Modification of Treatment Strategies Over a Period of 14 Years Has Markedly Reduced Cardiac Events Among Post-Myocardial Infarction Patients

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Recent trends in the treatment of post-myocardial infarction (MI) patients and the factors accounting for the improvement in outcome are presented. A total of 6,602 post-MI patients (5,320 males, 1,282 females; 58.9 ± 10.4 years of age) enrolled between 1986 and 1999 were followed up for an average of 12.6 ± 16.3 months. The incidence of cardiac events, which included fatal and nonfatal recurrent MIs, sudden death and death by congestive heart failure, was highest (44.9 events/1,000 person·year) in 1986–1987, but decreased steadily to 22.5 events/1,000 person·year by 1997–1999 (Trend $p < 0.0001$). This trend accompanied the increased use of coronary thrombolysis, percutaneous transluminal coronary angioplasty and coronary artery bypass graft surgery, increased prescription of antiplatelet agents (51.5%–83.4%), lipid-lowering agents (29.8%–52.6%) and angiotensin-converting enzyme inhibitors (5.3%–41.0%), and reduced prescription of calcium antagonists (68.5%–41.0%) and nitrates (60.7%–45.7%). These changes in treatment have led to a decreased incidence of angina pectoris, wall motion abnormalities and abnormal Q waves on electrocardiograms. The decline in the incidence of cardiac events among post-MI patients in the 14 years between 1986 and 1999 reflects implementation of new therapeutic modalities proven to be effective in clinical trials and in daily practice. (Circ J 2002; 66: 881–885)

Key Words: Cardiac events; Recurrent myocardial infarction; Secondary prevention

The short-term prognosis of patients with acute myocardial infarction (MI) has been markedly improved by the introduction of reperfusion therapy: in Israel the 30-day hospital mortality among acute MI patients was reduced from 17.0% in the pre-reperfusion era of 1981–1983 to 10.8% in 1992–1994¹ and the Minnesota Heart Survey also reported that 3-year mortality among 28-day survivors of acute myocardial infarction declined from 17 (person per 100,000) in 1985 to 13 in 1995 in men and from 22 to 11 in women.² Investigating the trends in the treatment of MI among a population of 1.5 million patients entered in the National Registry of Myocardial Infarction in the United States, Rogers et al found that the use of β -blockers, aspirin and angiotensin-converting enzyme inhibitors (ACEI) increased over the period from 1990 to 1999, and hospital mortality declined from 11.2% to 9.4% during the same period.³ They concluded that the recommendations of recent clinical trials and published guidelines were indeed being implemented, resulting in more frequent use of therapies known to reduce mortality and diminished use of therapies, such as prescription of short-acting nifedipine, now known to be ineffective.

There has also been improvement in the long-term prognosis of post-MI patients. For example, among 2,733

post-MI patients discharged from Japanese hospitals between 1983 and 1988, 172 (6.3%) had recurrent MI during a mean follow-up period of 2.9 years.⁴ By contrast, the incidence of cardiac events, including recurrent MI, sudden death and death by congestive heart failure, among 1,483 Japanese post-MI patients discharged between 1986 and 1996 was 4.8% (33 events per 1,000 person·year) during a mean follow-up period of 17.4 ± 20.9 months.⁵ The purpose of the present study was to assess by how much the long-term prognosis in post-MI patients has been improved, what changes in treatment modality might account for this improvement, and what we can do to improve further the prognoses of these patients.

Methods

Subjects

A total of 6,602 post-MI patients treated in hospital were studied.

Enrollment

Subjects were consecutively enrolled in the study from January 1986 to December 1999, including all MI patients from the Department of Cardiology. The diagnosis of MI was based on history, electrocardiogram (ECG) changes and a significant elevation of myocardial serum enzymes. All inpatients with acute MI were registered after 8 days of onset; all outpatients with a healed MI were registered on their first visit to the Department. If a patient had a nonfatal recurrent MI and revisited the hospital, he/she was registered as a new patient upon return. If a patient visited another hospital but returned to the primary hospital for

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Table 1 Characteristics of the Post-MI Patients in the 14 Years of the Study

	1986–1987 n=1,089	1988–1990 n=1,099	1991–1993 n=1,478	1994–1996 n=1,585	1997–1999 n=1,351	p value [†]
Sex, male %	81.8	78.5	81.9	80.9	79.4	
Age, years	59.5±11.6	59.8±11.0	58.5±10.1*	58.8±10.1	58.3±9.7**	0.0010
Mean observation period, months	16.0±21.1	15.0±19.5	14.7±18.3	10.4±11.2	8.3±8.7***	0.0010
Blood pressure, mmHg						
Systolic	128±22	127±20	125±19***	124±18***	126±18*	0.0001
Diastolic	77±13	75±12***	73±11***	73±11***	73±11***	0.0001
Heart rate, beats/min	65±11	65±11	66±12	67±11**	66±12	0.0170
Characteristics of first MI						
Anterior wall infarction, %	43.1	34.2***	38.4*	41.2	40.3	
Killip class, I%	81.4	88.3***	82.5	83.4	87.5***	
Number of involved vessels, IVD%	41.0	43.2	45.1*	44.6	46.5*	
Peak CK, U/L	2,415±2,073	2,489±2,095	2,638±2,165**	2,810±2,307***	2,952±2,430***	0.0001
Interventional therapy						
Coronary thrombolysis, %	27.8	33.2**	42.8***	48.2***	45.6***	0.0001
PTCA, %	4.2	17.5***	27.2***	36.0***	45.6***	0.0001
CABG, %	1.9	5.7***	7.7***	13.5***	16.6***	0.0001
Wall motion index by echocardiogram	8.7±6.0	8.2±5.7	6.7±5.6***	6.9±5.2***	6.4±5.1***	0.0001
ECG QRS score	6.1±4.0	5.1±3.5***	5.1±3.5***	4.5±3.6***	4.6±3.5***	0.0001
Post-MI angina, %	37.3	33.5	28.8***	22.2***	14.0***	0.0001
Coronary risk factors, %						
Hyperlipidemia	53.8	50.3	50.8	52.3	51.5	
Hypertension	45.2	49.2	45.8	49.8**	48.9	
Smoking including ex-smokers	63.9	67.8	71.4***	73.9***	70.6***	0.0001
Diabetes mellitus	27.1	29.3	26.7	30.1	29.8	
Obesity	16.0	22.6***	25.9***	31.7***	30.3***	0.0001
Laboratory findings during follow-up						
Total cholesterol, mg/dl	214±43	206±40***	197±37***	194±36***	199±34***	0.0001
Triglycerides, mg/dl	163±94	181±118***	153±95**	147±87***	152±80**	0.0001
HDL cholesterol, mg/dl	41±13	41±13	44±12***	42±12*	41±12	0.0001
Positive exercise ECG test, %	37.1	46.6***	40.9*	42.7*	31.2**	
Drug treatment, %						
Antiplatelet agents	51.5	62.8***	72.7***	78.9***	83.4***	0.0001
Lipid-lowering agents	29.8	33.8*	41.7***	45.2***	52.6***	0.0001
ACE I	5.3	11.4***	23.3***	34.8***	41.0***	0.0001
-blockers	53.4	64.5**	63.1***	61.7***	60.4***	0.0001
Warfarin	23.1	26.4	34.4***	27.4*	16.3***	
Calcium antagonists	68.5	59.1***	48.0***	41.5***	41.0***	0.0001
Nitrates	60.7	69.3***	68.9***	54.8**	45.7***	0.0360
Antiarrhythmic agents	8.6	10.6	9.8	8.9	8.1	

Mean±standard deviation.

MI, myocardial infarction; IVD, one vessel disease; CK, serum creatine kinase activity; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft surgery; ACE I, angiotensin converting enzyme inhibitors.

Difference between 1986, 1987. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

[†]The Mantel-Haenszel test assessed trends by serial time intervals over the duration of the registry.

any reason, the earlier and later observations were registered separately. Likewise, if a patient had coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty, observations made before and after those procedures were registered separately. If there were any changes in the prescription of one or more of the antiplatelet agents, lipid-lowering agents, ACEI, -blockers, warfarin, calcium antagonists, nitrates or antiarrhythmic agents, observations made before and after administration of the new medications were registered separately.

Follow-up Examination

Serial blood tests, exercise ECGs, and echocardiography were carried out several times for hospitalized patients and approximately twice a year for outpatients. Left ventricular wall motion abnormality was evaluated using echocardiography according to Heger et al.⁶ QRS scores on ECGs were calculated as an index related to infarct size according to Wagner et al.⁷ Hyperlipidemia was considered to be present if the patient had a past history of total cholesterol >220 mg/dl and a history of hypertension was defined as

casual systolic blood pressure >160 mmHg or diastolic pressure >95 mmHg. Obesity was considered to be present if patients had a body mass index >25.

Exclusion and Lost-to-Follow

Because the present study focused on the long-term prognoses of patients with healed MI, cardiac events occurring within 7 days of onset of symptoms were excluded. If a patient ceased visiting the hospital, efforts were made to contact him/her by telephone and determine the reason so as to avoid overlooking cardiac or other medical events. Those patients who stopped coming in for unknown reasons and whom we failed to contact were defined as lost-to-follow.

Primary End-Points

The primary end-points were cardiac events, which included fatal and nonfatal recurrent MI, sudden death and death by congestive heart failure.

Table 2 Cardiac Events in Post-MI Patients in the 14 Years of the Study

	1986–1987 n (%)	1988–1990 n (%)	1991–1993 n (%)	1994–1996 n (%)	1997–1999 n (%)	p value [†]	All n (%)
<i>Re-MI</i>	n=1,089	n=1,099	n=1,478	n=1,585	n=1,351		n=6,602
Fatal	9 (0.8%)	8 (0.7%)	5 (0.3%)	4 (0.3%)	4 (0.3%)	0.0340	30 (0.5%)
Nonfatal	42 (3.9%)	21 (1.9%)**	28 (1.9%)**	16 (1.0%***	10 (0.7%***	0.0001	117 (1.8%)
Sudden death	12 (1.1%)	9 (0.8%)	7 (0.5%)	2 (0.1%***	3 (0.2%***	0.0010	33 (0.5%)
Death by CHF	2 (0.2%)	3 (0.3%)	5 (0.3%)	1 (0.1%)	4 (0.3%)		15 (0.2%)
Total (cardiac events)	65 (6.0%)	41 (3.7%)**	45 (3.0%***	23 (1.5%***	21 (1.6%***	0.0001	195 (3.0%)
<events/1,000 person·year>	<44.9>	<29.8>**	<24.8>**	<16.7>**	<22.5>**	0.0001	<28.1>
Non-cardiac death	27 (2.5%)	31 (2.8%)	21 (1.4%)*	19 (1.2%)*	4 (0.3%***	0.0020	102 (1.5%)
Total mortality	50 (4.6%)	51 (4.6%)	38 (2.6%)*	26 (1.6%***	15 (1.1%***	0.0001	180 (2.7%)
Lost-to-follow-up	6 (0.6%)	4 (0.4%)	4 (0.3%)	12 (0.8%)	4 (0.3%)		30 (0.5%)

Re-MI, recurrent myocardial infarction; CHF, congestive heart failure.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs 1986, 1987.

[†]The Mantel-Haenszel test assessed trends by serial time intervals over the duration of the registry.

Statistical Analysis

Data are presented as means±one standard deviation. For categorical data, the Mantel-Haenszel chi-square test was used as the measure of trends.³ Differences between 2 values were tested using the ² test. Two-sided probability values are presented; values of $p < 0.05$ were considered significant.

Results

Study Population

During the 14-year study period, a total of 6,602 post-MI patients (5,320 males, 1,282 females; mean age, 58.9±10.4 years at onset) were registered. The mean time from onset of symptoms to registry was 34.4±42.5 months, and the mean observation period was 12.6±16.3 months. Patients were grouped in 5 time periods as shown in Table 1. Peak serum creatine kinase activity after the first MI was higher among patients enrolled during 1997–1999, and more of those patients were treated with coronary thrombolysis, percutaneous transluminal coronary angioplasty and coronary artery bypass graft surgery than in earlier periods. Among patients with multivessel disease, 4.2% had bypass surgery in 1986–1987; this increased to 10.2% in 1988–1990, 13.5% in 1991–1993, 24.0% in 1994–1996 and 28.2% in 1997–1999. The incidence of wall motion abnormalities and QRS scores on ECGs declined over the course of the study period, as did the incidence of angina pectoris.

Coronary Risk Factors

During 1986–1987, 386 patients reported a history of hypertension; their mean blood pressure was 138±23/80±14 mmHg. During 1997–1999, 625 patients reported a history of hypertension; in this group, the mean blood pressure was 130±18/75±11 mmHg, whereas in those with no history of it was 122±17/70±11 mmHg. Among the former group of patients, both systolic and diastolic blood pressures were significantly ($p < 0.01$) lower in 1997–1999 than in 1986–1987. The percentage of smokers, including ex-smokers, remained high throughout the study period. There were 232 diabetic patients enrolled during 1986–1987 and 384 during 1997–1999. Hemoglobin A1c (8.3±2.9 vs 6.8±1.1; $p < 0.01$) and total cholesterol (218±46 vs 199±36 mg/dl; $p < 0.01$) were both significantly lower in 1997–1999 than in 1986–1987. On the other hand, the inci-

Reduction of cardiac events and trends in drug use in these 14 years

Fig 1. Reduction in cardiac events and trends in drug use in the 14 years of the study.

dence of obesity trended upward, nearly doubling over the course of the study period.

Laboratory Findings

Laboratory findings showed no remarkable changes over the course of the study period, though total cholesterol trended downward. During 1986–1987, 465 patients reported a history of hyperlipidemia: the mean total cholesterol was 236±41 mg/dl and 14.0% were taking statins. In 1997–1999, by contrast, 653 patients reported a history of hyperlipidemia: total cholesterol was 211±35 mg/dl ($p < 0.01$ vs 1986–1987), and 89.5% were on statins.

Trends in Drug Treatment

Drug treatment showed a marked shift toward antiplatelet agents over the course of the study period, with 51.5% of patients receiving antiplatelet agents in 1986–1987 vs 83.4% in 1997–1999. During 1986–1987 aspirin alone was taken by only 2.0% of patients, but aspirin combined with other antiplatelet agents was taken by 48.1% of patients. During 1997–1999, however, 49.8% of patients took aspirin alone, and combined use had declined to 39.5%. The use of warfarin also reduced during this period. Prescription of lipid-lowering agents increased over the years from 29.8% to 52.6%, with 80.5% of those prescribed during 1997–1999 being statins. Use of ACEI also increased, and β -blockers were used consistently in more than half of post-MI patients (53.4–64.5%), and among the 1,854 patients who were 65 years or older at onset, 1,005 (54.2%) were prescribed β -

blockers. Use of calcium antagonists trended downward, as did that of nitrates, though they were still taken by 41.0% and 45.7% of patients, respectively, during 1997–1999. Antiarrhythmic agents were used in a limited number of patients.

Trends in Cardiac Events (Table 2, Fig 1)

Among the 6,602 post-MI patients, 195 cardiac events were recorded over the course of the study period (3.0%, 28.1 events/1,000 person·year). There was no statistical difference between the number of cardiac events occurring in males and females: 159 cardiac events (3.0%, 27.6 events/1,000 person·year) among the 5,320 male patients and 36 events (2.8%, 30.3 events/1,000 person·year) among the 1,282 female patients. There were 78 cardiac deaths (1.2%, 11.2 events/1,000 person·year) and 147 recurrent MIs (2.2%, 21.2 events/1,000 person·year). There was a downward trend in the incidence of post-MI cardiac events throughout the study period, with the number of cardiac events declining from 44.9 events/1,000 person·year in 1986–1987 to 22.5 events/1,000 person·year in 1997–1999 ($p<0.01$).

Discussion

Recent Decline in Cardiac Events in Post-MI Patients

According to the Framingham Study published in 1993⁸ following a first MI, there were 68.4 coronary deaths and 39 recurrent MIs per 1,000 person·year among males and 110.6 coronary deaths and 42.2 recurrent MIs per 1,000 person·year among females during a 34-year follow-up from 1948 to 1981 (no gender difference). This was substantially higher than the 11.2 cardiac deaths and 21.2 recurrent MIs per 1,000 person·year observed during the 14-year period evaluated in the present study and is likely the result in part to differences in race and community. In addition, the Framingham Study was initiated and ended many years before the present study, suggesting that improved health habits and better treatment modalities also contributed to the observed improvement in the long-term prognosis of post-MI patients.

Successful Use of Reperfusion Therapies

The risk factors that affect clinical outcome following acute MI are multifactorial, so it is difficult to identify any single factor contributing to the improvement in the outcome for post-MI patients shown in the present study. Nevertheless, one would expect limitation of infarct size by myocardial salvage and preservation of left ventricular function to be major determinants affecting patient prognosis. For instance, in 1986–1987 only 27.8% of patients received coronary thrombolysis at the onset of symptoms; this increased to 45.6% by 1997–1999. In Japan, we used urokinase as a thrombolytic agent in 1985; tissue-type plasminogen activator (tPA), which gave a higher rate of reperfusion was adopted in 1991, and then in 1998 mutant tPA became available. Reduction of wall motion abnormalities and QRS scores on the ECG may reflect the successful use of such reperfusion therapy during the acute phase. There has also recently been a tremendous increase in the number of patients receiving percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery. In particular, bypass surgery in cases of multivessel disease may have contributed much to the improved long-term prognosis. With the use of such interventional

therapy, the incidence of post-MI angina pectoris has been reduced by more than half. However, only 28.2% of patients with multivessel disease in the present study population received bypass surgery and we would encourage greater use of this technique.

Effective Secondary Prevention of MI

Accumulating evidence is clarifying which drugs are effective for secondary prevention of MI and which are not.^{9,10} In that regard, randomized clinical trials have had a measurable influence on the patterns of medical practice. For example, in 1994 the Antiplatelet Trialists Collaboration concluded that with respect to every category of high-risk patient, antiplatelet therapy was definitely protective.¹¹ In addition, Stafford reported that aspirin use among outpatients with coronary artery disease in the United States increased from 5.0% of patients in 1980 to 26.6% in 1996.¹² In the present study population, aspirin was used more in 1997–1999, possibly encouraged by the results, which showed aspirin (50 mg/day) plus either dipyridamole (150 mg/day) or ticlopidine (200 mg/day) was effective in preventing recurrent MI.¹³ Based on convincing evidence that lowering serum lipid is effective at preventing cardiac events,¹⁴ 52.6% of patients were taking lipid-lowering agents (mostly statins) by 1997–1999. ACEI are effective in patients following MI, particularly those with the signs and symptoms of heart failure or with chronic left ventricular dysfunction.⁹ Consistent with those findings, we also found that increased use of ACEI likely contributes to improved long-term prognosis. The important role of β -blockers for secondary prevention of MI has been pointed out repeatedly,^{15,16} but their use is limited, especially among elderly patients.¹⁷ Use of β -blockers in our study population was high compared with that described by Heller et al, who reported that the use of β -blockers among elderly survivors of acute MI (>65 years of age) increased from 39.6% in 1994 to 58.6% in 1997.¹⁸ Based in part on the recent evidence indicating the efficacy of β -blockers in preventing cardiac events,¹⁹ their use at our institution is relatively high, even among elderly patients, and still higher (71–72%) usage of β -blockers in post-MI patients has been reported in Finland and Sweden.²⁰ Warfarin is effective for prevention of thrombotic events in some patients, and antiarrhythmic agents were used in a selected group within the study population.

Despite the availability of new types of calcium antagonists,²¹ their use has been declining, possibly because of reports that indicated them to be ineffective at preventing secondary MI.^{22,23} In addition, GISSI-3²⁴ and ISIS-4²⁵ have both shown that long-term use of nitrates does not reduce mortality in post-MI patients; indeed studies from Japan^{26,27} indicate long-term use of nitrates may even be deleterious. Although, we found a slight decline in the use of nitrates since 1986, 45.7% of patients were still taking nitrates in 1997–1999. Among elderly survivors of acute MI, 74.8–76.5% are reportedly taking nitrates and other vasodilators,¹⁸ and Rogers et al found that approximately 30% of patients are discharged with nitrates.³ A randomized trial to evaluate long-term nitrate use in coronary artery disease would thus seem warranted.

Coronary Risk Factors

Approximately half the present patients had high serum total cholesterol or a history of hyperlipidemia. Mean total cholesterol declined from approximately 214 mg/dl in

1986–1987 to 199 mg/dl in 1997–1999, perhaps thanks to the increased use of statins. Blood pressure control is important to improve long-term prognosis in post-MI patients.²⁸ Blood pressure was also lower in hypertensive patients in 1997–1999 than in 1986–1987, and among diabetic patients, hemoglobin A1c as well as total cholesterol was markedly lower during the same period. These positive findings among outpatients would be expected to have also contributed to the improved long-term prognosis. However, it was surprising how many post-MI patients have a history of smoking or are presently smokers, and there has been an increase the incidence of obesity among our patients. Perhaps additional patient education for reducing these coronary risk factors may further improve the long-term prognosis of post-MI patients.

Study Limitation

The results of the present study are drawn from post-MI patients at a single institution, and thus may not represent the national trend in Japan. To reach a national consensus on the proper advice for medical doctors and their patients, observations from many institutions in many districts will be needed.

Conclusion

There has been a marked decline in the incidence of cardiac events in post-MI patients during the 14 years of the study. The implementation of the findings of recent clinical trials and more use of therapies known to reduce cardiac events have contributed much to the improvement in long-term prognosis of these patients.

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