non-fatal MI, and stroke rate with both revascularization techniques (PCI 8.7% vs. CABG 9.1%; p = NS). In the present study, we are describing the five-year clinical follow-up results of the patients randomized in the ERACI II study.

METHODS

Details of the ERACI II trial have been previously published in this journal (11). This trial included patients with multi-vessel coronary artery disease and clinical indication of myocardial revascularization. In these patients, completed

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Abbreviations and Acronyms

AMI	= acute myocardial infarction
ARTS	= Artery Revascularization Therapies Study
CABG	= coronary artery bypass grafting
CAD	= coronary artery disease
ERACI II	= Argentine Randomized Study: Coronary Angioplasty with Stenting Versus Coronary Bypass Surgery in Multi-Vessel Disease
LAD	= left anterior descending
LIMA	= left internal mammary artery graft
MACE	= major adverse cardiovascular events
PCI	= percutaneous coronary intervention
PTCA	= percutaneous transluminal coronary angioplasty

functional revascularization could be achieved by either PCI or coronary bypass surgery. A total of 5,619 patients underwent coronary angiography in the participating centers of the ERACI II between October 1996 and September 1998 (11). Of this group, 2,759 patients had an indication for revascularization, and of these, 1,076 patients met the entrance criteria for randomization. Of these 1,076 patients, 450 patients were randomized, and are the subject of this study. Six hundred twenty-six patients with angiographic and clinical criteria for randomization were not randomized because they refused or because of their referral physician preference (335 patients had PCI and 291 had CABG). The other 1,683 patients treated with either PCI or CABG did not meet the randomization criteria and were included in the registry. Angioplasty procedures were performed in 1,396 of these patients because the following reasons: single-vessel disease (67.5%), two-vessel disease (1.5%), previous CABG (5%), acute MI (AMI) (10%), and previous PCI (16%). Of the 287 patients in the registry who underwent CABG, 16% were selected for a protocol of minimal invasive surgery, 27% had significant main left stenosis, 1.7% had previous CABG, 27% had poor left ventricular function, and 28.3% had multi-vessel disease not amenable to PCI. Patients were eligible for inclusion if they had severely limiting stable angina (Canadian class III/IV), unstable angina according Braunwald criteria (11), or mild symptoms but with a large area of myocardium at risk determined by thallium scintigraphy. Coronary stent deployment and surgical techniques were performed with standard methods as previously described (10–17). The patients were required to have >50% stenosis in more than one major pericardial vessel and >70% in at least one of the major epicardial vessels by visual estimation. The vessel should also be suitable for stent deployment. Patients with unprotected severe left main stenosis could be included if they were amenable to a single stent procedure according to the interventionalist's point of view. Patients with post-AMI were also included.

Patients with poor left ventricular function (left ventricular ejection fraction <35%), concomitant severe valvular heart disease, evolving AMI (<24 h), previous CABG, previous percutaneous transluminal coronary angioplasty (PTCA) in the last year with predominant vessel occlusion (two or more), and/or limited life expectancy were excluded from the study.

Study end points. The composite primary end point of the study was the occurrence of combined MACE, defined as death, Q-wave MI, stroke, and need for repeat revascularization procedures at 30 days, 1 year, 3 years, and 5 years of follow-up. Death included mortality from all causes.

Secondary end points included: angina status and functional class at one, three, and five years of follow-up; completeness of revascularization, determined by stress thallium at one month; and follow-up cost and cost-effectiveness of both techniques. The major in-hospital complications and follow-up events (mortality, MI, stroke, angina, and the need of additional revascularization procedures) were recorded. A trained staff was responsible for data collection of variables and clinical follow-up information. Randomization of patients fulfilling the inclusion criteria was performed by the coordinating center in 10-patient blocks. A randomization sequence was developed so that an equal number of patients were assigned to each treatment strategy at each center. Patients or their referring physician during the five years of follow-up were contacted every six months by trained staff, using personal interviews, letters, or telephone. At five years, clinical follow-up was obtained in 92% of hospital survivors.

The organization and analysis of the results of the study were conducted by a central coordinating executive committee. The study was monitored by a Safety and Data Monitoring Committee.

Statistics. The primary analysis of angiographic and clinical outcomes was based on the intention-to-treat principle.

The results are expressed as mean ± standard deviation. For comparison of the continuous variable between the two treatment groups, the unpaired two-tailed Student *t* test was used. Comparison of categorical variables between the two groups was performed with the chi-square and Fischer exact test methods. Comparison of the composite clinical end point (MACE) was performed with the Kaplan-Meier and log-rank tests (18). All tests were two-tailed, and a p value of <0.05 was considered statistically significant. As previously reported, the power of the study to detect differences during the first 30 days was 90% (11).

RESULTS

Patient population. The two randomized groups were well-matched for baseline demographic, clinical, and angiographic characteristics (Table 1). The incidence of unstable angina IIb, IIIa, and C was high in the overall cohort of patients (91.1%) and similar in PCI (92%) and CABG (91%). Post-AMI angina was present in 10% of the patients. In the registry, the incidence of patients with unstable coronary syndromes was also high. Unstable angina

JACC Vol. 46, No. 4, 2005
August 16, 2005:582–8

Table 1. Baseline Demographic, Clinical, and Angiographic Characteristics: ERACI II (11)

	PTCA (n = 225)	CABG (n = 225)
Male	77.3%	81.4%
Age	62.4%	61.3%
Hypertension	71%	70.5%
Smokers	54.3%	49.5%
Diabetic	17.3%	17.3%
High cholesterol	62.5%	60.2%
Previous infarction	28.5%	27.7%
Obesity	28.8%	23.5%
Unstable II/III/C	92.1%	90.7%
Peripheral disease	19.1%	26.6%
Double vessel	40%	38%
Three vessel	54.7%	58%
Left main	5.3%	4%

All p values not significant.
CABG = coronary artery bypass graft surgery; ERACI II = Argentina Randomized Study Coronary Angiopasty with Stenting Versus Coronary Bypass Surgery in Patients with Multiple Vessel Disease; PTCA = percutaneous transluminal coronary angioplasty.

was present in 61.3%, and the incidence of non–ST-segment elevation MI was 12%.

Concomitant peripheral or vascular disease was present in 23% of the patients (27% in CABG arm). Glycoprotein IIb and IIIa inhibitors were used in 28% of the patients in the PCI group (Table 1). There were also no differences in the incidence of two- and three-vessel disease between the two strategies of revascularization. Proximal left anterior descending coronary artery (LAD) stenosis (before the take-off of the first diagonal branch) was present in 113 patients randomized to PCI and in 117 patients randomized to CABG. After randomization, and before the index procedure was performed, 3 patients from the PCI group crossed over to CABG, whereas 16 patients from the CABG group crossed over to PCI (1.4% vs. 7.6%, p = 0.04). In the PCI group, at least 99% of the patients had one vessel successfully treated, and 80.5% of the patients had two vessels successfully treated; whereas 91.5% of planned vessels were successfully treated. Excluding those patients with chronic total occlusions, only 8.8% of the patients had severe residual stenosis in one major epicardial vessel after the PCI procedure. The number of chronic occlusions not attempted by PCI, as we reported previously, was 23.4% (11). The overall 448 lesions attempted in the PCI arm were treated with either 315 stents (Gianturco Rubin II design in 92% of lesions) or balloon angioplasty. Thus, in the stent arm, the planned vessels PCI strategy was successfully performed in 91.5% of the patients using 1.4 stent per patient. In the surgical group, arterial conduits were used in 88.5% of the patients.

Initial and one-year follow-up. As previously published (11), 30-day MACE were significantly lower with stent therapy than with bypass surgery (3.6% vs. 12.3%, p = 0.002). One-month mortality was also significantly lower with stent therapy (0.9% vs. 5.7%, p = 0.013). Although this study was not designed to assess hospital outcomes according to angina class, there was a trend toward a higher 30-day mortality rate in patients with unstable angina treated with surgery. There were no hospital mortalities with surgery in patients with stable angina, whereas it reached 5.6% and 7.9% in patients with unstable class II and unstable class III or C. Compared with PCI, only surgically treated patients with unstable class III or C angina have a greater in-hospital mortality (p = 0.06 in favor of PCI). Owing to the above differences during the initial hospital period with the two revascularization techniques, survival during the first year of follow-up was better with PCI compared with surgery (96.9% vs. 92.5%, p = 0.017). Survival with freedom from non-fatal MI was also better with PCI therapy than with surgery (97.7% vs. 93.7%, p = 0.017). In contrast, despite the liberal use of stents, freedom from new revascularization procedures and incidence of angina were significantly better with bypass surgery. Hospital and follow-up costs did not show any differences between the two revascularization techniques.

In the subgroup of diabetic patients included in the randomization population (39 patients), there was a trend to higher mortality in the PCI diabetic patients compared with PCI in non-diabetic patients (10% vs. 6.4%, p = 0.663). In contrast, in the patients randomized to surgery, the five-year mortality in the diabetic population was 10.2%, whereas it was 11.8% in the non-diabetic population (p = 0.637).

Surgical mortality was 2.1% in the 287 patients undergoing surgical revascularization in the registry. These patients in the registry included those patients who were included in a protocol of minimally invasive surgery. They had left internal mammary artery graft (LIMA) to LAD, because they had either single-vessel LAD disease, or because they were candidates for hybrid procedures (LIMA to LAD + PCI to right coronary artery or circumflex). In contrast, 30-day surgical mortality was 7.1% in the rest of patients who underwent surgery in the registry. They included a cohort of patients with poor left ventricular function (n = 77), patients with severe main left stenosis (n = 77), patients with multi-vessel disease and lesions not amenable to PCI (n = 81), and patients with previous cardiac surgery (n = 11).

Five-year follow-up results. Clinical follow-up was obtained in 92% of living patients (100% complete five-year follow-up).

MORTALITY. In the CABG group, a total of 26 patients died during the five years of follow-up; 13 of these deaths occurred during the first 30 days after the procedure, and 13 additional patients died during the rest of the five years of follow-up. Five of these deaths were non-cardiac in origin (pulmonary emphysema, stroke, renal insufficiency, and prostate and lung cancer). In the PCI group, 16 patients died during the five years of follow-up, 7 during the first year, and 9 more between the first and fifth years of follow-up. Four of these deaths were non-cardiac in origin (renal insufficiency, lung cancer, pulmonary emphysema, and mesenteric infarction). There were no significant dif-

ferences in mortality from all causes between the CABG and the PCI arms (11.5% vs. 7.1%, p = 0.182).

The corresponding actuarial survival curves during the five years of follow-up for these two groups of patients also showed a trend toward better outcomes with PCI compared with bypass surgery (92.8% vs. 88.4%, log-rank test, p = 0.095) (Fig. 1).

The five-year mortality in diabetic patients with surgery was 10.2% (4 of 39); with two-vessel disease, 10.6% (10 of 94); and with three-vessel disease, including left main stenosis, 12.2% (16 of 131).

NON-FATAL MI. In the CABG group, 14 patients (6.2%) sustained a new non-fatal Q-wave MI within the five years of follow-up, with all of them occurring during the first year. In the PCI group, six patients (2.8%) sustained a new non-fatal Q-wave MI within the five years of follow-up, five during the first year of follow-up. There were no significant differences in the incidence of new non-fatal MI between the PCI and CABG group (2.8% vs. 6.2%, respectively, p = 0.128). The corresponding actuarial survival curves with freedom from non-fatal MI during the five years of follow-up for these two groups of patients showed no significant differences between PCI and CABG (97.3% vs. 94%, log-rank test, p = 0.159) (Fig. 2).

REPEAT REVASCULARIZATION PROCEDURES. A total of 64 patients (28.4%) in the PCI group and 17 patients (7.2%) in the coronary bypass surgery group underwent a second revascularization procedure (PTCA or CABG) during the entire follow-up period (p = 0.0002). In the PCI arm, 66.6% occurred during the first year of follow-up. Most of the repeat procedures performed in the PCI group either in the first year or thereafter were new PCI procedures. Of note: only 19 patients in the PCI group crossed over to CABG during the five years of follow-up (8.4%).

The corresponding actuarial survival curve with freedom from repeat revascularization procedures during the five years of follow-up were significantly better with coronary bypass surgery than with PCI (92.4% vs. 71.5%, p = 0.00001) (Fig. 3). The comparison in the number of repeat

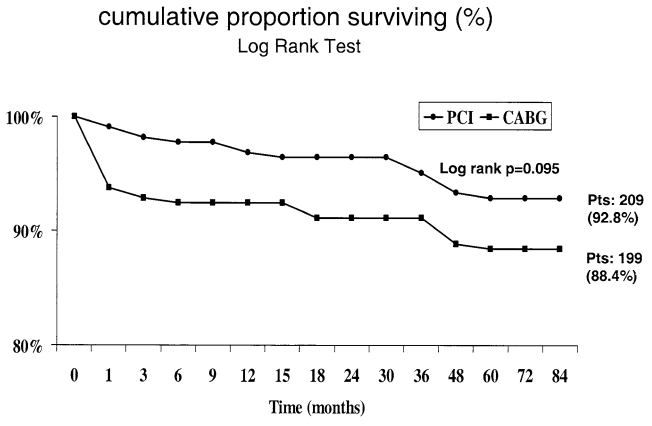

Figure 1. Comparison of survival of patients treated with coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI).

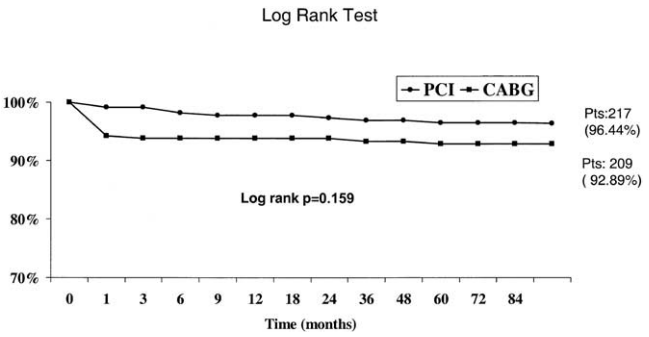

Figure 2. Comparison of non-fatal myocardial infarction of patients treated with coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI).

revascularization procedures with our previously published ERACI I trial showed an improvement of late outcome with stents compared with balloon angioplasty (1,9). At five years, there was less incidence of repeat PTCA/CABG in the ERACI II trial versus the three years follow-up of the ERACI I trial (28.4% vs. 37%, p = 0.053). Furthermore, the numbers of patients who required cross-over to surgery was significantly lower in the ERACI II trial compared with the ERACI I trial (8.4% vs. 22%, respectively, p = 0.016).

INCIDENCE OF ANGINA. During the first year of follow-up, the ERACI II trial patients assigned to CABG were more frequently free of angina than those assigned to PCI (92% vs. 84.5%, p = 0.01); however, as shown in Figure 4, after new revascularization procedures were performed, the incidence of angina was similar in the two groups. At the end of the follow-up period, a similar number of patients in each group were asymptomatic or in Canadian class I angina (86% in PCI and 82% in CABG, p = 0.916).

Event-free survival (MACE). The primary end point of the study was "event-free survival" (freedom from death, non-fatal MI and repeat revascularization (PCI or CABG), and stroke). At one year of follow-up, we reported no significant differences between the two strategies of revascularization (11).

In the present study, during the five years of follow-up, 78 patients in the PCI group and 53 patients in the CABG group suffered one or more cardiac events (Fig. 5); thus, the corresponding actuarial survival curve of freedom from MACE showed a better outcome with CABG (76.4% vs. 65.3%, p = 0.019). This difference was due solely to the

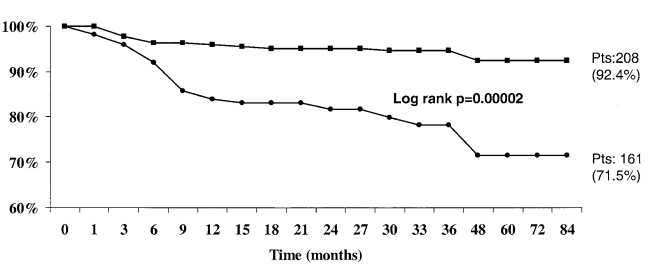

Figure 3. Comparison of repeat revascularization procedures (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) of patients treated with CABG **(square symbols)** versus PCI **(round symbols)**.

JACC Vol. 46, No. 4, 2005
August 16, 2005:582–8

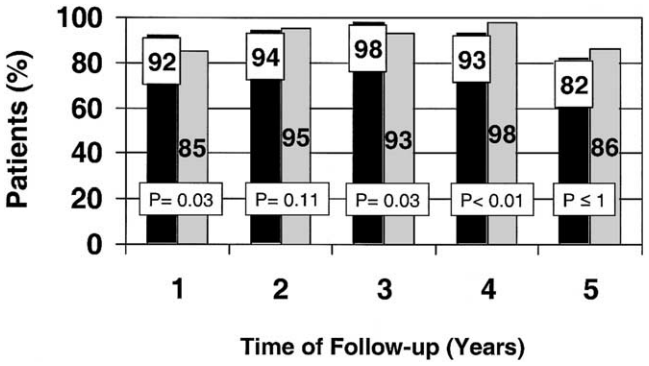

Figure 4. Comparison of freedom from angina between patients treated with coronary artery bypass grafting **(solid bars)** versus percutaneous coronary intervention **(gray bars)**.

presence of a greater incidence of repeat revascularization procedures in the PCI arm.

Long-term follow-up costs. During the first year of follow-up, both strategies of revascularization had similar cost. Cost included the cost of initial procedure, hospital charges, procedural resources (PTCA devices others than balloon, medications other than glycoprotein inhibitors), and professional fees.

During the five years of follow-up, the number of patients requiring new revascularization procedures between the first and fifth year were still significantly higher with PCI, resulting in an additional cost, between one- and five-year follow-up in the PCI group, of $236,000 to the overall cost at one-year (14 PCI and 9 CABG). In contrast, there was an additional one- to five-year follow-up cost in the CABG group of $45,000 (four PCI and one redo-CABG).

Thus, at the end of the five years of follow-up, comparison of overall cost of the two strategies of revascularization showed a trend toward higher cost with PCI ($3,056,615 in PCI and $2,556,500 in CABG, $p = 0.069$). Thus, the cost-per-patient was significantly higher with stent therapy ($13,584 vs. $11,362 for the PCI and the CABG groups respectively, $p = 0.04$).

DISCUSSION

In the present study, patients with multi-vessel disease and a high prevalence of unstable angina (91%) included in the ERACI II trial, treated initially with PCI with liberal use of bare metal stents, had similar survival and incidence of non-fatal MI at five years of follow-up when compared with those initially treated with CABG. Even though survival was higher in PCI-treated patients, that difference was not significant at five years of follow-up.

The findings of this long-term follow-up changed our previously reported safety-benefit findings at short-term outcome with PCI randomized patients. The incidence of repeat procedures and angina was significantly higher with stents; however, at the end of the follow-up, a similar number of patients in each group were asymptomatic or with class I angina, and only 8.4% of the patients in the PCI group crossed over to surgery during the entire follow-up period.

The end point of freedom from MACE showed fewer events with surgery, due to the greater numbers of patients in the PCI group requiring new revascularization procedures.

Overall costs of both procedures (according to the modules of practices of the Social Security System of Argentina) showed that current PCI resources in this group of patients had a trend for higher costs than CABG at the end of the five years of follow-up.

We previously published (11) the 30-day and one-year outcomes of the ERACI II trial. The hospital results of this trial showed lower in-hospital death and MI in those patients treated with stents when they had unstable angina or post-AMI angina at the time of randomization. In agreement with these findings, others trials and registries have reported higher hospital mortality with surgery in those patients with refractory unstable angina or post-MI angina (19–27).

Even though other randomized comparisons between stents and surgery, such as the ARTS (10) and the Stent or Surgery trials (12), reported a lower hospital mortality with surgery than the ERACI II trial, the baseline clinical and angiographic characteristics of these two studies differ from our trial. These differences in baseline patient populations could explain these results. In fact, when similar cohorts of patients of the ERACI II and the ARTS trials were compared, the hospital and one-year results from the two trials were identical (23). More recently, a randomized comparison between CABG and PCI (the Angina With Extremely Serious Operative Mortality Evaluation study) showed a 5% incidence of 30-day mortality with surgery in patients with refractory myocardial ischemia (13,21).

It has been well established that the use of coronary bare metal stents, compared with balloon angioplasty, has been associated with both lower acute complications and restenosis (16,24,25). Consequently, we witnessed a significant change in the incidence of repeat revascularization procedures at five years of follow-up with the use of bare metal stents. Compared with the ERACI I trial, stent use in the ERACI II trial reduced the gap between PCI and CABG by 24%. In contrast, requirements of new revascularization procedures with surgery remained stable during the last

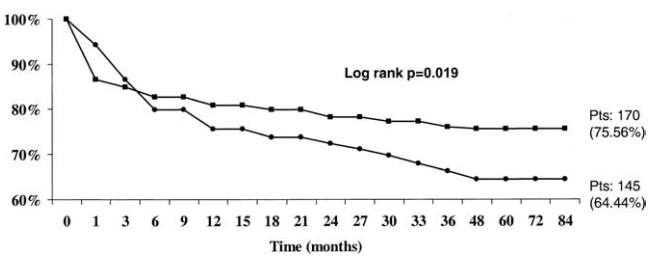

Figure 5. Comparison of freedom from major adverse cardiovascular events (alive and free of non-fatal myocardial infarction or stroke or repeat revascularization procedures) of patients treated with coronary artery bypass grafting **(square symbols)** versus percutaneous coronary intervention **(round symbols)**.

decade (6.3 vs. 6.2% in the ERACI I and ERACI II trials, respectively) (1).

Furthermore, patients in the PCI arm who needed to cross over to surgery also were significantly reduced in stent era. A large meta-analysis from eight randomized studies comparing balloon angioplasty with bypass surgery (8), at 2.5 years of follow-up, showed that 18% of patients with balloons needed to cross over to CABG. This value was higher than the 8.4% showed by our study with the liberal use of stents in the PCI arm. And the cross-over to CABG rate was 22% at three years in the balloon angioplasty group of the ERACI I trial.

Both lower acute hospital complications and restenosis improved the long-term outcomes in those patients treated with bare metal stents compared with old balloon PTCA techniques. Therefore, freedom from MACE at five years of follow-up in the ERACI II trial was better when compared with the three-year incidence of MACE of the ERACI I trial (1,9) (65% vs. 49%, respectively, $p = 0.02$).

In accordance with the number of repeat revascularization procedures, the incidence of angina during the entire follow-up period was significantly better with bypass surgery, reflecting restenosis or incomplete revascularization in the coronary stent group (14,26,27). This difference is attenuated during later follow-up, however, so by the end of the five years of follow-up, the prevalence of angina was similar in the two groups as a consequence of a higher rate of additional coronary revascularization procedures during the follow-up in the PCI patients.

In the past, initial and mid-term follow-up of percutaneous revascularization techniques was less expensive than the conventional coronary bypass surgery with arterial or vein graft conduit (1–9); nevertheless, this initial advantage declined over the long-term follow-up.

In the present study, the liberal use of stents during the PCI procedure increased the cost of percutaneous interventions significantly in Argentina compared with several years ago (1,9). In contrast, the cost of conventional coronary bypass surgery remained stable. In comparison with the ERACI I trial, which enrolled patients at the end of 1980, the ERACI II trial, performed in 1988, was more expensive. Thus, at five years of follow-up, our current study showed that percutaneous interventions had a trend toward higher costs, compared with conventional surgery. The relatively high proportion of glycoprotein inhibitors used in this study in the PCI arm (28%), due to the large number of patients treated with acute coronary syndromes, also helped explain the increase of cost in the stent group. We should remember, however, that cost-effectiveness of either revascularization procedure requires consideration of acute and long-term safety and of efficacy demonstrated for each revascularization procedure in different subsets of patients.

Study limitations. As previously cited (11), our study involved a large cohort of patients with unstable coronary syndromes at high risk for in-hospital morbidity and mortality.

Because the differences in major events largely occurred during the hospital period and mainly in patients with more severe unstable angina, these results could change if the clinical profiles of the patients treated were different (21). In fact, these differences in our study were not reported previously in those patients with stable angina.

The numbers of repeat revascularization procedures at three years in the PCI group could be associated with the stent design used in our study (GRII, Cook Cardiology Inc., Bloomington, Indiana) that was reported higher than other stent designs (28). Furthermore, a significant reduction of restenosis in the new era of drug-eluting stents (29–31) has recently been demonstrated and could change the long-term outcome and efficacy of percutaneous interventions. The cost-effectiveness of these percutaneous techniques compared with conventional or mid-CABG will need prompt new comparisons.

Conclusions. This multicenter randomized study comparing stent therapy with coronary bypass surgery demonstrates that in patients with multi-vessel coronary artery disease who have had lower 30-day mortality and incidence of MI when treated with routine bare metal stent therapy, at five years of follow-up, the two groups did not have significant differences either in survival or freedom from non-fatal MI. Compared with CABG patients, however, patients with multi-vessel disease treated with PCI continue to have an increased incidence of repeat revascularization procedures at follow-up.

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APPENDIX

For the ERACI II five-year follow-up study organization and participants, please see the online version of this article.