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### Management of acute coronary syndromes - Reply

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**Publication date**  
2005

**Published in**  
The New England journal of medicine

[Link to publication](#)

**Citation for published version (APA):**

de Winter, R. J., Windhausen, A., & Tijssen, J. G. P. (2005). Management of acute coronary syndromes - Reply. *The New England journal of medicine*, 353(25), 2716-2717.

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CORRESPONDENCE



## Management of Acute Coronary Syndromes

**TO THE EDITOR:** The Invasive versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) trial reported by de Winter et al. (Sept. 15 issue)<sup>1</sup> shows that an early invasive strategy was not superior to a conservative strategy in patients who had acute coronary syndromes without ST-segment elevation and with an elevated cardiac troponin T level. However, we disagree with the authors' statement that they "studied a high-risk population," because such a conclusion is not supported by the data that they present (i.e., <50 percent of the patients were older than 65 years of age, <15 percent had diabetes, and <50 percent had ST-segment deviation of at least 0.1 mV on electrocardiography). Moreover, the cumulative one-year rate of death or nonfatal myocardial infarction in the conservative-strategy group was less than 9 percent according to the definition of myocardial infarction used in the TACTICS-TIMI 18 (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive Conservative Strategy-Thrombolysis in Myocardial Infarction 18) trial, whereas previous observations have shown that an early invasive strategy is most beneficial if the risk of death or myocardial infarction is greater than 20 percent.<sup>2</sup>

The results of the ICTUS trial therefore sug-

gest that an elevated troponin level is not a specific indicator of high risk. Instead, a more comprehensive method of risk stratification is needed for the treatment of patients who have acute coronary syndromes without ST-segment elevation, because the benefit of an early invasive strategy is proportional to the risk of adverse events as estimated by a TIMI risk score above 2, a GRACE (Global Registry of Acute Coronary Events) risk score above 133, or a PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin) score above 14.<sup>2</sup>

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1. de Winter RJ, Windhausen F, Cornel JH, et al. Early invasive versus selectively invasive management for acute coronary syndromes. *N Engl J Med* 2005;353:1095-104.
2. de Araujo Goncalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTEMI-ACS. *Eur Heart J* 2005;26:865-72.

**TO THE EDITOR:** Cautious interpretation of the results of the ICTUS trial is necessary because of the small sample (about 600 per group), the high intervention rate in the group receiving "conservative" treatment (54 percent), and the extraordinarily low one-year mortality rate of 2.5 percent, as compared with 6.0 percent in previous trials.<sup>1</sup> The use of clopidogrel and intensive lipid-lowering therapy is unlikely to account for the last observation, since neither agent reduces mortality in this population.<sup>2,3</sup>

The authors did not report how many patients were excluded and what their one-year mortality

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was. Patients who underwent randomization were at low risk, arousing concern about selection bias in recruitment, particularly since patients at low risk do not benefit from routine early intervention.<sup>4</sup>

Follow-up in the ICTUS trial was relatively short, and the neutral effect on one-year mortality is consistent with previous meta-analyses.<sup>1</sup> However, the RITA-3 (Third Randomized Intervention Treatment of Angina) trial<sup>4</sup> showed that benefits of early invasive management in terms of mortality emerge only with longer-term (five-year) follow-up. As with previous revascularization trials, the early hazard associated with intervention may be outweighed by long-term benefits.

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1. Mehta SR, Cannon CP, Fox KA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA* 2005;293:2908-17.
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**TO THE EDITOR:** We consider the validity of the conclusion reached by de Winter et al. to be questionable for several reasons. First, the variation in the number of patients contributed by individual centers (range, 1 to 105) suggests disparities in procedural volumes. Some of the participating hospitals perform more than 2000 procedures a year, whereas others perform only 500.<sup>1</sup> The volume of interventional activity correlates with the rate of procedural success and the rate of complications.<sup>2</sup> Benefits of an early invasive strategy may have been diluted by the inclusion in the ICTUS trial of patients from low-volume centers who had worse outcomes.

Second, the clinical significance of periprocedural release of the MB isoform of creatine kinase (CK-MB) is uncertain.<sup>3</sup> The criterion for myocar-

dial infarction (a CK-MB level greater than the upper limit of normal) is influenced predominantly by procedural rather than patient-related variables, making the lack of procedural and lesional information disappointing. The use of a widely accepted definition (a CK-MB level more than three times the upper limit of normal) annuls the difference in the incidence of myocardial infarction between groups (shown in Table 3 of the article). Finally, given the linear relation between troponin levels and major adverse cardiac events,<sup>4</sup> treating troponin levels dichotomously is unlikely to capture the effect of treatment on outcomes.

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**TO THE EDITOR:** De Winter et al. suggest that patients with acute coronary syndromes without ST-segment elevation could be treated safely with the use of a selective approach to coronary intervention. This strategy could potentially reduce the number of costly coronary procedures. However, we believe that the study design was suboptimal, precluding such a conclusion, for several reasons.

First, long delays between admission and coronary procedures are reported in both groups (23 hours in the early-invasive-strategy group and 11.8 days in the group assigned to a selectively invasive strategy), suggesting longer hospital stays in the conservative group. Were long delays necessary for therapeutic adjustments in the conservative group before noninvasive testing was performed? Second, the cost of both strategies is not reported. Given the differences in the duration of hospital stays, it seems highly improba-

ble that the conservative strategy was cost-effective. What was the influence on the quality of life and long-term employment status?

Finally, data on the medical therapy administered in the conservative group are incomplete: there are no data on anti-ischemic therapy such as beta-blockers. What therapeutic regimen were the patients receiving before noninvasive testing?

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**TO THE EDITOR:** De Winter and colleagues report that an early invasive strategy was not superior to a selectively invasive strategy in patients with acute coronary syndromes without ST-segment elevation and with an elevated cardiac troponin T level with respect to the composite end point of death, nonfatal myocardial infarction, or rehospitalization for anginal symptoms within a year. Even though permuted-block randomization was performed, in analyzing Table 1 of the article we could see that a clinical history of coronary artery disease (i.e., myocardial infarction, percutaneous intervention, or coronary-artery bypass grafting) was significantly more frequent in the early-invasive-management group ( $P=0.001$ ). Considering that a clinical history of coronary artery disease is a well-known negative prognostic indicator,<sup>1</sup> it would be of interest to perform a subgroup analysis according to the clinical history of coronary artery disease, even if the relatively small number of patients in these subgroups would preclude detection of a significant difference between the groups.

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1. Bertrand ME, Simoons ML, Fox KA, et al. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2003;24:485.

**TO THE EDITOR:** De Winter and colleagues report that, contrary to the recommendations of current guidelines, an early invasive strategy for high-risk

patients with acute coronary syndromes without ST-segment elevation does not improve survival as compared with a selectively invasive strategy. As pointed out by the authors, one of the main differences between the management of acute coronary syndromes in their trial and that in the trials on which the recommendations are based<sup>1-3</sup> is the early use of clopidogrel and intensive lipid-lowering therapy in the study of de Winter et al.

Although the use of clopidogrel and statins at discharge is reported, no information is given concerning their use in the early management of acute coronary syndromes in the two groups. We wonder whether the use of these drugs differed between the two strategies and whether this factor could have influenced the results. Since the role played by the early use of clopidogrel and statins may have been crucial in the ICTUS trial's reaching a result that was so discordant with the previous literature, we believe that this information should be available to put in perspective the results of the ICTUS trial.

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1. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999;354:708-15.

2. Fox KA, Poole-Wilson PA, Henderson RA, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. *Lancet* 2002;360:743-51.

3. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;344:1879-87.

**THE AUTHORS REPLY:** Newby and Fox suggest that the low event rate observed in the ICTUS trial was the result of the inclusion of low-risk patients owing to selection bias in recruitment. In addition, Tarantini et al. suggest that an analysis with the use of comprehensive risk stratification is needed. Patients who have acute coronary syndromes without ST-segment elevation and with an elevated cardiac troponin T level are designated high-risk patients for whom an early invasive strategy is recommended. Although several studies have shown the largest benefit in the pa-

tients who are at the highest risk, our preliminary subgroup analysis did not show a benefit of early invasive management among the higher-risk patients in the ICTUS trial.<sup>1</sup>

We agree with Newby and Fox that longer follow-up in the ICTUS study is needed. Although comparing the various “strategy trials” is complex, the long-term results of the RITA-3 trial show that “intermediate intensive revascularization” in patients who have acute coronary syndromes without ST-segment elevation of 55 to 60 percent at one year (the early-invasive group in the RITA-3 trial and the selectively-invasive-management group in the ICTUS trial) may be optimal.

The low event rate in the ICTUS trial is due in part to the fact that all revascularization procedures were performed in high-volume tertiary centers. The low-volume center mentioned by Ionescu and Garg did not perform percutaneous coronary intervention on ICTUS patients at the time the study was conducted. The definition of myocardial infarction that we used is from the Joint European Society of Cardiology–American College of Cardiology Committee.<sup>2</sup> We agree that the clinical significance of smaller periprocedural myocardial infarctions is uncertain, but we showed that, independent of the definition of myocardial infarction, there was no difference in outcome with early invasive management as compared with selectively invasive management. The correlation between cardiac troponin levels and outcome is complex and requires further study.<sup>3</sup>

Spaulding et al. ask about hospital stay, quality of life, employment status, and cost. We did not measure quality of life or employment status in our patients but agree that such factors are important for the decision to choose an early-invasive-management approach. We did collect cost data in the ICTUS trial, but the data have not yet been analyzed.

In response to Costantino et al.: the primary end point occurred in 46 of 196 patients with coronary artery disease (23.5 percent) in the early-invasive-strategy group, as compared with 41 of 165 (24.8 percent) in the selectively-invasive-strategy group (relative risk, 0.95; 95 percent confidence interval, 0.66 to 1.37). Among patients without coronary artery disease, the end point occurred in 91 of 408 patients (22.3 percent) in the early-invasive-strategy group and 85 of 431 (19.7 percent) in

the selectively-invasive-strategy group (relative risk, 1.13; 95 percent confidence interval, 0.87 to 1.47).

Garcia-Pavia et al. request additional data about the use of clopidogrel and statins. The protocol of the ICTUS trial included a recommendation to start both agents as soon as possible. We recorded medication use only at randomization and at discharge.

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1. Hirsch A, Windhausen F, Tijssen JG, et al. An early invasive strategy is not superior to a selective invasive strategy regardless of the number of risk factors at admission in troponin positive patients with non-ST-elevation acute coronary syndromes. Presented at the American Heart Association Scientific Sessions 2005, Dallas, November 13–16, 2005. abstract.

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**THE EDITORIALIST REPLIES:** Drs. Newby and Fox are incorrect in asserting that the use of clopidogrel and intensive lipid-lowering therapy does not reduce mortality in this population of patients with acute coronary syndromes. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial<sup>1</sup> (comparing clopidogrel plus aspirin with aspirin alone) and the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial<sup>2</sup> (comparing high-dose atorvastatin with pravastatin) both showed significantly lower rates of death, myocardial infarction, and stroke at one year of follow-up, supporting the likelihood that these medical therapies played an important role in the low observed event rates in both groups in the ICTUS trial. It also seems difficult to understand why revascularization of the culprit coronary stenoses in the RITA-3 trial<sup>3</sup> would have no benefit in terms of death or myocardial infarction during the first year of follow-up, a time when the benefits of early intervention were clearly evident in other trials (Fragmin and Fast Revasculariza-

tion during Instability in Coronary Artery Disease [FRISC] II<sup>4</sup> and TACTICS<sup>5</sup>). It seems more plausible that the late (five-year) clinical benefit observed in the RITA-3 trial might have been a consequence of the more systemic effects of robust medical therapy given to high-risk patients in the routine-invasive-strategy group, which in turn lessened the likelihood of a new plaque rupture in one or more of the native coronary arteries that did not initially have a flow-limiting stenosis. Thus, cautious interpretation might be well advised for both the ICTUS and RITA-3 trials.

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1. The Clopidogrel in Unstable Angina to Prevent Recurrent

Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502. [Errata, *N Engl J Med* 2001;345:1506, 1716.]

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3. Fox KA, Poole-Wilson PA, Henderson RA, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. *Lancet* 2002;360:743-51.

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## Protective Conditioning for Acute Graft-versus-Host Disease

**TO THE EDITOR:** Lowsky et al. (Sept. 29 issue)<sup>1</sup> report a conditioning regimen associated with an impressively low incidence of graft-versus-host disease (GVHD). However, the dynamics of engraftment are unclear. The authors mention that “donor T cells subsequently declined in number and were markedly reduced or undetectable within 75 to 200 days after transplantation in 6 of the 37 patients.” This finding suggests that late graft failure occurred in a substantial proportion of patients and consequently could in part explain the low incidence of GVHD.

In addition, in the setting of nonmyeloablative transplantation, the time to the onset of acute GVHD is significantly delayed,<sup>2</sup> so the 100-day limit used by Lowsky et al. may not reflect the true incidence of acute GVHD.

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1. Lowsky R, Takahashi T, Liu YP, et al. Protective conditioning for acute graft-versus-host disease. *N Engl J Med* 2005;353: 1321-31.

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and the apparently high rate of late graft loss reported in our study. The diagnosis and grading of acute and chronic GVHD in our study were performed according to established consensus criteria.<sup>1,2</sup> With a period of observation now ranging from 492 to 1339 days after transplantation, only 1 of the 37 patients (<3 percent) died from complications related to either acute or chronic GVHD — a number we consider to be impressively low, especially given the fact that almost 40 percent of the patients received grafts from unrelated donors.

Six patients in our study had graft loss within 75 to 200 days after transplantation. However, in four of these patients, the graft loss was associated with tumor progression or relapse of disease in the bone marrow. Thus, only 2 of the 37 patients (5 percent) had non-relapse-related graft loss — a fraction that is consistent with other nonmyeloablative host-conditioning regimens.

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**THE AUTHORS REPLY:** Drs. Ayala and Kharfan-Dabaja question the low incidence of acute GVHD