

# Prolonged antithrombotic pretreatment increased risk for MI or death in unstable coronary syndromes

Neumann FJ, Kastrati A, Pogatsa-Murray G, et al. Evaluation of prolonged antithrombotic pretreatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. *JAMA*. 2003;290:1593-9.

## QUESTION

In patients with unstable coronary syndromes, is prolonged antithrombotic pretreatment for 3 to 5 days more effective than early intervention and pretreatment for  $\leq 6$  hours before cardiac catheterization?

## DESIGN

Randomized {allocation concealed\*}†, blinded (monitoring committee),\* controlled trial with 30-day follow-up (Intracoronary Stenting With Antithrombotic Regimen Cooling-Off [ISAR-COOL]).

## SETTING

2 tertiary care centers in Germany.

## PATIENTS

410 patients (mean age 70 y, 67% men) who had angina pectoris at rest or with minimal exertion, with the last episode occurring within 24 hours, and myocardial ischemia confirmed by ST-segment depression or elevated cardiac troponin T levels. Exclusion criteria were large myocardial infarction (MI), hemodynamic instability, or contraindication to study medication. Follow-up was complete.

## INTERVENTION

Patients were allocated to prolonged antithrombotic pretreatment for 3 to 5 days

( $n = 207$ ) or pretreatment for  $\leq 6$  hours ( $n = 203$ ) before coronary intervention. Antithrombotic pretreatment consisted of intravenous (IV) unfractionated heparin, administered to achieve a partial thromboplastin time of 60 to 85 seconds; aspirin, 500-mg intravenous loading dose then 100 mg twice daily; clopidogrel, 600-mg loading dose and 75 mg twice daily; and IV tirofiban, initial 10  $\mu\text{g}/\text{kg}$  bolus and continuous infusion of 0.10  $\mu\text{g}/\text{kg}$  per minute.

## MAIN OUTCOME MEASURES

Composite endpoint of large MI (new Q waves in  $\geq 2$  contiguous electrocardiographic leads, new left-bundle branch block, or elevation of creatine kinase-MB levels to  $\geq 5$  times the upper limit of normal) or all-cause mortality at 30 days. Bleeding complications were also assessed.

## MAIN RESULTS

Analysis was by intention to treat. The composite endpoint was reached by more patients in the prolonged pretreatment group than the early intervention group (Table). Adjustment for baseline variables did not alter the result (odds ratio 2.17, 95% CI 1.01 to 4.76). Groups did not differ for major bleeding events (Table).

## CONCLUSION

In patients with unstable coronary syndromes, prolonged antithrombotic pretreatment before cardiac catheterization increased the risk for large myocardial infarction or death at 30 days.

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\*See Glossary.

†Information provided by author.

## Prolonged antithrombotic pretreatment vs early intervention before cardiac catheterization‡

Outcomes at 30 d	Prolonged pretreatment	Early intervention	RRI (95% CI)	NNH (CI)
Large myocardial infarction or death	11.6%	5.9%	96% (2.3 to 278)	18 (9 to 486)
Major bleeding	3.9%	3.0%	31% (-52 to 255)	Not significant

‡Abbreviations defined in Glossary; RRI, NNH, and CI calculated from data in article.

## COMMENTARY

Over the past decade, much clinical investigation has focused on the best strategies for treating patients with acute coronary syndromes without persistent ST-segment elevation (NSTEMI/ACS). Among high-risk patients, early cardiac catheterization followed by coronary revascularization is now preferred over "watchful waiting," where angiography is reserved for those with recurrent ischemia.

Unlike ST-elevation acute MI, where time to reperfusion is unequivocally linked to improved survival, optimal timing of cardiac catheterization in NSTEMI/ACS remains uncertain. Older observational reports from the era of balloon angioplasty have, in fact, suggested a benefit of medical "cooling down" before intervention. Aspirin, heparin, clopidogrel, and glycoprotein IIb/IIIa inhibitors are therefore the cornerstone of acute treatment for these patients. Additionally, recent large randomized trials have shown antiplatelet therapies to be beneficial when given both before and after interventional procedures (1, 2).

In ISAR-COOL, Neumann and colleagues tested the hypothesis that there would be an incremental benefit of prolonged antiplatelet and antithrombin therapies before angiography and revascularization in high-risk patients with ACS. Although small, the trial showed that the delayed strategy was inferior to a very early one and that the benefit came from reducing ischemic events before delayed catheterization.

What does this study tell us about how best to combine medical and

mechanical therapies for NSTEMI/ACS? Although ISAR-COOL has limited generalizability because of its small sample size, has a limited number of endpoint events, and was done in just 2 centers, it strongly suggests that waiting for angiography and revascularization may be harmful, as even very potent antithrombotic therapies do not attenuate all the ischemic risk that accrues during the waiting period. Unlike treatment of an earlier era, in which balloon angioplasty was the preferred coronary intervention and aspirin and unfractionated heparin constituted all antithrombotic therapy, ISAR-COOL shows no increased early hazard associated with rapid invasive procedures.

The recent call for specialized centers of excellence (3) for treating ACS patients fits the scheme studied in this trial. Patients presenting with high-risk ACS should be rapidly given potent antithrombotic therapies and considered for angiography within the next working day. Centers without cardiac catheterization laboratories should consider transferring high-risk ACS patients to offer them the best evidence-based care.

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## References

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