Addition of clopidogrel to aspirin, but not early use of metoprolol, improved overall outcome in acute myocardial infarction

COMMIT Collaborative Group. **Addition of clopidogrel to aspirin in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial.** Lancet. 2005;366:1607-21.

Clinical impact ratings: Hospitalists ★★★★★★★ Cardiology ★★★★★★☆ Emergency Med ★★★★★★☆

COMMIT Collaborative Group. **Early intravenous then oral metoprolol in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial.** Lancet. 2005;366:1622-32.

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QUESTION

In patients hospitalized within 24 hours of suspected acute myocardial infarction (AMI), does the addition of clopidogrel to aspirin and the early use of metoprolol improve outcomes?

METHODS

Design: Randomized placebo-controlled trial with 2 × 2 factorial design (Clopidogrel and Metoprolol in Myocardial Infarction Trial [COMMIT]).

Allocation: Concealed.*

Blinding: Blinded {clinicians, patients, and outcome assessors}†.*

Follow-up period: Until first hospital discharge or 28 days.

Setting: 1250 hospitals in China.

Patients: 45 852 patients (mean age 61 y, 72% men) hospitalized within 24 hours (mean 10 h) of onset of symptoms of AMI, with ST elevation (87%), left-bundle branch block (6%), or ST depression (7%) and no clear indication for or against the study medications. Those with moderate heart failure were eligible. Patients scheduled for primary percutaneous coronary intervention (PCI) and those with small likelihood of benefit or high risk for adverse effects were excluded.

Interventions: Clopidogrel, 75 mg once daily (n = 22 961), or placebo (n = 22 891); all patients also received aspirin, 162 mg once daily. Intravenous (IV) metoprolol, 5 mg, up to 3 doses administered over 2 to 3 minutes and spaced 2 to 3 minutes apart (provided heart rate > 50 beats/min and systolic blood pressure > 90 mm Hg), then oral metoprolol, 50 mg every 6 hours for 2 days, followed by oral controlled-release metoprolol, 200 mg once daily (n = 22 929), or placebo (n = 22 923). 54% of patients also received fibrinolytic therapy.

Outcomes: Clopidogrel study: composite endpoint (death, reinfarction, or stroke), all-cause mortality, reinfarction, stroke, and life-threatening bleeding (hemorrhagic stroke or major noncerebral bleeding). Metoprolol study: composite endpoint (death, reinfarction, or cardiac arrest), all-cause mortality, reinfarction, ventricular fibrillation, other cardiac arrest, and cardiogenic shock.

Patient follow-up: > 99.99% (100% in intention-to-treat analyses).

MAIN RESULTS

Clopidogrel study: Clopidogrel plus aspirin reduced risk for the composite endpoint and the single endpoints of death and reinfarction more than aspirin alone (Table 1). Groups did not differ for stroke alone or life-threatening bleeding (Table 1). For the composite endpoint, the efficacy of clopidogrel increased with shorter intervals between onset of symptoms and study entry, but did not differ by days since study entry, patient age, use of fibrinolytic therapy, or allocation to metoprolol.

Metoprolol study: Metoprolol and placebo did not differ for the composite endpoint (Table 2). Metoprolol reduced risk for reinfarction and ventricular fibrillation; it increased risk for cardiogenic shock (Table 2). Risk for shock was elevated on the first 2 days but not subsequently. Combining the composite endpoint and shock, there was no overall net benefit or harm of metoprolol (Table 2), but this result varied by time since study entry: harm on day 0, no net effect on day 1, and benefit from day 2 onward. Risk for harm with metoprolol was higher in patients ≥ 70 years of age, rated as Killip class III, or with systolic blood pressure < 120 mm Hg or heart rate ≥ 110 beats/min.

CONCLUSIONS

In patients hospitalized within 24 hours of suspected acute myocardial infarction, adding clopidogrel to aspirin (and other standard treatments) reduced risk for the composite endpoint of death, reinfarction, or stroke and did not increase the risk for major bleeding. Early intravenous then oral metoprolol did not reduce risk for the composite endpoint of death, reinfarction, or cardiac arrest; it increased risk for cardiogenic shock, especially in the first 2 days after admission, but reduced the risk for reinfarction and ventricular fibrillation.

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*See Glossary.

†Information provided by author.

Table 1. Clopidogrel plus aspirin vs aspirin alone for acute myocardial infarction at up to 28 days‡

Outcomes	Clopidogrel plus aspirin	Aspirin	RRR (95% CI)	NNT (CI)
Composite endpoint§	9.2%	10.1%	8.2% (2.7 to 13)	122 (78 to 367)
Death	7.5%	8.1%	6.5% (0.9 to 12)	192 (103 to 1349)
Reinfarction	2.1%	2.4%	14% (2.9 to 24)	302 (176 to 1413)
Stroke	0.9%	1.1%	14% (–3.0 to 28)	Not significant
			RRI (CI)	NNH
Major bleeding	0.58%	0.55%	6.9% (–16 to 36)	Not significant

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

§Death, reinfarction, or stoke.

(continued on page 59)

(continued from page 58)

Table 2. Metoprolol vs placebo for acute myocardial infarction at up to 28 days‖

Outcomes	Metoprolol	Placebo	RRR (95% CI)	NNT (CI)
Composite endpoint¶	9.4%	9.9%	3.6% (–0.9 to 9.1)	Not significant
Death	7.7%	7.8%	0.9% (–4.6 to 7.4)	Not significant
Reinfarction	2.0%	2.5%	18% (7.8 to 28)	229 (147 to 517)
Ventricular fibrillation	2.5%	3.0%	17% (6.8 to 24)	199 (135 to 483)
			RRI (CI)	NNH (CI)
Other cardiac arrest	3.0%	2.8%	7.8% (–2.9 to 20)	Not significant
Cardiogenic shock	5.0%	3.9%	29% (18 to 39)	91 (67 to 143)
Composite endpoint¶ or shock	10.9%	10.8%	1.8% (–3.6 to 7.1)	Not significant

‖Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article.
¶Death, reinfarction, or cardiac arrest.

COMMENTARY

The metoprolol arm of COMMIT is an example of a so-called "negative" trial having a positive effect on clinical practice. Perhaps these results should not come as too much of a surprise. First, the bulk of the data concerning β-blocker use in AMI comes from the prefibrinolytic era. The largest trial from the "fibrinolytic era," comparing immediate IV followed by oral β-blockers versus deferred (6-d) oral β-blockers, also showed no effect on mortality at 6 weeks but did show a lower risk for recurrent infarction (1). Immediate β-blocker use was believed to be safe, but the trial was about one thirtieth the size of COMMIT and thus could have underestimated adverse consequences. Second, hemodynamic stability is probably at play. As a corollary, despite the benefit of angiotensin-converting enzyme (ACE) inhibitors in the setting of AMI, their early IV administration has been shown to mitigate this benefit. The Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS-II) showed that early IV followed by oral enalapril was associated with nonsignificantly higher mortality than placebo (2). Hypotension was significantly more common in the ACE-inhibitor group (12% vs 3%) and may have been the culprit. Similarly, hypotension induced by IV nitroglycerine can mitigate its favorable effect on left ventricular remodeling in AMI (3).

That the addition of clopidogrel to aspirin in the setting of ST-segment elevation AMI (STEMI) is modestly effective and safe comes as no surprise. Similar magnitudes of benefit (about 10 composite events per 1000 treated at 1 mo) were shown in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial among patients with acute coronary syndromes (4). A slightly larger, albeit not statistically significant, effect (18 events prevented per 1000 treated by 30 d) was seen in the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)–Thrombolysis in Myocardial Infarction (TIMI) 28 study among patients with STEMI treated with aspirin and fibrinolytics (5). COMMIT supports those results, but it should be noted that it was done against a background of a very low rate of invasive procedures. Can one apply the COMMIT results widely and, in particular, to locales where a more "invasive" approach is the norm? I believe one can. Observational substudies of CLARITY and CURE showed that a greater absolute benefit with clopidogrel was seen among patients having PCI (6, 7). Moreover, benefit was seen to emerge between randomization and PCI in both these studies.

Clopidogrel is expensive—will it have value for money? Using a back-of-the-envelope approach, I suspect it will. Consider that tissue plasminogen activator is regarded as cost-effective compared with streptokinase, based on 10 fewer deaths per 1000 treated (counterbalanced by 1 nonfatal but disabling and expensive-to-treat stroke) and a cost differential of about U.S. $2500. Based on COMMIT, clopidogrel use would result in 6 fewer deaths (and fewer recurrent AMIs and no excess strokes) per 1000 treated and a cost differential over a month of perhaps U.S. $100.

Routine early IV β-blocker use in STEMI is potentially hazardous and should be avoided. Consideration of routine oral β-blockers after the hemodynamics have stabilized is a more prudent approach. As most of the hazard occurs within the first day or so, it should be safe to initiate β-blockers after that period in response to symptoms of recurrent ischemia or for treatment of hypertension, ventricular ectopy, or congestive heart failure.

In the absence of bleeding concerns, clopidogrel should be given with aspirin in patients with STEMI whether the plan is to use fibrinolysis or to do direct PCI. I would use a 300-mg loading dose followed by 75 mg daily. While optimal duration of therapy is not known, I would continue clopidogrel for at least 9 to 12 months (4, 8).

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