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Impact of Bisoprolol on Ventricular Arrhythmias in Experimental Myocardial Infarction

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Following acute myocardial infarction (AMI), early use of beta-blockers (BBs) reduced the incidences of ventricular arrhythmia (VA) and death in the pre reperfusion era. However, some studies have reported a worsening of clinical outcomes and therefore, this study used a porcine model of AMI to evaluate the efficacy of bisoprolol on VAs and mortality. Twenty pigs were divided into two groups with one group using oral bisoprolol which was given for 3 hours before the experiment and then maintained for 7 days. A loop recorder was implanted, AMI was induced by balloon occlusion for 60 min, and then, reperfusion. One week later, the echocardiography and loop recorder data were analyzed in the surviving animals. Bisoprolol did not increase the heart rate (62.9±14.5 vs 79.0±20.3; p=0.048), lower the rate of premature ventricular contractions (PVC) (0.8±0.8 vs 11.0±12.8; p=0.021) or tend to lower recurrent VA (0.6±0.5 vs 1.1±1.1; p=0.131) during coronary artery occlusion. After reperfusion, bisoprolol did reduce VA in the early AMI period (0.1±0.3 vs 4.2±4.6; p=0.001) and it was not associated with the extent of myocardial recovery. In this porcine model, early oral bisoprolol might help reduce the incidences of PVC and recurrent VA and determine whether effects are more pronounced during the early AMI period. Our results suggest that bisoprolol might help reduce lethal VA and cardiac death following AMI in this reperfusion era.

Key Words: *Myocardial Infarction; Cardiac Arrhythmia; Adrenergic beta-Antagonists*

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INTRODUCTION

Early use of beta-blockers (BBs) after acute myocardial infarction (AMI) has been found to reduce the incidence of ventricular arrhythmia (VA) and mortality, and their oral use within 24 hours is recommended for patients with myocardial infarction (MI).[1,2] However, most of these studies were conducted in the pre-reperfusion era, before the introduction and use of renin–angiotensin–aldosterone system blockers, statins, and new antiplatelet agents. Although several observations have confirmed the beneficial clinical effects of early beta blockade after MI following primary angioplasty,[3-5] the role of BBs in the treatment of AMI remains controversial. Moreover, in two recent studies, the early use of BBs in patients with AMI undergoing primary angioplasty was associated a deterioration of clinical outcomes.[6,7] Additionally, one study found that prior use of BBs increased inpatient mortality and should be considered a high-risk marker for AMI.[8]

Bisoprolol is a beta 1-selective adrenoceptor antagonist, which has been widely used after AMI. However, there have been few studies comparing the use of bisoprolol and other BBs in patients with AMI. During the early stages of AMI, VA is a frequent cause of cardiac-related mortality, which often occurs within minutes after the onset of clinical symptoms, and occasionally even before the patient has established contact with a medical health care system. Since out-of-hospital VA following AMI is sudden and unexpected, there is relatively little information on this available from clinical studies. The study of VA following AMI in humans is challenging, therefore, our study was designed to evaluate the effect on VA and mortality, of an early treatment with oral bisoprolol after AMI, in a porcine model.

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MATERIALS AND METHODS

1. Animal preparation

Twenty Yorkshire Landrace F1 crossbred castrated boars weighing 25-30 kg each were exposed to daily premedication with aspirin and clopidogrel for 5 days before any surgical procedure (The protocol is described in Fig. 1). The pigs were divided into two groups (n=10 each): BB treated and control. Bisoprolol fumarate (Concor®, Merck Ltd.) 100 mg/kg was administered orally in the BB group 3 h before the experiment and maintained for 7 days afterwards.

2. Loop recorder implantation

After anesthesia, a loop recorder (Confirm®, St. Jude Medical, Inc., USA) was implanted subcutaneously and programmed for the detection of cardiac arrhythmias and death. The basic requirements were an R-wave amplitude of at least 0.3 mV and a peak-to-peak R-wave amplitude at least twice the peak T- and P-wave amplitudes.

3. Two-dimensional (2-D) echocardiography

2-D echocardiography was performed in all pigs before the procedure, and 1 week after. The left ventricular (LV) ejection fraction (LVEF) and LV volumes (LV end-systolic volume and LV end-diastolic volume) were measured using a modified biplane method in 2- and 4-chamber views.

4. Induction of AMI

Firstly, baseline coronary angiogram via the left carotid artery sheath was obtained and then AMI was induced by balloon inflation (8 atm) in the middle left anterior descending coronary artery (LAD) just distal to the first diagonal branch for 60 minutes. The balloon size was adjusted to the coronary vessel size with reference to the 7-Fr guiding catheter diameter (2.31 mm). Continuous electrocardiographic monitoring was performed to detect cardiac arrhythmias. All VAs were terminated by DC cardioversion and defibrillation (Biphasic 200J). Each animal was observed carefully for 60 minutes and then returned to the holding facility and monitored until recovery.

5. Follow-up angiogram, echocardiography, and pathology

One week later, animals underwent follow-up 2-D transthoracic echocardiography and coronary angiography in the same orthogonal views to determine vessel patency. At the end of the experiment, pigs were anesthetized and euthanized with an overdose of potassium chloride. Hearts were extracted and 1-cm sections were made using a microtome. Sections were then immersed in 2,3,5-triphenyltetrazolium chloride (TTC) solution and infarct size (% LV area) was measured from digital photographs of TTC-stained sections, by outlining LV areas and TTC negative infarcted areas. Next macroscopic and microscopic examinations were performed to evaluate changes in ischemia. After a gross examination, the extracted hearts were fixed with 10% formalin and embedded in paraffin to create a formalin-fixed, paraffin-embedded (FFPE) block. The FFPE was cut using a microtome to generate thin sections of tissue (2 mm) and stained with hematoxylin and eosin, or used for immunohistochemical staining, or Masson's trichrome staining. Finally, we confirmed ischemic changes such as necrosis, inflammation, and fibrosis using a light microscope.

6. Analysis of loop recorder data

Each stored episode in the explanted loop recorder was interpreted by two cardiologists blinded to the experimental groups. Arrhythmic events were automatically stored according to the following criteria: sinus arrest as a pause $\geq$3 seconds, ventricular tachycardia (VT) as a heart rate $\geq$200 bpm and sustained VT as lasting $\geq$30 seconds.[9] The QRS complex that interrupts the T wave of the preceding beat was defined as an R on T arrhythmic beat. Premature ventricular complexes (PVCs) were counted in 300 consecutive heart beats immediately preceding VA. VAs during AMI and are typically classified based upon their onset time: acute phase (within 1 hour) or early period (1 hour to 1 week).[10]

7. Statistical analysis

All data was expressed as the mean±standard deviation. Statistical analyses were performed using SPSS statistics (version 21.0; IBM Corp., Armonk, NY, USA). Comparisons between the two groups were analyzed by Mann–Whitney nonparametric U tests for continuous variables, and Fisher's exact tests for categorical variables as appropriate. p-values of <0.05 were considered to be statistically significant. Interobserver differences were analyzed using Kappa statistics to determine consistency among the raters and that there were no inter-observer differences when interpreting events [Kappa 0.943 (p<0.001), 95% CI (0.933,0.952)]. Arrhythmic episodes during the follow up period were evaluated using a Poisson regression model.

8. Ethical statement

This animal study was approved by the Ethics Commit-

1. Premedication of aspirin, clopidogrel, bisoprolol 100 μg/kg (only BB group)
2. Anesthesia/implantation of loop recorder, EGM recording
3. Induction of acute myocardial infarction, EGM recording
4. Monitor for spontaneous arrhythmias for 1 hour, EGM recording
5. Aspirin, clopidogrel, bisoprolol 100 μg/kg (only BB group) medication for 1 week
6. Follow-up coronary angiogram, EGM recording
   Heart extraction, measurement of myocardial infarct size, analysis of loop recorder

FIG. 1. Schematic representing the study protocol.

tee of Chonnam National University Medical School and Hospital, South Korea (CNU IACUC-H-2013-18) and conformed to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

RESULTS

1. ILR data analysis

ILR data and analysis are listed in Table 1 and the mean R-wave amplitude was 0.67±0.24 mV. There were no complications during implantation of the ILRs.

1) Ventricular arrhythmia in the acute phase (≤1 hour): Eighteen episodes of ventricular fibrillation (VF) occurred during the 60 minutes of coronary artery occlusion and no differences were seen in the total number of pigs developing VF between the two groups (six in each). There were no differences in the time to VF occurrence between the two groups (37.3±10.0 min in the BB vs 40.0±6.1 min in the control; p=0.747; Table 1). However, the total number of episodes of VF tended to be lower in the BB group (0.6±0.5 in the BB vs 1.1±1.1 in controls, p=0.131) and all VF episodes could be terminated by defibrillation (Biphasic 200 J).

2) Frequency of PVCs in the acute phase (≤1 hour): Before coronary occlusion, there were close to zero PVCs. Immediately preceding the onset of VF however, the frequency of PVCs increased in both groups but were significantly lower in the BB group (0.8±0.8 in the BB vs 11.0±12.8 in the control; p=0.021) (Table 1). All VFs were triggered by PVCs (R on T arrhythmic beat, Fig. 2).

3) Heart rate during the experiment: The mean baseline heart rate was 68.5±12.7 bpm with no differences seen between the two groups (68.0±10.3 bpm in the BB vs 69.0±15.2 bpm in the control; p=0.968). In the BB group, the heart rate was not found to be increased following AMI when compared to the control group (62.9±14.5 bpm in the BB vs 79.0±20.3 in the control; p=0.048, Fig. 3) and heart rates returned to baseline in all surviving pigs after 1 week.

4) Ventricular arrhythmia in the early period (1 hour to 1 week): Seven of the pigs died during follow up. VF occurred within 24 hours after infarction in all pigs, as assessed by the ILR data and the incidence of VF was lower in the BB group in the early period (two in the BB vs five

TABLE 1. Ventricular arrhythmias after AMI

	BB (n=10)	Control (n=10)	p value
Acute phase (<1 hour)			
Total number of pigs developed VF	6 (60%)	6 (60%)	1.000
PVC (%)	0.8±0.8	11.0±12.8	0.021
Total number of VF (<1 hour)	0.6±0.5	1.1±1.1	0.131
VF onset time after AMI (minutes)	37.3±10.0	40.0±6.1	0.747
Early period (1 hour-1 week)			
Total number of VF (>1 hour)	2 (20%)	5 (50%)	0.170
Total number of NSVT	0.13±0.35	4.20±4.65	0.001
Total number of sustained VT	0	1.2±1.09	0.001

AMI: acute myocardial infarction, NSVT: non sustained ventricular tachycardia, BB: beta blocker, PVC: premature ventricular complex, VA: ventricular arrhythmia, VF: ventricular fibrillation, VT: ventricular tachycardia.

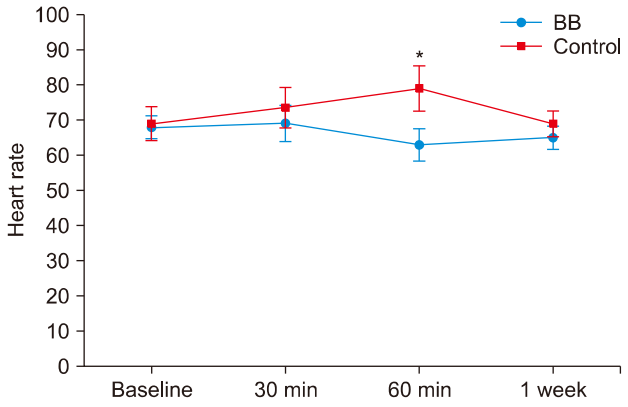

FIG. 3. Heart rate (HR) during the experiment. In the beta-blocker (BB) group, HR was not increased following acute myocardial infarction when compared to the control group (62.9±14.5 bpm in the BB vs 79.0±20.3 in the control; *p=0.048). HR returned to baseline in all surviving pigs after 1 week.

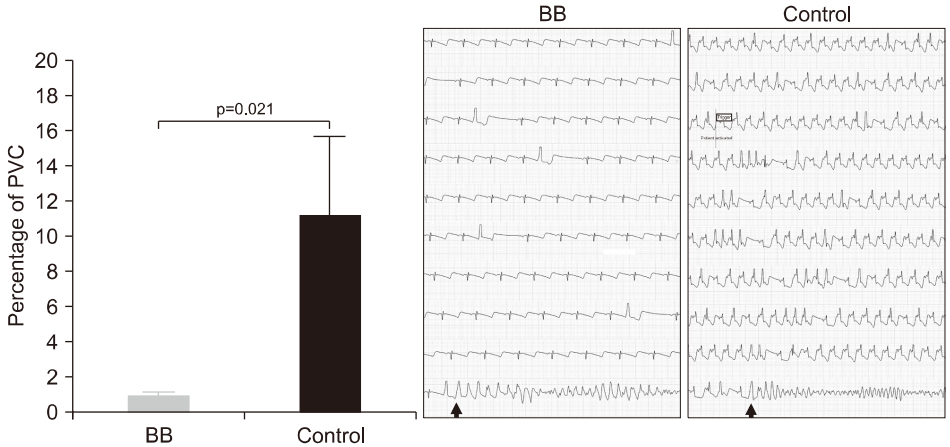

FIG. 2. Effects of the beta-blocker (BB) on the occurrence of spontaneous premature ventricular contractions (PVCs) following acute myocardial infarction. PVC occurred less in the BB group. PVC triggered ventricular fibrillation (black arrow).

in the control; p=0.170). Six pigs had sustained ventricular tachycardia (VT) (monomorphic) in the control group. In addition, the total number of non-sustained VT was lower in the BB group (0.1±0.3 in the BB vs 4.2±4.6 in the control; p=0.001; Table 1).

2. Two-dimensional echocardiography results

There were no differences in LV function or volumes at baseline between the two groups (Table 2). At 1 week, the LV ejection fraction (%) was significantly lower, but there was no significant difference (38.2±5.6 in the BB vs 36.9±5.7 in the control; p=0.700).

TABLE 2. Two dimensional echocardiography results

	BB (n=10)	Control (n=10)	p value
Baseline			
LVEF (%)	59.3±2.9	58.3±5.7	0.405
LVEDV index (ml/m^2)	56.5±7.1	56.2±7.8	0.925
LVESV index (ml/m^2)	24.9±2.5	24.3±2.5	0.604
	BB (n=8)	Control (n=5)	p value
1 week			
LVEF (%)	38.2±5.6	36.9±5.7	0.700
LVEDV index (ml/m^2)	67.8±8.7	62.2±6.90	0.231
LVESV index (ml/m^2)	45.0±5.1	41.9±4.78	0.292

AMI: acute myocardial infarction, LVEDV: left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction, LVESV: left ventricular end-systolic volume.

3 Histopathology

TTC staining clearly demonstrated infarction localized at the cardiac apex and left ventricular septal wall, and these extracted heart tissues showed ischemic injury under both macroscopic and microscopic examination (Fig. 4). The hearts from the 13 surviving pigs showed no significant difference between the two groups in myocardial mass of the ischemic area (% LV area) (16.2±4.4 in the BB vs 13.8±5.3 in the control; p=0.286).

DISCUSSION

This study raises important clinical conceptual questions, as to whether bisoprolol can reduce premature ventricular contractions and recurrent VA during occlusion and reperfusion of the coronary artery. Our results suggest that bisoprolol might help reduce lethal VA regardless of the coronary artery reperfusion status and myocardial protection status and whether effects are more pronounced during the early AMI period.

VA remains the major cause of mortality in patients suffering from AMI[11] and prompt revascularization and phar-

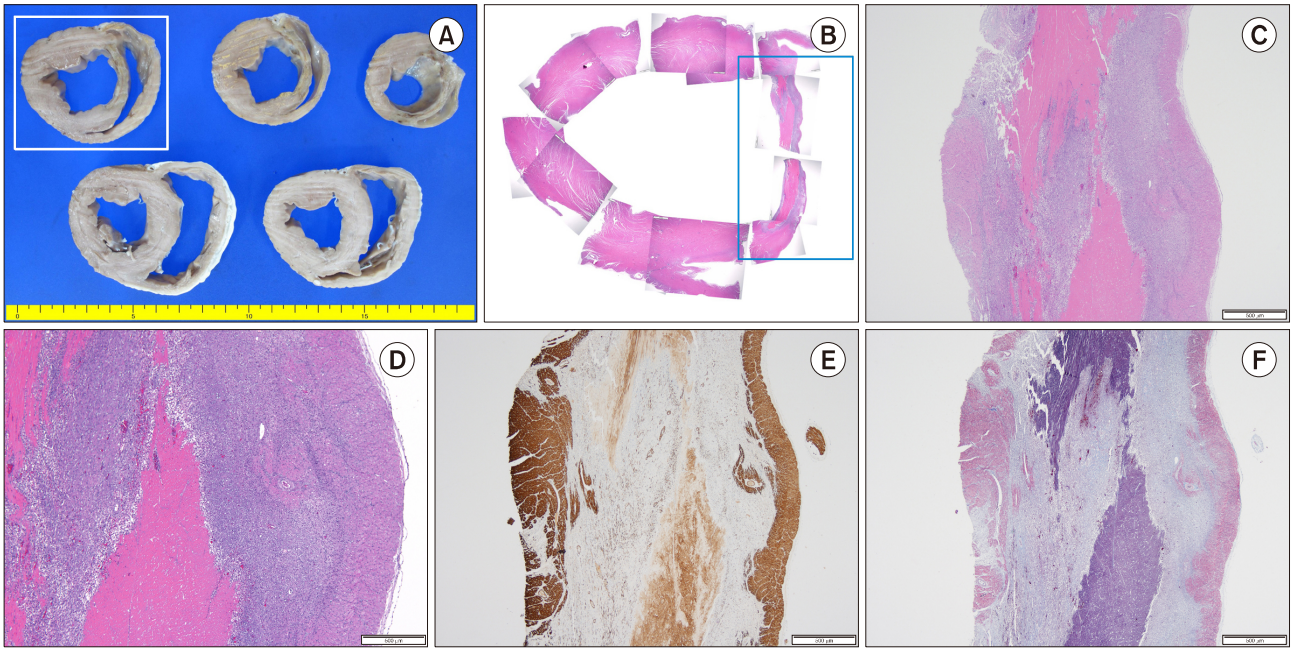

FIG. 4. Macroscopic and microscopic examination of the representative infarcted heart. (A) Macroscopic examination revealed a fibrotic and hemorrhagic lesion, and wall thinning in the apex and anterior portion of the left ventricular free wall and interventricular septum. (B) Microscopic examination of representative section showed an ischemic lesion and a wall thinning in the interventricular septum (H&E, mag ×12.5). (C) The infarcted myocardium was noted in the interventricular septum and the myocardium which was relatively free from infarction, was also noted in both sides of the endocardium (H&E, mag ×20). (D) Cardiomyocyte coagulation necrosis with loss of nuclei, cytoplasmic hypereosinophilia; neutrophilic infiltration; phagocytosis of cardiomyocyte debris; granulation tissue formation, and early fibrotic change was also noted (H&E, mag ×40). (E) Viable cardiomyocytes in both sides of the endocardium showed positivity to the immunohistochemical stain for desmin (mag ×20). (F) An early fibrotic change was also noted in the middle portion of the interventricular septum (Masson's trichrome stain, mag ×20).

macologic therapies, including antiplatelet agents, statins, angiotensin-converting enzyme (ACE) inhibitors and BBs, have markedly decreased the incidence of VA.[12-14] In the 1980s, up to early 2000s, BBs were the most important and effective agents used to combat MI. They were used effectively in patients with AMI, to reduce major cardiac events such as sudden cardiac death.[3] In a recent meta-analysis study, BBs reduced all-causes of mortality in patients with AMI undergoing percutaneous coronary intervention[15] and it was beneficial to give BBs to patients who do not have a contraindication, such as hemodynamic instability after AMI.[1] Thus, current guidelines recommend the use of oral BBs within the first 24 hours in patients with AMI. Although BBs are recommended as a standard medical treatment after AMI, most studies supporting their use were conducted in the pre-reperfusion era. There have been mixed results regarding the impact of BBs on mortality rates following AMI, for example in the ClOpidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), studies found BBs were effective during early oral administration, in particular metoprolol, in more than 4,000 patients with MI, and with fibrinolysis in approximately half of them.[16] Metoprolol decreased the incidence of MI and VA but increased the frequency of cardiac shock. A meta-analysis published in 2014 listed 60 trials involving 102,003 patients, with cases stratified into pre-perfusion and reperfusion eras found that BBs lost their beneficial effects on the reduction of mortality after AMI in the reperfusion era.[17]

Among the different types of BBs in use, bisoprolol represents a beta 1-selective adrenoceptor antagonist, which is devoid of intrinsic sympathomimetic activity. It is a lipophilic drug (like carvedilol and metoprolol), which is beneficial in all causes of mortality when compared with hydrophilic BBs (e.g., atenolol and nadolol).[18] It can improve the perfusion of the ischemic myocardium and prevent VA.[19] However, there have been few studies looking at the use of bisoprolol in patients with AMI, whereas other BBs (such as carvediol and metoprolol) have already been proven to be effective following AMI in a randomized controlled trial.[20,21]

In our experiment, bisoprolol was shown to be ineffective at preventing VA, but this is not surprising as most beta-adrenoceptor antagonists, including propranolol and sotalol, fail to prevent VA after ligation of the coronary artery when used in a similar model to ours.[22,23] With complete vascular occlusion, the differences in perfusion of the normal and the acutely ischemic myocardium, and in perfusion of the different layers of the ischemic segment, are not affected by pharmacological agents.[24] These results are consistent with other studies whereby prior BB use was not associated with inpatient mortality following AMI because they were ineffective in the prevention of VA, which is the major cause of mortality in patients suffering AMI.[8]

In our study, VF occurred 18 times within the first hour during coronary artery occlusion and bisoprolol significantly reduced the occurrence of spontaneous PVCs and recurrent VA after reperfusion. The use of BBs has been found to increase the VF threshold in some studies[25] and can also decrease heart rate, prolonging diastole and improving coronary diastolic perfusion and reduced afterdepolarizations and triggered activity. After balloon induced deflection and revascularization of myocardial flow, these flow differences between the various myocardial areas were attenuated, and bisoprolol reduced the incidence of fatal VA. Furthermore, it decreased the frequency of VAs (VF, non-sustained or sustained VT) for 1 week. Finally, it also decreased VA following AMI which was more pronounced in the hours and days after the AMI.

Our study however, failed to show the ability of bisoprolol to decrease MI size during a 1-week follow up period. Some preclinical studies have suggested that BBs can decrease the myocardial infarct size, whereas others have shown no effect.[22,26,27] In one experiment, early intravenous metoprolol treatment during acute coronary occlusion increased myocardial salvage as assessed by cardiac magnetic resonance imaging (MRI) in a porcine model.[28] Our experiment differed from that study because of our relatively short follow-up period (1 week), and methods used to assess cardiac status (2-D echocardiography, not MRI), as well as the lack of a comedication such as amiodarone.

1. Study limitations

This study presented with various limitations, firstly, the small sample size could bias the results when using some of statistical tests. Secondly, the use of ILR for recording arrhythmias has several limitations in recording arrhythmias, some related to inherent limitations on the detection channel and others related to the prespecified arrhythmia detection criteria. It is therefore possible that other important forms of arrhythmia were missed because of these inherent limitations and restricted memory. In particular, there are differences between surface ECG and eletrocardiogram measurements recorded by ILR, as well as different filter settings and different positions of the lead axis, which represents a potential source of bias. Thirdly, the experiment was designed to occlude the middle LAD instead of the proximal LAD, which is of greater prognostic significance. Since occlusion in the proximal LAD induced high mortality cardiogenic shock (pump failure), it was difficult to determine the effect of bisoprolol on arrhythmia. Fourthly, we did not administer statins as part of the premedication as these have an antiarrhythmic effect independent of their lipid-lowering capacity, and therefore, they could have a confounding effect when looking at bisoprolol effects on arrhythmias. Finally, there are no non-invasive methods available for serial blood pressure measurements in pigs and therefore, we were unable to determine the optimal tolerable doses of bisoprolol which would give a beneficial effect after experimental AMI. This may affect both positive and negative outcomes of the study.

2. Conclusions

In this porcine model, early oral bisoprolol might help reduce the incidences of PVC and recurrent VA irrespective

of coronary artery reperfusion status and myocardial salvage status and determine whether effects are more pronounced during the early AMI period. Our results suggest that bisoprolol might help reduce lethal VA and cardiac death following AMI in this reperfusion era.

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CONFLICT OF INTEREST STATEMENT

None declared.

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