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Ranolazine: a new antiarrhythmic agent for patients with non-ST-segment elevation acute coronary syndromes?

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SYNOPSIS

BACKGROUND—Ranolazine is a novel antianginal agent that has also been shown to have electrophysiological properties in laboratory models. This is the first clinical evaluation of the antiarrythmic effects of ranolazine.

OBJECTIVE—To compare the incidence of cardiac arrhythmias in patients with non-ST-segment elevation acute coronary syndromes (NSTE ACS) receiving ranolazine with that in patients receiving placebo.

DESIGN AND INTERVENTION—This was a subanalysis of the international, randomized, double-blind, placebo-controlled MERLIN-TIMI 36 trial, which was conducted from 8 October 2004 to 24 May 2006. Patients with NSTE ACS and at moderate to high cardiovascular risk were enrolled within 48 h of their last ischemic symptoms. A detailed description of the inclusion and exclusion criteria has previously been published. Patients were randomized to receive ranolazine (intravenous followed by oral administration) or matching placebo, alongside standard medication and interventional therapy. All patients underwent continuous electro cardiographic (cECG; Holter) monitoring for the first 7 days after randomization.

OUTCOME MEASURE—The primary end point was the incidence of clinically significant arrhythmia (supraventricular tachycardia >120 beats per min lasting at least four beats, ventricular tachycardia of at least three beats, ventricular pause >2.5 s, new-onset atrial fibrillation [AF], or complete heart block).

RESULTS—A total of 6,560 patients were enrolled in the trial, of whom 6,351 (97%) had interpretable cECG recordings (ranolazine = 3,162; placebo = 3,189). The baseline characteristics were similar in both groups. The mean age was 63 years and around a third of patients were female. Approximately 4% of patients in each group had a prior ventricular arrhythmia, approximately 34% in each had a prior myocardial infarction, and the majority of patients had a Thrombolysis in Myocardial Infarction (TIMI) risk score of 3−4. The median time from symptom onset to randomization was 23.9 h in the ranolazine group and 23.3 h in the placebo group. Overall, the mean duration of cECG monitoring was 6.8 days, after which time significantly fewer patients in the ranolazine group than in the placebo group had experienced ventricular tachycardia lasting for more than three (52.1% vs 60.6%, risk ratio [RR] 0.86, 95% CI 0.82−0.90; P <0.001), four (20.9% vs 29.5%, RR 0.71, 95% CI 0.60−0.78; P <0.001), or eight (5.3% vs 8.3%, RR 0.63, 95% CI 0.52−0.76;

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Competing interests The author has declared associations with the following companies: AstraZeneca, Cardiome, and CV Therapeutics. See the article online for full details of the relationships.

PRACTICE POINT Ranolazine could offer a new approach to the management of atrial and ventricular arrhythmias, particularly in patients at moderate-to-high cardiovascular risk

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P <0.001) beats. Similarly, ranolazine was associated with a lower incidence of supraventricular tachycardias than was placebo (44.7% vs 55.0%, RR 0.81, 95% CI 0.77−0.85; *P* <0.001). There were only two cases of torsade de pointes, one in each group. There was also a trend towards a lower rate of new-onset AF in the ranolazine group, although the difference was not significant (*P* = 0.08).

CONCLUSION—Ranolazine is associated with reduced incidences of ventricular and supraventricular arrhythmia in moderate-to-high-risk patients with NSTE ACS.

Keywords

acute coronary syndromes; arrhythmia; ischemia; myocardial infarction; ranolazine

COMMENTARY

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The MERLIN-TIMI 36 study evaluated the efficacy and safety of ranolazine during long-term treatment of patients with NSTE ACS. The study, which included cECG monitoring of 6,351 patients and led to the creation of one of the largest known Holter databases to date, concluded that ranolazine is not associated with increased incidence of all-cause mortality, sudden cardiac death, or clinically significant arrhythmias. In addition to demonstrating the safety of ranolazine, the paper by Scirica *et al*. reported that patients treated with this drug had significantly lower incidence of ventricular and supraventricular tachycardia. The incidence of new-onset AF was approximately 30% lower in ranolazine-treated patients, just missing statistical significance. Notably, patients at high risk for arrhythmic events also benefited from ranolazine treatment, with a 47−49% reduction in the relative risk of developing ventricular tachycardia of eight beats or more (*P* <0.01). This subgroup also showed a trend towards decreased sudden cardiac death at 12 months (2.7% vs 4.9%, hazard ratio 0.49; *P* = 0.07).

The antiarrhythmic effects of ranolazine revealed in the MERLIN-TIMI 36 trial corroborate the results of previously reported preclinical studies. In the ventricle, ranolazine has been shown to most potently inhibit both the late sodium current (late INa) and the rapidly activating delayed rectifier potassium current (IKr), producing opposing effects on action potential duration and resulting in a modest increase in the rate-corrected QT interval.[1] The potent inhibitory effect of ranolazine on late INa is capable of suppressing arrhythmogenesis induced by IKr blockers and other QT-prolonging agents.[1] The late-INa-blocking action of ranolazine is thought to underlie the drug's capacity to suppress early after-depolarization-induced triggered activity as well as its action of reducing transmural dispersion of repolarization, and it is also likely to be responsible for the antiarrhythmic effects of ranolazine in the ventricle. These observations provide further evidence to support the hypothesis that agents with IKr-blocking activity, even when associated with some degree of QT prolongation, might lack proarrhythmic proclivity and in fact demonstrate antiarrhythmic efficacy owing to their additional inhibitory effect on late INa.

In experimental models, ranolazine has been shown to produce a profound rate-dependent reduction of peak INa in the atrium and, thereby, to suppress AF.[2] The atrial-selective capacity of ranolazine to inhibit peak INa seems to result in part from the fact that steady-state inactivation of the sodium channels is shifted to more negative potentials in atrial than in ventricular cells. These findings are consistent with the significant reduction in supraventricular tachycardia and impressive, although nonsignificant, reduction in new-onset AF observed in MERLIN-TIMI 36.

Both preclinical and clinical data, therefore, provide compelling evidence in support of an antiarrhythmic action of ranolazine and indicate that studies evaluating the potential role of ranolazine as an antiarrhythmic are warranted. Ranolazine's unique interaction with the sodium

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channel and its proven safety profile make it a promising candidate for further evaluation in the management of arrhythmias, including AF and excessive implantable cardioverter-defibrillator shocks. Ranolazine may provide a safe alternative to currently available antiarrhythmic drugs, which are associated with clinically significant adverse effects and are contraindicated in specific populations.[3,4]

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