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The optimal revascularization strategy for multivessel coronary artery disease: The debate continues

ABSTRACT

Mortality rates were lower among patients with multivessel coronary artery disease who underwent coronary artery bypass grafting (CABG) than among similar patients who underwent percutaneous coronary intervention (PCI) in an analysis of data from New York State registries (N Engl J Med 2005; 352:2174–2183). This finding appears to run counter to the results of randomized controlled trials, which found both procedures equivalent with regard to mortality. What are we to believe?

KEY POINTS

In the New York study, at 3 years the adjusted mortality rate was at least 25% lower with CABG than with PCI, and the trend was consistent in all subgroups studied.

Restenosis rates after PCI for the treatment of multivessel disease have gradually improved over the past decade, although they probably do not yet really match those of CABG.

Observational studies and randomized controlled studies each have strengths and weaknesses. Although the latter generally provide a higher level of evidence, they usually exclude a large portion of patients.

In clinical practice, physicians use PCI and CABG to treat different types of patients with multivessel disease: PCI for multifocal discrete disease and CABG for diffuse disease and multiple chronic total occlusions.

WHAT IS THE OPTIMAL revascularization strategy for patients with multivessel coronary artery disease: percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)? Although both procedures have been available for 30 years, the debate remains unresolved.

A recent analysis of data from registries in the state of New York has added fuel to this debate.¹ In contrast to prior studies, which were randomized and indicated that mortality rates were equivalent with either approach, this retrospective analysis found a significantly lower mortality rate with CABG in all anatomic and clinical subgroups of patients with multivessel coronary artery disease that were studied.

See related editorials, pages 329 and 340

This review summarizes the findings of the study and provides a critical analysis of their impact on the continuing debate.

THE NEW YORK REGISTRY STUDY

Hannan et al¹ used the Percutaneous Coronary Intervention Reporting System and the Cardiac Surgery Reporting System registries for the state of New York to identify patients who underwent revascularization for multivessel coronary artery disease between January 1997 and December 2000.

Multivessel coronary artery disease was defined as stenosis of 70% or greater in at least two of the three main coronary arteries.

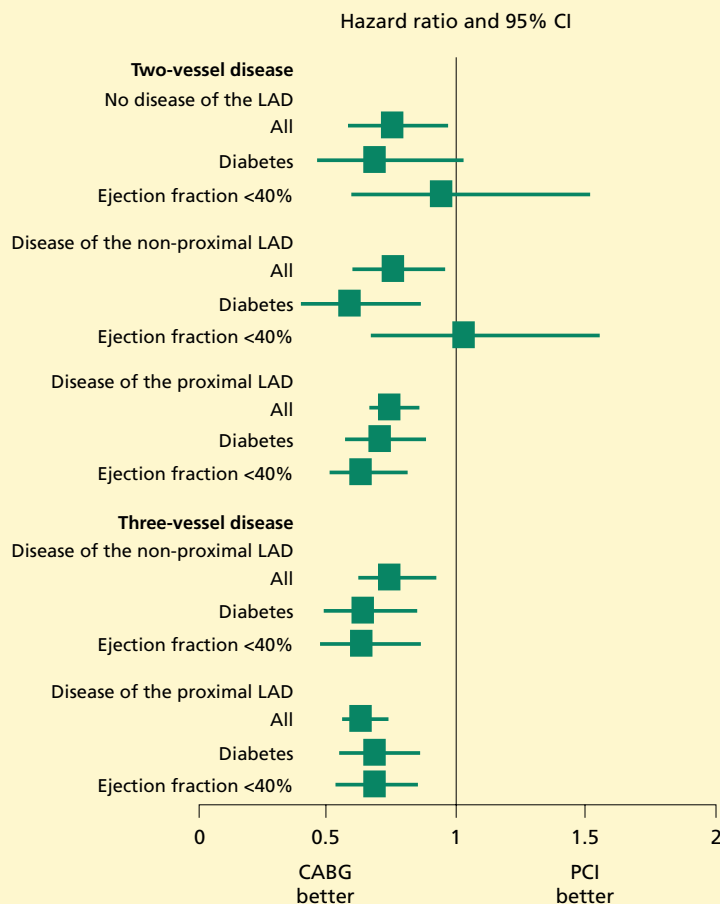


FIGURE 1. Outcomes in subgroups in the New York registry study. LAD = left anterior descending artery; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

DATA FROM HANNAN EL, RACZ MJ, WALFORD G, ET AL. LONG-TERM OUTCOMES OF CORONARY-ARTERY BYPASS GRAFTING VERSUS STENT IMPLANTATION. *N ENGL J MED* 2005; 352:2174-2183.

Patients were excluded if they had previously undergone revascularization, if they had significant left main coronary artery disease, or if they had suffered a myocardial infarction within the preceding 24 hours.

Approximately 22,000 patients underwent PCI and 37,000 underwent CABG. In general, the CABG group patients were older, had a higher prevalence of significant medical comorbidities, had lower ejection fractions, and were more likely to have three-vessel coronary artery disease.

Patients were divided into five anatomic subgroups on the basis of the pattern of their

disease (**FIGURE 1**). Within each of these subgroups, further prespecified subset analyses were performed according to whether the patient had diabetes mellitus or impaired left ventricular function (ie, ejection fraction < 40%). The end points of the study were death and repeat revascularization between the time of the index procedure and December 2000.

Findings

At 3 years, after adjustment for differences in the baseline characteristics between the CABG patients and the PCI patients, the mortality rate was at least 25% lower with CABG than with PCI in all anatomic subgroups (**FIGURE 1**), and the difference was statistically significant. The survival curves began to diverge remarkably early in favor of CABG, and the difference steadily increased over the 3-year follow-up period (**FIGURE 2**).

Among patients with diabetes the difference was even greater: the mortality rate was at least 30% lower with CABG than with PCI in all anatomic subgroups. The rate was also at least 30% lower with CABG in patients with reduced left ventricular ejection fraction with three-vessel disease or two-vessel disease involving the proximal left anterior descending artery (LAD).

Only 4.9% of patients who underwent CABG needed a repeat revascularization procedure, compared with 35.1% for those treated with PCI ($P < .001$).

To adjust for the obvious selection bias inherent in such an observational study, the authors identified clinical variables that were significant predictors of the type of revascularization strategy chosen and matched patients with a similar anatomic distribution of disease on the basis of their propensity to receive PCI. In this “propensity analysis,” there was also a consistent survival benefit with CABG vs PCI.

Comparison with previous data

Before this study was published, the prevailing opinion about revascularization for patients with multivessel coronary artery disease was that CABG entails less need for repeat revascularization compared with PCI (including

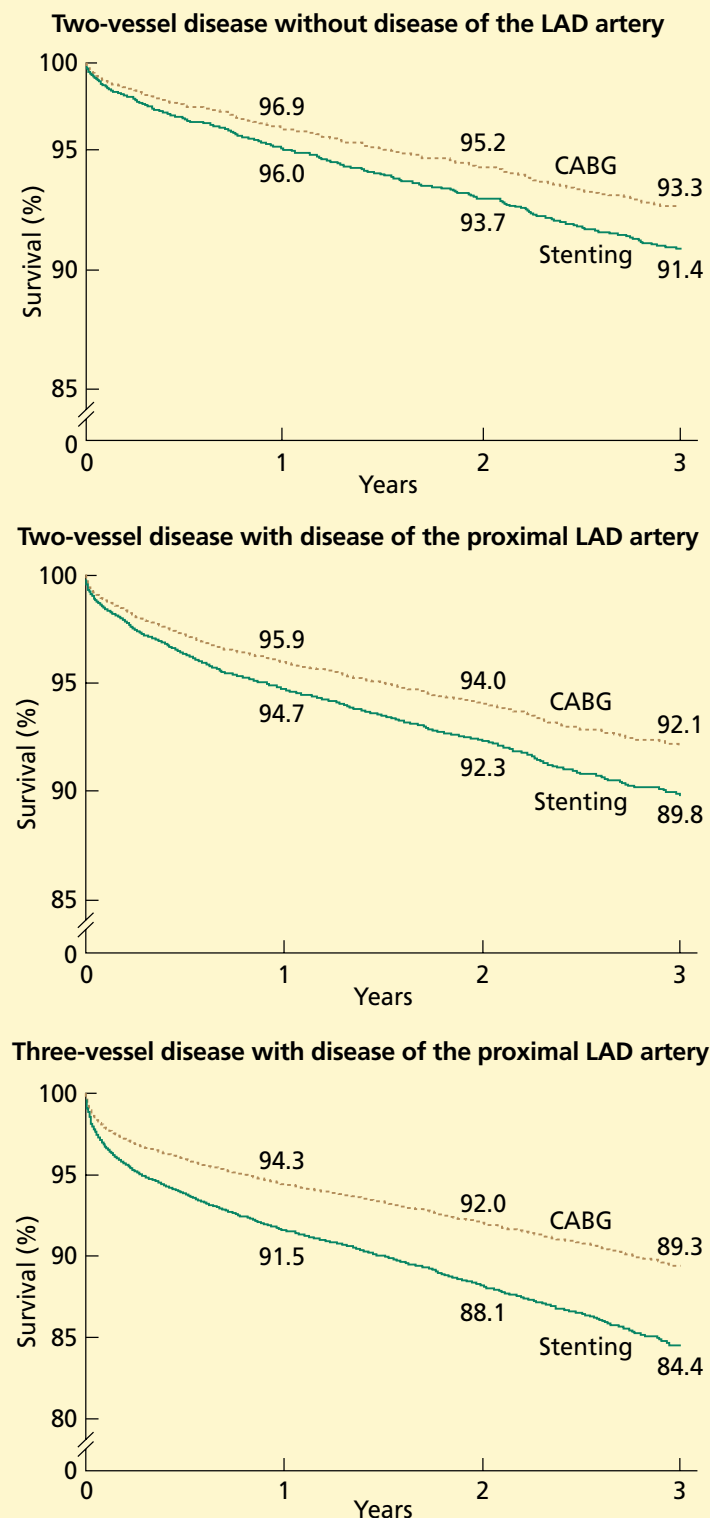


FIGURE 2. Adjusted survival curves in the New York registry study.

FROM HANNAN EL, RACZ MJ, WALFORD G, ET AL. LONG-TERM OUTCOMES OF CORONARY-ARTERY BYPASS GRAFTING VERSUS STENT IMPLANTATION. *N ENGL J MED* 2005; 352:2174-2183.

stenting) and provides more effective relief from symptoms of angina, but offers no survival benefit over PCI except in patients with diabetes.

This opinion was based on the results of several randomized controlled trials and registries that can be broadly divided into three groups (TABLE 1):

- Trials that compared multivessel PCI with angioplasty vs CABG
- Trials that compared multivessel PCI with stenting vs CABG
- Registries of patients who underwent multivessel PCI with drug-eluting stents.

These groupings reflect the changing practice of PCI over time and the efforts of investigators to compare CABG with contemporary PCI techniques.

With advances in PCI technology, from balloon angioplasty alone to bare metal stents and subsequently to drug-eluting stents, repeat revascularization rates after initial PCI have declined significantly. For example, in the group that underwent balloon angioplasty without stenting in the Bypass Angioplasty Revascularization Investigation (BARI) trial, the repeat revascularization rate at 5 years was 54%,² compared with 28% in the group that underwent PCI with stenting in the second Argentine Randomized Study of Coronary Angioplasty (ERACI II),³ and 30% in the Arterial Revascularization Therapies Study (ARTS).⁴ Although 5-year revascularization rates with drug-eluting stents for the treatment of multivessel coronary artery disease are not available, the 1-year rate of repeat revascularization of 7.4% reported in the ARTS II registry is approximately half that reported in trials of bare metal stents vs CABG.

At the same time, 5-year revascularization rates with CABG have remained relatively constant at 5% to 10%, which is still superior to those achieved with bare metal stenting. Although drug-eluting stents have narrowed the gap, it appears unlikely that the 5-year revascularization rates with these stents will rival those achieved with CABG.

With respect to mortality, none of the individual multivessel angioplasty-vs-CABG trials showed either strategy to be significantly better. However, a meta-analysis of all multi-

**TABLE 1****Studies comparing PCI with CABG for multivessel coronary artery disease****PCI alone vs CABG**

BARI (Bypass Angioplasty Revascularization Investigation)
CABRI (Coronary Angioplasty vs Bypass Revascularization Investigation)
RITA (Randomized Intervention Treatment of Angina)
EAST (Emory Angioplasty versus Surgery Trial)
GABI (German Angioplasty Bypass Surgery Investigation)
ERACI (Argentine Randomized Study of Coronary Angioplasty)

PCI with stenting vs CABG

ARTS (Arterial Revascularization Therapies Study)
SoS (Stent or Surgery)
ERACI II
AWESOME (Angina With Extremely Serious Operative Mortality Evaluation)

PCI with drug-eluting stenting vs CABG

ARTS II

PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting

vessel angioplasty-vs-CABG trials found an absolute difference of 2.3% ($P = .025$) in favor of CABG at 5 years in the entire cohort.⁵ Additionally, a post-hoc analysis of diabetic patients in the BARI trial showed a 5-year survival rate of 80% in the CABG group vs 65% in the PCI group ($P = .003$).² We should point out that when these studies were performed in the late 1980s and early 1990s, medical therapy for atherosclerosis and antiplatelet and anticoagulant regimens at the time of PCI was rudimentary compared with current standards.

Of the randomized trials of CABG vs PCI with stenting, the ERACI II and ARTS trials showed no statistically significant difference in mortality rates at 5 years between CABG and PCI (11.5% vs 7.1% in ERACI II, $P = .182$; and 7.6% vs 8% in ARTS, $P = .83$).^{3,4} while the Stent or Surgery (SoS) trial reported a mortality benefit in favor of surgery at 1 year (2% vs 5%, $P .01$).⁶

In the high-risk patient cohort studied in the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) trial (with stent use in 54% of patients), survival rates at 3 years were equivalent in both treatment groups (79% with CABG vs 80% with PCI, $P = .46$).⁷ In the subset of patients with diabetes, the mortality

rate at 3 years was 19% with PCI vs 28% with CABG.⁸ However, in the ARTS trial the rates at 5 years in this subset were 13.4% with PCI vs 8.3 with CABG.⁴

In aggregate, these data suggested that stenting might have narrowed any potential mortality benefit that was seen with CABG in earlier trials in which angioplasty alone was the PCI strategy, and may also have had a similar effect in the diabetic subset of patients.

The only data about mortality with multivessel stenting with drug-eluting stents come from a single registry study with limited follow-up: ARTS II. At 1 year, the mortality rate was 1%, which compared favorably to that with CABG (2.7%) and PCI with stenting (2.7%) in the original ARTS trial.⁹

■ EXPLAINING THE DISPARITY IN OUTCOMES

Given the data outlined above, how can we explain the disparity in mortality outcomes between the New York registry and prior, randomized controlled trials? A potential explanation lies in the fundamental differences between the New York registry and the con-

Are randomized trials valid if they exclude most 'real world' patients?

trolled trials, including their sample sizes, study populations, and study designs.

The randomized trials were smaller

The New York registry was remarkably large, with about 60,000 patients. In contrast, the BARI trial, which was the largest of the randomized trials, had about 1,800 patients,² and ARTS, which was the largest trial of CABG vs PCI with stenting, included about 1,200 patients.⁹ Because the numbers of patients in these trials were relatively small, composite end points were used that included all major adverse cardiac events. As a result, these studies did not have enough power to demonstrate a difference in the single end point of mortality favoring either mode of revascularization. This problem was magnified when studying the outcomes of important subsets of patients such as those with diabetes.

The similar mortality rates with CABG and with PCI in the randomized controlled trials were reassuring: if there is a difference, it should be modest. Nevertheless, it is plausible that a much larger study could unmask a significant difference.

The randomized trials excluded many patients

The New York registry study used broad inclusion criteria and therefore included most of the patients with multivessel coronary artery disease who underwent revascularization in that state. In contrast, the randomized controlled trials enrolled only an estimated 4% to 10% of all patients with multivessel disease, owing to restrictive inclusion criteria and operator and patient preference.

For example, the major criterion for inclusion in these randomized studies was obstructive coronary disease that could be fully revascularized by either percutaneous or surgical strategies. This resulted in the selection of a reasonably homogenous subset of patients with multivessel coronary artery disease whose anatomic distribution of disease was similar and who likely had a lower atherosclerotic burden than the entire cohort of patients with multivessel coronary artery disease.

The general effect of the restricted enrollment was to exclude sicker patients with a greater atherosclerotic burden and important

subsets such as those with significant left ventricular dysfunction. As a result, the broader applicability of the findings of randomized controlled trials has been constantly questioned. The inclusion of sicker patients in the New York registry study may explain the lower mortality rate with CABG that was observed in this study, and is consistent with the “gradient-of-risk” hypothesis, which argues that higher-risk patients gain the most from surgical vs percutaneous revascularization.

On the other hand, a comparison of patients undergoing PCI in the state of New York, where public reporting of operator and hospital outcomes is mandatory, and the state of Michigan, where it is not, shows significant differences in the case mixes between the two states.¹⁰ In New York, the scrutiny of public reporting seems to have resulted in a case selection bias favoring lower-risk cases, which has influenced decisions regarding surgical revascularization. Therefore, the New York registries may represent a unique population of patients with multivessel coronary artery disease, and the findings of this study may not be universally applicable.

Study design

The New York registry study was an observational analysis. Within the cohort studied, there is little doubt that there were patients who underwent PCI who, based on clinical factors or the anatomic distribution of disease, would never be referred for surgery, and similarly, there were patients who underwent CABG who would never have been referred for PCI. For example, patients with multifocal discrete stenoses are generally referred for PCI, whereas those with diffuse disease and multiple chronic total occlusions are generally referred for CABG. Can we really compare these two fundamentally different patient groups (ie, compare apples with oranges)?

In addition, even among patients who appear similar on the basis of the variables that were recorded, there are other clinical, angiographic, and social variables that influence the decision to proceed to PCI or CABG that the registry did not record. Many of these unrecorded variables are often very compelling in favoring a particular revascularization strategy, and some have a strong influ-

In New York, public scrutiny of outcomes may influence the choice of PCI or CABG

TABLE 2

Current trials comparing PCI and CABG for multivessel coronary artery disease

| | CARDIA | SYNTAX | FREEDOM |
|---------------------------|--|--|---|
| No. of patients | 600 | 1,500 | 2,400 |
| Location | UK/Ireland | United States | United States |
| Sponsors | Boston Scientific Bristol Myers Squibb Cordis Eli Lilly Guidant Hammersmith Hospitals Special Trustees Medtronic Sanofi-Synthelabo | Boston Scientific | NHLBI |
| Inclusion criteria | Diabetic patients with multivessel CAD or complex single-vessel disease | Patients with 3-vessel disease, LM disease, or LM equivalent | Diabetic patients with multivessel CAD |
| Randomization | CABG vs PCI (using sirolimus drug-eluting stents and adjunctive abciximab) | CABG vs PCI (using paclitaxel drug-eluting stents) | CABG vs PCI (using sirolimus drug-eluting stents) |
| Primary end point | 12-month MACCE [†] | 12-month MACCE [‡] | 5-year mortality |

[†]Death, myocardial infarction (MI), cerebrovascular accident

[‡]All-cause death, cerebrovascular event, MI, repeat revascularization

NHLBI: National Heart, Lung, and Blood Institute, UK: United Kingdom, CAD: coronary artery disease, LM: left main coronary artery, CABG: coronary artery bypass surgery, PCI: percutaneous coronary intervention, MACCE: major adverse cardiovascular and cerebrovascular event

FREEDOM: Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease

CARDia: Coronary Artery Revascularization in Diabetes

SYNTAX: Synergy Between PCI With Taxus and Cardiac Surgery

In practice, PCI and CABG are complementary rather than competitive strategies

ence on subsequent mortality. An imbalance in these variables between treatment groups may seriously confound the observed outcome. The statistical methods used in this registry, including the propensity analysis, can only attempt to adjust for differences in the recorded baseline characteristics of the CABG-treated and PCI-treated cohorts.

Again, this raises serious doubts about whether one is truly comparing similar groups of patients. The great advantage of randomization is that it balances these potential confounding variables between the two treatment groups.

THE 'TRUTH'

Given these considerations, are we to believe the data from the New York registry or those from previous, randomized controlled trials? In other words, do the large sample size and broader inclusion criteria of the New York registry trump the randomized design of the randomized controlled trials? This question is highly contentious, and there is a tendency for opinions to be strongly influenced by one's own inherent bias toward PCI or CABG.

In general, observational studies provide a lower level of evidence than do randomized

controlled trials, and there is particular reason to be suspicious of registry data when studying multivessel coronary artery disease. This disease is highly heterogeneous, and in the real world clinicians are strongly inclined to use PCI to treat multifocal discrete disease and CABG to treat diffuse disease and multiple chronic total occlusions. In other words, in clinical practice, PCI and CABG are *complementary* rather than *competitive* revascularization strategies.

As a result, patients who undergo PCI (ie, apples) are fundamentally different from patients who are referred for CABG (ie, oranges). Therefore, despite the use of contemporary statistical techniques, the validity of retrospective comparisons of “apples” and “oranges” is highly uncertain, and the results of such studies should not result in a significant change in clinical practice.

There is an additional concern regarding the biological plausibility of the temporal pattern of mortality benefit favoring CABG over PCI observed in the New York registry. The adjusted survival curves began to separate almost immediately, even though the in-hospital mortality rate was higher with CABG (1.75% vs 0.68%).

Although stent thrombosis is an early hazard of stent implantation, typically occurring within 30 days of the procedure, its incidence in large series of patients who receive bare metal stents is 0.5% to 1.9%; about 10% of patients in whom it develops die, making the absolute mortality rate from this complication 0.05% to 0.2%.¹¹ Therefore, stent thrombosis does not explain the magnitude of the early divergence in outcome.

Since PCI treats only the lesion site but CABG bypasses the entire proximal segment of the vessel, some have argued that CABG produces a lower mortality rate by protecting from the consequences of progression of atherosclerotic disease or plaque rupture proximal to the bypassed epicardial segment. However, one would expect the temporal pattern of this benefit to be gradual over time, and it is also uncertain whether this would translate into a mortality benefit.

Many believe, with some evidence, that the mortality benefit associated with CABG is



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closely linked to the use of left internal mammary arterial grafts to the LAD.^{12,13} For this reason, the mortality benefit associated with CABG in patients with two-vessel coronary artery disease without LAD involvement in the New York registry is puzzling. In fact, the magnitude of the benefit at 3-year follow-up in this subgroup was roughly equivalent to that seen in patients with two-vessel coronary artery disease with proximal LAD involvement (1.9% vs 2.3%). The absence of a plausible explanation for this finding raises additional suspicion about the overall findings of the study.

Despite these reservations, we must acknowledge the current limitations of randomized controlled trials and the potential contribution of registry studies. Ongoing randomized studies of multivessel coronary artery disease continue to restrict enrollment to the subset of patients who can be completely revascularized by either CABG or PCI (TABLE 2), and with the exception of the Future Revascularization Evaluation in Patients with Diabetes Mellitus (FREEDOM) trial, they remain underpowered to detect a mortality difference between revascularization strategies.

Additionally, the 5-year follow-up data from the current generation of studies will not be available until about 2010. As a result, we have to rely on registry data to provide assessments of contemporary practice and to provide insights into clinical outcomes of patient subsets not enrolled in randomized controlled trials.

Finally, it should be emphasized that it is advances in medical therapy for the prevention of atherothrombosis and the treatment of lipid disorders (eg, agents that raise high-density lipoprotein cholesterol levels), diabetes mellitus (eg, thiazolidinediones), hypertension, smoking addiction, and obesity, that have the greatest potential to prevent deaths following either CABG or PCI. The overall framing of the debate as a competition between CABG and PCI may be counterproductive. Incorporating the best of both approaches, such as with hybrid revascularization procedures, and optimizing medical therapy, may ultimately provide the optimal outcome for our patients.



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