Clinical Investigations

PREVENTION

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Contemporary Trends of Optimal Evidence-Based Medical Therapy at Discharge for Patients Surviving Acute Myocardial Infarction From the Korea Acute Myocardial Infarction Registry

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ABSTRACT

Background: Temporal trends of evidence-based optimal medical therapy (OMT) at discharge after acute myocardial infarction (AMI) have not been investigated in recent years.

Hypothesis: OMT should have been increased in AMI and gap between guidelines and practices in its use should have been narrowed.

Methods: We examined discharge medications of 17,578 post-MI patients who had no documented contraindications to antiplatelet agents, β-blockers, angiotensin-converting enzyme inhibitors, or statins across a 6-year period (divided into subperiods of November 2005 to December 2006 [period 1], 2007 [period 2], 2008 [period 3], 2009 [period 4], 2010 [period 5], and January to June 2011 [period 6]) in the Korean AMI Registry. OMT was defined as use of all 4 indicated medications.

Results: Marked increases in OMT (48.6% to 63.2%) were seen irrespective of age and sex, mainly attributed to marked increases in the use of β-blockers (70.3% to 83.7%) and statins (76.9% to 82.6%) from period 1 to period 6. The gap in use of OMT between men and women narrowed over time between the first and second 3 periods, but not between the young and the elderly. Advanced age (odds ratio [OR]: 0.88, $P = 0.04$) was independently associated with underuse of OMT. Adjusted ORs for OMT from period 1 to period 6 were as follows: 1, 1.14 ($P = 0.024$), 1.21 ($P = 0.001$), 1.40 ($P < 0.001$), 1.47 ($P < 0.001$), and 1.69 ($P < 0.001$), respectively.

Conclusions: Despite gradual increase in OMT over time, the gap between guidelines and practices in use of OMT continues to exist.

Introduction

Although previous studies reported that the use of evidence-based optimal medical therapy (OMT), defined as the use of all 4 indicated medications such as antiplatelet agents, β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs), and lipid-lowering drugs (statins), in hospital patients after acute myocardial infarction (AMI) increased markedly over time, OMT remains underused for secondary prevention in Asia as well as in Western countries.[1–12] Therefore, current guidelines for the management of AMI have recommended increasing utilization

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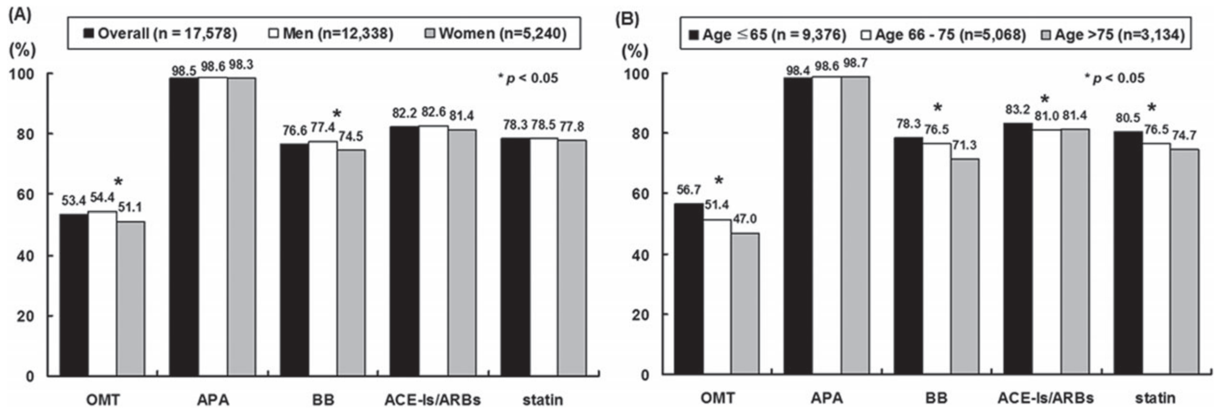

Figure 1. Use of each medication at discharge according to (A) sex and (B) age. Abbreviations: ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; APA, antiplatelet agents; BB, β-blockers; OMT, optimal medical therapy.

rates of OMT in all post-MI patients unless contraindicated.[13,14] Accordingly, clinicians may wonder how many patients are receiving OMT year by year in the current guideline-directed medical therapy era. There are several investigations about the recent trends in discharge medications[15−17]; however, those studies did not primarily focus on the temporal trend of discharge medications, but rather on guideline adherence at the time of discharge and during follow-up.

The primary objective of this study was to describe the current status of, as well as temporal change in, prescription of 4 effective cardiac medications in post-MI patients between 2005 and 2011. Although guidelines for the use of these medications do not differentiate treatment on the basis of age or sex, women and the elderly are treated less aggressively with OMT than men and younger post-MI patients.[10−12,18] However, limited data are available for the recent trend of OMT according to age and sex. Therefore, a secondary goal of this study was to determine whether the use of 4 effective cardiac medications at discharge differs on the basis of age or sex.

Methods

The Korean AMI Registry is a prospective, open, observational, multicenter, online registry of AMI established with support of the Korean Society of Cardiology. It has been in operation since November 2005.[3]

Between November 2005 and June 2011, 29999 patients with a final diagnosis of AMI at admission were recruited into the Korean AMI Registry. Of these patients, baseline clinical data were available for 29 819. The in-hospital mortality was 6.0% (n = 1795); thus, 28 024 patients with AMI survived to hospital discharge.

AMI was diagnosed on the basis of characteristic clinical presentation, serial changes on electrocardiogram suggesting infarction, and increase in cardiac enzymes.[19] All patients were considered to be eligible for antiplatelet agents unless they had a history of life-threatening bleeding, coagulopathy, or thrombocytopenia. Contraindications to β-blockers were defined as significant bradycardia (heart rate <50 bpm) or hypotension (systolic blood pressure <90 mm Hg). ACEIs/ARBs were indicated in patients with heart failure, left ventricular dysfunction (left ventricular ejection fraction [LVEF] <40%), hypertension, or diabetes mellitus (DM) for non−ST-segment elevation MI, and in patients with anterior location, heart failure, or LVEF ≤40% for ST-segment elevation MI unless they had hypotension and severe renal dysfunction (serum creatinine [sCr] >2.5 mg/dL in men or >2.0 mg/dL in women). All patients with AMI were considered to be eligible for statins unless they had a statin intolerance. In the present study, we excluded 2683 (9.6%) patients with incomplete data for discharge medications, 4886 (17.4%) patients who were not indicated in ACEI/ARB use, and 3118 (11.1%) patients with documented contraindications to antiplatelet agents, β-blockers, or ACEIs/ARBs. The number of patients with contraindications to these medications was as follows: 1086 (3.9%), significant bradycardia; 1084 (3.9%), hypotension; 880 (3.1%), severe renal dysfunction; and 68 (0.2%), major bleeding. Finally, 17 578 patients with AMI who survived to hospital discharge were included in analysis. All data were recorded on an electronic Web page−based case-report form. The protocol was approved by the ethics committee of each participating institution.

Data are expressed as mean ± SD for continuous variables and percentages for categorical variables. Differences in various characteristics of patients prescribed OMT across the 6-year period were assessed using analysis of variance (ANOVA) for continuous variables and the χ^2 test for categorical variables. Changes over time in the percentage of patients treated with the 4 cardiac medications were examined using χ^2 tests for trends. Univariate analyses were performed to determine the clinical predictors of OMT. Variables associated with the use of OMT were assessed using the Student *t* test for continuous variables and the χ^2 test for categorical variables. Multivariate logistic-regression models were constructed to examine changing trends in the use of OMT overall and according to age and sex while controlling for factors possibly affecting prescription of the medications. These factors included variables with a *P* value <0.05 on univariate analysis, such as patient age, sex, body mass index, type of MI, location of MI, Killip class, LVEF, previous coronary heart disease (CHD), hypertension, hyperlipidemia, smoking status, sCr levels, percutaneous coronary intervention, and coronary

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Table 1. Characteristics in Patients Receiving OMT According to Study Period

	Entire, N = 17578	Period 1 Nov 2005–Dec 2006, n = 4911	Period 2 2007, n = 3162	Period 3 2008, n = 3545	Period 4 2009, n = 3189	Period 5 2010, n = 1959	Period 6 2011 Jan-Jun, n = 812
Prescription rates of OMT[a]	9338 (53.4)	2386 (48.6)	1595 (50.4)	1908 (53.8)	1841 (57.7)	1145 (58.4)	513 (63.2)
Demographics							
Age, y							
≤65[a]	5312 (56.7)	1384 (51.6)	915 (53.1)	1095 (58.2)	1006 (60.2)	640 (62.9)	272 (68.2)
66–75[a]	2604 (48.6)	667 (47.1)	461 (49.7)	501 (48.9)	521 (57.4)	315 (56.5)	139 (58.9)
>75[a]	1472 (47.0)	335 (41.3)	219 (42.8)	312 (48.8)	314 (51.5)	190 (49.5)	102 (57.6)
M sex[a]	6710 (54.4)	1722 (50.4)	1132 (50.7)	1352 (54.7)	1304 (57.6)	820 (59.7)	380 (65.2)
F sex[a]	2678 (51.1)	664 (44.5)	463 (49.7)	556 (51.7)	537 (58.0)	325 (55.5)	133 (58.1)
BMI (kg/m²)	24.3 ± 3.2	24.2 ± 3.2	24.4 ± 3.2	24.3 ± 3.3	24.3 ± 3.2	24.3 ± 3.2	24.1 ± 3.2
Initial presentation							
SBP (mm Hg)	134.7 ± 25.4	134.4 ± 26.0	135.1 ± 25.3	135.3 ± 24.9	134.9 ± 25.5	133.1 ± 24.9	135.0 ± 25.5
Heart rate (bpm)	79.9 ± 17.1	79.5 ± 17.5	80.6 ± 16.8	80.0 ± 17.3	79.5 ± 17.0	79.9 ± 16.7	80.4 ± 17.0
STEMI (%)[a]	5711 (55.6)	1503 (50.1)	997 (52.3)	1171 (56.8)	1108 (60.9)	669 (61.3)	263 (65.9)
Anterior MI[a]	5114 (55.9)	1397 (50.5)	894 (52.8)	1060 (57.5)	868 (61.3)	622 (61.9)	273 (63.9)
Inferior MI[a]	2237 (51.6)	592 (45.4)	401 (47.3)	470 (53.8)	396 (57.7)	257 (58.4)	121 (64.7)
Killip class >1[a]	2325 (48.4)	560 (41.3)	373 (44.8)	510 (48.8)	526 (55.8)	228 (54.0)	128 (61.8)
LVEF, %[a]	51.7 ± 12.7	51.0 ± 15.3	51.2 ± 11.8	52.2 ± 12.0	52.0 ± 11.7	52.6 ± 11.3	51.7 ± 11.1
Past history							
Previous CHD[a]	1309 (47.1)	364 (44.0)	208 (44.7)	258 (45.5)	243 (48.4)	146 (53.1)	90 (61.6)
HTN[a]	5238 (54.4)	1300 (49.3)	879 (51.6)	1045 (54.3)	1039 (59.3)	660 (58.9)	315 (64.9)
DM[a]	2721 (53.1)	711 (49.4)	463 (51.0)	535 (52.9)	537 (57.2)	327 (56.8)	148 (60.2)
Hyperlipidemia[a]	1184 (59.6)	216 (51.3)	218 (58.3)	273 (62.6)	228 (66.5)	172 (58.5)	77 (65.3)
Current smoking[a]	4097 (55.5)	1044 (50.5)	722 (53.4)	847 (55.6)	806 (60.1)	480 (61.1)	198 (64.3)
Laboratory findings							
Glucose (mg/dL)	168.6 ± 75.6	169.9 ± 76.6	168.2 ± 73.6	165.9 ± 73.6	168.4 ± 72.8	169.5 ± 81.2	173.4 ± 80.6
sCr (mg/dL)[a]	0.97 ± 0.26	0.99 ± 0.26	0.98 ± 0.26	0.97 ± 0.27	0.97 ± 0.27	0.95 ± 0.27	0.93 ± 0.26
Peak CK-MB (ng/mL)[a]	132.2 ± 257.1	149.0 ± 302.7	148.5 ± 323.1	127.1 ± 176.2	116.9 ± 163.5	116.5 ± 318.8	111.5 ± 131.4
Total cholesterol (mg/dL)[a]	188.5 ± 44.9	188.5 ± 45.1	188.4 ± 44.1	188.6 ± 43.6	190.6 ± 47.2	159.5 ± 44.2	179.7 ± 44.2
TG (mg/dL)	133.3 ± 107.5	131.7 ± 105.2	129.7 ± 114.9	133.3 ± 99.9	135.4 ± 112.0	140.4 ± 108.6	128.6 ± 102.0
HDL-C (mg/dL)[a]	45.0 ± 18.9	46.0 ± 19.7	46.4 ± 28.4	45.2 ± 12.4	44.5 ± 17.2	42.9 ± 12.9	42.6 ± 13.3
LDL-C (mg/dL)[a]	118.8 ± 39.5	117.9 ± 40.1	118.8 ± 39.7	118.7 ± 39.3	121.2 ± 39.3	120.8 ± 39.1	111.8 ± 38.2
PCI at index hospitalization[a]	8590 (57.3)	2113 (52.5)	1423 (54.4)	1771 (57.0)	1713 (61.5)	1086 (62.7)	484 (66.9)
CABG at index hospitalization[a]	205 (37.3)	22 (19.6)	9 (15.0)	19 (32.2)	119 (53.1)	36 (43.4)	0 (0.0)
Multivessel disease[a]	4959 (55.2)	1283 (50.7)	855 (53.2)	1033 (56.0)	908 (57.8)	592 (60.2)	288 (64.9)

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; CHD, coronary heart disease; CK-MB, creatine kinase-MB; Dec, December; DM, diabetes mellitus; F, female; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; Jan, January; Jun, June; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; M, male; MI, myocardial infarction; Nov, November; OMT, evidence-based optimal medical therapy; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; sCR, serum creatinine; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; TG, triglycerides.
Data are expressed as mean ± SD or n (%).
[a] $P < 0.05$.

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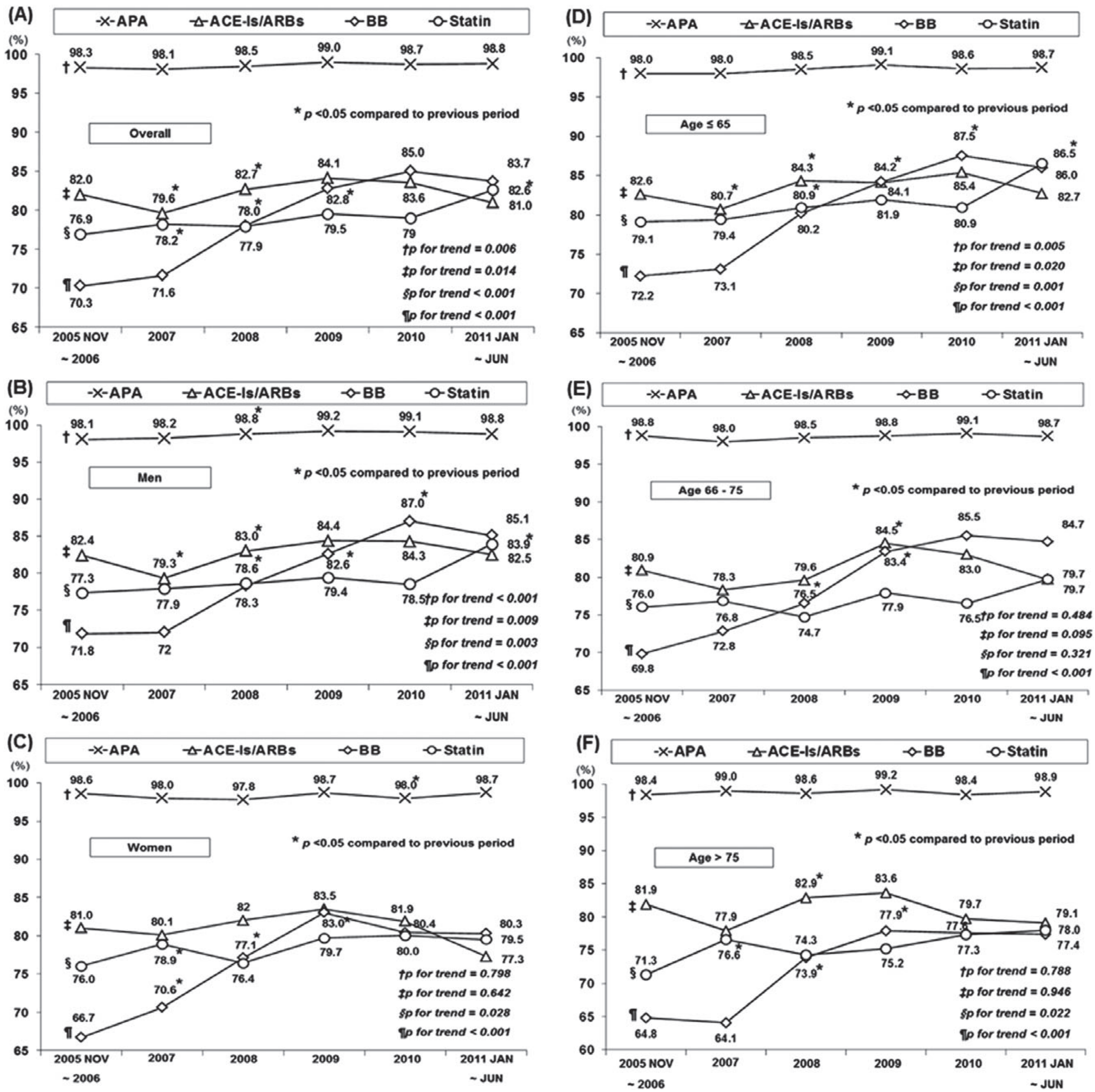

Figure 2. Time trends in the prescription of selected medications for (A) overall, (B) men, (C) women, and those according to age: (D) age ≤65 years, (E) age 66 to 75 years, and (F) age >75 years. Abbreviations: ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; APA, antiplatelet agents; BB, β-blockers.

artery bypass grafting at hospitalization. Study period was also included as a variable. For all analyses, a 2-sided P value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL).

Results

The OMT was prescribed at discharge in 54.4% of men and 51.1% of women ($P < 0.001$; Figure 1A). Among OMT, β-blockers were more frequently prescribed in men than in women ($P < 0.05$). Optimal medical therapy was prescribed at discharge in 56.7% of patients age ≤65 years, 51.4% of patients age 66 to 75 years, and 47.0% of patients age >75 years (P for trend <0.05; Figure 1B). β-Blockers, ACEIs/ARBs, and statins were more frequently prescribed in younger patients than in the elderly (P for trend <0.05, respectively).

Factors associated with the use of OMT over time are shown in Table 1. Marked increases in the use of OMT (from 48.6% to 63.2%; $P < 0.001$) occurred from period 1 to period 6. The increased use of OMT was evident both in men (from 50.4% to 65.2%) and women (from 44.5% to 58.1%) over time (P for trend <0.001, respectively). In the

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first 3 periods, there was significant difference in the use of OMT between men and women (51.8% vs 48.1%; $P < 0.001$). However, there was no significant difference in the use of OMT between men and women in the second 3 periods (59.4% vs 57.2%; $P = 0.117$). The gap in the prescription rate of OMT between men and women narrowed over time between the first 3 periods and the second 3 periods (from 3.7% point to 2.2% point). Marked increase in the use of OMT was noted across all age strata (P for trend <0.001, respectively): ≤65 years (from 51.6% to 68.2%), 66 to 75 years (from 47.1% to 58.9%), and >75 years (from 41.3% to 57.6%). There were significant differences in the use of OMT among 3 age groups, both in the first 3 periods (54.0% vs 48.4% vs 44.1%; $P < 0.001$) and the second 3 periods (62.1% vs 57.3% vs 51.8%; $P < 0.001$). The gap in the prescription rate of OMT among 3 age groups did not narrow over time. These trends were similarly observed in patients with high-risk clinical features such as ST-elevation MI, higher Killip class, past history of CHD, hypertension, DM, hyperlipidemia, current smoking, and multivessel disease.

Increases were consistently observed in the singular use of each component of the OMTs examined. Particularly, marked relative increases from period 1 to period 6 were observed in the use of β-blockers (from 70.3% to 83.7%) and statins (from 76.9% to 82.6%), whereas less dramatic increases were noted in the use of ACEIs/ARBs (Figure 2A). Few increases in the use of antiplatelet drugs occurred over time because most (approximately 98%) AMI patients in hospital were treated with this therapy. In both men and women, the prescription of β-blockers and statins increased more over time (Figure 2B,C). In contrast, increased use of antiplatelet agents and ACEIs/ARBs was more evident in men than in women.

The prescription rate of β-blockers increased more over time across all age groups (Figure 2D–F). In contrast, in patients age 66 to 75 years and >75 years, the prescription of antiplatelet agents and ACEIs/ARBs increased less over time. The increased use of statins was more evident in patients age ≤65 years (from 79.1% to 86.5%) and in patients age >75 years (from 71.3% to 78.0%) than in patients age 66 to 75 years (from 76.0% to 79.7%).

In multivariate logistic regression analysis, a progressive increase over time occurred in the prescription of OMT after adjustment for several confounding factors (Table 2). The odds ratios (ORs) for the use of OMT from period 1 to period 6 were as follows: 1, 1.14 ($P = 0.024$), 1.21 ($P = 0.001$), 1.40 ($P < 0.001$), 1.47 ($P < 0.001$), and 1.69 ($P < 0.001$), respectively. Age >75 years, Killip class >1, LVEF <40%, previous CHD, sCr levels, and coronary artery bypass grafting surgery were negative predictors of OMT use, whereas body mass index, anterior MI, hypertension, hyperlipidemia, and percutaneous coronary intervention were positive predictors of OMT use. Female sex was not an independent predictor of the use of OMT.

Multivariate analyses were also performed separately in men and women (Figure 3A). The ORs for the use of OMT from period 1 to period 6 were as follows: 1, 1.12 ($P = 0.106$), 1.20 ($P = 0.006$), 1.24 ($P = 0.003$), 1.43 ($P < 0.001$), and 1.71 ($P < 0.001$), respectively, in men; and 1, 1.17 ($P = 0.124$), 1.21 ($P = 0.065$), 1.88 ($P < 0.001$), 1.54 ($P = 0.01$), and 1.62 ($P = 0.007$), respectively, in women.

Table 2. Multivariate Logistic Regression Analysis for Prescribing of OMT at Discharge

Variables	OR	95% CI	*P* Value
Study period			
November 2005–December 2006	Ref		
2007	1.14	1.02-1.27	0.024
2008	1.21	1.08-1.34	0.001
2009	1.40	1.24-1.58	<0.001
2010	1.47	1.28-1.68	<0.001
2011 January–June	1.69	1.40-2.03	<0.001
Age, y			
≤65	Ref		
66–75	0.95	0.87-1.04	0.289
>75	0.88	0.78-0.99	0.040
F sex	1.01	0.92-1.12	0.795
BMI	1.03	1.02-1.05	<0.001
STEMI	1.03	0.92-1.10	0.941
Anterior MI	1.14	1.04-1.24	0.003
Killip class >1	0.87	0.80-0.95	0.002
LVEF <40%	0.81	0.73-0.89	<0.001
Previous CHD	0.86	0.77-0.96	0.007
HTN	1.17	1.07-1.27	<0.001
Hyperlipidemia	1.25	1.11-1.41	<0.001
Current smoking	1.04	0.96-1.14	0.343
sCR	0.81	0.70-0.94	0.006
PCI	2.39	2.11-2.70	<0.001
CABG surgery at hospitalization	0.32	0.22-0.47	<0.001

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; CHD, coronary heart disease; CI, confidence interval; F, female; HTN, hypertension; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OMT, evidence-based optimal medical therapy; OR, odds ratio; PCI, percutaneous coronary intervention; Ref, reference; sCR, serum creatinine; STEMI, ST-segment elevation myocardial infarction.

Increases in the use of OMT at discharge were also observed in 3 age groups examined (Figure 3B). In multivariate logistic regression analyses, the ORs for the use of OMT from period 1 to period 6 were as follows: 1, 1.11 ($P = 0.18$), 1.33 ($P < 0.001$), 1.26 ($P = 0.006$), 1.51 ($P < 0.001$), and 1.76 ($P < 0.001$), respectively, in patients age ≤65 years; 1, 1.22 ($P = 0.061$), 1.04 ($P = 0.73$), 1.68 ($P < 0.001$), 1.40 ($P = 0.009$), and 1.56 ($P = 0.01$), respectively, in patients age 66 to 75 years; and 1, 1.12 ($P = 0.417$), 1.19 ($P = 0.20$), 1.51 ($P = 0.005$), 1.50 ($P = 0.013$), and 1.75 ($P = 0.009$), respectively, in patients age >75 years.

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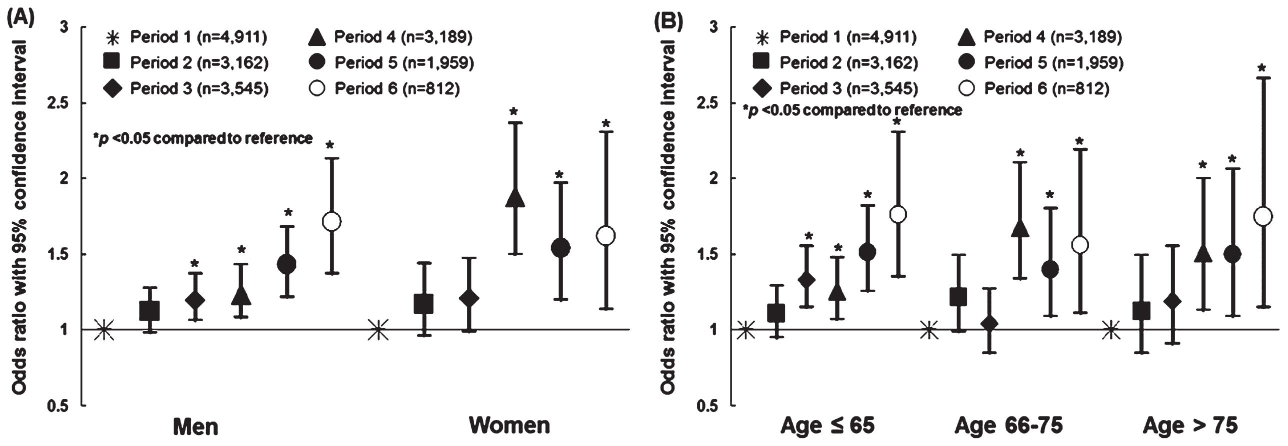

Figure 3. Multivariate logistic regression analysis for prescription of OMT at discharge according to (A) sex and (B) age by 6 time periods, with period 1 as the reference. The multivariate model includes all variables used in Table 2. Abbreviations: OMT, optimal medical therapy.

Discussion

Although recommended cardiac drugs are still prescribed at suboptimal rates, significant improvement was seen year by year in the use of OMT at discharge in post-MI patients. The gap in the use of OMT between men and women narrowed over time in recent years; however, a significant gap still remained in the use of OMT between the young and the elderly. Advanced age, but not female sex, was independently associated with the underprescription of OMT.

The most intriguing finding of this study is that the gaps in the use of OMT between men and women narrowed over time during the study period. Although female sex has been associated with underprescription of OMT in post-MI patients at discharge in studies conducted more than 5 years previously,[10–12,18] the current study showed that trends in prescribing OMT according to sex were changing. However, underprescription of OMT in older patients has not changed over time in recent years. Moreover, advanced age was independently associated with lower use of OMT, and this is consistent with the results of previous studies.[2,10,20–22] Although emerging evidence suggests that older patients can receive similar benefits from aggressive cardiac therapy,[23–25] clinicians are usually reluctant to prescribe aggressive medical therapies for older patients because advanced age may be associated with an increased prevalence of comorbidities and higher incidence of adverse drug effects.[3] However, despite clinicians' unwillingness, in our study we observed marked increases in the prescription of each of the OMT medications examined, and combinations thereof, in the elderly over time. Although this is not sufficient to overcome the gap between the young and the elderly, these encouraging trends in the elderly might influence the prescription rate of OMT in the female sex. Because women are nearly a decade older than men at the time they present with AMI, increased prescription rates of OMT in the elderly may contribute to increase of the prescription of OMT in women. As a result, female sex was not independently associated with lower use of OMT in the present study.

Two plausible explanations exist for the encouraging trends of OMT in the elderly and female sex over time. First, contemporary adherence to current guidelines for management of AMI appears to be influencing the increased prescription of OMT in patients of both sexes and across all ages.[13,14] However, prescriptions at discharge are not necessarily equated to medications taken. Continuing educational approaches might encourage clinicians to treat these high-risk patients in a more optimal manner.[26–28]

Second, a unique quality improvement program (QIP) in Korea might have influenced decisions regarding discharge medication. Quality assessment, as legally stipulated in Korea, has been one of the main roles of the Health Insurance Review & Assessment Service since 2000.[29] The QIP evaluated performance of 181 health care providers and disclosed the results to the public with a small incentive. The trial projects for AMI were completed between July 2007 and December 2010, and the program was implemented in 2011. The program aims to reduce the quality gap among health care providers and improve service quality to reach a certain level. The quality assessment of AMI utilized both administrative and clinical data, including rate of aspirin prescribed at discharge and rate of β-blockers prescribed at discharge.[30] This might help explain why most post-MI hospital patients were treated with antiplatelet agents (approximately 98%) and the prescription of β-blockers markedly increased over time, irrespective of age and sex.

Study Limitations

Our study had several potential limitations. First, the reasons for nonprescription of each medication, such as statin intolerance, and details regarding dosages of prescribed medications or use of specific medications within a class of agents were not obtained from patients and their physicians. As a result, we were unable to accurately exclude patients with contraindications from our analyses, and we may have underestimated the prescription rates for the 4 individual drug classes examined. Second, data on the use of aldosterone receptor blockade were not sufficient for analysis of a temporal trend and predictors of this effective medication in the present study. However, the limitations of the study should not undermine our assessment of discharge medication use among post-MI hospital patients.

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Conclusion

The prescription rates of guideline-directed medical therapy have continued to rise year by year during the recent study period. The previously observed inequality in medication practices between men and women has been attenuated. Despite these encouraging trends, the gap between guidelines and practices in the use of OMT continues to exist in the older patients. Filling this gap will require concerted efforts such as continued educational programs and novel QIPs.

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