Acute myocardial infarction treatment : from prehospital care to secondary prevention

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Chapter 7

Acute Myocardial Infarction Treatment of Young versus Elderly patients: Insights from the Leiden MISSION! program.

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ABSTRACT

Background

Lack of data about outcome of aggressive acute myocardial infarction (AMI) treatment in older patients may potentially contribute to significant underutilization of optimal treatment in this cohort. The authors evaluated clinical success of AMI treatment in the elderly population and analyzed several contributing factors.

Methods

A total of 1002 consecutive and unselected AMI patients were admitted between 2006 and 2009. Patients were divided into 2 groups according to age: 841(84%) patients <75years and 161(16%) patients ≥75years. All were treated according to the MISSION! AMI protocol. Baseline characteristics, time delay from onset of symptoms to arrival at the catheterization room, 1year mortality, medication at discharge and compliance at 12months were documented.

Results

Age group ≥75years had 20% less male patients, as well as lower prevalence of risk factors for coronary artery disease. More than 90% of AMI patients in both age groups were treated with primary PCI, with similar initial procedural success. Patients ≥75years had significantly longer time delays than patients <75years (median 193minutes vs. 150minutes respectively, p=0.033). In-hospital mortality was significantly higher in older AMI patients. However, age was only a significant independent predictor of 90day mortality. After 3months, low ejection fraction and diabetes were more important predictors. Patients ≥75years attending the outpatient clinic 1year post MI were as persistent with their medication as younger patients.

Conclusions

Despite a significantly higher mortality <3months post-MI in older patients, surviving patients have the potential to gain significant advantage from aggressive reperfusion, optimal medication and regular follow-up in the first year post-MI.

INTRODUCTION

Despite the greater incidence and risk of acute myocardial infarction (AMI) among older patients[1-3], there is still a considerable lack of data regarding success of aggressive AMI treatment in this group and factors contributing to clinical outcome. Several factors thought to contribute to the higher AMI mortality associated with older age are a higher prevalence of atypical clinical presentation delaying diagnosis[3], less persistent use of medication[4], as well as cardiovascular structural and physiological changes that predispose patients to more adverse outcomes with and without reperfusion therapy[5-8]. Nevertheless, patients 75 years of age and older with AMI, constitute a heterogeneous group and lack of data about outcome of aggressive AMI treatment may potentially contribute to significant underutilization of optimal AMI treatment in this cohort[3;9]. Moreover, the need for data regarding clinical characteristics and outcome of elderly AMI patients is ever increasing, as they constitute a rapidly growing group in the Western world[10]. The present study aims to provide more insight into the clinical profile, presentation delays, medication compliance and outcome of treatment in the elderly AMI population up to one year post myocardial infarction (MI).

METHODS

Patient population and protocol

Consecutive and unselected patients presenting from January 2006 to January 2009 with AMI at the Leiden University Medical Center were included in the present study. Patients were all treated according to the MISSION! AMI protocol, as previously described in detail[11]. The protocol is based on ACC/AHA/ESC guidelines[2] for the treatment of AMI and focuses on the reduction of onset of symptoms-to-balloon time, optimization of pharmacological treatment, and structured secondary prevention during follow-up. In brief, all patients considered eligible for primary percutaneous coronary intervention (PCI) had electrocardiographic ST segment changes and additional evidence supporting the clinical diagnosis of an acute MI, including prolonged ischemic signs and symptoms (≥20 minutes), biomarker evidence of myocardial necrosis, or both[12]. Eligible patients were transferred directly to the PCI center's Cardiac Care Unit. The catheterization room was operational within 20 minutes, 24 hours a day, 7 days a week. Before the procedure all patients received 300 mg of aspirin, 300 to 600 mg of clopidogrel, and an intravenous bolus of abciximab (25 μg/kg), followed by a continuous infusion of 10 μg/kg/min for 12 h. At start of the procedure, 5,000 IU of heparin was given. Lesions were treated according to current interventional practice. MI was confirmed by detection of rise and/or fall of cardiac biomarkers with at least one of the following: (1) symptoms of ischemia: (2) ECG changes indicative of new ischemia development of the pathological Q wave, (3) imaging of new loss of viable myocardium or new regional wall motion abnormality.

Follow-up

After hospital discharge, patients were offered a cardiac rehabilitation program and benefited from intensive out-patient follow up for the period of 1 year[11]. Outpatient clinic visits were scheduled for 30 days, 3 months, 6 months and 12 months after the index event.

Data collection

Data of all patients (including baseline characteristics, time delay, cardiac history, and medication up to one year) was recorded by medical staff at the department of cardiology. All data was documented in the departmental electronic patient system (EPD-Vision®, LUMC, Leiden, The Netherlands). Survival status at 12 months was ascertained by medical records and data from the community population registry.

Endpoints

Baseline clinical characteristics, time delay (minutes) from onset of symptoms to arrival at the catheterization room, 1-year mortality, medication at hospital discharge, and medication compliance at 12 months were all points of interest.

Statistical analysis

Continuous data are expressed as mean (±standard deviation) or as median (25^{th}-75^{th} percentile); dichotomous data are presented as numbers and percentages. Differences between categorical data were tested for statistical significance using a Pearson chi-square test using continuity correction where appropriate. Continuous normally distributed data were tested by student t-tests or in the case of a non-Gaussian distribution by a nonparametric test for independent samples. Survival was analyzed by method of Kaplan-Meier with corresponding log-rank test for differences in distribution between the curves. Univariate and multivariate Cox regression analysis was performed to determine a relation between potential risk factors at baseline and the incidence of all cause death. All variables with an unadjusted p value of <0.10 entered the multivariate regression model. A wide range of variables were considered including age, gender, clinical characteristics such as risk factors for CAD, cardiac history, treatment delay, and procedure and infarction related characteristics (see table 1). Only adjusted Hazard Ratio (HR) is reported in the text with the corresponding 95% confidence interval (CI). Also, univariate and multivariate logistic regression analysis was performed using the same methodology as described above to determine a relation between potential risk factors at baseline and time delay $\geq$150 minutes. Variables considered included age, gender, risk factors for CAD and cardiac history. Only adjusted Odds Ratio (OR) is reported in the text with the corresponding 95% CI. All tests were two-sided, a p-value of < 0.05 was considered significant.

RESULTS

Patient population

A total of 1002 consecutive AMI patients were admitted at the PCI center between 2006 and 2009. For study purposes, patients were divided into two groups according to age at presentation: 841 (84%) patients younger than 75 years and 161(16%) patients ≥75 years.

Clinical characteristics

Clinical characteristics according to age group are shown in Table 1 and figure 1. The statistically most significant differences between patients ≥75 years and patients <75 years were a 20% lower proportion of male patients in the older patient group (Figure 1, panel A), as well as a lower prevalence of risk factors such as smoking, hyperlipidemia, BMI ≥30 kg/m^2 and family history of coronary artery disease (CAD). In addition, Figure 1, Panel B demonstrates that older patients were less likely to have ≥3 risk factors for CAD. Table 1 furthermore shows that more patients aged ≥75 years were using cardiovascular and antiplatelet agents prior to the index event compared to younger patients.

More than 90% of AMI patients in both age groups were treated with percutaneous coronary intervention (Table 1). Significantly more patients in the age group ≥75 years were observed with multi-vessel disease, however LAD related infarctions were equally distributed between the two age groups. A similar percentage of patients failed to attain a postprocedural Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 in both age groups (Table 1).

Time delay and infarct size

Figure 1, Panel C, shows that older patients had significantly longer time delays from onset of symptoms to arrival at the catheterization room than patients younger than 75 years (median 193 minutes versus 150 minutes respectively, p=0.033). Due to the larger proportion of female patients in the older group, an additional analysis was conducted to evaluate how gender influenced the difference in time delay between the age groups. When split up by gender, male patients ≥75 years had a median 20 minute longer time delay than younger male patients. Older female patients had a median 45 minute longer time delay when compared to female patients <75 years. When considering age and gender in a multivariate logistic regression analysis, age ≥75 years remained a significant predictor of time delay ≥150 minutes from symptom onset to arrival at the catheterization room (OR 1.51, 95% CI 1.05-2.16, p=0.026), while gender did not (OR 1.31, 95% CI 0.95-1.80, p=0.098). However, interaction between age ≥75 years and female gender was observed, increasing the OR to 2.15 (95% CI 1.25-3.70, p=0.006) for a time delay ≥150 minutes.

In line with these findings, peak troponin T values were significantly higher in older patients compared to the younger patients (median 4.31 µg/L versus 3.22 µg/L respectively,

Table 1. Baseline characteristics

Age group (years)	<75y (n=841)	≥75y (n=161)	p-value
Male gender	669 (79%)	93 (58%)	<0.001*
Mean age (years±SD)	57±10	80±4	<0.001*
Range (min-max)	22-74	75-91	
Risk factors			
Smoking	494 (59%)	47 (29%)	<0.001*
Family History	380 (45%)	30 (19%)	<0.001*
Hyperlipidemia †	181 (22%)	18 (11%)	0.003*
Hypertension ‡	287 (34%)	75 (47%)	0.002*
Diabetes Mellitus	104 (12%)	28 (18%)	0.08
BMI ≥30 kg/m^2	156 (19%)	21 (13%)	0.19
Cardiac History			
Prior Myocardial Infarction	90 (11%)	21 (13%)	0.36
Prior percutaneous coronary intervention	72 (9%)	8 (5%)	0.14
Prior coronary artery bypass grafting	17 (2%)	9 (6%)	0.018*
Medication before MI			
Beta-blocker	163 (19%)	44 (27%)	0.020*
Aspirin	137 (16%)	48 (30%)	<0.001*
Statin	165 (20%)	30 (19%)	0.81
ACE-inhibitor	97 (12%)	31 (19%)	0.007*
Angiotensine II-antagonist	61 (7%)	17 (11%)	0.14
Diuretic	85 (10%)	31 (19%)	0.001*
Ca-antagonist	76 (9%)	28 (17%)	0.001*
Time delay:			
Onset symptoms-cath. room (median min [interquartile range])	150 (101-281)	193 (120-288)	0.033*
Procedure related:			
Percutaneous coronary intervention	788 (94%)	149 (93%)	0.59
Coronary artery bypass grafting	5 (1%)	2 (1%)	0.70
Conservative treatment	48 (6%)	10 (6%)	0.80
Multivessel disease	427 (51%)	106 (66%)	0.001*
Related to left anterior descending artery	340 (40%)	65 (40%)	0.99
Postprocedural TIMI flow grade <3	66 (8%)	16 (10%)	0.34
Infarction size related:			
Peak troponin T (median µg/L [interquartile range])	3.22 (1.20-6.75)	4.31 (1.71-8.08)	0.008*
Peak CPK (median U/L [interquartile range])	1322 (586-2635)	1366 (634-2442)	0.96
LVEF 3 months post-MI (%)	56 (46-63)	57 (47-66)	0.44
In-hospital deaths	6 (1%)	17 (11%)	<0.001*

* p<0.05; † Total cholesterol ≥190 mg/dl or previous pharmacological treatment.
‡ Blood pressure ≥140/90 mm Hg or previous pharmacological treatment.

p=0.008) (Table 1). Of note, when patients who died in-hospital were excluded from this

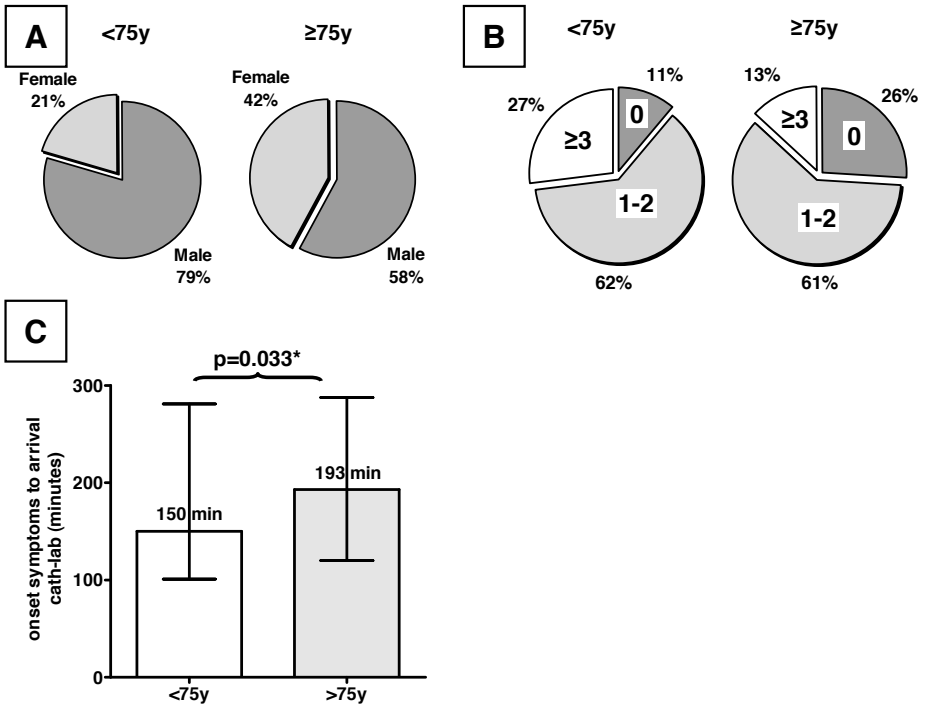

Figure 1. Baseline characteristics according to age group.
Panel A: Gender distribution (%).
Panel B: Prevalence of 0, 1-2 and ≥3 risk factors for coronary artery disease per age group (%).
Panel C: Bar graph showing time interval from onset of symptoms to arrival at the catheterization room (minutes) per age group. Top of bar represents median time (minutes). Error bars indicate 25th and 75th percentiles.

analysis, peak troponin T values were not significantly different between the old and young age groups (median 3.83 µg/L versus 3.19 µg/L respectively, p=0.083). Correspondingly, at 3 months post-MI the mean left ventricular ejection fraction (LVEF, derived ^{99m} tetrofosmin gated myocardial perfusion SPECT) of surviving patients was similar between the age groups (Table 1).

Survival

One year survival data was complete for all patients (n=1002). In-hospital mortality was significantly higher in patients aged 75 years and older when compared to younger patients (17/161, 11% versus 6/841, 0.7%, respectively; p<0.001). All of these early deaths were caused by complications related to the index event.

Figure 2 demonstrates 1-year cumulative all-cause mortality stratified by age group. Panel A demonstrates that the trend of higher mortality in the age group ≥75 years compared to the age group <75 years was continued throughout the first year (p<0.001). Eighteen

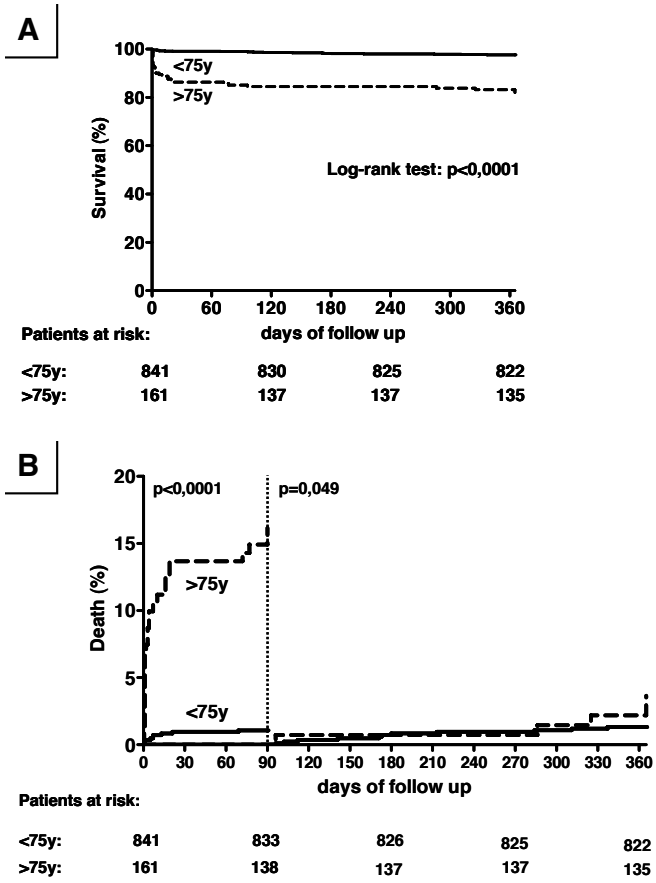

Figure 2. Mortality
Panel A: Kaplan-Meier plot of the cumulative incidence of all-cause death.
Panel B: Landmark incidence analysis plot of the cumulative incidence of all-cause death.

percent of patients (n=29) died within the first year post-MI in the age group ≥75 years, compared to 2% of patients (n=20) in the age group <75 years. Panel B emphasizes the more pronounced difference in the cumulative rate of relatively early deaths post-MI (landmark set at 90 days) and shows that both early and late (from 90 days to 1 year) mortality was significantly higher in the group aged ≥75 years. Multivariable Cox regression analysis of 0 to 90 day mortality revealed that age (adjusted HR 1.14, 95%CI 1.08-1.19, p<0.001), post-procedural TIMI flow grade <3 (adjusted HR 8.74, 95%CI 3.72-20.52, p<0.001), and time from onset of symptoms to arrival at the catheterization room (adjusted HR 1.001, 95%CI 1.00-1.001, p=0.009) were strong independent predictors of early mortality with TIMI flow grade <3 being the strongest predictor (Table 2). Multivariable Cox regression analysis of 90 day -1 year mortality revealed only diabetes (adjusted HR 4.39, 95% CI 1.24-15.6, p=0.022)

Table 2. Association with mortality 0-90 days post-MI and 90 days - 1 year post-MI.

	Mortality 0 - 90 days			
	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age	1.12 (1.10-1.16)	<0.001	1.14 (1.08-1.19)	<0.001*
Male gender	0.55 (0,27-1.11)	0.093	1.01 (0.40-2.50)	0.99
Treatment delay	1.000 (1.00-1.001)	0.014	1.001 (1.00-1.001)	0.009*
Multivessel disease	1.97 (0.90-4.32)	0.091	1.37 (0.52-3.60)	0.53
TIMI flow grade <3	6.29 (3.03-13.0)	<0.001	8.74 (3.72-20.52)	<0.001*
	Mortality 90 days – 1 year			
	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age	1,05 (1.01-1.10)	0.020	1.05 (0.98-1.12)	0.19
Diabetes Mellitus	4.06 (1.48-11.18)	0.007	4.39 (1.24-15.6)	0.022*
Prior MI	2.73 (0.88-8.46)	0.082	1.81 (0.43-7.63)	0.42
LVEF	0.94 (0.90-0.98)	0.001	0.94 (0.89-0.98)	0.005*

Only significant variables shown. These were the variables that were incorporated into the multivariate model (variables with an unadjusted p-value of <0.10). Unadjusted and adjusted Hazard Ratio (HR) is reported with the corresponding 95% confidence interval (CI). * p<0.05

and left ventricular ejection fraction (adjusted HR 0.94, 95% CI 0.89-0.98, p=0.005) as significant independent predictors of death (Table 2).

Medication prescription and compliance

Table 3 shows medication prescription at hospital discharge, the number of (alive) patients that failed to attend the 12 month appointment at the outpatient clinic and the percentage of patients (as proportion of the patient group that did attend) that were still on optimal medication at 12 months.

Medication prescription at discharge was more or less optimal in both age groups. When aspirin was not prescribed at discharge, it was often due to anticoagulant treatment (alongside clopidogrel). In such cases aspirin was withheld in order to avoid increased risk of bleeding complications. Anticoagulants were prescribed in case of atrial fibrillation, severely impaired LV function or LV aneurysm.

A significantly larger percentage of patients in the age group ≥75 years failed to return to the outpatient clinic at 12 months when compared to the younger age group (37% of 132 alive patients versus 16% of 820 alive patients, respectively; p<0.001). However, medication compliance in the patients that did attend at 12 months was high and similar between the age groups.

Table 3. Medication prescription, follow-up and compliance.

Age group (years)	<75y	≥75y	p-value
Hospital discharge:	(n=841)	(n=161)	
Alive at discharge	835/841 (99%)	144/161 (89%)	<0.001*
Aspirin	793/835 (95%)	135/144 (93%)	0.49
Statin	818/835 (98%)	140/144 (97%)	0.60
Beta blocker	793/835 (95%)	132/144 (92%)	0.28
Clopidogrel	810/835 (97%)	140/144 (97%)	1.00
ACE inhibitor	810/835 (97%)	135/144 (94%)	0.08
Alive 1 year post-MI	820/841 (98%)	132/161 (82%)	<0.001*
Failed to attend 12 month visit	131/820 (16%)	49/132 (37%)	<0.001*
12 Month Visit:	(n=689)	(n=83)	
Aspirin	623/689 (90%)	72/83 (87%)	0.29
Statin	664/689 (96%)	78/83 (94%)	0.44
Beta blocker	636/689 (92%)	75/83 (90%)	0.54
Clopidogrel	656/689 (95%)	78/83 (94%)	0.82
ACE inhibitor	666/689 (97%)	78/83 (94%)	0.36

* $p<0.05$

DISCUSSION

Key findings of this study were (1) AMI patients in the age group of ≥75 years presented with significantly less modifiable risk factors of CAD than younger AMI patients; (2) In-hospital mortality was significantly higher in older AMI patients than in younger AMI patients despite similar postprocedural TIMI flow grades, and: (3) Despite a significantly higher cumulative incidence of mortality 1 year post-MI in older AMI patients, age was only a significant independent predictor of 90 day mortality. In the period of 90 days to 1 year post-MI other contributing risk factors such as LV ejection fraction and diabetes were more important predictors of mortality.

Elderly patients included in this study had less modifiable risk factors of CAD than younger patients, a so-called "survivor effect" that was also seen in other studies [3;13]. It is not unreasonable that older patients, who experience MI at a later stage in life, are likely to have less risk factors for CAD than those who experience MI at a younger age. Furthermore, as patients were unselected and consecutively enrolled in the study, they truly reflect the patient population in the region of the PCI center, which may be a more healthy population than the patients enrolled in other studies [14;15]. The significantly longer treatment delays in the older patient group were in part caused by the larger proportion of female patients as demonstrated by multivariate logistic regression analysis, but other contributing factors that were not considered may include atypical symptoms, electrocardiographic presentations that

were difficult to interpret, a greater likelihood that patients were first transported to a center without PCI facility as seen in previous studies, and perhaps a greater inclination of elderly patients to wait longer before alerting emergency services [3;16;17].

It is well known that elderly patients are more likely to experience an AMI and to die after a MI than younger patients [18]. However, though it is well known that age is a significant risk factor for post-MI death, not all older patients are equally vulnerable to poor functional outcomes [14;19].

Older patients surviving the index event had similar cardiac function compared to the younger patients at three months post-MI. After 3 months the difference in mortality between the two age groups was less pronounced than in the first three months post-MI (borderline significant: p=0.049) and results of the multivariate analysis confirmed that age was no longer a significant predictor of 1-year mortality in patients surviving the first three months post-MI. This outcome is consistent with findings from a recent large registry study, which found that two out of three patients experienced a favorable functional outcome (neither death nor functional decline) at 1 year post-MI regardless of age [14]. Other studies often included a patient population in which older patients were treated less aggressively and with less patients undergoing primary PCI than the younger patients [3] or included patients from a time period when AMI treatment was not up to current standards [13]. Also, most of these studies divided mortality into 30 day mortality and 1 year mortality, not looking at other time windows.

Although older post-MI patients have consistently been shown to receive fewer evidence-based treatments, even when eligible[20-23], patients surviving the acute phase post-MI have similar potential for favorable outcomes to those of younger patients as evidenced by results of the present study and other studies [14] where patients of both age groups were treated equally aggressive. Prescription of beneficial cardiovascular medication at discharge was optimal in post-MI patients of all ages in the population studied, an encouraging finding as medication underuse at discharge is not uncommon in older patients [15]. Of the surviving patients at 1 year post-MI 20% more patients of the older age group failed to return to the outpatient clinic compared to younger patients, possibly related to more comorbidities or the perception that follow-up was not needed. It has been reported before that older patients are less likely to be persistent with evidence-based cardiovascular medicine after discharge from an acute coronary syndrome event [4]. However, surviving patients of the older age group that returned to the outpatient clinic were as persistent with their medication regimen as the younger patients, possibly a positive effect of the intensive follow-up of the MISSION! outpatient protocol [11].

Limitations

There are potential limitations to the present study that should be considered when interpreting the results. As this was a single center, single region study, conclusions may not pertain to patients of other centers or regions. Furthermore, as data on prevalence of baseline risk

factors and baseline medication use was derived largely from patient self-report, it should be considered with the necessary caution.

Finally, as this is an observational study, there is a possibility of unmeasured confounding. However, due to the large amount of data that was available for the study population, it was possible to adjust for a wide range of potential confounders in the multivariable analysis, and these did not alter the findings.

CONCLUSION

Given that old age is associated with greater morbidity and mortality after a MI, most clinicians would have considered age to remain the most important risk factor of mortality throughout the first year post-MI. However, results demonstrated that older patients surviving the first 3 months post-MI have similar outcomes to younger patients in terms of cardiac function and that age was a not a significant risk factor of 1-year mortality in survivors three months after MI. Therefore, though conservative treatment may be the adequate choice for some patients, results of this study suggest that older patients have the potential to gain significant advantage from aggressive and invasive AMI treatment and that age alone should not preclude intensive treatment after an MI.

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