The Effectiveness of β -blockers in Women With Congestive Heart Failure

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BACKGROUND: β -blockers have been shown to improve survival in patients with congestive heart failure (CHF). However, few studies have looked at the effects of these medications specifically in women.

OBJECTIVE: To determine the effectiveness of β -blockers in women with CHF.

PATIENTS: We conducted a retrospective cohort study that used administrative databases of all patients >65 years of age discharged with a diagnosis of CHF between January 1998 and March 2003 in Quebec, Canada. Follow-up information was available until March 31, 2004.

METHOD: The cohort included 27,837 patients. Subjects with filled prescription for a β -blocker (14,083 users) were compared with those who never filled such prescription (12,254 nonusers). The primary outcome was survival in women and men by β -blocker use.

RESULTS: There were 14,693 women (52% were prescribed β -blockers) and 13,144 men (49% were prescribed β -blockers). Women were older and had more hypertension, whereas men had more myocardial infarction. There was a significant survival benefit with β -blockers use in both sexes (hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.75–0.83 in women, and 0.76, 95% CI 0.72–0.80 in men). Sensitivity analyses adjusting for selection bias showed similar survival benefits in both sexes. Overall, men had a worse survival than women (HR 1.2, 95% CI 1.2–1.3 in men).

CONCLUSIONS: β -blockers appear to improve survival from CHF as much in women as in men. Clinical trials involving large numbers of women are necessary to demonstrate potential treatment benefits.

KEY WORDS: β -blockers; women; congestive heart failure.

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Nearly 5 million Americans have congestive heart failure (CHF) with approximately 50% of these patients being women.¹ The incidence of CHF approaches 10 of 1,000 population in people ≥ 65 years. About 20% of all hospital

admissions in persons ≥ 65 years are caused by CHF; hospitalizations for CHF increased by 159% over the past decade, with women having a greater rate of increase. Hospitalized women with CHF have less improvement in physical health status and perceive their quality of care to be lower than that of men.² Moreover, 62.5% of total CHF mortality occur in women compared to 37.5% in men.³

CHF appears to have different characteristics and etiologies in men and women. Women tend to have more hypertension and diastolic dysfunction and men have more ischemic changes.^{4,5} Randomized clinical trials showed that β -blockers (as well as the angiotensin converting enzyme inhibitors [ACEi]) are mainstays in the treatment of CHF. However, few studies have looked at the effects of β -blockers specifically in women. Harris and colleagues⁶ studied the enrollment of women in cardiovascular trials funded by the National Heart, Lung, and Blood Institute from 1965 to 1998. Although efforts to increase women representation in such studies were moderately successful, women were underrepresented in heart failure studies with only 26% of total enrollment. The average proportion of women enrolled in β -blocker trials in CHF patients was 24%.² Moreover, there is a lack of definitive randomized trials in patients with diastolic CHF, a group of patients who are predominantly women.¹

Yet, current guidelines indicate the same treatment for both sexes.⁷ A study specifically looking at the effects of β -blockers in women with CHF is unlikely to be undertaken, and subgroup analyses of women in studies have been underpowered.^{1–4} Thus, an important question that still needs to be addressed is whether β -blockers have similar beneficial effects on mortality in women as in men with CHF. We undertook this study to determine the effectiveness of β -blockers in men and women with CHF.

METHODS

Study Population

The Quebec hospital discharge summary databases, which include information on all CHF hospitalizations, were linked to provincial physician and drug claims database. Patients were identified if they were admitted to a hospital with a primary diagnosis of CHF (International Classification of Disease Ninth revision, code 428) (and no hospitalizations for CHF within the preceding 3 years) between January 1, 1998 and March 31, 2003 (index admission). The 3-year wash-out period for a hospitalization for CHF was used to ensure that groups were of comparable severity of illness, and also to minimize the proportion of patients for whom the β -blocker prescription was not new. The reliability of coding for the diagnosis of CHF in

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administrative databases is high^{8,9} and the physician and drug claims database was validated for the accuracy of prescription claims.¹⁰ Follow-up information was available until March 31, 2004.

Only patients ≥ 65 years were included, as data on medication are available for this age group alone. We excluded patients ≥ 105 years ($n=97$), patients with CHF coded as an in-hospital complication, or those with a previous admission for CHF within 3 years before the index hospitalization ($n=26,543$). Patients discharged to long-term care institution, rehabilitation center, another province, or psychiatric cares ($n=1,840$) were also excluded for lack of information on medication prescriptions. Also different hospital admissions involving transfers to another acute care facility were excluded to avoid including several hospitalizations for the same reason at the same period of time for the same patient. We considered the admission to the first hospital as the index admission. We calculated the total length of hospital stay by adding up the length of stay in each hospital that the patient was transferred to, if a transfer occurred.

The cohort for the present analysis included 27,837 patients (14,693 women and 13,144 men) and contains information on all inpatient and outpatient diagnostic and therapeutic procedures.

Clinical Characteristics

Covariates of importance for CHF were based on the *American Heart Association/American College of Cardiology* guidelines for heart failure management.⁷ They were selected based on a clinical model specific to CHF established by Lee and colleagues¹¹ to predict mortality in patients with CHF using administrative database. These variables are age, hypertension, diabetes, myocardial infarction (MI), atrial fibrillation, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, chronic renal failure, liver disease, rheumatologic disease, cancer, and dementia. Cardiac medications that could influence survival rates in CHF were identified at the time of hospital discharge including ACEi, angiotensin receptor blockers (ARBs), calcium channel blockers, hydralazine, loop diuretics, spironolactone, metolazone, other diuretics, nitrates, digoxin, amiodarone, statins, warfarin, and clopidogrel/ticlopidine. Information on the treating physician (cardiologist, general practitioner, or internist), teaching university affiliation, and hospital's annual volume of CHF admissions (low ≤ 31 , medium ≤ 121 and >31 , and high >121 admissions for CHF/year) were obtained.

β -blocker Use

β -blocker use was defined as a filled prescription at any time during the study, whereas no β -blocker use was defined as no filled prescription ever. This classification requires that a person survives until the date of their filled prescription, introducing an artificial survival advantage of the users, irrespective of the effectiveness of the treatment. To minimize this survival bias in our study, the method of "prescription time distribution matching" was used.^{12,13} The time that a user filled her/his prescription was considered as time zero. The number of days from hospital discharge to time zero (the time that the first β -blocker prescription was filled) was assessed for users. For nonusers, a time zero was matched and assigned to them, in a manner that the overall distribution of time zero of the nonusers was matched to that of

the users' time of first prescription. Both groups were followed from time zero to death, or the end of the study follow-up, whichever came first. Nonusers who had an event before the assigned time zero were excluded from the analysis (752 women and 748 men). This method minimizes the artificial survival advantage of the β -blocker users.

We calculated several measures to determine the extent to which patients followed their treatment regimens. Among patients with β -blocker use, we calculated the proportion of time for which a patient was covered by prescriptions during the study, or until death if the patient died earlier. These measures were calculated on the basis of a variable indicating the duration of each filled prescription available in the drug claims database. We also calculated the mean time to first prescription, the percent target dose achieved, and any β -blocker switch within the same class of medication.

Outcomes

The primary outcome was survival in women and men by β -blocker use. We performed an intention-to-treat analysis (based on the initial treatment intent). This type of analysis is done to avoid crossover and dropout effects.

Statistical Analysis

Data are presented as mean values $\pm$ standard deviation (SD) unless otherwise indicated. All variables were compared according to sex and β -blocker use. Clinical characteristics of women and men were compared by the chi-square test. Continuous variables were compared by the Student's *t* test. Kaplan-Meier curves were generated and results were compared using the log-rank test.

Adjusted survival curves from proportional hazards models were constructed as described by Ghali and colleagues¹⁴; survival curves are first calculated for each combination of covariates in a database. A weighted average of these individual curves is then calculated, with weights proportional to the number of individuals at each level of covariates.

To identify the independent determinants of mortality, a multivariate analysis was performed using a Cox proportional hazards model. Adjustments were made for age, sex, baseline comorbidities, admitting service, cardiac procedures, other discharge medications, year of CHF (to account for temporal trends), and hospital characteristics. In a separate model we also adjusted for β -blocker use within the preceding 3 years from the index admission, to test whether previous β -blocker use for indications other than CHF (i.e., for hypertension) could affect our findings. Results are expressed as hazard ratios (HRs) with 95% confidence intervals (CIs).

Sensitivity Analyses

Apart from the main multivariate Cox proportional hazards model, several additional analyses were performed to test the robustness of our results.

Our primary analyses used "prescription time distribution matching" to minimize the survival bias. The analyses were also performed using different classifications for users and nonusers. In one analysis, the group of users included only those subjects who filled a β -blocker prescription during the first 90 days after hospital discharge; the nonusers included those who never filled a β -blocker prescription. Another classification defined users as

Table 1. Characteristics of 27,837 Men and Women With Congestive Heart Failure

Variable	Women (N=14,693)	Men (N=13,144)	P value
Age (y)	79.9 $\pm$ 7.5	76.7 $\pm$ 7.0	<.0001
Comorbidities (%)			
Systemic hypertension	44	30	<.0001
Diabetes mellitus	32	33	.016
Myocardial infarction	19	25	<.0001
Atrial fibrillation and flutter	41	39	.0006
Cerebrovascular disease	9	9	.457
Peripheral vascular disease	5	10	<.0001
Chronic obstructive pulmonary disease	27	38	<.0001
Chronic renal failure	15	22	<.0001
Liver disease	1	1	.0007
Rheumatologic disease	3	1	<.0001
Malignancy	3	6	<.0001
Dementia	4	3	<.0001
Admitting physician (%)			
Cardiologist	31	34	<.0001
General practitioner	58	56	.0006
Internal medicine	11	10	.0196
Procedures (%)			
Coronary artery bypass graft surgery	1	1	<.0001
Primary percutaneous coronary intervention	1	2	.0063
Angiography	6	8	<.0001
Length of hospital stay	11.1 $\pm$ 12.3	9.8 $\pm$ 11.4	<.0001
Events (deaths)	7,769	7,476	<.0001

those subjects with a filled β -blocker prescription within 90 days from discharge, and nonusers as both subjects who never filled a prescription and subjects who filled a β -blocker prescription after the first 90 days.

We performed sensitivity analyses using the Charlson Comorbidity Index to assess subjects' disease severity with disease outcome.¹⁵ This is a validated method of classifying comorbidities to predict mortality from medical records.^{16,17} Subjects with an index <2 were considered less sick than those with an index of ≥ 2 . We also used a different cutoff point of this index (0 [no comorbidities] versus >0) to construct a different model. As subjects were classified into different groups according to comorbidities included in the Charlson Index, we could only adjust in the multivariate model for baseline covariates other than those included in this index.

In a different analysis, the effect of β -blocker use was examined in patients discharged with additional cardiac medications (digoxin, amiodarone, hydralazine, spironolactone, or metolazone) and in patients discharged without any of these additional medications.

We performed an intention-to-treat analysis. However, we also performed a separate analysis in 65% of women and 67% of men who had an ongoing β -blocker prescription for $\geq 80\%$ of the time (compliant patients) to confirm the robustness of our findings.

Ethics Approval

All the data used for study analyses were anonymous and confidential. All personal identifiers were scrambled by the provincial government agencies before we received the data. The study was approved by the McGill University Ethics Review Board.

RESULTS

Patient Characteristics

The cohort includes 14,693 (53%) women and 13,114 (47%) men (Table 1). Women were older and less likely to be admitted by cardiology. More women had hypertension when compared with men (44% vs 30%, respectively); whereas more men had MI (25% vs 18%, respectively). Men also had more chronic obstructive pulmonary disease, malignancy, and chronic renal failure. Procedures were performed more often in men than women during the admission (Table 1).

In both sexes, a greater number of β -blocker users had diabetes, hypertension, and MI, whereas more nonusers had

Table 2. Characteristics of 27,837 Men and Women With Congestive Heart Failure by β -blocker Use

Variable	Women (N=14,693)		Men (N=13,144)	
	Nonusers	Users	Nonusers	Users
N	7,109	7,584	6,645	6,499
Age (y)	81 $\pm$ 7.6	79 $\pm$ 7.2*	78 $\pm$ 7.1	75 $\pm$ 6.7*
Comorbidities (%)				
Systemic hypertension	40	48*	27	33*
Diabetes mellitus	29	34*	30	36*
Myocardial infarction	15	22*	21	29*
Atrial fibrillation and flutter	43	40*	41	37*
Cerebrovascular disease	9	9	10	9
Peripheral vascular disease	5	6*	10	10
Chronic obstructive pulmonary disease	36	18*	49	27*
Chronic renal failure	16	14*	24	21*
Liver disease	1.1	0.6**	1.4	1.1
Rheumatologic disease	3	3	1	1
Malignancy	4	3	7	5*
Dementia	6	3*	4	2*
Admitting physician (%)				
Cardiologist	27	34*	29	39*
General practitioner	62	55	60	51
Internal medicine	11	11	11	9
Procedures (%)				
Coronary artery bypass graft surgery	0	1*	1	2*
Primary percutaneous coronary intervention	0	2*	1	3*
Angiography	3	10*	5	12*
Length of hospital stay	11.5 $\pm$	10.6 $\pm$	10.3 $\pm$	9.2 $\pm$
	13.1	11.4	12.2	10.5
Events (deaths)	4,508	3,261	4,536	2,940

* $P < .0001$ users versus nonusers

** $P = .001$ users versus nonusers

Table 3. Discharge Medical Therapy in 27,837 Men and Women With Congestive Heart Failure by β -blocker Use

Variable	Women (N=14,693)		Men (N=13,144)	
	Nonusers	Users	Nonusers	Users
N	7,109	7,584	6,645	6,499
Medications use (%)				
Angiotensin-converting enzyme inhibitors	33	38*	35	41*
Angiotensin receptor blockers	5	7*	3	4
Calcium channel blockers	19	18	15	14
Hydralazine	1	2	2	2
Loop diuretics	52	58*	51	56*
Spironolactone	6	8*	8	10*
Metolazone	1	0	1	1
Other diuretics	3	3	2	2
Nitrates (long acting)	27	35*	26	33*
Digoxin	20	18	21	21
Amiodarone	5	5	7	6
Statins	5	12*	6	15*
Warfarin	16	20*	15	20*
Clopidogrel / ticlopidine	1	3*	1	3*

* $P < .0001$ users versus nonusers

chronic obstructive pulmonary disease and chronic renal failure. When the admitting physician was a cardiologist, more subjects were prescribed β -blockers in both sexes. Also, more β -blocker users underwent examination by angiography than nonusers in both sexes (Table 2).

Medical Therapy

Fifty-one percent (14,083) of the patients filled a β -blocker prescription and 44% (12,254) of the patients never filled a β -blocker prescription (Table 3). There were 7,584 (52%) women and 6,499 (49%) men prescribed β -blockers. In both groups β -blocker users had more prescriptions for ACEi, loop diuretics, spironolactone, nitrates, statins, and warfarin.

Prescription Characteristics

The extent to which patients followed their treatment regimens was similar for both men and women (Table 4). Both groups highly adhered to β -blockers once prescribed. There were few exchanges of β -blockers within the same class of medication, and the mean duration of follow-up was about 2^{1/2} years in both sexes.

Effectiveness of β -blockers on Mortality

There was a significant improvement in survival associated with β -blocker use in both sexes. The unadjusted HR and 95% CI were 0.67, 95% CI 0.64–0.70 in women; and 0.64, 95% CI 0.61–0.67 in men. The 1-year mortality was 23% (3,388) in women (13% nonusers and 10% users) and 25% (3,294) in men (15% nonusers and 10% users). The total mortality was 53% (7,769) in women (31% in nonusers and 22% in users) and 57% (7,476) in men (35% in nonusers and 22% in users).

Adjusted HR and 95% CI in women was 0.79, 95% CI 0.75–0.83; and 0.76, 95% CI 0.72–0.80 in men (Table 5). The other

protective factors were the presence of hypertension and cardiologist as admitting physician. ACEi and statin prescription at hospital discharge also improved survival in both sexes. Discharge prescription of ARBs and warfarin improved survival only in women. There was a survival benefit in both women and men who had an angiography during the hospital admission. Coronary artery bypass graft improved survival only in men.

When all subjects were considered together, men had a worse survival than women (HR 1.2, 95% CI 1.18–1.28 for men; Fig. 1), and there was no interaction between sex and β -blocker use. β -blocker use, presence of hypertension, admission by cardiology, ACEi, and statin use provided a better survival in all subjects. Older age, diabetes, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, liver disease, chronic renal failure, and malignancy conferred worse survival.

Sensitivity Analyses

Limiting follow-up to 1 year post hospital discharge similarly demonstrated that β -blocker use significantly improves survival in CHF in both sexes (HR 0.72, 95% CI 0.67–0.78 in women, and 0.70, 95% CI 0.65–0.76 in men).

Different classifications of the groups of users and nonusers revealed similar survival benefit of β -blockers in both sexes. When the users included only those with a filled prescription within 90 days compared to those who never filled a prescription, the HR was 0.73 (95% CI 0.69–0.77) in women, and 0.69 (95% CI 0.65–0.73) in men. Classification of the group of users as those who filled a prescription within 90 days of hospital discharge, and the group of nonusers as both those who filled a prescription after 90 days from hospital discharge and those who never filled a β -blocker prescription, demonstrated a HR of 0.84 (95% CI 0.80–0.88) in women, and 0.81 (95% CI 0.76–0.85) in men.

Table 4. Pattern of β -blocker Prescription in Men and Women With Congestive Heart Failure

N	Women	Men	P
	7,584	6,499	
Mean time during which a patient had an ongoing prescription, %*	77±0.3	77±0.3	.1
Proportion of patients who had an ongoing prescription for 80% or more of the time, %*	65	67	.02
First prescription meets target dose, %†	11		<.001
Achieved target dose at any time during the follow up, %†	19	23	<.001
β -blocker switch within 1 year, %‡	8	8	.6
β -blocker switch at any time during the follow up, %‡	16	16	.8
Median number of prescription per year	12	12	<.001
Mean time to first prescription, days§	144	134	.08
Duration of follow-up, days	781	804	.01

*During the first year after discharge or until death, if patient died in the year after discharge

†The target dose of each drug was identified from randomized, controlled trials as follows: metoprolol 150 mg/day, atenolol 100 mg/day, carvedilol 50 mg/day, bisoprolol 10 mg/day, and acebutolol 400 mg/day.

‡ β -blocker switch within the same class

§Time between CHF hospital discharge and date the first prescription was filled

Table 5. Factors Included in the Multivariable Proportional Hazard Model Associated With Survival in Women And Men

N	Women		Men	
	14,693		13,144	
Factor	HR	95% CI	HR	95% CI
β -blocker non-users (reference)	—	—	—	—
β -blocker users	0.79	0.75–0.83	0.76	0.72–0.80
Baseline characteristics and comorbidities				
Age	1.04	1.04–1.04	1.03	1.03–1.04
Systemic hypertension	0.81	0.77–0.85	0.83	0.79–0.88
Diabetes mellitus	1.34	1.27–1.41	1.25	1.18–1.31
Myocardial infarction	1.05	0.99–1.12	1.03	0.97–1.09
Atrial fibrillation and flutter	1.04	0.98–1.10	0.99	0.94–1.05
Cerebrovascular disease	1.20	1.12–1.30	1.15	1.06–1.24
Peripheral vascular disease	1.27	1.15–1.40	1.17	1.08–1.26
Chronic obstructive pulmonary disease	1.09	1.04–1.15	1.11	1.05–1.17
Chronic renal failure	1.51	1.43–1.61	1.39	1.31–1.47
Liver disease	1.48	1.18–1.86	1.40	1.14–1.71
Rheumatologic disease	1.15	0.99–1.34	1.11	0.90–1.37
Malignancy	1.93	1.72–2.16	1.92	1.75–2.10
Dementia	1.40	1.27–1.55	1.33	1.16–1.51
Cardiac medication (at discharge)				
Angiotensin converting enzyme inhibitor	0.87	0.82–0.92	0.84	0.79–0.89
Angiotensin receptors blockers	0.85	0.76–0.95	1.07	0.94–1.22
Calcium-channel blocker	1.01	0.94–1.07	0.93	0.87–1.00
Hydralazine	1.21	0.99–1.47	1.34	1.14–1.56
Loop diuretics	0.97	0.91–1.02	0.96	0.90–1.01
Spironolactone	1.15	1.04–1.27	1.01	0.92–1.11
Metolozone	2.90	2.19–3.83	2.80	2.23–3.53
Other diuretics	0.91	0.78–1.06	1.05	0.87–1.26
Nitrates (long acting)	1.10	1.04–1.16	1.18	1.11–1.25
Digoxin	1.08	1.01–1.15	1.10	1.03–1.17
Amiodarone	1.14	1.01–1.28	1.04	0.94–1.15
Statins	0.83	0.75–0.92	0.82	0.75–0.90
Warfarin	0.84	0.78–0.91	0.97	0.90–1.05
Clopidogrel / ticlopidine	0.97	0.80–1.17	1.09	0.90–1.33
In-hospital procedure				
Coronary artery bypass graft surgery	0.77	0.53–1.13	0.50	0.36–0.70
Primary percutaneous coronary intervention	0.97	0.70–1.33	0.85	0.64–1.13
Angiography	0.70	0.60–0.81	0.65	0.57–0.74
Length of hospital stay	1.01	1.00–1.01	1.01	1.01–1.01
Physician and hospital characteristics				
Cardiologist	0.91	0.86–0.97	0.94	0.88–0.99
General practitioner (reference)	—	—	—	—
Internal medicine	1.01	0.93–1.10	1.07	0.98–1.16
Teaching hospital	1.04	0.97–1.11	1.12	1.04–1.20
High CHF volume (reference)	—	—	—	—
Medium CHF volume	0.94	0.80–1.10	0.95	0.81–1.12
Low CHF volume	0.97	0.91–1.03	0.95	0.89–1.01
Year of index CHF admission				
1997–1998	0.97	0.88–1.07	0.99	0.90–1.09
1998–1999 (reference)	—	—	—	—
1999–2000	1.04	0.98–1.12	0.91	0.85–0.97
2000–2001	0.98	0.91–1.05	0.93	0.87–1.00
2001–2002	0.96	0.89–1.04	0.90	0.83–0.98
2002–2003	0.99	0.90–1.09	0.87	0.78–0.96

CHF = congestive heart failure

When the Charlson Index was used to classify subjects into groups with different disease severity, the results did not change; both sexes had a better survival when β -blockers were used independent of the comorbidity index (0.76, 95% CI 0.71–0.81, and 0.79, 95% CI 0.74–0.85 in women; 0.77, 95% CI 0.71–0.83, and 0.74, 95% CI 0.69–0.79 in men, for patients with less severe and more severe disease, respectively).

Different models also demonstrated a survival advantage of β -blocker use for both groups of patients—not on cardiac medications and on cardiac medications—in both sexes (0.77, 95% CI 0.73–0.82 and 0.75, 95% CI 0.68–0.82 in women; 0.73, 95% CI 0.69–0.78 and 0.77, 95% CI 0.70–0.84 in men, for those not on cardiac medication and those on cardiac medication, respectively).

In a separate analysis, in 65% of women and 67% of men who had an ongoing β -blocker prescription for $\geq 80\%$ of the time (compliant patients) we found a nonsignificant trend for further improvement in survival in all 6 different models that we used (all compliant patients, compliant women, compliant men, with and without adjustment for pre-index-admission use of β -blockers; HRs ranged from 0.68 to 0.76—results not shown). These analyses further supported the robustness of our data, as the less beneficial effect of β -blockers in less compliant patient was removed.

We tested for interactions between β -blocker use and hypertension, β -blocker use and MI, β -blocker use and ACEi use at discharge, and β -blocker use and ARB use at discharge. All interaction terms were nonsignificant, suggesting that the effect of the drug is not through the comorbidity for which the drug would be given and which could be associated with the outcome.

DISCUSSION

Our results demonstrate that β -blocker use is associated with improved survival from CHF as much in women as in men. The number of women (14,693) in this large unselected population of CHF patients is much higher than any prior CHF trials combined.

A meta-analysis of 12 large randomized trials of ACEi and β -blockers in patients with CHF and left ventricular systolic dysfunction was performed by Shekelle and colleagues.¹⁸ The combined number of females in the 5 major β -blocker trials (CIBIS-II, COPENICUS, MERIT-HF, BEST, and US CARVEDILOL HF) was 2,134. This analysis was inconclusive regarding the effectiveness of β -blockers in women (HR 0.75, 95% CI 0.51–1.09) compared to a definitive survival benefit in men (HR 0.68, 95% CI 0.51–0.89). This lack of benefit was most likely caused by the insufficient power of the meta-analysis; females represented only 21% of patients, and included only subjects with systolic dysfunction. There was substantial heterogeneity between the studies, and the authors were unable to control for possible differences between subpopulations in the etiology of heart failure. It is important to note that the survival advantage in men in our study (HR 0.76, 95% CI 0.72–0.80) was similar to that found in the meta-analysis. This lends support to the validity of the HR found for women in our study.

In the only post-hoc analysis of the women ($n=898$) in MERIT-HF,¹⁹ there was a 21% reduction in the primary end point of all-cause mortality and hospitalizations with β -blocker usage, but it did not lead to a significant reduction in mortality

Figure 1. Risk-adjusted survival curves were plotted from the proportional hazards model using the corrected group prognosis¹⁴ comparing β -blocker use and nonuse in men and women.

when viewed as separate end points. The women in the MERIT-HF study had New York Heart Association (NYHA) class II–IV with a left ventricular ejection fraction (LVEF) <40%, and 58% of them had an ischemic etiology for their CHF. The above-mentioned study shows benefits of β -blockers in women with systolic CHF. Population studies showed that most females have preserved left ventricular function or mild systolic dysfunction.^{20–24}

A growing evidence point to fundamental sex-related differences in the nature and extent of myocardial hypertrophy and adaptation, which might account for the survival advantage for women.^{25,26} There is evidence for sex differences in myocardial adaptation to pressure overload, lower rates of aging-related cardiac myocyte cell loss and reactive hypertrophy; also, sex differences may exist in up-regulation of left ventricular ACEi activity during pressure overload hypertrophy.^{27–29} Thus, there is a need to identify therapies specifically beneficial for women and tested in a large women population.

Our study included all women with discharge diagnosis of CHF and demonstrated an association between the use of β -blockers and improved survival. Furthermore, β -blocker use, presence of systemic hypertension, admission by cardiology, ACEi and statin use are associated with better survival in all subjects. The paradox that the presence of systemic hypertension is protective might be explained by the fact that hypertensive subjects are more likely to be prescribed β -blockers (as an indication for their hypertension) and, therefore, benefit from the effect of these drugs on CHF. It was shown that when β -blockers are prescribed for cardiovascular disorders other than hypertension (such as CHF and post-MI), the mortality reductions exceed that seen in patients without these cardiovascular complications.³⁰

The limitations of our study included the inability to accurately determine the specific etiologies of CHF in the database used and the lack of other detailed clinical information. However, these factors are unlikely to have changed the outcome as we adjusted for multiple potentially confounding variables, and the results of our sensitivity analyses, based on censoring after 1 year and reclassification of the groups of β -blocker users and nonusers, are consistent with our main analysis. Our results apply only to those ≥ 65 years who were hospitalized with CHF (median age 75 years). As in most pharmacoepidemiologic studies,³¹ filled

prescriptions were used as a measure of “exposure time” to β -blockers and may not accurately reflect actual pill intake. Patients with filled β -blocker prescriptions were assumed to be receiving the drug throughout the follow-up based on the intention-to-treat analysis. This method is unlikely to have altered our outcome as there was high adherence to β -blockers; the mean time during which a patient had an ongoing prescription was high in both groups as well as the proportion of patients who had an ongoing prescription for $\geq 80\%$ of the time. Moreover, the median number of prescriptions filled for β -blockers was 12/year in both groups, which suggest that most subjects were regularly taking their β -blockers. Furthermore, our results were confirmed by the findings of analyses including only compliant patients (with an ongoing β -blocker prescription for $\geq 80\%$ of the time). We did not consider the β -blocker use as a time-dependent variable. However, we have previously performed an analysis of the class-effect of ACEi using a fixed effect model and a time-dependent variable model. The time-dependent analyses yielded very similar results for between-drug comparisons with the fixed model.³²

Another important issue is the possibility of confounding by indication. That is the possibility that patients with worse prognosis or more comorbidities are prescribed certain types of cardiovascular medications. The severity of CHF could not be directly evaluated. This is a known limitation of administrative databases as echocardiography results, information on systolic or diastolic dysfunction, LVEF and NYHA functional classification system results are not available. However, we attempted to identify any bias caused by comorbidities and disease severity by subclassifying subjects into different levels of disease severity based on the validated method of Charlson index and on the presence or absence of prescriptions for other cardiac medications. These analyses demonstrated similar magnitude of benefit with β -blocker use in both sexes independent of the presence of comorbidities and the severity of the disease. However, although sensitivity analyses and tests for interactions were performed to exclude confounding by indication, the presence of residual confounding cannot definitely be ruled out.

We did not perform a class-effect analysis of β -blocker drugs. Bisoprolol and carvedilol had only a small share of the β -blocker prescriptions (a total of 18.92%). These β -blocker drugs have been shown to decrease mortality. However, it is unlikely

that they explain the beneficial effect of β -blockers on mortality found in our study by their own, suggesting that other β -blockers may also have such an effect. We believe that class-effect is a very interesting issue and such analysis of the data should be included in a different project.

This is the first analysis of a large administrative population-based database that examines the effectiveness of β -blockers in the treatment of CHF specifically in women. β -blockers is associated with improved survival from CHF similarly in men and women. The results of this study lend support to the current management of women with CHF.

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