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Age-Related Differences in Management of Heart Disease: A Study of Cardiac Medication Use in an Older Cohort

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BACKGROUND: Previous studies have suggested suboptimal use of cardiac medications for secondary prevention after myocardial infarction (MI) and atrial fibrillation (AF), especially among older people.

OBJECTIVE: To determine whether patients older than 75 years are less likely than those aged 65 to 74 to be prescribed medications with evidence-based indications, including angiotensin-converting enzyme (ACE) inhibitors for left ventricular dysfunction (LVD) and/or diabetes mellitus (DM), aspirin and/or β -blockers for those with a history of MI, and warfarin for chronic AF.

DESIGN: A retrospective cohort study.

SETTING: Twenty-nine hospitals, predominantly tertiary-care institutions.

PARTICIPANTS: A total of 407 patients randomized to ventricular or dual-chamber pacing from February 26, 1993, to September 30, 1994, in the Pacemaker Selection in the Elderly (PASE) trial.

MEASUREMENTS: A review of the patient's medical history and a physical exam at study enrollment, three follow-up timepoints, and a study closeout.

RESULTS: Patients older than 75 years with LVD and/or DM were less likely to be prescribed ACE inhibitors (OR = .56 (0.31–1.00)); patients older than 75 with a history of MI were less likely to be taking aspirin (OR = .43 (0.19–.95)), and patients older than 75 with AF were less likely to be prescribed warfarin (OR = .18 (0.05–.61)). Patients older than 75 years of age with any or all of the conditions studied were less likely to be prescribed indicated medications than those ages 65 to 74 (OR = .35 (0.18–.70)), after controlling for between-group differences in comorbidity, gender, and number of noncardiac medications.

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CONCLUSION: Older age is a significant independent negative correlate of evidence-based cardiac medication use in this cohort. Causes for this finding need to be explored. *J Am Geriatr Soc* 47:145–150, 1999.

Key words: variation in care; age; cardiovascular disease treatment

Well designed clinical studies can identify a preferred treatment strategy for the management of a cardiovascular disease and its complications, but the implementation of such strategies is uneven. Evidence from randomized efficacy trials during the past 10 years supports the use of angiotensin-converting enzyme (ACE) inhibitors in patients with left ventricular dysfunction (LVD),^{1–5} aspirin, and β -blockers prescribed after myocardial infarction (MI)^{6,7} and warfarin prescribed for atrial fibrillation (AF).^{8–10} ACE inhibitors have also been shown to benefit some patients with diabetes mellitus (DM).¹¹ However, studies suggest that many patients, especially older patients, are not being prescribed these effective medications after diagnosis of MI or AF.^{12–20} Using data from patients enrolled in a clinical trial of dual-versus single-chamber pacing, we sought to determine whether persons older than age 75 with LVD, DM, history of MI, and/or AF were less likely to be managed with evidence-based medications than those ages 65 to 74.

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METHODS

Patient Population

The Pacemaker Selection in the Elderly study (PASE) was a single-blind, 29-center trial that randomized 407 patients to ventricular or dual-chamber pacing.²¹ Patients were eligible for the study if they required a permanent pacemaker for the prevention or treatment of bradycardia, were aged 65 or older and in sinus rhythm, and gave informed consent for research participation. Patients were excluded from the study if they (1) could not participate in quality of life assessments; (2) had clinically overt congestive heart failure (CHF) that required treatment before consideration of pacemaker implantation; (3) had AF without any documented sinus mechanism for more than 6 months; (4) had a serious noncardiac illness; or (5) had inadequate atrial capture or sensing thresholds.

Data Collection

Clinical Data

Patients were recruited from February 26, 1993, to September 30, 1994, and were followed until clinical closeout, which began on June 1, 1995, and ended August 31, 1995. At study enrollment, each clinical site recorded the age, sex, and race of participants. Each participant also underwent a medical history, including a review of all current medications and chronic medical conditions, as well as a detailed cardiovascular physical examination, which documented vital signs and any evidence of cardiovascular compromise such as the presence of rales or an S3 gallop suggestive of CHF. Additionally, 12-lead electrocardiograms were obtained. The examining physician was asked to record whether the patient had a history of CHF, AF, or MI. At 3-month, 9-month, 18-month, and closeout follow-up visits, physical exams and electrocardiograms were repeated, and any changes in medications, as well as new cardiovascular diagnoses, were recorded.

Definition of Prevalent and Incident LVD

Participants were classified with prevalent LVD if any of the following were true at baseline: (1) their physicians indicated they had CHF; (2) they exhibited clinical signs of CHF (rales \geq 1/3 of chest or S3 gallop on physical exam); or (3) they had a left ventricular ejection fraction of less than 40% on diagnostic testing or left ventricular function was qualitatively described as "moderately depressed" or "severely depressed." The rationale for the composite definition of LVD is that it describes a group of persons for whom ACE inhibitor therapy would be indicated based on results from randomized controlled trials. We used sensitivity analyses to see if the specific case definition for LVD influenced the conclusions from our models. When looking at incident LVD during follow-up, we used only the physician's impression that a patient had developed CHF.

Definition of Indicated Medication Use for Incident LVD and AF

For both incident LVD and incident AF, if a patient was found to be on the indicated therapy at any follow-up time point after the incident was recorded, we considered this "indicated use." If information about use of the medication was missing after the event, this patient was excluded from the analysis ($n = 5$ for incident CHF, $n = 6$ for incident AF).

Medical Comorbidity

We computed an unweighted sum of comorbidities as 0, 1, 2, or 3 or more. These comorbidities, based on the Charlson Comorbidity Index,²² included peripheral vascular disease, cerebrovascular disease, hemiplegia, dementia, diabetes with end-organ damage, moderate or severe renal disease, chronic pulmonary disease, connective tissue disease, mild liver disease, moderate or severe liver disease, any tumor, leukemia or lymphoma, metastatic solid tumor, and AIDS. Past MI, CHF, DM, and ulcer disease were not included in the comorbidity sum in order to assess the independent effects of these variables on medication use.

Cardiac and Noncardiac Medications

PASE questionnaires included a checklist for the following cardiac medications: ACE inhibitors, aspirin, β -blockers,

calcium antagonists, warfarin, digitalis, diuretics, nitrates, various classes of antiarrhythmic drugs (amiodarone, flecainide/encaïnide, procainamide, propafenone, quinidine, and sotalol), and other. The baseline noncardiac medication checklist included insulin, oral hypoglycemics, thyroid hormone, estrogen, nonsteroidal anti-inflammatory drugs, and other. We coded the number of noncardiac medications (a "yes" response for other medication was counted) as 0, 1, or 2 or more for use in the multivariate analysis as an indicator of polypharmacy.

Statistical Analysis

To evaluate the influence of age on compliance with evidence-based guidelines for the management of LVD, DM, AF, and post-MI patients, we dichotomized the population into those aged 65 to 74 and those 75 years and older (sample median age: 76). To determine whether the observed relationship between age and medication use was a function of the cut-point, we analyzed age both as a dichotomous and as a continuous variable in the pooled analysis (see below) and found that age was a significant correlate of medication use in both models.

All unadjusted comparisons utilized the chi-square test. We performed chi-square analyses on prevalent data to test the association between age and (1) use of ACE inhibitors for those with LVD (the strongest indication); (2) use of ACE inhibitors for persons with a specific indication (DM or LVD); (3) use of aspirin and β -blockers among participants who had a previous MI; and (4) use of warfarin among those with AF. We considered comparisons statistically significant at $P \leq .05$.

Because differences in other characteristics between age groups could confound our analysis, we also constructed multivariate logistic regression models that adjusted for the independent effects of gender, comorbidity, and use of other medications on medication use for each of the clinical conditions described above. For the multivariate analysis of aspirin use among study participants with a previous MI, we adjusted for between-group differences in peptic ulcer disease (a known contraindication) and warfarin use. For patients with AF, we also created a multivariate model in which aspirin and/or warfarin use was the outcome variable since both therapies have been shown to reduce the risk of stroke, and some patients may have had contraindications to warfarin but not to aspirin.

Because the observed effect of age was similar across the various evidence-based indications, we conducted a pooled analysis. The outcome variable was use of condition-specific, evidence-based medications. Patients were managed according to indication if they received all evidence-based medications indicated by their conditions. However, in a post-MI patient with AF, we considered aspirin use and/or warfarin use to be a positive outcome, because of the lack of clear evidence at the time of the study to support aspirin alone, warfarin alone, or aspirin with warfarin in this patient group.

For cases of incident LVD and AF, we looked at use of indicated medications after the incident, using chi-square analyses to compare the proportion using evidence-based treatments in each age group. We did not examine medication use after incident myocardial infarction because there were too few cases ($n = 5$). Multivariate analyses for incident LVD and AF included all variables that achieved a signifi-

cance of $P \leq .10$ in our multivariate analyses of prevalent LVD and AF.

RESULTS

Study Sample

The 407 patients (41% female, 86% white) included 177 patients less than 75 years of age (43%) and 230 patients aged 75 and older (57%) (Table 1). A total of 148 patients had prevalent LVD, 133 had a previous MI, and 97 had a history of atrial fibrillation or flutter. There was no difference in the distribution of these conditions by age group. However, significantly fewer older patients had DM. Older persons also had poorer cardiovascular function as measured by the Specific Activity Scale (SAS, $P = .005$).

Medication Use: Prevalent Data

In the overall cohort, ACE inhibitors were used by 47% of those with LVD and by 44% of patients with a specific indication for these drugs (LVD and/or DM). Patients with a history of MI received aspirin and β -blockers at rates of 54% and 19%, respectively. Patients with a history of AF received warfarin at a rate of 17% and received aspirin and/or warfarin at a rate of 49%.

Bivariable Analysis (Table 2, Figure 1)

Among patients with LVD, the trend toward less ACE inhibitor use in those aged 65 to 74 compared with those 75 years of age or older was not statistically significant (RR =

Table 2. Unadjusted Cardiac Medication Use by Age

	RR (95% CI)* for Age ≥ 75
Pts. with LVD [†] (n = 148)	
On ACE inhibitors [†]	0.79 (0.56–1.10)
On digitalis	1.03 (0.61–1.74)
On diuretics	1.09 (0.85–1.39)
On nitrates	0.86 (0.58–1.26)
Pts. w/LVD and/or DM [†] (n = 206)	
On ACE inhibitors	0.72 (0.53–0.98)
Pts. w/history of MI [†] (n = 133)	
On aspirin	0.73 (0.53–0.99)
On beta blockers	0.57 (0.28–1.16)
Pts. w/history of AF [†] (n = 97)	
On warfarin	0.27 (0.10–0.71)

*Bold represents statistically significant relative risks at $P \leq .05$.
[†]ACE: angiotensin-converting enzyme; LVD: left ventricular dysfunction; DM: diabetes mellitus; MI: myocardial infarction; AF: atrial fibrillation or flutter.

.79 (0.56–1.10)). Digitalis, diuretic, and nitrate use were also similar between the two age groups. Patients with a specific indication for an ACE inhibitor (LVD and/or DM) were less likely to receive that therapy if they were 75 or older (RR = .72 (0.53–.98)). In addition, patients with a history of MI who were aged 75 or older were less likely to be prescribed aspirin (RR = .73 (0.53–.99)). The trend toward less β -blocker use among older patients with a history of MI (RR = .57 (0.28–1.16)) was not statistically significant. In patients with a history of atrial fibrillation or flutter, those aged 75 and older were less likely to be prescribed warfarin than those age 65 to 74 (RR = .27 (0.10–.71)). Overall, all trends were for less medication use in those aged 75 and older. Furthermore, an adjusted pooled analysis examining evidence-based medication use among patients with any or all of the conditions studied showed a significant age effect (Table 3).

Multivariable Analysis by Medication (Table 3)

Age was a significant correlate of medication use — after controlling for gender, comorbidity, and use of other medications — in the specific cases of ACE inhibitors for LVD and/or DM, aspirin and MI, and warfarin and AF. In addition, patients with AF who were older than age 75 were less likely to be taking aspirin and/or warfarin. Factors in our multivariate models, such as female sex, comorbidity, and number of noncardiac medications, were not associated significantly with medication use.

Medication Use: Incident Data

Of 47 cases of incident LVD, 24 were less than age 75, and 23 patients were aged 75 years and older. Of patients younger than age 75, 83% were found to be taking ACE inhibitors following the diagnosis of LVD versus 61% of patients aged 75 and older (RR = .73 (0.50–1.06)). Among 67 patients with incident AF, 29 were less than age 75 and 38 were age 75 and older. Of patients younger than 75 years of age, 38% were taking warfarin at some point after their incident AF versus 50% of patients aged 75 and older (RR = 1.32 (0.75–2.31)).

Table 1. Demographic and Medical Characteristics of the Study Sample

	Age <75 n (%)	Age ≥ 75 n (%)	P Value
All patients (n = 407)	177 (43)	230 (57)	
Female	57 (32)	108 (47)	.003
White	152 (86)	199 (87)	.68
Prevalent LVD*	61 (34)	87 (38)	.48
History of MI*	56 (32)	77 (33)	.70
History of AF*	36 (20)	61 (27)	.15
Diabetes mellitus	58 (33)	50 (22)	.01
Hypertension	88 (50)	123 (54)	.45
Peptic ulcer disease	12 (7)	28 (12)	.07
Other comorbidities			
0	92 (52)	127 (55)	.33
1	60 (34)	62 (27)	
2	18 (10)	25 (11)	
3 or more	7 (4)	16 (7)	
SAS class*			.005
I	84 (47)	71 (31)	
II	31 (18)	60 (26)	
III	60 (34)	93 (40)	
IV	2 (1)	6 (3)	
No. of noncardiac medications			.56
0	67 (38)	87 (38)	
1	69 (39)	99 (43)	
2 or more	41 (23)	44 (19)	

*LVD: left ventricular dysfunction; MI: myocardial infarction; AF: atrial fibrillation or flutter; SAS: Specific Activity Scale.²⁸

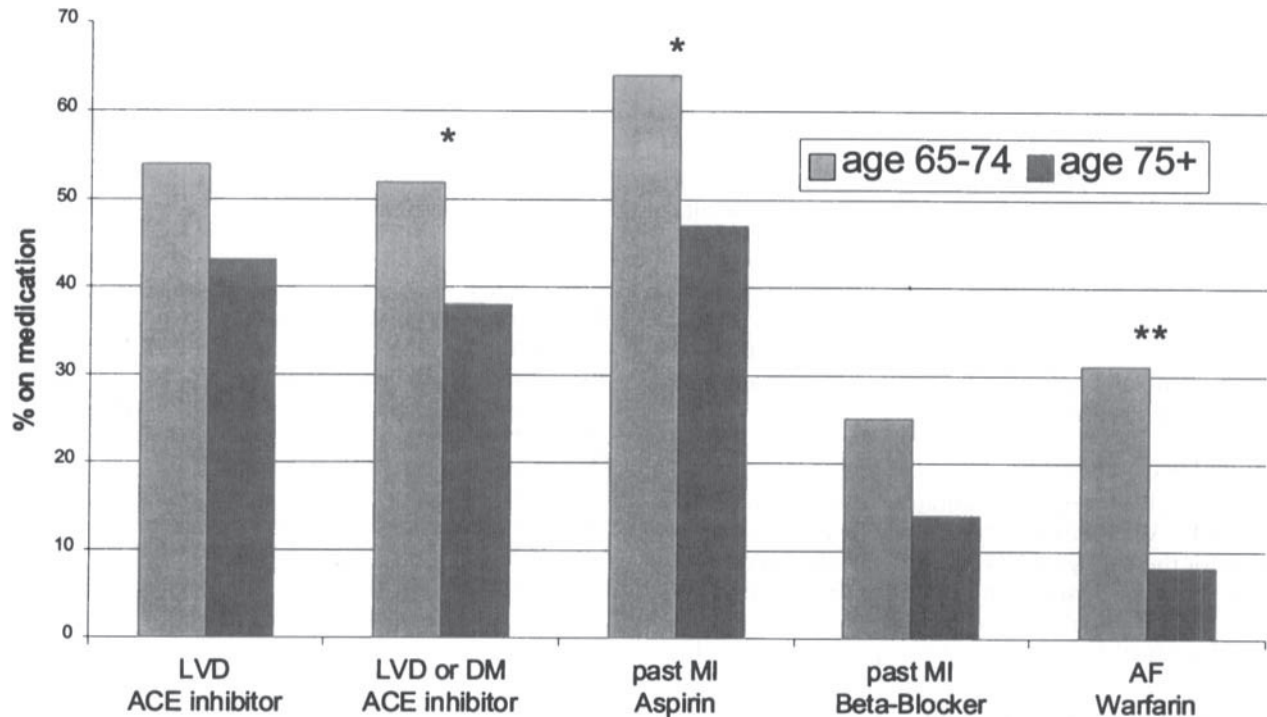


Figure 1. Unadjusted comparisons of medication usage by age group. The upper row of labels along the x-axis indicates the group of patients in whom medication use was assessed. The lower row of labels indicates the medication being used. ACE = angiotensin converting enzyme, LVD = left ventricular dysfunction, DM = diabetes mellitus, MI = myocardial infarction, AF = history of atrial fibrillation or flutter. Chi-square analysis was performed to test for statistical significance: * = significantly different at $P < .05$; ** = significantly different at $P < .01$.

Table 3. Factors Associated with Prevalent Medication Use in Selected Diagnostic Groups (Odds Ratio and 95% Confidence Intervals from Multivariate Models)*

	Age ≥ 75	Female	Comorbidity	No. of Noncardiac Medications
Pts. with LVD (n = 148)				
On ACE inhibitors	0.64 (0.33–1.25)	0.85 (0.43–1.71)	1.05 (0.75–1.47)	0.97 (0.64–1.47)
Pts. with LVD and/or DM (n = 206)				
On ACE inhibitors [†]	0.56 (0.31–1.00)	0.95 (0.51–1.80)	0.95 (0.70–1.30)	0.90 (0.62–1.31)
Pts. with history of MI (n = 133)				
On aspirin [‡]	0.43 (0.19–0.95)	0.47 (0.20–1.08)	0.73 (0.50–1.06)	1.32 (0.78–2.23)
On β -blockers [§]	0.47 (0.18–1.22)	0.78 (0.26–2.33)	0.77 (0.45–1.29)	1.10 (0.57–2.11)
Pts. with history of AF (n = 97)				
On warfarin	0.18 (0.05–0.61)	0.71 (0.21–2.34)	1.20 (0.53–2.69)	0.47 (0.20–1.12)
On warfarin and/or aspirin [¶]	0.40 (0.16–0.98)	0.60 (0.25–1.42)	0.97 (0.57–1.67)	1.16 (0.66–2.05)
Pooled analysis (n = 274)				
On evidence-based medications	0.35 (0.18–0.70)	1.30 (0.65–2.60)	0.68 (0.44–1.03)	0.96 (0.61–1.51)

*Bold represents statistically significant odds ratios.

[†]Also controlled for hypertension and history of MI.

[‡]Also controlled for LVD, DM, warfarin use, and ulcer disease.

[§]Also controlled for LVD and DM.

[¶]Also controlled for history of MI.

^{||}Also controlled for number of indications ($P < .001$), hypertension, and ulcer disease.

DISCUSSION

In this sample of older adults with underlying cardiac disease, we found low rates of use of all of the medications examined — ACE inhibitors (47% of those with LVD), aspirin (54% of those post-MI), β -blockers (19% of those post-MI), and warfarin (17% of those with a history of AF). These results are similar to population-based studies among

those aged 65 and older that have shown suboptimal rates of discharge prescription of ACE inhibitors (45%),²³ aspirin (76%),¹⁵ and β -blockers (21%)¹⁷ among post-MI patients without contraindications. However, this study sample had substantially lower rates of warfarin use among patients in AF than previous studies among patients without contraindications, which showed a usage rate of 79% at a Massachu-

setts HMO²⁴ and 64% at a group of five Pennsylvania hospitals.²⁵ Unmeasured contraindications such as risk of falling could account for some of the observed difference in usage rates for warfarin. In addition, evidence supporting anticoagulation with warfarin for paroxysmal AF, which comprised the vast majority of AF seen among PASE participants, might not have altered practice patterns by the time of this trial. However, when we broadened our definition of evidence-based preventive therapy for stroke to include aspirin and/or warfarin (which would diminish the pool of patients with contraindications), we still found that only 49% of patients in AF were using either or both medications. It is clear that although results from randomized controlled clinical trials do influence medical practice,²⁶ evidence alone is inadequate for dissemination and implementation.

Examination of evidence-based medication use by age showed that ACE inhibitors are used less frequently in persons aged 75 and older with a specific indication for their use, that aspirin is used less frequently among patients aged 75 and older with a past MI, and that warfarin is used less frequently among patients aged 75 and older with AF. In the pooled analysis, patients older than 75 were less likely to be prescribed evidence-based medications than patients ages 65 to 74. There are many possible explanations for less frequent use of chronic treatments with established efficacy among older persons. First, some clinicians challenge the generalizability of findings from randomized controlled clinical trials with age-based exclusions, such as those in clinical trials for acute myocardial infarction,²⁷ or trials whose conditions are difficult to duplicate in practice, as may be the case for warfarin use in patients with AF.²⁴ Additionally, the greater prevalence of absolute contraindications to medication, potential for adverse drug interactions, and competing medical needs may all be reasons why older people are less likely to be using otherwise indicated medication. However, these reasons are less likely to be significant in PASE patients, since medical comorbidity and usage of other medications did not differ by age in this study. In addition, adjusting our analyses for polypharmacy and medical comorbidity did not diminish the independent effect of age on evidence-based medication use. Another explanation for the observed differences in evidence-based medication use by age is that physicians may be slower to adopt these newer therapies for older people, based on concern about the potential side effects that are likely to occur in the short-term (for example, a gastrointestinal bleed with aspirin) versus possible long-term benefits that are not clinically obvious (the prevention of a second MI). Consistent with this explanation is that use of three long-standing therapies to relieve symptoms of CHF (digitalis, diuretics, and nitrates) was balanced among the younger and older groups.

It is important to point out that at the time of this study, information on the use of warfarin for patients older than age 75 with AF was limited, and many experts recommended aspirin rather than warfarin for older persons with AF. When we analyzed the use of aspirin and/or warfarin for patients with AF, we still found that older patients were less likely to be taking aspirin and/or warfarin, but this difference was not as marked as in the case of warfarin alone.

This study had a number of important limitations that need to be considered when interpreting its findings. First, since we considered multiple endpoints, the reader should be aware of the potential for false positives. Also, by definition,

PASE patients were participating in a clinical trial. Persons who are willing to be randomized to a therapy such as a pacing modality may be different in unmeasured ways from the population at large. For this reason, care must be taken when generalizing these findings. However, the principal finding of underuse of medications in these carefully monitored patients, who are predominantly from tertiary-care settings, should bias the analyses toward the null hypothesis. It is probable that the effect of age on medication use would be even greater in community-based settings.

In summary, age is an independent negative correlate of evidence-based cardiac medication use in this cohort. This finding suggests that physicians use chronological age when deciding whether to prescribe these medications to their patients even though physiological age might be a more relevant criterion. The age bias noted in our study exists against a background of low rates of evidence-based medication use that are similar to rates observed in population-based samples. These findings suggest that there may be potential to decrease morbidity and mortality by altering prescription patterns. Prospective studies that measure absolute and relative contraindications to specific medication use comprehensively are needed to identify factors that cause clinicians to withhold potentially effective treatments for cardiac conditions from the older patient.

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