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Relation of Pre-Event Use of Inhibitors of the Renin-Angiotensin System With Myocardial Infarct Size in Patients Presenting With a First ST-Segment Elevation Myocardial Infarction

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Agents that block the renin-angiotensin system (RAS), including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, are of proven benefit in patients after ST-segment elevation myocardial infarction (STEMI). However, no studies have evaluated the benefit of pre-event use of RAS inhibitors before STEMI. A retrospective review was performed of patients admitted to a single hospital with the diagnosis of STEMI and without a history of coronary disease or the equivalent, including diabetes mellitus, peripheral vascular disease, or stroke. Patients were stratified according to the use of RAS inhibitors before STEMI. Compared to patients not taking RAS inhibitors, patients who were taking RAS inhibitors had a lower peak troponin I level (79 vs 120 ng/dl, $p = 0.016$). Of the patients who had medically treated hypertension, those receiving RAS inhibitors had a significantly lower peak troponin I compared to those receiving non-RAS agents (79 vs 130 ng/dl, $p = 0.015$), despite equivalent blood pressure across the 2 groups. The beneficial effect of RAS inhibitor pretreatment remained when concomitant aspirin and statin use were controlled for. In conclusion, in patients presenting with a first STEMI, pretreatment with RAS inhibitors conferred a cardioprotective effect. The mechanism of this benefit appears to be independent of an effect on blood pressure control and was not wholly due to the effect of concomitant use of other medicines known to be protective in patients with STEMI. **(Am J Cardiol 2010;106:646–649)**

In the present study, we examined the protective effect of pretreatment with inhibitors of the renin-angiotensin system (RAS) on myocardial injury in the setting of a first ST-segment elevation myocardial infarction (STEMI) in patients without history of coronary artery disease (CAD) or the equivalent.

Methods

A retrospective review was performed using a computerized database of all patients admitted from January 2004 to April 2008 to Lehigh Valley Hospital (Allentown, Pennsylvania) with the diagnosis of STEMI. Patients included in the present review were those who had no history of coronary, cerebral, or peripheral vascular disease according to either clinical events or abnormal diagnostic test results. Additionally, the patients with a history of diabetes mellitus were not included in the present study. Patients with a pre-event history of angina were included if the diagnosis of CAD was not confirmed by diagnostic testing. All patients in the study underwent diagnostic cardiac catheterization within 4 hours of presentation or transfer to the study center. Data, including baseline characteristics, medical history, medicine use, admission laboratory study results, and hospital course, were extracted from an electronic medical record database.

The coronary anatomy and degree of stenosis were determined by the catheterizing physician with ≥2 views of each coronary artery. A coronary artery was defined as diseased if the major epicardial vessel or any major branches had >50% stenosis. The left ventricular ejection fraction was assessed qualitatively at cardiac catheterization by ventriculography in 2 planes. The serum lipid levels were assessed within 48 hours of admission, with the patient in a fasting state. The cardiac troponin I (TnI) levels were measured immediately on presentation and at 6 and 24 hours after admission. The patients were included in the RAS group if they had been treated with either angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers for ≥1 week before the index STEMI.

The baseline and end point analyses were performed with unpaired *t* tests for continuous data and chi-square tests for categorical data using the SigmaStat software (SYSTAT Software, San Jose, California). The institutional review board of the Lehigh Valley Health Network approved the study.

Results

A total of 511 patients met the criteria for inclusion in the present study. Of the total population, 266 were men (53%). The average patient age was 60 years (range 31 to 97). A total of 196 (36%) had a family history positive for premature CAD, and 267 (53%) were smokers. Of the 158 patients (31%) with a diagnosis of hypertension, 66 (13%) were taking RAS inhibitors (35 taking ACEIs and 31 taking angiotensin receptor blockers).

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Table 1
Patient characteristics stratified by renin-angiotensin system (RAS) inhibitor pretreatment status

Characteristic	RAS Use		p Value
	Yes (n = 66)	No (n = 445)	
Men	37 (56%)	229 (52%)	0.60
Age (years)	62.3	59.2	0.05
Hypertension	66 (100%)	90 (20%)	<0.001
Current smoker	26 (39%)	241 (54%)	0.02
Family history	24 (36%)	172 (38%)	0.79
Statin use	17 (25%)	68 (15%)	0.028
Aspirin use	39 (59%)	18 (4%)	<0.05
Systolic blood pressure (mm Hg)	124	130	0.22
Diastolic blood pressure (mm Hg)	69	77	0.32
Total cholesterol (mg/dl)	179.6	173.7	0.43
Low-density lipoprotein (mg/dl)	115.4	112.1	0.73
High-density lipoprotein (mg/dl)	37.9	37.2	0.60
Triglycerides (mg/dl)	173.0	149.5	0.10
Serum creatinine (mg/dl)	1.02	0.96	0.33

Table 2
Angiographic and outcome data stratified by renin angiotensin system (RAS) pretreatment status

Variable	RAS Use		p Value
	Yes (n = 66)	No (n = 445)	
Infarct location			
Anterior	36 (54%)	117 (26%)	0.02
Lateral	11 (16%)	86 (19%)	0.68
Inferior	28 (42%)	247 (55%)	0.07
Posterior	4 (6%)	40 (9%)	0.57
No. of diseased vessels			
1 Vessel disease	26 (39%)	181 (41%)	0.53
2 Vessel disease	22 (33%)	154 (34%)	
3 Vessel disease	19 (28%)	106 (24%)	
Left main	2 (3%)	35 (8%)	0.23
Need for coronary artery bypass grafting	5 (7%)	45 (10%)	0.58
In-hospital death	3 (4%)	3 (1%)	0.17
Vasopressor use	7 (10%)	59 (13%)	0.63
Ventricular tachycardia/ventricular fibrillation	12 (18%)	91 (20%)	0.37

When the cohort was stratified by pretreatment with RAS inhibitors (Table 1), the 2 groups were similar in terms of age, gender, and a family history of CAD. Fewer patients smoked in the RAS group than in the non-RAS group. In contrast, as would be expected, a significantly greater percentage of patients had hypertension in the RAS inhibitor group than the non-RAS inhibitor group. The use of both aspirin and statins was more common in patients receiving RAS inhibitors than in the remainder of the cohort. Compared to patients treated with non-RAS inhibitors, the patients receiving RAS inhibitors had lower systolic and diastolic blood pressures. However, neither of these reached statistical significance.

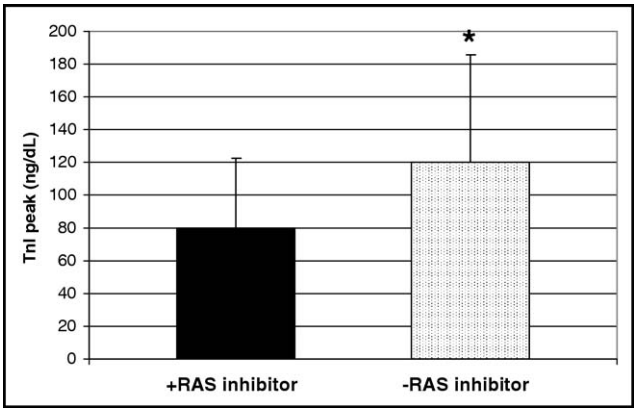

Figure 1. Peak TnI level in patients pretreated and not pretreated with RAS inhibitor. *p = 0.016.

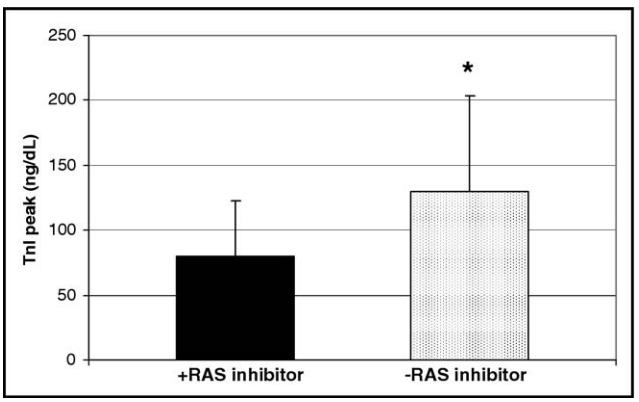

Figure 2. Peak TnI level in patients with medically treated hypertension, stratified by RAS inhibitor pretreatment. *p = 0.003.

The geographic infarct location, coronary disease burden, and STEMI-related complications were compared between the RAS and non-RAS pretreated patients (Table 2). Significantly more patients who had been pretreated with RAS inhibitors were found to have anterior myocardial infarction (54% vs 26%, p = 0.02); otherwise the number of diseased vessels, the incidence of left main CAD, the need for urgent coronary artery bypass grafting, and vasopressor use did not differ between the 2 groups. Likewise, the occurrence of ventricular tachycardia/fibrillation and death did not differ between the 2 groups.

The degree of myonecrosis due to the index STEMI was assessed for the RAS inhibitor pretreated and nonpretreated patients, as defined by the peak TnI (Figure 1). The patients treated with RAS inhibitors had a significantly lower peak TnI compared to the those not treated with RAS inhibitors (79.8 vs 120.0 ng/dl, p = 0.016). This protective trend persisted but failed to reach clinical significance when we compared only those patients pretreated with ACEIs and nonpretreated patients (77.6 vs 120.0 ng/dl, p = 0.062, data not shown) or only those patients pretreated with angiotensin receptor blockers and nonpretreated patients (82.0 vs 120.0 ng/dl, p = 0.115, data not shown). The lack of significance in these subgroup

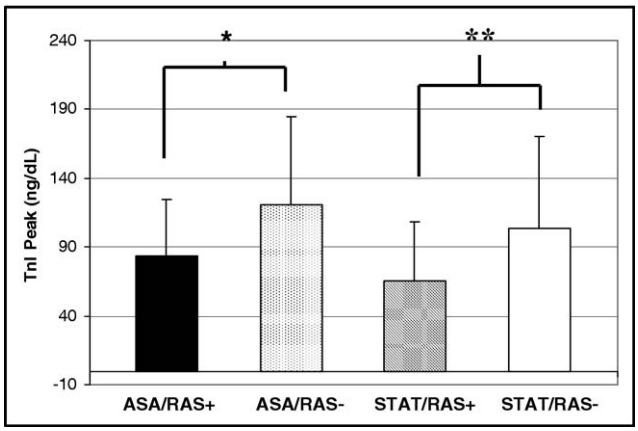

Figure 3. Peak TnI level in pretreatment RAS inhibitor group versus nonpretreated patients. Subgroup analysis of patients treated with aspirin *(Left bars)* and statins *(Right bars)*. *p = 0.047; **p = 0.23.

analyses was likely due to the small size of the ACEI and angiotensin receptor blocker groups.

To determine whether the effect of RAS inhibitor pretreatment on the peak TnI level was wholly due to the attenuation of blood pressure by the RAS inhibitors and not specifically an effect due to modulation of the RAS system, we compared the peak TnI level between those patients pretreated with RAS inhibitors and those treated with other antihypertensive agents. Compared to patients treated with non-RAS antihypertensive agents, those treated with RAS inhibiting agents demonstrated a significantly lower peak TnI level (79.8 vs 146.2 ng/dl, p = 0.003; Figure 2).

Given that the patients treated with RAS inhibitors were more likely to be treated with aspirin and statins, it would be reasonable to conclude that the beneficial effect of RAS inhibitors on TnI leak might actually have resulted from the effect of aspirin or statin pretreatment, because previous studies have shown a beneficial effect of the chronic use of these agents on TnI release in patients with STEMI.[1,2] Therefore, we performed a subanalysis of the effect of RAS inhibitor pretreatment on TnI release only in those patients in the cohort who were treated concomitantly with aspirin or statins (Figure 3). The beneficial effect of RAS inhibitor pretreatment persisted, even with a "background" of chronic aspirin use (83.5 vs 120.4 ng/dl, p = 0.047), providing evidence that the RAS inhibitor pretreatment effect was not simply an effect of greater aspirin use within this group. With a background of statin use, the patients treated with RAS inhibitors maintained a lower peak TnI level, although this difference failed to reach statistical significance, possibly owing to the small number of patients concomitantly treated with statins and RAS inhibitors (65.6 vs 104.0 ng/dl, p = 0.23).

Discussion

Pivotal trials have elucidated a role of RAS inhibitors in the prevention of cardiac events in high-risk patients,[3] and the early use of RAS inhibitors after STEMI has been shown to reduce the morbidity and mortality by limiting the pathologic cardiac remodeling and preservation of left ventricular function after myocardial infarction.[4] In addition, it has now been established that patents with acute coronary syndrome are less likely to have repeat events if treated chronically with RAS inhibitors for secondary prevention.[5] In the present study, we evaluated the effect of the pre-event use of RAS inhibitors on modulating the damage resulting from a first STEMI using the measurement of the peak TnI level as a surrogate for infarct size. The relation of the peak TnI level and the extent of myocardial damage has been confirmed in several recent trials.[6–8] We have demonstrated in our study for the first time that use of RAS inhibitors before STEMI is also associated with a decreased peak TnI level and that this effect was both independent of the blood pressure at presentation and was not equally afforded by non-RAS antihypertensive agents. These data suggest that this protective effect is at least partially due to mechanisms beyond the nonspecific blood pressure lowering effect of RAS inhibitors. Furthermore, the results of the present study have provided evidence that this protective effective might be additive to that previously shown to be afforded by the use of aspirin and statins.[1,2]

The mechanism of the protective effect of RAS inhibitor pretreatment at the time of STEMI is unknown. Pretreatment with ACEIs has been shown to attenuate ischemic reperfusion injury during coronary revascularization.[9] That the pre-event use of RAS inhibitors demonstrated greater cardioprotection at STEMI compared to non-RAS antihypertensive agents is somewhat discordant with recently published large trials examining the effect of specific antihypertensive agents on cardiac events.[10,11] Our trial differed from those studies in several ways. First, most of the patients enrolled in these trials had established CAD. In contrast, the present trial specifically excluded patients with a history of CAD. In addition, unequal blood pressure lowering across antihypertensive classes was proposed as a possible reason at least one of these trials failed to show superior cardioprotection for the angiotensin receptor blocker valsartan versus amlodipine.[11] Although the present trial was limited in fact that blood pressure was only recorded at a patient's presentation with STEMI, we detected no difference in blood pressure between antihypertensive classes at that point.

Our analysis of the effect of RAS inhibitors on the peak TnI levels in patients with STEMI included both ACEIs and angiotensin receptor blockers in the RAS cohort. This was important given the controversy surrounding the comparative effect of angiotensin receptor blockers versus ACEIs on the prevention of cardiovascular events in patients without established CAD.[12] Our study was of insufficient size to make conclusions regarding the differential efficacy across these 2 classes of RAS inhibitors, and this possibility will be the subject of a future study.

The lower peak TnI level in the RAS inhibitor-treated group was present despite a significantly greater proportion of anterior wall myocardial infarcts in this group. Given that anterior wall myocardial infarctions are associated with larger degrees of myonecrosis and infarct size than myocardial infarctions in other geographic locations,[13] this finding was somewhat surprising. The mechanism of the association of RAS inhibitor pretreatment and anterior infarct location could not be ascertained by our data; however, that the RAS inhibitor treated patients had smaller infarcts de-

spite this association highlights the protective effect of RAS inhibitors in this population.

Our study has expanded on previously published reports supporting a protective effect of pre-event use of RAS inhibitors in patients presenting with acute coronary syndrome. A previous study demonstrated a reduction in the odds of TnI release and peak TnI levels in patients chronically treated with RAS inhibitors before non–ST-segment elevation acute coronary syndrome.[14] That study included a large proportion of patients with a history of CAD and diabetes mellitus. The present study specifically excluded these high-risk patients yet nonetheless still demonstrated a protective effect of pretreatment with RAS inhibitors. Such a finding supports the role for RAS inhibitors as first-line agents even for patients with hypertension who do not have specific co-morbidities such as vascular disease or diabetes mellitus. Additional randomized prospective trials are required to better define the incremental benefit of treatment with RAS inhibitors in patients who present with STEMI as a CAD-defining first event.

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