Seven-Year Outcome in the RITA-2 Trial: Coronary Angioplasty Versus Medical Therapy

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OBJECTIVES
This study was designed to compare the long-term consequences of percutaneous transluminal coronary angioplasty (PTCA) and continued medical treatment.

BACKGROUND
The long-term effects of percutaneous coronary intervention need evaluating, especially in comparison with an alternative policy of continued medical treatment.

METHODS
The Second Randomized Intervention Treatment of Angina (RITA-2) is a randomized trial of PTCA versus conservative (medical) care in 1,018 patients considered suitable for either treatment option. Information on clinical events, interventions, and symptoms is available for a median seven years follow-up.

RESULTS
Death or myocardial infarction (MI) occurred in 73 (14.5%) PTCA patients and 63 (12.3%) medical patients (difference 2.2%, 95% confidence interval 2.0% to 6.4%, p = 0.21). There were 43 deaths in both groups, of which 41% were cardiac-related. Among patients assigned PTCA 12.7% subsequently had coronary artery bypass grafts, and 14.5% required additional non-randomized PTCA. Most of these re-interventions occurred within a year of randomization, and after two years the re-intervention rate was 2.3% per annum. In the medical group, 35.4% required myocardial revascularization: 15.0% in the first year and an annual rate of 3.6% after two years. An initial policy of PTCA was associated with improved anginal symptoms and exercise times. These treatment differences narrowed over time, mainly because of coronary interventions in medical patients with severe symptoms.

CONCLUSIONS
In RITA-2 an initial strategy of PTCA did not influence the risk of death or MI, but it improved angina and exercise tolerance. Patients considered suitable for PTCA or medical therapy can be safely managed with continued medical therapy, but percutaneous intervention is appropriate if symptoms are not controlled. (J Am Coll Cardiol 2003;42:1161–70) © 2003 by the American College of Cardiology Foundation

The optimal management of patients with angina pectoris remains controversial, but options include anti-anginal medication, percutaneous coronary intervention (PCI), or coronary artery bypass surgery. Several randomized clinical trials have compared percutaneous and surgical methods of myocardial revascularization, and some have reported long-term results (1–3). Overall, these trials suggest that percutaneous intervention is slightly less effective at relieving angina than is coronary artery bypass surgery, but there is no evidence that either revascularization strategy provides a prognostic advantage in the majority of patients.

For some patients with angina, revascularization is not considered essential for symptom relief or for prognostic reasons. Several small trials have compared percutaneous intervention with alternative medical treatment strategies in such patients, but most have reported only limited follow-up data (4–8). A meta-analysis of data available in 1998 concluded that percutaneous transluminal coronary angioplasty (PTCA) provides superior relief of angina at the cost of more coronary artery bypass surgery, but it could not reliably estimate the effects of the two treatment strategies on the risk of death or myocardial infarction (MI) (9).

The second Randomized Intervention Treatment of Angina (RITA-2) trial was designed to compare PTCA with continued medical treatment in patients in whom either strategy was considered a clinically acceptable treatment option. The primary trial end point was the five-year rate of death or non-fatal MI. The trial recruited 1,018 patients, and interim results have been published (10,11). In this article we report extended follow-up of the RITA-2 patients to a median seven years.

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Abbreviations and Acronyms

CABG = coronary artery bypass graft
CAD = coronary artery disease
LV = left ventricular
MI = myocardial infarction
PCI = percutaneous coronary intervention
PTCA = percutaneous transluminal coronary angioplasty
RITA = Randomized Intervention Treatment of Angina

METHODS

Trial design. The design of RITA-2 has been reported previously (10). Patients were recruited at 20 centers in the U.K. and Ireland, and the ethics committee of each participating center approved the trial protocol. In brief, patients with arteriographically proven coronary artery disease (CAD) were considered for the trial if the supervising cardiologist thought that continued medical therapy and PTCA were both acceptable treatment options. Patients had to be over 18 years of age, but there was no upper age limit. Patients were not required to have current symptoms, but patients with multi-vessel disease, occluded coronary arteries, or impaired left ventricular (LV) function were potentially eligible for the trial. Patients with previous myocardial revascularization, significant left main stem disease, recent (within seven days) acute coronary syndrome, hemodynamically significant valve disease, or life-threatening non-cardiac disease likely to have a major influence on survival were excluded. Patients in whom revascularization was considered necessary for symptom relief or for prognostic reasons were also ineligible.

Before randomization, a participating interventional cardiologist reviewed the coronary arteriogram of a potentially eligible patient and identified at least one significant coronary stenosis in a major epicardial vessel that could be treated by coronary angioplasty. Patients who satisfied the eligibility criteria and consented to participate were subsequently randomized to initial treatment strategies of PTCA or continued medical management. Patients were stratified by center and by extent of disease (single or multi-vessel disease).

The trial protocol required that patients assigned to PTCA underwent dilation of the target stenosis (or stenoses) within three months of randomization. Stents and other coronary interventional techniques were used only if the initial balloon angioplasty result was unsatisfactory. The choice of medication after a randomized PTCA was not mandated, although clinicians were encouraged to discontinue anti-anginal drugs if a patient no longer had symptoms of angina. Patients in the PTCA group underwent additional coronary arteriography and revascularization procedures if considered appropriate by the supervising clinician, with the objective of detecting and treating restenosis.

Patients randomized to an initial strategy of medical management were prescribed appropriate anti-anginal medication for symptom relief. Coronary arteriography was repeated only for compelling clinical reasons, and myocardial revascularization procedures were reserved for patients whose symptoms were not controlled by optimal anti-anginal medication (usually a beta-adrenoceptor blocker, with a calcium antagonist, and/or with long-acting nitrate in maximally tolerated doses).

Data collection. Patients were assessed at three months, six months, and yearly intervals after randomization. Research assistants at each participating center recorded trial data on specially prepared forms.

The pre-defined primary trial end point was the five-year rate of death and definite MI. An independent event validation committee, unaware of treatment assignment, reviewed all available information on deaths and MIs. The cause of death was classified as cardiac, other cardiovascular, or non-cardiovascular. Definite MI was diagnosed when new pathological Q-waves appeared on a follow-up electrocardiogram, or when a convincing clinical history was associated with electrocardiographic changes consistent with non-Q-wave infarction and cardiac enzyme activity above twice the upper limit of normal on at least two relevant serum samples.

As previously reported, angina was assessed with the Canadian Cardiovascular Society classification and breathlessness and physical activity were assessed by ordinal scales (10,12). Symptom-limited exercise tolerance tests were carried out using the Bruce protocol at three and six months and one and three years after randomization. Left ventricular function was assessed from LV angiograms using a wall motion score.

Statistical analysis. A total of 1,018 patients were randomized at 20 participating centers. All data were analyzed by intention to treat, using standard methods. The percentages of patients with the primary end point of death or MI at five years in each treatment group were compared using Kaplan-Meier estimates. Times to death and death/MI are presented using Kaplan-Meier curves. The percentages of patients reporting other outcomes from follow-up interviews were compared using chi-squared tests. Analysis of co-variance was used to compare exercise time at three months and three years. Prognostic factors were determined by forward stepwise regression modeling: for the outcome of cardiac death or non-fatal MI, Cox regression was used, and for angina grade 2+ at five years, logistic regression was used.

RESULTS

The 1,018 patients were randomized to coronary angioplasty (n = 504) or continued medical treatment (n = 514) from July 1992 to May 1996. Follow-up to September 30, 2001, is included in this report, the median follow-up period being seven years. Eighteen patients (1.8%) have been lost to follow-up. The five-year follow-up rate is 99.1%.
Baseline data and randomized PTCA. Detailed information on baseline comparability and the randomized PTCA has been published earlier (10). In brief, 60% of patients had single-vessel disease, 53% had angina grade 2 or worse, 18% were female, and the median age was 58 years. At randomization 53% were receiving two or more anti-anginal drugs, 13% were taking lipid-lowering medication, 47% had had a previous MI, and 9% were treated for diabetes. The PTCA and medical treatment groups were similar with regard to all these baseline features.

The intended randomized PTCA was performed on 471 (93%) patients in the PTCA group, the median time from randomization to PTCA being five weeks. Angioplasty was attempted in a mean 1.4 vessel segments per patient (means 1.2, 1.6, and 1.9 segments for those with significant disease in 1, 2, and 3 epicardial vessels, respectively), of which 93% were successfully dilated. The randomized PTCA was complicated by emergency coronary artery bypass graft (CABG) in seven patients, non-fatal MI in seven patients (of whom 4 developed new electrocardiographic Q-waves), and one procedure-related death. Patient recruitment began before the widespread use of coronary stents, which were implanted during 44 (9%) randomized PTCA. Of these, 32 occurred in the 160 patients randomized to PTCA during 1995 and 1996, the last 17 months of patient recruitment.

Death and MI. To date, 43 patients have died in both treatment groups (Table 1). The survival plot (Fig. 1A) reveals comparable mortality between groups over eight years of follow-up. At five years follow-up, the mortality rate was 4.6% and 4.7% in the PTCA and medical groups, respectively (difference −0.1%, 95% confidence interval [CI] −2.7% to +2.5%).

Almost half the deaths were from non-cardiovascular causes. Although there were fewer cardiac deaths in the PTCA group—13 PTCA versus 22 medical—this difference is not statistically significant. Three of the seven cardiovascular deaths in the PTCA group were due to stroke.

To date, 32 and 23 patients in the PTCA and medical groups respectively have had a definite non-fatal MI (Table 1), five of whom (2 PTCA, 3 medical) have subsequently died. Thus, death or definite MI has occurred in 73 PTCA and 63 medical patients. The time-to-event plot (Fig. 1B) reveals an excess risk of this combined end point in the PTCA group in the first two months after randomization, which can be attributed to the eight procedure-related events mentioned earlier. Thereafter, the plots run parallel with a steady rate of end points up to eight years of follow-up. If the eight events related to the randomized PTCA are discounted, the subsequent rates of death or definite MI in the PTCA and medical groups are 2.0 and 1.8 per 100 patient-years of follow-up, respectively (difference +0.2, 95% CI from −0.5 to +0.8).

The pre-defined primary end point of death or definite
MI at five years (including procedure-related events) occurred in 47 PTCA patients (9.4%) and 39 medical patients (7.6%) (difference +1.8%, 95% CI −1.7% to +5.2%, p = 0.31).

**Subsequent interventions.** Since randomization, 64 patients randomized to PTCA (12.7%) and 63 (12.3%) patients randomized to medical treatment have had CABGs (Table 1). This includes the seven emergency CABGs after randomized PTCA and nine CABGs performed instead of the intended randomized PTCA.

In the PTCA group, additional non-randomized PTCA was required in 86 patients, 13 of whom also had CABG and 17 of whom required two or more such PTCA. In the medical group, 139 patients subsequently had a first PTCA, of whom 20 also needed CABG during follow-up.

In total, the PTCA and medical groups had 106 and 174 non-randomized PTCA during follow-up, and stents were implanted during 36% of these procedures in each group. Stent use increased over time: in 1992 to 1994, in 1995 to 1997, and in 1998 to 2001, the numbers of non-randomized PTCA with stent insertion are 9 of 94 (9.6%), 42 of 113 (37.2%), and 50 of 73 (68.5%), respectively. There was no evidence of a difference in any outcome between patients with stents and those without stents.

In both treatment groups, the rate of non-randomized interventions (further PTCA and/or CABG) is much higher in the first year of follow-up (Fig. 2). In the PTCA group, 14.9% of patients required re-intervention in that first year (one-third of whom required CABG). This fell to a re-intervention rate of 3.8% in the next year and an average of 2.3% per annum over years 3 to 8 post randomization. In the medical group, 15% of the patients underwent a coronary intervention procedure in the first year (one-fifth of whom required CABG). In year 2, this fell to 6.4%, and in years 3 to 8 their coronary intervention rate averaged 3.6% per annum.

Over five years of follow-up, 10.5% of the PTCA group had a CABG, compared to 9.3% in the medical group. In the PTCA group, the five-year rate of re-intervention (PTCA and/or CABG) was 23.3% (16.2% and 28.9%, respectively, for patients with baseline angina grade <2 and ≥2). Information about coronary arteriography before these non-randomized revascularization procedures was available for 71 of 106 PTCA patients, and restenosis was demonstrated in 63%. By contrast, in the medical group 28.8% of patients had at least one coronary revascularization procedure by five years (20.2% and 37.5%, respectively, for patients with baseline angina grade <2 and ≥2), but 71.2% did not require any revascularization procedure.

**Angina and breathlessness.** The prevalence of angina declined in both treatment groups during the first five years of follow-up (Fig. 3), but this symptomatic improvement was much more rapid in the PTCA group. At three months after randomization, 19.4% and 35.9% of the PTCA and medical groups, respectively, had angina grade 2 or worse (difference 16.5%, 95% CI 11.0% to 21.9%). By five years follow-up, the prevalence of angina grade 2 or worse in the PTCA group remained steady at 15.0%, whereas in the medical group the prevalence of angina was reduced to 21.4%. The five-year treatment difference is thus much smaller, 6.4% in favor of PTCA (95% CI 1.5% to 11.3%, p = 0.011). During the next three years, the prevalence of angina begins to increase slightly in both treatment groups.

The above results are based on analysis by intention to treat, but it is also relevant to consider the impact of non-randomized procedures on anginal symptoms. Figure 4 relates mean angina grade to time before and after the first non-randomized intervention; the vertical line at time 0 represents the moment of intervention. Patients without non-randomized interventions are not shown on these graphs. The angina grades are smoothed using a nearest-neighbor running-line smoother, with the data before and after the non-randomized intervention smoothed separately to allow a discontinuity. Pointwise 95% confidence intervals are also shown. The mean angina grade increases during the 6 to 12 months before the non-randomized intervention; the vertical line at time 0 represents the moment of intervention. Patients without non-randomized interventions are not shown on these graphs. The angina grades are smoothed using a nearest-neighbor running-line smoother, with the data before and after the non-randomized intervention smoothed separately to allow a discontinuity. Pointwise 95% confidence intervals are also shown. The mean angina grade increases during the 6 to 12 months before the non-randomized intervention; the vertical line at time 0 represents the moment of intervention. Patients without non-randomized interventions are not shown on these graphs.
marked with a triangle (Fig. 4) and is consistent with the prior trend. After the non-randomized intervention, angina grade improves rapidly, especially where a CABG was done (Figs. 4B and 4D).

Patients in the PTCA group had less use of anti-anginal drugs up to eight years follow-up compared with the medical group. For instance, at five years 70% and 83% of the PTCA and medical groups, respectively, were receiving at least one anti-anginal drug, 23% and 34% were receiving two drugs, and 8% and 11% were receiving triple-drug therapy. Anti-anginal treatment included a beta-blocker in 42% of the PTCA group and 53% of the medical group. In the PTCA group, 92% were taking aspirin, compared with 91% of the medical group. The use of HMG CoA reductase inhibitors increased over time, and at five years 51% of the PTCA group and 47% of the medical group were prescribed lipid-lowering medication. Angiotensin-converting enzyme inhibitors were prescribed for 20% of the PTCA group and 17% of the medical group.

The highly significant treatment difference in prevalence of breathlessness in early follow-up had largely disappeared after a few years: 42% versus 57% breathless at three months ($p < 0.001$) in the PTCA and medical groups, respectively, compared to 46% versus 50% at three years ($p = 0.30$).

Similarly the mean difference in Bruce exercise treadmill time at three months, $+37$ s in favor of PTCA based on 864 patients (95% CI 21 to 52 s), had reduced to $+25$ s mean benefit based on 749 patients (95% CI 6 to 44 s) by three years follow-up.

Prognostic factors. In determining which patient baseline factors are linked to subsequent prognosis we considered two outcomes:

1) The combined incidence of cardiac death and definite non-fatal MI, excluding the eight such events related to randomized PTCA, since they are likely to have a different etiology. Thus 78 patients experienced this outcome.

2) The presence of angina grade 2 or worse five years after randomization: this affected 173 of 948 patients seen at five years.

For each outcome the following baseline factors were considered: angina grade, unstable angina in the past three months, number of anti-anginal drugs, breathlessness grade, exercise treadmill time, age, gender, previous MI, treatment for diabetes mellitus (with diet, drugs, or insulin), treatment for hypertension, blood pressure, serum cholesterol, weight, height, body mass index, smoking history, electrocardiographic abnormality, LV function score, number of diseased vessels, and $>50\%$ stenosis in the proximal left anterior descending or other proximal vessel. By using forward stepwise regression modeling procedures the predictive models shown in Table 2 were derived.

For cardiac death and non-fatal MI, angina grade at randomization was the strongest predictor. Patients with both proximal left anterior descending and at least one other diseased proximal vessel (i.e., $\geq 50\%$ stenosis) had an estimated three-fold increase in risk, but there were only 71 patients in this category. There was no treatment difference in risk after adjusting for these two factors.

For prevalence of angina grade $2+$ after five years, the baseline exercise time and breathlessness at baseline were strongly predictive. Patients with more severe angina at baseline also had an increased risk; but angina grade was strongly associated with breathlessness and exercise time, and after taking these variables into account, baseline angina grade was less independently predictive of outcome. After adjusting for these three factors, there remained a 33% odds reduction in angina at five years for PTCA versus medical treatment ($p = 0.031$).
There was a trend for the 90 patients with diabetes mellitus to be at greater risk of death or MI (hazard ratio 1.17, 95% CI 0.56 to 2.43) or angina grade 2+ during follow-up (odds ratio 1.43, 95% CI 0.80 to 2.58), but there was no evidence of an interaction between diabetes and treatment for these two outcomes. Other subgroup analyses were explored for each of the baseline variables listed above, but for neither outcome were there any statistically significant interactions between treatment group and baseline factors.

**DISCUSSION**

The RITA-2 trial provides the only currently available randomized evidence comparing the long-term consequences of PCI and medical treatment in patients with
angina. Over a median seven years follow-up, we have demonstrated that initial policies of PTCA and medical therapy in patients considered suitable for either treatment are comparable with regard to risk of death and non-fatal MI, but an initial policy of PTCA was associated with a lower prevalence of angina and improved exercise tolerance.

The patients in our trial were selected from a large group of patients undergoing coronary arteriography and ranged from patients with no angina and single-vessel disease to those with severe symptoms and advanced coronary disease (10). Nevertheless our patients were at low cardiovascular risk, with a mortality of <1% per annum in both groups. The trial results therefore cannot be generalized to all patients undergoing PCI but are relevant to a substantial group of patients for whom optimal treatment has been uncertain and for whom percutaneous intervention or continued medical therapy both seem appropriate.

Other trials of coronary angioplasty versus medical therapy (4–8) provide important additional information but are too small to reliably estimate the effects of the two treatment
strategies on mortality or risk of MI, and most have not reported long-term follow-up data. The TIME and ACIP trials are also relevant, but these trials compared a policy of early myocardial revascularization with continued medical therapy, and the long-term effects of percutaneous and surgical treatment cannot easily be separated (13,14).

The clinical significance of MI during PCI has recently been the subject of intense research interest. Some investigators report that the extent of myonecrosis, defined by the serum cardiac enzyme level, correlates closely with mortality during long-term follow-up (15,16). Other studies suggest that a small peri-procedural rise in cardiac enzyme level is related myocardial injury may have been underestimated. Nevertheless, this procedural risk did not translate into increased mortality during follow-up, and although RITA-2 was not designed to compare the effects of the two treatments on long-term mortality, the data suggest that early coronary intervention is a safe strategy in low-risk patients with symptomatic CAD.

Many interventional cardiologists advocate dilation of severe coronary stenoses irrespective of symptoms, in the belief that this reduces the risk of progression to coronary occlusion, prevents MI, and improves prognosis. Our data do not support this belief, and in RITA-2, dilation of one or more coronary stenoses did not subsequently affect the incidence of MI or death over eight years of follow-up. Patients with more extensive CAD may gain prognostic benefit from coronary artery bypass surgery (20), but whether contemporary PCI influences prognosis in such patients can be elucidated only by additional randomized clinical trials.

Angina and exercise tolerance. The RITA-2 data suggest that the main advantage of PTCA over medical management is an improved angina status and exercise tolerance over many years, but the long-term symptom data require careful interpretation. Shortly after randomization, there is a substantial reduction in anginal symptoms among patients treated by PTCA compared with patients assigned medical therapy. Thereafter this treatment difference attenuates because of symptomatic improvement in the medical management group, which can be largely explained by the effects of myocardial revascularization procedures in 35% of medical patients (Fig. 4). Thus, the intention-to-treat results for angina prevalence (grade 2 or worse) at five years show only 30% proportionately fewer cases in the PTCA group compared with the medical group. This narrowing of the observed treatment difference over time should not be interpreted as a decline in the effectiveness of an interventional strategy but as an inevitable consequence of the most severely affected medical group patients requiring coronary interventions. More complex statistical modeling of these issues has been undertaken and confirms this interpretation (21).

It is relevant to note that the most powerful predictors of symptomatic status at five years are breathlessness, exercise time, and angina grade at baseline. Furthermore, more severe angina grade at baseline is the strongest predictor of cardiac death or MI. By comparison, there was no evidence that other baseline variables, including the number of diseased vessels and LV function score, predict subsequent symptoms or cardiac events. This analysis has limited statistical power but implies that the management strategy for patients with coronary disease for which revascularization is not considered essential on prognostic grounds can be predominantly determined by symptoms. In RITA-2, patients with mild symptoms at baseline had a better prognosis, and among such patients the use of coronary angioplasty and the associated procedural risk can reasonably be delayed until worsening symptoms mandate intervention, particularly as the economic cost of the interventional strategy exceeds the cost of conservative care (22).

**Study limitations.** The RITA-2 trial enrolled patients from 1992 to 1996, since when there have been considerable

### Table 2. Multivariate Predictors of Cardiac Death and Non-Fatal MI, and Angina Grade 2 or Worse at Five Years

<table>
<thead>
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<th>Risk Factor</th>
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<th>p Value</th>
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<td>1.22 to 3.52</td>
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<td>1.40 to 5.24</td>
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*Among 889/1,018 (87%): 64 patients did not have the baseline Bruce exercise test.

LAD = left anterior descending coronary artery. Other abbreviations as in Table 1.
advances in both medical and interventional treatment. The use of coronary stents has increased markedly, and developments in stent design and deployment techniques, together with adjunctive use of clopidogrel and glycoprotein IIb/IIIa receptor antagonists, have all contributed to improvements in outcome after PCI (23,24). Randomized trials of multi-vessel stenting versus CABG, such as ARTS (25), ERACI-2 (26), and SOS (27) provide valuable information, but their follow-up period is still relatively short. The introduction of drug-coated stents has been heralded as a major advance, but there are no data concerning the long-term effects of this new technology (28). Other changes in practice include increasing use of hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors (29,30), angiotensin-converting enzyme inhibitors (31), and thienopyridines (32) in patients with CAD.

The long-term prognostic and symptomatic implications of all these developments for patients considered eligible for PCI remain largely unexplored to date. The Clinical Outcome Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial is testing the hypothesis in more than 3,000 patients that optimal catheter-based coronary revascularization combined with intensive medical therapy is superior to intensive medical therapy alone (33). Further data will be available from the BARI-2D trial, a comparison of medical therapy and revascularization in patients with type 2 diabetes mellitus. These trials will be important contributions; but recruitment in both trials is ongoing, and hence, long-term results will not be known for several years. Meantime RITA-2 provides the best currently available insight into outcome many years after initial policies of percutaneous intervention or conservative management in patients with angina.

Conclusions. In conclusion, we have demonstrated that PTCA reduces anginal symptoms and improves exercise tolerance in the long-term for patients who are considered suitable for treatment by percutaneous intervention or by continued medical therapy. However, among such patients PTCA does not appear to influence the disease natural history favorably with regard to risk of death and non-fatal MI. Treatment choice can therefore be determined principally by symptom status. Patients with mild to moderate angina can be safely managed with continued medical therapy, but percutaneous intervention is appropriate if symptoms are not controlled by medication. Other trial evidence is needed to update these long-term findings regarding percutaneous interventional treatment, in the light of increased use of coronary stents and recent developments in medical treatments.

Acknowledgments

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REFERENCES


APPENDIX

For a complete list of participants in the RITA-2 trial, please see the October 1, 2003, issue of JACC at www.cardiosource.com/jacc.html.