Clinical Trial

Improvement of Guideline Beta-Blocker Prescribing in Heart Failure: A Cluster-Randomized Pragmatic Trial of a Pharmacy Intervention

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ABSTRACT

Background: Treatment with specific beta-blockers and doses recommended by guidelines is often not achieved in practice. We evaluated an intervention directed to the pharmacy to improve prescribing.

Methods and Results: We conducted a pragmatic cluster-randomized trial, where facilities (n = 12) with patients (n = 220) were the clusters. Eligible patients had a beta-blocker prescription that was not guideline concordant. Level 1 intervention included information to a pharmacist on facility guideline concordance. Level 2 also provided a list of patients not meeting guideline goals. Intervention and follow-up periods were each 6 months. Achievement of full concordance with recommendations was low (4%−5%) in both groups, primarily due to lack of tolerability. However, compared with level 1, the level 2 intervention was associated with 1.9-fold greater odds of improvement in prescribing (95% confidence interval [CI] 1.1−3.2). Level 2 patients also had greater odds of a higher dose (1.9, 95% CI 1.1−3.3). The intervention was aided by the patient lists provided, the electronic medical record system, and staff support.

Conclusions: In actual practice, full achievement of guideline goals was low. However, a simple intervention targeting pharmacy moved patients toward guideline goals. As health care systems incorporate electronic medical records, this intervention should have broader feasibility. (*J Cardiac Fail 2013;19:525−532*)

Key Words: Target dose, quality improvement, pharmacy intervention, health information technology, pragmatic trial.

For the treatment of heart failure with reduced left ventricular ejection fraction (HF), American College of Cardiology/American Heart Association Guidelines recommend 1 of 3 beta-adrenergic blockers—bisoprolol, carvedilol, or metoprolol succinate—with efforts to achieve the target dose studied in clinical trials.[1−10] Although beta-blocker use in HF has increased,[1] the agents or doses are often not guideline concordant.[11−13] In a retrospective study, only 4% of patients on metoprolol succinate and 25% of patients on carvedilol achieved target dose, with the median

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dose of the last prescription at 25% of target for both medications.[13] It is recognized that some patients do not tolerate guideline-recommended therapy.[12,14] Even in large clinical trials, the average dose achieved can be substantially lower than target.[15] Nevertheless, the observation that interventions such as an HF clinic[14] or an intensive medication management program[16] can increase dose relative to target indicates that some improvement is achievable.

Pharmacists can be important contributors to quality improvement (QI) intervention teams[17–19] as shown in studies of the "explanatory" type,[20,21] ie, where interventions are tested under study-specific "ideal" conditions. For example, Lowrie et al[22] reported on an HF intervention in which pharmacists were hired and trained to conduct medication review and intervention clinics and had regular contact with the study team or pharmacist specializing in HF. Although it is necessary to evaluate an intervention under structured facilitating conditions, there is also a need to design and test interventions that are applicable to usual practice conditions, ie, in a "pragmatic" trial. The Pharmacy Benefits Management (PBM) Services of the Veterans Health Administration (VHA) has a national drug safety QI program. Using VHA electronic health information resources,[23] PBM's medication safety center (VAMedSAFE)[17] is able to identify patients with prescriptions of potential concern. This information is transmitted electronically to VHA facilities for follow-up as part of usual practice. Such QI activities are conducted as needed and are largely unpublished. However, those that have been published[24–26] illustrate the ability of VAMedSAFE to effect change within the confines of existing facility resources by leveraging VHA's health information technology and network of pharmacists.

We evaluated 2 methods for promoting prescribing according to practice guidelines for beta-blocker therapy in VHA patients with HF with reduced left ventricular ejection fraction. We focused on HF patients already treated with beta-blocker therapy (as reflected in VHA's national pharmacy database) but where the dose or agent was not in accordance with guideline recommendations. The intervention was based on established components (audit, feedback, and education[27,28]) that we have used successfully in our safety interventions.[24–26] Because the literature suggests that full concordance might be limited despite intervention,[12,14,16,29] we included a comparator group to facilitate interpretation of potentially modest intervention effects.

Methods

Trial Design Overview

We conducted an unmasked pragmatic cluster-randomized trial, randomizing 12 VHA facilities to 1 of 2 levels of intervention intensity (Table 1). We used administrative databases (see below) to obtain patient prescription data to determine initial and final eligibility and prescription outcomes. Facilities with patients comprised the 12 clusters, and the intervention was directed to the pharmacy through a representative who agreed to participate. The methods were designed to be consistent with the goal of a pragmatic trial,[20,21] ie, to reflect, as much as feasible, the intervention's effect when applied in the natural environment. Therefore, the burden of participation in the research elements (eg, data collection) was designed to be as low as possible to (a) encourage participation by nonresearchers and (b) minimize unanticipated changes in participant behavior that might not be replicated when the intervention is subsequently used for routine QI.[20]

Patient Eligibility

Initial patient eligibility was determined by querying VHA electronic administrative databases for prescription and diagnostic criteria. To produce a manageable facility work load, we limited the

Table 1. Study Intervention and Methods

Methods in common to randomized clusters		
Intervention		(a) Education (see Supplemental Materials 1 and 2) (b) Feedback on guideline concordance: facility, overall VHA (c) Request to improve concordance in 6 months
Primary data collection		(a) Facility characteristics (b) Description of local response (c) Summative evaluation
Primary Measure:		Each patient's final follow-up prescription was categorized as: • *concordant:* total daily dose for carvedilol ≥50 mg or metoprolol succinate ≥200 mg* • *with progress:* change to a guideline agent or dose increase of a guideline agent • *with regression:* change to a nonguideline agent or dose decrease of a guideline agent
Methods specific to randomized clusters (6 facilities each)		
	Level 1	Level 2
Intervention	Nothing additional	Audit: received a list of specific patients (eligibility described in text) with potentially suboptimal therapy Accountability: asked to provide data on patients (see below)
Primary data collection	Nothing additional	Reason for final follow-up status if not guideline-concordant (7 options) Provider type for the prescription Helpfulness of additional study resources (patient list, data collection form)

*No prescriptions were found for bisoprolol.

study sample by including only patients meeting criteria within specific time windows. Patients met the prescription criterion if they had a VHA beta-blocker prescription within a 4-month window that (a) was not guideline concordant and (b) was not preceded by a prescription that was consistent with a concordance attempt within the preceding 12 months. The 4-month window was July−October 2009 (10 sites) or June−September 2010 (2 sites). Patients met the diagnostic criterion if they had an admission for HF (International Classification of Diseases, 9th Edition, Clinical Modification [ICD-9CM] primary diagnosis code 428.xx [except 428.3x, which is diastolic dysfunction/HF with preserved ejection fraction], 402.01, 402.11, 402.91, 404.01, 404.11, or 404.91) that was 3−9 months before the eligibility prescription. From this initial pool, final eligibility for the analytic cohort required that a patient fill a prescription within VHA for a beta-blocker within 6 months after randomization (ie, in the intervention period) and survive for 6 months' follow-up after the first such fill. Patient-prescription outcomes were assessed after 6 months of follow-up.

Study Intervention

Both intervention groups received background materials (Supplemental Materials 1 and 2), including estimates of concordance with guideline that were generated using the administrative databases (both for the specific facility and for the VHA overall). The study did not dictate methods to be used locally to influence prescribing. The goal was a pragmatic trial, ie, to assess the effect of an intervention as it is expected to be applied for routine use. In our case, routine use is initiation of the intervention at the central administrative level, with the local response left to the discretion of the participating facilities. Participants were asked only to improve prescribing and to describe their methods. The key difference in the study interventions was that only level 2 received a list of patients, for whom the pharmacist was to provide data (Table 1). This patient-specific data collection effected accountability and is therefore part of the intervention.

Data Sources

Prescription, diagnostic, and identifier data for all patients were obtained from the VHA electronic administrative databases. The sources were the national patient files (inpatient admissions, demographic information, ICD-9CM diagnosis codes, vital status[23]) and the prescription data from the PBM database (PBM v3.0). Only prescriptions filled by VHA were included. Data from these databases were linked via unique patient identifiers.

Primary data were collected from the participating pharmacists (Table 1). Level 2 submitted additional data on specific patients. After the intervention ended, respondents were surveyed to: 1) describe the local procedures used to implement the intervention, particularly the methods used to interact with providers; and 2) evaluate the intervention. In the summative evaluation, pharmacists rated the helpfulness/usefulness of materials or recommendations by choosing among response choices (*not at all*, *somewhat*, *very, not used*; *somewhat* and *very* were later combined in analysis owing to small numbers). Respondents at level 2 facilities were asked 2 additional questions about the patient list and data collection form (which were specific to level 2 intervention). All respondents were asked to include comments and to identify and rank the 3 most important barriers and facilitators related to implementation of the intervention. Content analysis of free-text data was used to identify conceptual themes. Themes were drafted independently by 2 investigators, then iteratively refined and affirmed through consensus during telephone conferences. All primary data were transmitted electronically according to VHA security regulations.

Statistical Methods

Facilities were randomized with the use of Proc Plan (SAS v9.2; SAS Institute, Cary, North Carolina). Analysis of outcomes was at the patient level, accounting for clustering within facility and adjusting for confounding as indicated (Proc Genmod; SAS v9.2). We provide descriptions of distributions as well as proportional odds ratios with 95% confidence intervals (CIs) to assess trend in outcome measures of concordance and final dose (after testing, with the use of the Score test, that the proportional odds assumption was not violated). The proportional odds ratio is similar to the odds ratio for a dichotomous response (eg, event occurs/does not occur) except that it applies to ≥3 ordered categories. It reflects the odds of a patient being in a higher category instead of a lower category.

Regulatory Concerns

The trial was approved by local research and development committees and human subjects subcommittees with waivers of documentation of informed consent of pharmacy staff and of Health Insurance Portability and Accountability Act for patient data. The trial was registered with Clinicaltrials.gov (NCT01002456).

Results

The total number of patients initially identified at the facilities as eligible for intervention (indicative of study work load) was 277. On average, 21% were ultimately ineligible for analysis because of death or lack of a prescription fill during the intervention period. The total number of patients meeting final/analytic criteria was 220 (98 at level 1 and 122 at level 2).

Baseline Facility and Patient Characteristics

Key baseline measures are presented for facilities in Table 2 and patients in Table 3. Per eligibility criteria, all patients were on beta-blocker therapy at baseline. Of those prescribed guideline-recommended beta-blockers at baseline (72% of level 1 and 53% of level 2), the dose was only about one-third (33% and 35% for levels 1 and 2, respectively) of the recommended target dose. For both levels at baseline, carvedilol was prescribed in

Table 2. Baseline Characteristics of Participating Facilities [Mean (SD) or n (%)]

Characteristic	Level 1 (n = 6)	Level 2 (n = 6)
% patients at goal or with prior attempt (facility mean)	38 (16.6)	36 (14.6)
Patients in intervention cohort (facility mean)	21 (9.9)	25 (9.1)
Patients in analytic cohort (facility mean)	16 (8.2)	20 (8.1)
Facilities with heart failure clinic	3 (50%)	3 (50%)

Table 3. Baseline Characteristics of Patients

Patient Characteristic	Level 1 (n = 98)	Level 2 (n = 122)
Age, y, mean (SD)	70 (11.5)	71 (11.0)
Gender, male (%)	97	98
Loop diuretic	93	95
Potassium-sparing diuretic	37	25
Angiotensin-converting enzyme inhibitor	68	65
Angiotensin II inhibitor	21	29
Digitalis glycosides	24	25
Antianginal	42	34
Anticoagulants	41	36
Platelet aggregation inhibitors	28	18
Antiarrhythmics	13	6
Antilipidemic	84	82
Nonopioid analgesics	56	68
Opioid analgesics	32	37
Antidepressants	36	34
Bronchodilators, sympathomimetic, inhaled	29	33
Oral hypoglycemic	26	30
Insulin	24	31

Values for medications are percentage with a fill (≥28 days) in the preceding year.

twice as many patients as metoprolol succinate, and the most common nonguideline agent was metoprolol tartrate. Table 3 lists the drug classes for which patients filled ≥1 prescription (with a supply of ≥28 days) in the preceding year. Included are HF and other cardiovascular drug classes, as well as the more common classes reflective of comorbidity.

Change in Prescription Concordance

By definition for the studied cohort, concordance with guideline targets was zero at baseline. Prescription outcomes after 6 months are presented in Table 4. There was only modest improvement for fully meeting goals regarding use of recommended agents at target doses, ie, gains of 4% (level 1) and 5% (level 2). However, the pattern of change showed a shift in level 2 toward greater progress toward goal with less regression from goal. There was a trend for greater odds of improvement ($P = .024$) in level 2. Although most patients were on a guideline-recommended agent at baseline, by chance the percentage was smaller in level 2. Nevertheless, adjusting for baseline agent (guideline-concordant or not) had little effect on the estimate for improvement trend (adjusted proportional odds ratio 1.8).

Target Dosing

At the end of follow-up, approximately two-thirds of patients in both groups (n = 151) were on guideline-recommended agents. The distributions into dose categories (relative to target) of <50%, 50%, and >50% were, respectively: level 1: 69%, 25%, and 6%; and level 2: 43%, 44%, and 13%. The crude proportional odds ratio for trend toward higher dose was 1.6 (95% CI 0.8−3.2) for level 2 compared with level 1. When adjusted for baseline agent (guideline-concordant or not), the proportional odds ratio was 1.9 (95% CI 1.1−3.3; $P = .025$). The mean doses at the end of follow-up, as percentage of target, were level 1:32% (95% CI 23.3−41.1) versus level 2:41% (95% CI: 31.5−51.3), ie, 28% higher in level 2 facilities.

Patient-Level Measures

At baseline, level 1 had 72% of patients already on a guideline-recommended agent, and an increase in the dose of the guideline drug accounted for most (78%) of the change toward goal for level 1. Level 2 had 53% of patients on a guideline-recommended drug at baseline. Positive changes were due equally to dose increase for those drugs (54%) and to switching to a guideline-recommended agent (46%).

Level 2 facilities had received a list of patients with prescriptions not meeting goal and collected data on these patients. Pharmacists recorded the primary reason a patient did not meet goal during follow-up from a list of choices (Table 5). The rank order of reasons was similar whether the provider was in primary care (65%) or cardiology (33%). Despite our attempts to exclude patients with preserved ejection fraction with the use of ICD-9CM codes, pharmacist review identified many such patients on the study list. Although the presence of patients with preserved ejection fraction on the lists was cited as a barrier, a sensitivity analysis of level 2 data excluding those patients still showed low goal achievement. Full concordance was 5%, 24% showed progression, and 7% showed regression. The

Table 4. Prescription Changes After 6 Months' Follow-Up, n (%)

Prescription Status	Level 1	Level 2	Proportional OR (95% CI)
Concordant with guideline goals	4 (4)	6 (5)	1.9 (1.1−3.2)
Not at goal but with progression*	10 (10)	22 (18)	
No change relative to goal	74 (76)	88 (72)	
Not at goal and with regression†	10 (10)	6 (5)	

OR, odds ratio with level 1 as the reference group; CI, confidence interval.

*Change to a guideline agent or dose increase of a guideline agent.

†Change to a nonguideline agent or dose decrease of a guideline agent.

Table 5. Main Reason Guideline Goal Not Achieved During Follow-Up in Level 2 (n = 122)

Reason	n
Adverse events (eg, bradycardia, hypotension, etc)	34
Nonsystolic/preserved ejection fraction heart failure*	32
Pharmacist's inability to engage the provider	17
Patient logistics	5
Insufficient facility resources	5
Nonguideline beta-blocker required for co-morbidity	4
Other	3

Values shown are percentage of patients in predefined category options. Data were not collected for level 1.

*Rank order of reasons was the same with this group removed.

Table 6. Local Response at Level 2 Facilities (n = 6)

No. of pharmacists involved, median (range)	1 (1−9)
Method of communication with provider about specific patients, n (%)	
Electronic medical record	4 (67%)
E-mail	3 (50%)
Face to face	2 (33%)
Telephone	1 (17%)
Frequency of communication with provider about specific patients, n (%)	
More than once per patient, as needed	2 (33%)
Usually once per patient	3 (50%)
Not for all patients*	1 (17%)
Ability to modify therapy without provider approval, n (%)	1 (17%)
Local implementation strategies (n = 5), n (%)	
Involved additional pharmacist(s)	2 (40%)
Contacted provider	5 (100%)
Reviewed charts for specific elements	5 (100%)
Reviewed records for reasons for discordance with guidelines	3 (60%)
Recommendation given to provider regarding patient	5 (100%)

*This pharmacist indicated *insufficient resources* as the main reason for not achieving concordance for 4/15 patients.

rank order of reasons was the same as in Table 5 for the full cohort.

Response of Facilities to the Intervention

Both level 1 and level 2 participants were asked to complete a survey on their strategies to implement the study intervention. For level 1, 2 participants did not return the survey, 2 returned the survey but indicated that they did not contact providers about patients, and 2 submitted details on their local implementation. Per design, we did not give level 1 the lists of patients meeting study criteria nor did we collect patient-level data from level 1. Because we do not know the extent to which eligible patients included in our analysis were targeted by level 1 facilities, we describe response details only for level 2 (Table 6). All level 2 participants made use of the patient lists. For each level 2 patient, a provider type and final status reason was coded (Table 5), indicating that each patient's record was reviewed by the facility.

Summative Evaluation

Eleven facilities (92%) responded to the evaluation survey. Most (80% of level 1 and 83%−100% of level 2) facilities found study resources helpful. The same percentages (80% of level 1 and 83%−100% of level 2) found the estimates of VHA and facility concordance useful. All level 2 facilities found the patient lists to be helpful, although the inclusion of HF patients with preserved ejection fraction was a distraction.

Facilitator themes were staff support (titration clinics, staff engagement, clinical pharmacist's role) and the protocol resources. Of the 7 sites that submitted facilitator information, 5 responded with the theme of staff support as the primary facilitator. Barrier themes were aspects of the protocol (short duration, regulatory/Institutional Review Board [IRB] issues, inaccurate patient identification), provider issues (identification, engagement), and inadequate staffing. Of the 10 sites submitting barrier information, eight responded with the theme of aspects of the protocol as the primary barrier (including 3 each specifying short duration or regulatory/IRB issues).

Discussion

We found that established QI methods applied at the level of the pharmacy were effective in improving prescribing of beta-blockers in HF. Our methodology was based on our past pharmacy-directed interventions which were focused on safety issues.[24−26] Similarly to those, there was no special funding or training for the contact at the pharmacy. We distributed educational, feedback, and audit information to pharmacies, asked them to bring prescriptions closer to guideline recommendations when possible, and allowed them flexibility in their local approach to this request. Our pragmatic trial extends the work of others who have demonstrated the effectiveness of pharmacists in improving prescribing under more structured and resource-intensive protocols that usually include routine patient contact.[14,16,17,22] Our findings raise the possibility that simpler interventions directed at the pharmacy could be used routinely to good effect.

Similarly to other studies, we found that conversion to fully meeting guideline goals was infrequent. Whellan et al reported that the percentage of patients at target dose increased from 6% to only 13% with an intensive medication management program.[16] These figures are similar to ours for the percentage of patients achieving greater than one-half of target dose for the 2 interventions. In the study by Lowrie et al,[22] only 20%−22% of patients were using ≥100% of the recommended dose at baseline. After intervention, 5% (usual care) and 8% (pharmacist intervention) increased dose to ≥100%. Jain et al[14] found that, after institution of an HF clinic, the proportion of patients on ''medium'' or ''high'' doses of beta-blockers increased from 18% to 57%. In our analysis, the percentage of patients at one-half or greater of target dose was 31% for level 1 and 57% for level 2.

The report by Galatius et al[12] is unusual in its quantification of reasons for beta-blocker use that was discordant with guidelines. Their study, intervening at the patient level, identified tolerability as the main reason, as did our study. We did not find evidence that the provider type was associated with tolerability, but the small number treated by cardiologists limits interpretation. Furthermore, we do not know if the patient profile was similar across provider types. Note, however, that we intervened at the pharmacy level, and our findings are most relevant from a system perspective. From a broader system perspective, there were other notable barriers, eg, lack of engagement of the provider and contamination of the identified pool of patients with patients to whom the guidance does not apply. Future work might explore ways to reduce these

barriers. Our findings on dose are consistent with reports that achievement of target dose in usual practice is not common, even with intervention.

What are the implications of subtarget dosing? Bristow et al[30] randomized patients to a range of target doses of carvedilol. Although their study was underpowered for conclusions about individual doses, the results were consistent with some benefit of lower doses (25%−50% of target). Metra et al showed that carvedilol was superior to a comparator (metoprolol tartrate), even in patients achieving only low doses of both drugs.[31] Finally, a trial of metoprolol succinate reported a reduction in mortality of 38% in both the low-dose (mean 38% of target) and high-dose (mean 96% of target) treatment groups compared with placebo.[32] The hypothesis that dose, per se, may be less important than titration to heart rate response might account for these findings, although such a mechanism remains controversial.[31,33,34] Nevertheless, an increase in use of medications according to clinical practice guidelines has been associated with a significant reduction in health care utilization despite only modest change in guideline adherence (from 37% to 41%).[35] Thus, despite the barriers to fully meeting guideline goals, modest improvement may be beneficial.

The VHA is a staff-model health care system. The applicability of our methodology to other health care systems may depend not only on their model, but also on the extent to which they can incorporate our facilitators, minimize the barriers, and have the resources and culture to support the local response. VHA informatics[23] has long been used to support research and QI in the VHA. Health care systems with such resources should be able to similarly leverage their data, once an interface is in place to translate data into an actionable form for providers. In our study, the interface was multilayered, with VAMedSAFE personnel extracting the pertinent information from administrative databases and communicating it to pharmacies. The pharmacists, in turn, reviewed the identified patient records and communicated information or recommendations regarding patients to providers to effect change. Communication with providers was most often through the electronic medical record. Thus, local resources and culture supported the pharmacist's action without the need for the study to direct and monitor activities. Staff support was cited as an important facilitator in our study, and others also have identified teamwork as an important feature of change.[18] Regarding work load, our patient eligibility criteria were chosen such that ∼20 patients would be eligible per facility. We wanted to sufficiently challenge facility resources without overwhelming them, and it appears that we struck that balance. ''Insufficient facility resources'' was cited as the main limitation to achieving concordance in 5% of patients. Most of these patients were from a facility whose participating pharmacist worked part time. Therefore, we estimate a manageable workload of ∼20 patients over 6 months. Finally, the pharmacy data were of good quality, because no pharmacist cited errors in medication data as a problem.

Barriers that should be considered in applying our methods include identification of patients with preserved ejection fraction and exclusion of them from the patient lists, because they distracted study resources. We relied on administrative codes, for which reasonably sensitive selection algorithms have poor specificity,[36,37] so we were not fully successful in eliminating these patients. Advances in VHA informatics should permit better identification in the future through mining of medical records.[38,39] A period longer than 6 months may be useful, depending on patient availability and how quickly the system can incorporate the needed appointments. Although regulatory/IRB issues were cited as a barrier, in a pure QI setting this should be less of a barrier. Finally, the participating facilities had agreed to participate in the study, and there were some research tactics in place that may have enhanced participant engagement. In a pure QI effort applied across all facilities in a health care system, pharmacists may be less engaged.

Our study was not designed as an explanatory trial and therefore does not speak to the change in concordance that might be achieved under ideal conditions. Rather, we have provided estimates as to the change that might be expected when providing modest assistance and oversight in an usual-care setting. To design a pragmatic trial, it was necessary to impose as little as possible on the setting (other than our education/feedback/audit intervention) and restrict data collection and monitoring to the minimum consistent with study goals. Consistent with principles of pragmatic trials[20] and our successful safety QI interventions, we allowed facilities flexibility in their local response. We waited until after the intervention was complete to survey participants about their local methods to avoid an effect of data collection/observation on their activities.[20] There were consistent themes identified by the survey that can be used in extrapolating from our setting.

Our study is consistent with the body of work showing that target doses used in clinical trials are infrequently seen in usual-care settings. Future work should be directed at investigating whether progress toward guideline concordance, even when full concordance is rare, is associated with clinical benefit. Ongoing monitoring of all-cause mortality in our study cohort is consistent with clinical benefit of the level 2 intervention. If benefit can be demonstrated in an adequately powered study, simple interventions that shift patients closer to recommended therapy could be a useful tool for health care systems.

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Disclosures

All of the authors are employees of the VHA. There are no other conflicts to report.

Supplementary Material

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References

1. Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel. PBM-MAP clinical practice guideline for the pharmacologic management of chronic heart failure in primary care practice. Publication no. 00-0015. Washington, DC: Veterans Health Administration, Department of Veteran Affairs; 2007.
2. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al, American College of Cardiology Foundation/American Heart Association. 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in collaboration with the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 2009;53:e1−90.
3. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study (CIBIS-II): a randomised trial. Lancet 1999;353:9−13.
4. Willenheimer R, van Veldhuisen DJ, Silke B, Erdmann E, Follath F, Krum H, et al, CIBIS III Investigators. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite consequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation 2005;112:2426−35.
5. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al, US Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996;334:1349−55.
6. Packer M, Coats AJS, Fowler MB, Katus HA, Krum H, Mohacsi P, et al, Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651−8.
7. Poole-Wilson PA, Swedberg K, Cleland JGF, di Lenarda A, Hanrath P, Komajda M, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol or Metoprolol European Trial (COMET): randomized controlled trial. Lancet 2003;362:7−13.
8. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001−7.
9. Goldstein S, Fagerberg B, Hjalmarson A, Kjekshus J, Waagstein F, Wedel H, et al, MERIT-HF Study Group. Metoprolol controlled release/extended release in patients with severe heart failure: analysis of the experience in the MERIT-HF study. J Am Coll Cardiol 2001;38:932−8.
10. Fonarow GC, Yancy CW, Hernandez AF, Peterson ED, Spertus JA, Heidenreich PA. Potential impact of optimal implementation of evidence-based heart failure therapies on mortality. Am Heart J 2011;161:1024−30.
11. Steinman MA, Harlow JB, Massie BM, Kaboli PJ, Fung KZ, Heidenreich PA. Age and receipt of guideline-recommended medications for heart failure: a nationwide study of veterans. J Gen Intern Med 2011;26:1152−9.
12. Galatius S, Gustafsson F, Atar D, Hildebrandt PR. Tolerability of beta-blocker initiation and titration with bisoprolol and carvedilol in congestive heart failure—a randomized comparison. Cardiology 2004;102:160−5.
13. Rector TS, Anand IS, Nelson DB, Ensrud KE. Carvedilol versus controlled-release metoprolol for elderly veterans with heart failure. J Am Geriatr Soc 2008;56:1021−7.
14. Jain A, Mills P, Nunn LM, Butler J, Luddington L, Ross V, et al. Success of a multidisciplinary heart failure clinic for initiation and up-titration of key therapeutic agents. Eur J Heart Fail 2005;7:405−10.
15. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. Ann Intern Med 2009;150:784−94.
16. Whellan DJ, Gaulden L, Gattis WA, Granger B, Russell SD, Blazing MA, et al. The benefit of implementing a heart failure disease management program. Arch Intern Med 2001;161:2223−8.
17. Koshman SL, Charrois TL, Simpson SH, McAlister FA, Tsuyuki RT. Pharmacist care of patients with heart failure: a systematic review of randomized trials. Arch Intern Med 2008;168:687−94.
18. Odum L, Whaley-Connell A. The role of team-based care involving pharmacists to improve cardiovascular and renal outcomes. Cardiorenal Med 2012;2:243−50.
19. Santschi V, Chiolero A, Burnand B, Colosimo AL, Paradis G. Impact of pharmacist care in the management of cardiovascular disease risk factors: a systematic review and meta-analysis of randomized trials. Arch Intern Med 2011;171:1441−53.
20. Thorpe KE, Zwarenstein M, Oxman AD, Treweek S, Furberg CD, Altman DG, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. CMAJ 2009;180:E47−57.
21. Godwin M, Ruhland L, Casson I, MacDonald S, Delva D, Birtwhistle R, et al. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. BMC Med Res Methodol 2003;3:28.
22. Lowrie R, Mair FS, Greenlaw N, Forsyth P, Jhund PS, McConnachie A, et al, Heart Failure Optimal Outcomes from Pharmacy Study (HOOPS) Investigators. Pharmacist intervention in primary care to improve outcomes in patients with left ventricular systolic dysfunction. Eur Heart J 2012;33:314−24.
23. Hynes DM, Perrin RA, Rappaport S, Stevens JM, Demakis JG. Informatics resources to support health care quality improvement in the veterans health administration. J Am Med Inform Assoc 2004;11:344−50.
24. Sales MM, Cunningham FE, Glassman PA, Valentino MA, Good CB. Pharmacy benefits management in the Veterans Health Administration: 1995 to 2003. Am J Manag Care 2005;11:104−12.
25. Aspinall SL, Zhao X, Good CB, Stone RA, Boresi J, Cox S, et al. Intervention to decrease glyburide use in elderly patients with renal insufficiency. Am J Geriatr Pharmacother 2011;9:58−68.
26. Furmaga EM, Glassman PA, Cunningham FE, Good CB. Reducing the use of short-acting nifedipine by hypertensives using a pharmaceutical database. Implementation issues. In: Henriksen K, Battles JB, Marks ES, Lewin DI, editors. Advances in patient safety: from research to implementation, Vol. 3. Rockville, Maryland: Agency for Healthcare Research and Quality; 2005.
27. Wallin L. Knowledge translation and implementation research in nursing. Int J Nurs Stud 2009;46:576−87.

28. Grimshaw JM, Eccles MP, Lavis JN, Hill SJ, Squires JE. Knowledge translation of research findings. Implement Sci 2012;7:50.
29. Goldstein MK, Lavori P, Coleman R, Advani A, Hoffman BB. Improving adherence to guidelines for hypertension drug prescribing: cluster-randomized controlled trial of general versus patient-specific recommendations. Am J Manag Care 2005;11:677−85.
30. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, et al, MOCHA Investigators. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. Circulation 1996;94:2807−16.
31. Metra M, Torp-Pedersen C, Swedberg K, Cleland JG, di Lenarda A, Komajda M, et al. Influence of heart rate, blood pressure, and beta-blocker dose on outcome and the differences in outcome between carvedilol and metoprolol tartrate in patients with chronic heart failure: results from the COMET trial. Eur Heart J 2005;26:2259−68.
32. Wikstrand J, Hjalmarson A, Waagstein F, Fagerberg B, Goldstein S, Kjekshus J, et al, MERIT-HF Study Group. Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure: analysis of the experience in Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF). J Am Coll Cardiol 2002;40:491−8.
33. Flannery G, Gehrig-Mills R, Billah B, Krum H. Analysis of randomized controlled trials on the effect of magnitude of heart rate reduction on clinical outcomes in patients with systolic chronic heart failure receiving beta-blockers. Am J Cardiol 2008;101:865−9.
34. Gullestad L, Wikstrand J, Deedwania P, Hjalmarson A, Egstrup K, Elkayam U, et al, MERIT-HF Study Group. What resting heart rate should one aim for when treating patients with heart failure with a beta-blocker? Experiences from the Metoprolol Controlled Release/Extended Release Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF). J Am Coll Cardiol 2005;45:252−9.
35. Shafazand S, Yang Y, Amore E, O'Neal W, Brixner D. A retrospective, observational cohort analysis of a nationwide database to compare heart failure prescriptions and related health care utilization before and after publication of updated treatment guidelines in the United States. Clin Ther 2010;32:1642−50.
36. Quach S, Blais C, Quan H. Administrative data have high variation in validity for recording heart failure. Can J Cardiol 2010;26:306−12.
37. Li Q, Glynn RJ, Dreyer NA, Liu J, Mogun H, Setoguchi S. Validity of claims-based definitions of left ventricular systolic dysfunction in Medicare patients. Pharmacoepidemiol Drug Saf 2011;20:700−8.
38. Maveric Arc v2.0. Available at: http://arc.4thparadigm.org.
39. United States Department of Veterans Affairs. VHA Office of Health Information. Available at: www.ehealth.va.gov/CAPRI_for_VSOs.asp.