THERAPEUTICS

Reviparin reduced a composite endpoint of death, reinfarction, stroke, and ischemia at 7 and 30 days after acute MI

Yusuf S, Mehta SR, Xie C, et al. **Effects of reviparin, a low-molecular-weight heparin, on mortality, reinfarction, and strokes in patients with acute myocardial infarction presenting with ST-segment elevation.** JAMA. 2005;293:427-36.

Clinical impact ratings: Hospitalists ★★★★★★☆ Cardiology ★★★★★☆☆ Critical Care ★★★★★★☆

QUESTION

In patients with acute myocardial infarction (MI), does the low-molecular-weight heparin (LMWH), reviparin reduce death, reinfarction, stroke, and recurrent ischemia better than placebo?

METHODS

Design: Randomized placebo-controlled trial with a partial 2×2 factorial design (Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation [CREATE]).

Allocation: {Concealed}†.*

Blinding: Blinded (clinicians, patients, {data collectors, and outcome assessors}†).*

Follow-up period: 30 days.

Setting: 274 centers in China and 67 centers in India.

Patients: 15 570 patients (mean age 59 y, 77% men) presenting with suspected acute MI and ST-segment elevation or new left bundle-branch block within 12 hours of symptom onset. Exclusion criteria included high risk for bleeding, recent major surgery or trauma, systolic blood pressure ≥ 180 mm Hg, severe anemia, hemorrhagic stroke within the past 12 months, oral anticoagulant therapy, heparin-induced thrombocytopenia, and pregnancy.

Intervention: Patients were stratified by center and allocated to reviparin, 3436 IU Ph Eur antiXa units (5153 IU in patients who weighed 50 to 75 kg and 6871 IU for > 75 kg) subcutaneously every 12 hours for 7 days (n = 7780), or placebo (n = 7790). Study drugs were started before or within 15 minutes of initiation of thrombolytic therapy.

Outcomes: A composite endpoint of 7-day death, reinfarction, and stroke; and the composite endpoint plus ischemia with electrocardiogram changes. Secondary outcomes were individual components of the composite endpoint, any ischemia within 7 days, and outcomes at 30 days.

Patient follow-up: 99.96% (intention-to-treat analysis).

MAIN RESULTS

The 2 composite endpoints occurred in fewer patients who received reviparin than in those who received placebo (Table). A reduction in the individual components of death and reinfarction also occurred with reviparin (Table). Groups did not differ for stroke (0.8% vs 0.6%, P = 0.26). Results were similar at 30 days (Table). Reviparin was associated with an early increase in life-threatening or major bleeding (Table).

CONCLUSION

In patients with acute myocardial infarction, reviparin reduced a composite endpoint of death, reinfarction, stroke, and ischemia and mortality alone at 7 and 30 days, but increased the risk for major bleeding.

Source of funding: No external funding.

For correspondence: Dr. S. Yusuf, Hamilton General Hospital and McMaster University, Hamilton, Ontario, Canada. E-mail yusuf@mcmaster.ca. ■

*See Glossary.

†Information provided by author.

Reviparin vs placebo for acute myocardial infarction‡

Outcomes	Follow-up	Reviparin	Placebo	RRR (95% CI)	NNT (CI)
Composite endpoint	7 d	9.6%	11%	13% (4.1 to 20)	73 (43 to 231)
	30 d	12%	14%	13% (5.2 to 20)	59 (37 to 149)
Composite endpoint + ischemia	7 d	11%	13%	12% (4.0 to 19)	67 (40 to 207)
	30 d	14%	16%	12% (4.5 to 18)	56 (35 to 147)
Death	7 d	8.0%	8.9%	11% (0.8 to 19)	107 (56 to 1548)
	30 d	9.8%	11%	13% (4.2 to 20)	71 (43 to 224)
Reinfarction	7 d	1.6%	2.1%	24% (4.2 to 40)	201 (109 to 1283)
	30 d	2.0%	2.6%	23% (4.6 to 37)	174 (96 to 926)
				RRI (CI)	NNH (CI)
Life-threatening or major bleeding	7 d	0.9%	0.4%	154% (65 to 291)	181 (123 to 323)

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

COMMENTARY

In the first GUSTO trial, no benefit was seen from intravenous (IV) heparin compared with subcutaneous unfractionated heparin in patients receiving streptokinase for ST-elevation MI (1). Other, much smaller studies have suggested benefit from IV unfractionated heparin with more fibrin-specific agents, such as acylated plasminogen-streptokinase activator complex and tissue plasminogen activator, with regard to such surrogate endpoints as patency. Until now, no megatrial appropriately powered to detect a difference in mortality has compared an LMWH (or unfractionated heparin) with placebo when administered with a fibrinolytic agent. The CREATE trial is the first to show that the LMWH reviparin is superior to placebo in terms of clinical endpoints when administered with any of several fibrinolytic agents.

The pharmacokinetic properties of several of the LMWHs differ substantially from one another. Therefore, it is unclear if the demonstrated benefits of reviparin would be seen with other LMWHs. Reviparin is not available in the United States. Physicians practicing where it is available ought to administer reviparin over placebo. Whether reviparin would outperform other LMWHs, or IV unfractionated heparin with fibrin-specific lytics, remains unknown.

The CREATE trial was a partial factorial design. The other intervention evaluated was GIK. A remarkable similarity exists between studies of GIK in patients with acute ST-elevation MI and those examining the effect of magnesium in acute MI. A meta-analysis of smaller trials of magnesium in acute MI suggested an impressive reduction in mortality (odds ratio 0.44, 95% CI 0.27 to 0.71) (2). However, the massive fourth International Study of Infarct Survival (ISIS-4) trial randomized 58 050 patients with acute MI to IV magnesium or no magnesium and did not show a reduction in 30-day mortality with magnesium therapy. In fact, there was a trend toward increased mortality with magnesium (P = 0.07) (3).

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A glucose-insulin-potassium infusion did not reduce mortality, cardiac arrest, or cardiogenic shock after acute MI

Mehta SR, Yusuf S, Diaz R, et al. **Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial.** JAMA. 2005;293:437-46.

Clinical impact ratings: Hospitalists ★★★★★☆☆ Cardiology ★★★★☆☆☆ Critical Care ★★★★★☆☆

QUESTION

In patients with acute myocardial infarction (MI), does an infusion of glucose-insulin-potassium (GIK) reduce death and cardiac outcomes better than usual care?

METHODS

Design: Randomized controlled trial with a partial 2×2 factorial design (Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation–Estudios Cardiologicas Latin American Study Group [CREATE-ECLA]).
Allocation: {Concealed}†.*
Blinding: Unblinded.*
Follow-up period: 30 days.
Setting: 470 centers worldwide.
Patients: 20 201 patients (mean age 59 y, 78% men) presenting with suspected acute MI and ST-segment elevation or new bundle-branch block within 12 hours of symptom onset. Exclusion criteria included type 1 diabetes, renal impairment, and hyperkalemia.
Intervention: Patients were stratified by center and allocated to an infusion of 25% glucose, 50 U/L of regular insulin, and 80 mEq/L of potassium at 1.5 mL/kg per hour for 24 hours in addition to usual care (n = 10 091), or usual care alone (n = 10 110).
Outcomes: 30-day all-cause mortality. Secondary outcomes were composite endpoints of death or nonfatal cardiac arrest, death or cardiogenic shock, and death or reinfarction; and individual components of the composite endpoints. The study had 99% power to detect a 20% relative risk reduction in mortality with GIK infusion.
Patient follow-up: 99.85% (intention-to-treat analysis).

MAIN RESULTS

The GIK infusion and usual care groups did not differ for all-cause mortality or for any secondary outcomes (Table).

CONCLUSION

In patients with acute myocardial infarction, an infusion of glucose-insulin-potassium in addition to usual care did not reduce mortality, cardiac arrest, or cardiogenic shock.

Source of funding: No external funding.

For correspondence: Dr. S.R. Mehta, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada. E-mail smehta@mcmaster.

*See Glossary.

†Information provided by author.

Glucose-insulin-potassium (GIK) infusion vs usual care for acute myocardial infarction at 30 days‡

Outcomes	GIK	Usual care	RRI (95% CI)	NNH
Death	10%	9.7%	3.1% (–5 to 12)	Not significant
Death or cardiogenic shock	12%	11.7%	2.7% (–4.7 to 11)	Not significant
Death or cardiac arrest	11.1%	11.0%	1.2% (–6.4 to 9.4)	Not significant
Death or reinfarction	11.7%	11.4%	2.4% (–5.2 to 10)	Not significant
Cardiogenic shock	6.6%	6.3%	4.4% (–6 to 16)	Not significant
			RRR (CI)	NNT
Cardiac arrest	1.4%	1.5%	7.8% (–16 to 27)	Not significant
Reinfarction	2.3%	2.4%	4.3% (–14 to 20)	Not significant

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

COMMENTARY

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The GIK story is similar to that of magnesium. A previous meta-analysis of 16 trials with a total of nearly 5000 acute MI patients showed an 18% mortality reduction with GIK therapy (4). However, the CREATE-ECLA trial, which enrolled 20 201 patients, failed to show any benefit with GIK. In the case of magnesium and GIK, the public was lucky. Neither magnesium nor GIK has been shown to be harmful (except for phlebitis in 3.9% from IV potassium). (Patients with kidney disease in whom magnesium might be harmful were excluded from the magnesium trials; those with kidney disease and hyperkalemia in whom GIK might be harmful were excluded from GIK trials). However, an unknown but undoubtedly large number of other therapies are routinely administered to patients on the basis of underpowered randomized trials or even less reliable observational studies and anecdotal experience. Therefore, perhaps the most important lesson from CREATE-ECLA is that well designed, appropriately powered trials are needed to confirm benefit and identify the true risks associated with therapies. When we consider the recent example of hormone replacement therapy (5), it is quite likely that some therapies currently administered to untold numbers of patients on a daily basis are not only not beneficial, but are less innocuous than magnesium and GIK.

Peter B. Berger, MD
Duke Clinical Research Institute
Durham, North Carolina, USA

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