Changes in Adherence to Evidence-Based Medications in the First Year After Initial Hospitalization for Heart Failure

Observational Cohort Study From 1994 to 2003

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Background—The use of evidence-based medications in patients with heart failure has increased over the past 10 years. We aimed to determine whether adherence to these medications has also increased during this time.

Methods and Results—A retrospective cohort was created using administrative databases from the province of Saskatchewan, Canada. Subjects discharged alive from their first hospitalization for heart failure between 1994 and 2003 were eligible. Those filling a prescription for a β-blocker (BB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB) within 6 months of discharge were followed for 1 year after the initial prescription. Of 8805 eligible patients, 67% of BB users (941/1414) and 74% of ACEI/ARB users (4441/5991) exhibited optimal adherence at 1 year (defined as ≥80% adherence calculated from pharmacy refill records). When grouped by year of initial heart failure hospitalization, the proportion of optimally adherent patients improved from 54% to 75% with BB and from 67% to 80% with ACEI/ARBs between 1994/1995 and 2002/2003 (P for trend <0.001 for both). Mean 1-year adherence improved from 71% to 83% for BB and 80% to 88% for ACEI/ARBs. After adjustment using multivariable logistic regression, subjects discharged in 2003 were significantly more likely to exhibit optimal adherence to a BB (odds ratio, 2.04; 95% CI, 1.21 to 3.44) or an ACEI/ARB (odds ratio, 1.65; 95% CI, 1.30 to 2.08) than those prescribed therapy in 1994/1995.

Conclusions—One-year adherence to BB and ACEI/ARB is improving over time in patients discharged after first heart failure hospitalization. Patients taking multiple cardiac medications were not any less likely to exhibit optimal adherence than patients taking only 1 medication. (Circ Cardiovasc Qual Outcomes. 2009;2:228-235.)

Key Words: adherence □ heart failure

Studies reporting medication prescribing/use in heart failure (HF) patients indicate that the use of evidence-based therapies such as β-blockers (BB), angiotensin-converting enzyme inhibitors (ACEI), and angiotensin II receptor blockers (ARBs) has increased over time.1-4 Factors underlying the increased prescribing rates of evidence-based medication are not well characterized, but it is likely that physician, environment, or patient conditions could play important roles.5 Clearly, physicians have changed their therapeutic approach to patients with HF as evidenced by increased prescribing of BB, ACEI, and ARBs.1-4 We hypothesized that conditions associated with greater evidence-based prescribing of medications to HF patients may have also influenced medication adherence.

Recent studies have provided clues that medication adherence may be on the rise. For example, Gislason et al reported that heart failure patients were less likely to interrupt their BB therapy in 2003 to 2004 compared to 1995 to 1996.6 To our knowledge, no study has directly examined whether adherence to evidence-based medications has changed over time among patients with heart failure. Thus, we aimed to determine whether adherence with BB and ACEI/ARBs in the first year after a hospital discharge for heart failure has improved between 1994 and 2003.
WHAT IS KNOWN

- Evidenced-based medications are being used more frequently in patients with heart failure.
- Poor medication adherence is a well known barrier to chronic disease management but it is not known if this problem has grown, stabilized, or improved over the years.

WHAT THE STUDY ADDS

- Over a 10 year period, one-year adherence to ACE inhibitors/ARBs and beta-blockers significantly improved among patients recently discharged from a heart failure hospitalization.
- Improved adherence was observed in all subgroups examined and was maintained after controlling for multiple confounders.
- By 2003, 75% of beta-blocker users and 80% of ACE inhibitor/ARB users remained adherent throughout the first year after discharge for heart failure.

Methods

Data Source

All study data were provided from administrative databases in the province of Saskatchewan, Canada. The Government of Saskatchewan maintains several databases of health services use information, including prescription drug data, physician services data, vital statistics information, and hospital services data. Diagnoses in the hospital services database are coded with the International Classification of Disease, 9th (ICD-9; before April 1, 2001) and 10th (ICD-10-CA [Canadian Enhancement]; starting April 1, 2001) Revisions.7 These administrative databases are electronically linkable on an individual level using personal health numbers. Saskatchewan Health covers all residents of Saskatchewan except for federal penitentiary inmates and members of the armed forces and Royal Canadian Mounted Police (this accounts for less than 1% of the Saskatchewan population). All Saskatchewan Health beneficiaries are eligible for prescription drug benefits except those who receive drug benefits from the federal government, such as the First Nations population and some service-related drug use among veterans. Overall, drug data are available for approximately 90% of the population covered by Saskatchewan Health. These Saskatchewan Health databases have been used in numerous pharmaco-epidemiological studies, and are considered to be both comprehensive and of high quality.5,9

Study Population

We created a retrospective cohort of subjects discharged alive from hospital with their first primary or most-responsible diagnosis of heart failure between January 1, 1994, and December 31, 2003 (ICD-9 428 to 428.x and ICD-10-CA I50.xxx and I11; a most responsible diagnosis of I11 was only used if one of the other diagnoses on the same record was I50.xxx). These codes for heart failure appear to be highly sensitive (up to 77%) and specific (up to 99%) in both Canadian and American administrative databases.10–12 Subjects were excluded if they had previously been discharged for heart failure (primary or most responsible diagnosis) within 5 years before study entry.

Adherence Measure

In Saskatchewan, BB, ACEI, and ARBs are routinely dispensed in 1-month quantities (34-day supply).13 Consequently, we have used the “fill-frequency” measure of adherence as per previous Saskatchewan Health database studies.14,15 The fill-frequency is calculated by dividing the number of prescription dispensations by the number of months of observation. For example, 9 dispensations over a 1-year observation period would be considered at least 80% adherence (365 days/34 days per month=10.74 months per year; 9 fills/10.74 months=84% adherence).

To test the robustness of our adherence measure, we undertook a sensitivity analysis of our overall results using an alternate measure of adherence. We recalculated adherence rates by estimating the proportion of days covered (PDC) that is reproducible in datasets of hypertensive9 and post–myocardial infarction15 subjects in Saskatchewan.

Data Analysis

One-year adherence was calculated for subjects filling a BB or ACEI/ARB prescription within 6 months after the initial heart failure discharge date. To be included, all subjects were required to have follow-up data for at least 365 days after the initial prescription. Adherence was calculated from the date of the first prescription and adjusted for subsequent time spent in hospital. Adherence rates were limited to a maximum of 100%.16 The proportion of subjects exhibiting adherence of at least 80% (optimal adherence) in the first 12 months after their initial prescription was examined in 2-year intervals according to the year of initial heart failure hospitalization: 1994/1995, 1996/1997, 1998/1999, 2000/2001, and 2002/2003. This threshold of 80% is a well-accepted standard to identify high adherence.14,15,20,21 χ² was used to both evaluate for trend in the proportion of adherent subjects over time and to compare proportions in select subgroups demonstrating optimal adherence. As a sensitivity analysis, we also examined adherence trends among subjects who died within the first year of follow-up as well as all other subjects who did not have a full year of follow-up available. These groups demonstrated very similar trends to those reported in the primary analysis.

For the calculation of BB adherence, only prescriptions for atenolol, metoprolol, bisoprolol, or carvedilol were considered eligible. All of these BBs are guideline-recommended options in the management of heart failure, with the exception of atenolol. However, atenolol makes up approximately 40% of all BB use in our study sample, and others have also noted it to be the most commonly used BB in HF patients.22–24 In addition, as a sensitivity analysis, we calculated adherence for all available BBs on the market at the time of the study, including those agents possessing intrinsic sympathomimetic activity (acebutolol and pindolol) that are not typically used for patients with heart failure. For the ACEI/ARB adherence analysis, all available ACEI or ARBs on the market at the time of the study were grouped to determine adherence. In both cases, switching between medications within a class was allowed within each defined group (group 1, BB; group 2, ACEI/ARB).

We created 2 logistic regression models (1 for BB and 1 for ACEI/ARB) to adjust for confounding factors that may have influenced the proportion of subjects demonstrating optimal adherence (≥80%). The following variables were deemed to be clinically important and were included in both models regardless of their univariate significance: age, sex, Deyo comorbidity score,20,26 time from discharge to first medication fill, year of discharge, and a discrete variable representing multiple medication use (filling ≥1
prescription in at least 3 of the following 6 medication classes during the year of observation: digoxin, anti diabetic drugs, statin, warfarin, spironolactone, or antihypertensive medications excluding study drugs and diiltiazem/verapamil). Additional covariates (such as prior/concomitant drug use or number of hospital visits) were included within the multivariable logistic regression if they were significantly (P<0.05) associated with 1-year adherence on univariate analysis. As a sensitivity analysis, we included all available patient characteristics (28 variables) within each regression model and found only small differences compared to our reported findings and our conclusions remained unchanged.

When analyzing BB adherence, an estimate of high initial daily dose (≥50% of target as defined in the randomized trials proving the efficacy of BB in HF) was also included in the regression analysis. To estimate the daily dose, we identified the first BB fill for each subject and calculated the total number of milligrams of drug provided. Then, assuming the fill was intended to last 34 days, we divided the total milligrams dispensed by 34 to obtain the estimate of daily dose. The results of our calculation were very similar to BB doses reported in other observational studies.

As a final sensitivity analysis, we identified a cohort of subjects receiving histamine-2 receptor antagonists (H2RA) and analyzed 1-year adherence using the identical procedures described above. H2RA are not indicated for the management of HF and represent a natural control group to help identify the extent to which temporal changes in the Saskatchewan Drug Plan reporting system may have influenced our findings.

Analyses of the study population were carried out using SPSS version 15.0 for Windows (SPSS Inc) and STATA SE version 10 (StataCorp LP). This study was approved by the Biomedical Research Ethics Board at the University of Saskatchewan. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

There were 14,198 subjects newly hospitalized for heart failure in Saskatchewan between January 1, 1994, and December 31, 2003. One-year mortality (standardized by age and sex to the 2001 Saskatchewan population) varied from 19% in 1995% to 12% by the end of 2002. From those newly hospitalized for HF, 1145 (8%) subjects died during the initial hospitalization, and 4248 (29%) died or were lost to follow-up (study period ended or lost beneficiary status) within the first year; as per our a priori analytic plan, these patients were excluded from our primary analysis but were included in a sensitivity analysis.

The primary study sample included 8805 eligible subjects with at least 1 year of complete follow-up after hospital discharge. The mean age of these subjects was 77 (SD, 10.8) years, and 51% were male. Within the first 30 days, 984 (11%) filled a BB prescription and 5058 (57%) filled a prescription for an ACEI or ARB. By 6 months, 1414 (16%) filled a BB prescription, 5991 (68%) filled a prescription for an ACEI or ARB, and 1165 (13%) subjects filled prescriptions for both BB and ACEI/ARBs (Table 1). The proportion of subjects filling at least 1 prescription for a BB within the first 6 months increased dramatically from 5% in 1994/1995 to 32% in 2002/2003, whereas the rate of ACEI/ARB use remained relatively stable at approximately 70% over the same 10-year period. The proportion of subjects switching within medication classes was 2.2%, 7.0%, 4.9%, 7.3%, and 5.4% for BB users in 1994/1995, 1996/1997, 1998/1999, 2000/2001, and 2002/2003. The corresponding proportions for ACEI/ARB over the same time period were 11.9%, 14.1%, 18.2%, 17.4%, and 15.8%.

Mean 1-year adherence was 78% (SD, 31) for BB and 84% (SD, 27) for ACEI/ARBs. Because of the high rate of optimal adherence in these cohorts, the corresponding median values were 100% in both cases. Mean 1-year adherence improved in both the BB and ACEI/ARB cohorts from 71% (SD, 33) and 80% (SD, 28) in 1994/1995 to 83% (SD, 29) and 88% (SD, 23) in 2002/2003, respectively. The proportion of subjects maintaining adherence ≥80% at 1 year was 67% (941/1414) in the BB cohort and 74% (4441/5991) in the ACEI/ARB cohort. However, when grouped by year of initial hospitalization, the proportion of patients with optimal adherence increased from 54% (49/90) to 75% (238/317) with BB (P for trend <0.001) and from 67% (807/1239) to 80% (544/688) with ACEI/ARBs (P for trend <0.001) between 1994/1995 and 2002/2003. Adjusted proportions resulted in very little change compared to the crude observations for BB (Figure 1) and ACEI/ARBs (Figure 2) adherence. In addition, when all available BBs were examined, similar increases were seen in adherence from 55% (73/133) in 1994/1995 to 73% (100/363) in 2002/2003.

Year of the index HF hospitalization remained a significant predictor of both BB and ACEI/ARB adherence even after adjusting for covariates in logistic regression analyses. Patients who were discharged in 2002/2003 were more likely to exhibit optimal adherence than those discharged in 1994/1995 (BB: odds ratio [OR], 2.04; 95% CI, 1.21 to 3.44; P=0.007 and ACEI: OR, 1.65; 95% CI, 1.30 to 2.08; P<0.001; Tables 2 and 3). In addition, concurrent or prior medication use was associated with higher likelihood of optimal adherence. For instance, subjects receiving ≥1 dispensation for at least 3 additional cardiovascular medication classes during the first year were more likely to exhibit adherence ≥80% to both BB (OR, 1.31; 95% CI, 1.01 to 1.71; P=0.04) and ACEI/ARB (OR, 1.20; 95% CI, 1.02 to 1.40; P=0.024). In contrast, a negative trend was observed between high initial BB doses and adherence to a BB (OR, 0.79; 95% CI, 0.62 to 1.00; P=0.05). Also, nondihydropyridine (ie, rate-slowing) calcium channel blocker use negatively impacted adherence to both BB (OR, 0.71; 95% CI, 0.50 to 1.01; P=0.05) and ACEI/ARBs (OR, 0.82; 95% CI, 0.69 to 0.98; P=0.03). Although women and patients with higher comorbidity burden were more likely to exhibit optimal adherence with ACEI/ARB, these associations were not seen with BB adherence (Tables 2 and 3).

Adherence to both BB and ACEI/ARB medications was influenced by patient age. Subjects ≥65 years of age were less likely to exhibit optimal adherence to a BB (OR, 0.70; 95% CI, 0.51 to 0.97; P=0.03) but were more likely to exhibit optimal adherence to an ACEI/ARB (OR, 1.26; 95% CI, 1.06 to 1.50; P=0.01). When divided into subgroups, optimal adherence to BB was observed in 66% (764/1165) of subjects ≥65 compared to 71% (177/249) of those under 65. For ACEI/ARB, the corresponding rates were 75% (3912/5235) compared to 70% (529/756). Regardless, both the older and younger subgroups showed similar improvements in adherence to BB and ACEI/ARB over the 10-year timeframe of this study (data available from corresponding author on request).

Adherence to both BB and ACEI/ARB medications was also influenced by whether the index prescription was new.
The proportion of new BB users exhibiting optimal adherence at 1 year (63%, 421/672) was significantly lower than those who had taken these medications before the heart failure hospitalization (70%, 520/742; \( P < 0.003 \) for comparison). Similarly, optimal adherence was demonstrated by 69% of new ACEI/ARB users (2134/3104) compared to 80% (2307/2887) of those who had used them previously (\( P < 0.001 \) for comparison). However, similar improvements in adherence were observed over time for both new and prior users of BB and ACEI/ARBs. For example, from 1994/1995 to 2002/2003, the proportion of patients with at least 80% adherence over 1 year improved from 43% to 70% for new BB users (\( P \) for trend = 0.003) and from 62% to 79% in subjects who had used BB previously (\( P \) for trend = 0.02). For ACEI/ARBs, the corresponding rates for new and prior users were 62% to 74% (\( P \) for trend < 0.001) and 74% to 86% (\( P \) for trend < 0.001).

**Sensitivity Analyses**

Using the modified PDC adherence measure in place of the fill frequency, mean 1-year adherence to BB was 79% (SD, 32), with 68% of subjects exhibiting adherence of at least 80%. For ACEI/ARBs, mean 1-year adherence was 85% (SD, 27), with 75% of subjects exhibiting adherence of at least 80%. In addition, almost identical increasing trends were observed with the PDC measure of adherence. Using the PDC, the proportion of subjects exhibiting optimal adherence increased from 57% in 1994/1995% to 76% in 2002/2003 for BB and from 68% to 81% for ACEI/ARBs. Furthermore, the

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<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>77.0 (10.5)</td>
<td>77.3 (10.6)</td>
<td>77.0 (11.0)</td>
<td>77.5 (10.9)</td>
<td>77.7 (11.3)</td>
</tr>
<tr>
<td>Male</td>
<td>1016 (51.4)</td>
<td>967 (49.9)</td>
<td>1014 (50.4)</td>
<td>966 (50.7)</td>
<td>485 (49.6)</td>
</tr>
<tr>
<td>Prior IHD</td>
<td>872 (44.2)</td>
<td>857 (44.3)</td>
<td>875 (43.5)</td>
<td>849 (44.6)</td>
<td>398 (40.7)</td>
</tr>
<tr>
<td>Prior use of DM medication*</td>
<td>355 (18.0)</td>
<td>408 (21.1)</td>
<td>447 (22.2)</td>
<td>431 (22.6)</td>
<td>234 (23.9)</td>
</tr>
<tr>
<td>Hospitalization in the year before first HF hospitalization</td>
<td>1024 (51.8)</td>
<td>1001 (51.7)</td>
<td>1007 (50.0)</td>
<td>938 (49.3)</td>
<td>469 (48.0)</td>
</tr>
<tr>
<td>Deyo comorbidity score25,26</td>
<td></td>
<td></td>
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<tr>
<td>Score of 0</td>
<td>1309 (66.3)</td>
<td>1269 (65.5)</td>
<td>1339 (66.6)</td>
<td>1203 (63.2)</td>
<td>626 (64.0)</td>
</tr>
<tr>
<td>Score of 1</td>
<td>392 (19.8)</td>
<td>355 (18.3)</td>
<td>361 (17.9)</td>
<td>335 (17.6)</td>
<td>157 (16.1)</td>
</tr>
<tr>
<td>Score of ( \geq 2 )</td>
<td>274 (13.9)</td>
<td>312 (16.1)</td>
<td>312 (15.5)</td>
<td>366 (19.2)</td>
<td>195 (19.9)</td>
</tr>
<tr>
<td>Hospitalization in the first 6 months after index HF hospitalization</td>
<td>1025 (51.9)</td>
<td>984 (50.8)</td>
<td>979 (48.7)</td>
<td>896 (47.1)</td>
<td>417 (42.6)</td>
</tr>
<tr>
<td>BB use†</td>
<td>90 (4.6)</td>
<td>172 (8.9)</td>
<td>328 (16.3)</td>
<td>507 (26.6)</td>
<td>317 (32.4)</td>
</tr>
<tr>
<td>Atenolol‡</td>
<td>63 (70.0)</td>
<td>109 (63.4)</td>
<td>150 (45.7)</td>
<td>202 (39.8)</td>
<td>115 (36.3)</td>
</tr>
<tr>
<td>Metoprolol‡</td>
<td>27 (30.0)</td>
<td>57 (33.1)</td>
<td>128 (39.0)</td>
<td>216 (42.6)</td>
<td>150 (47.3)</td>
</tr>
<tr>
<td>Carvedilol‡</td>
<td>0</td>
<td>6 (3.5)</td>
<td>50 (15.2)</td>
<td>85 (16.8)</td>
<td>48 (15.1)</td>
</tr>
<tr>
<td>Bisoprolol‡</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4 (0.8)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>ACEI/ARB use†</td>
<td>1239 (62.7)</td>
<td>1265 (65.3)</td>
<td>1400 (69.6)</td>
<td>1399 (73.5)</td>
<td>688 (70.3)</td>
</tr>
<tr>
<td>Captopril‡</td>
<td>289 (23.3)</td>
<td>193 (15.3)</td>
<td>144 (10.3)</td>
<td>83 (5.9)</td>
<td>29 (4.2)</td>
</tr>
<tr>
<td>Enalapril‡</td>
<td>647 (52.2)</td>
<td>521 (41.2)</td>
<td>483 (34.5)</td>
<td>279 (19.9)</td>
<td>105 (15.3)</td>
</tr>
<tr>
<td>Lisinopril‡</td>
<td>226 (18.2)</td>
<td>402 (31.8)</td>
<td>422 (30.1)</td>
<td>325 (23.2)</td>
<td>94 (13.7)</td>
</tr>
<tr>
<td>Ramipril‡</td>
<td>6 (0.5)</td>
<td>14 (1.1)</td>
<td>53 (3.8)</td>
<td>400 (28.6)</td>
<td>280 (40.7)</td>
</tr>
<tr>
<td>Other ACEI‡</td>
<td>71 (5.7)</td>
<td>119 (9.4)</td>
<td>175 (12.5)</td>
<td>149 (10.7)</td>
<td>63 (9.2)</td>
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<tr>
<td>ARB‡</td>
<td>0</td>
<td>16 (1.3)</td>
<td>123 (8.8)</td>
<td>163 (11.7)</td>
<td>117 (17)</td>
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<tr>
<td>Both BB and ACEI/ARB use†</td>
<td>64 (3.2)</td>
<td>129 (6.7)</td>
<td>270 (13.4)</td>
<td>427 (22.4)</td>
<td>275 (28.1)</td>
</tr>
<tr>
<td>Multiple medication use§</td>
<td>195 (9.9)</td>
<td>265 (13.7)</td>
<td>395 (19.6)</td>
<td>483 (25.4)</td>
<td>259 (26.5)</td>
</tr>
</tbody>
</table>

IHD indicates ischemic heart disease; DM, diabetes mellitus.

*DM medication indicates all oral medication used in the treatment of diabetes and insulin.

†Patients had to fill a medication within 6 months and also had to have follow-up data for at least 1 year. The mean first daily dose dispensed for each BB is as follows: atenolol (42.4 mg; SD, 25.4), carvedilol (9.4 mg; SD, 7.3), metoprolol (61.1 mg; SD, 58.1), and bisoprolol (3.7 mg; SD, 1.4).

‡Denominator is the total number of BB or ACEI/ARB users rather than the total eligible subjects during each period.

§Filling at least 3 of the following during the year of observation: digoxin, antidiabetic drugs, statin, warfarin, spironolactone, or antihypertensive medications excluding study drugs and diltiazem/verapamil.
PDC and fill-frequency measures were highly correlated for both BB ($r=0.95$) and ACEI/ARB ($r=0.91$).

Examining patients excluded because of death/loss to follow-up within the first year not only revealed similar adherence rates to our study cohorts, but also similar time trends in adherence (data available from corresponding author on request).

In contrast to the findings with BB and ACEI/ARB use, the proportion of subjects exhibiting optimal adherence in the H2RA cohort ($n=1829$) in each of the consecutive time periods (1994/1995, 1996/1997, 1998/1999, 2000/2001, 2002/2003) were 43%, 45%, 51%, 47%, and 50% ($P$ for trend=0.14). Using 1994/1995 as the reference years, the corresponding adjusted ORs for exhibiting optimal adherence to H2RAs were 1.02 in 1996/1997, 1.35 in 1998/1999, 1.12 in 2000/2001, and 1.22 in 2002/2003. None of these periods achieved statistical significance except for the year 1998/1999 (OR, 1.35; 95% CI 1.02 to 1.81; $P=0.04$).

### Discussion

From 1994 to 2003, the absolute proportion of subjects demonstrating optimal adherence to a BB or an ACEI/ARB increased by 21% and 13%, respectively. Although we can only speculate about the reasons for these positive trends, we find it interesting that improved adherence was observed during the same period in which evidence-based prescribing also increased. In contrast, we have no clear evidence to suggest that Saskatchewan patients had become more adherent to other medications: for example, 1-year adherence to H2RAs did not exhibit the same time trends as we observed for BB and ACEI/ARB. Furthermore, prescription writing and dispensation policies remained unchanged during the course of our observation period. Ultimately, we believe that improved adherence in Saskatchewan was primarily driven by improved management of heart failure patients, including increased awareness of the issues surrounding adherence. Most importantly, we have observed improvements in one of the most important global obstacles to successful chronic disease management, and this was achieved without any known, focused, province level change. Whatever the cause, improved adherence to these evidence-based medications...
Table 3. Predictors of 1-Year Adherence to BB on Multivariable Analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sample Size (%)</th>
<th>Odds Ratio</th>
<th>P Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherent to an ACEI/ARB</td>
<td>885 (63)</td>
<td>1.59</td>
<td>0.002</td>
<td>1.18–2.15</td>
</tr>
<tr>
<td>Prior BB use†</td>
<td>742 (52)</td>
<td>1.32</td>
<td>0.03</td>
<td>1.02–1.70</td>
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<tr>
<td>High 1st dose of a BB‡</td>
<td>558 (39)</td>
<td>0.79</td>
<td>0.05</td>
<td>0.62–1.00</td>
</tr>
<tr>
<td>Multiple medication use§</td>
<td>443 (31)</td>
<td>1.31</td>
<td>0.04</td>
<td>1.01–1.71</td>
</tr>
<tr>
<td>Age ≥65</td>
<td>1165 (82)</td>
<td>0.70</td>
<td>0.03</td>
<td>0.51–0.97</td>
</tr>
<tr>
<td>Prior IHD</td>
<td>868 (61)</td>
<td>1.32</td>
<td>0.04</td>
<td>1.01–1.71</td>
</tr>
<tr>
<td>Antiarrhythmic use</td>
<td>182 (13)</td>
<td>0.60</td>
<td>0.003</td>
<td>0.43–0.85</td>
</tr>
<tr>
<td>NDP–CCB use</td>
<td>174 (12)</td>
<td>0.71</td>
<td>0.05</td>
<td>0.50–1.01</td>
</tr>
<tr>
<td>Hospitalization in the 1st 6 months after index HF hospitalization</td>
<td>769 (54)</td>
<td>0.56</td>
<td>0.0001</td>
<td>0.44–0.72</td>
</tr>
<tr>
<td>Index year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994 and 1995</td>
<td>90 (6)</td>
<td>1</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>1996 and 1997</td>
<td>172 (12)</td>
<td>1.05</td>
<td>0.86</td>
<td>0.61–1.81</td>
</tr>
<tr>
<td>1998 and 1999</td>
<td>328 (23)</td>
<td>1.42</td>
<td>0.17</td>
<td>0.86–2.35</td>
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<tr>
<td>2000 and 2001</td>
<td>507 (36)</td>
<td>1.47</td>
<td>0.12</td>
<td>0.91–2.39</td>
</tr>
<tr>
<td>2002 and 2003</td>
<td>317 (23)</td>
<td>2.04</td>
<td>0.007</td>
<td>1.21–3.44</td>
</tr>
</tbody>
</table>

IHD indicates ischemic heart disease; NDP–CCB, nondihydropyridine calcium channel blocker.

Gender, time to first BB fill, and Deyo comorbidity score were also evaluated but were not significant predictors of adherence.

*Total sample size of BB users = 1414.
†Fill within 5 years before the initial HF hospitalization.
‡The first dosage of the prescribed BB was estimated and was labeled high if it was ≥50% of the recommended target dose.
§Filling at least 3 of the following during the year of observation: digoxin, antiarrhythmic drugs, statin, warfarin, spironolactone, or antihypertensive medications excluding study drugs and diltiazem/verapamil.

should help to reduce the morbidity and mortality associated with heart failure.

Adherence rates are nearing optimal levels in this cohort of HF patients. By 2002/2003, the proportion of patients exhibiting high 1-year adherence to BB and ACEI/ARBs had increased to 75% and 80%, respectively. These high rates of adherence in a heart failure population are plausible, as patients with symptomatic heart failure are likely to perceive the severity of their condition, especially in our cohort of subjects who were all recently discharged from their first-ever HF hospitalization. Indeed, the perception of risk may be an important promoter of chronic medication adherence. In addition, these relatively high rates of adherence may have been influenced by the fact that approximately half of our patients were already using BB or ACEI/ARBs at the time of their first HF hospitalization, as it has been shown that adherence usually declines most rapidly in new users of medication. In our population, only 63% and 69% of new users of BB and ACEI/ARB maintained an adherence of ≥80% in the first year. However, we observed the same temporal improvements in adherence rates in new users as in experienced users of both medications.

Accumulating evidence suggests that multiple medication regimens are not necessarily barriers to optimal medication adherence. Although our results cannot directly confirm this theory, we found that several factors linked to the overall medication burden were positively associated with adherence. For example, prior use, concurrent use, and adherence to the other target medication (BB or ACEI/ARB) were positively associated with greater odds of being adherent to either BB or ACEI/ARB. Also, subjects filling prescriptions for ≥3 distinct cardiovascular medication classes (digoxin, antiarrhythmic drugs, statins, warfarin, spironolactone, or any nonstudy antihypertensive medication excluding diltiazem/verapamil) in addition to their target medications were also more likely to exhibit optimal adherence compared to those who used <3 of those classes. Interestingly, elderly subjects in our study demonstrated comparable adherence to younger patients, despite their greater likelihood for polypharmacy and multiple comorbidities.

Filling an ACEI/ARB within the first month after discharge significantly increased the odds of being adherent over the subsequent year. However, a similar trend was not observed with BB. Unfortunately, we were unable to determine whether delays in filling prescriptions were appropriate (eg, adding medications in a stepwise manner to improve tolerance) or related to primary nonadherence. Limited information is available to guide physicians about the optimal timing of ACEI/ARB or BB initiation in heart failure patients. BB use, although improving, is still quite low, and thus we only had a relatively small cohort of BB subjects, which precludes detailed scrutiny in regards to optimal timing of initiation. Further work in this area is needed.

Although our study has several strengths (population based data from an entire province with relatively complete follow-up, data on prescriptions in younger as well as older patients, unique group of subjects followed from their first hospitalization for HF, and multiple supporting sensitivity analyses), it does have some limitations. For example, we lacked clinical data which would have permitted analysis of adherence by clinical status such as severity of HF, or presence of systolic versus diastolic heart failure. Furthermore, we did not have access to specific reasons for nonadherence such as medication intolerance. However, all of these patients were followed from their first hospital discharge for HF and thus were likely at the same stage of disease. Also, we have no reason to believe that the baseline rate of medication intolerance would change between 1994 and 2003. In fact, BBs appear to be tolerated by the majority of HF patients, even those with very severe disease.

Second, although the use of ICD-9 code 428 has been demonstrated in North American databases to accurately identify cases of HF in administrative data such as we used, there is limited data on the sensitivity and specificity of using ICD-10-CA codes 150 and 111 to identify cases of heart failure. Although we used refill frequency as a surrogate for adherence, this is a well recognized and previously validated technique. Further, our sensitivity analysis, using a different method of calculating adherence, provided nearly identical results. Third, these findings may not be generalized to all heart failure patients because our study sample was restricted to those patients who had been hospitalized for their condition and all patients had to survive for...
at least 1 year. In addition, we restricted our analysis to subjects who received a primary or most responsible diagnosis of HF only.

Lastly, it is possible that adherence may have been affected by a change in the clinical profile of surviving subjects over time. Indeed, medication use, comorbidity, and 1-year mortality all changed to some degree over the course of our study period. However, logistic regression was used to control for factors that may have influenced adherence. Also, adherence rates were examined among subjects who were excluded because of a lack of 1-year follow-up. In the sensitivity analysis examining adherence in those patients who died in the first year, the proportion of subjects exhibiting optimal adherence (at the time of exit) was not only similar to our study cohort, but also increased in a similar manner over time.

In summary, adherence to evidence-based medications has significantly improved over the past 10 years in patients after a first hospitalization for HF. Most importantly, it appears that these improvements were not a result of focused interventions or strategic funding directed at patients, rather they occurred during a time when physician management of HF was evolving. Also, improved adherence was observed in all subgroups including young and old, as well as individuals receiving multiple other medications. Further study is required to elucidate the driving factors behind these observational trends and to confirm whether these improvements in adherence will lead to improvements in survival and reductions in hospitalizations.40

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Disclosures
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