

# Angiotensin-converting Enzyme Inhibitor Therapy for Coronary Artery Disease and Diabetes Mellitus

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**Objectives:** To use a population management strategy to increase the proportion of patients with coronary artery disease (CAD) and diabetes receiving target-dose angiotensin-converting enzyme (ACE) inhibitor therapy and to assess the safety and tolerability of this initiative.

**Study Design:** Prospective cohort.

**Methods:** Patients were eligible for enrollment if they were not receiving target-dose ACE inhibitor therapy. Clinical pharmacy specialists were responsible for initiation, titration, and appropriate follow-up of ACE inhibitor therapy.

**Results:** A total of 453 subjects were enrolled. Their mean age was 67.9 years and 77% were male. At baseline, 30.9% (n = 140) of eligible patients were on no ACE inhibitor therapy and no patients were at the target dose. The mean systolic blood pressure, serum creatinine, and serum potassium values were 128.0 mm Hg, 1.0 mg/dL, and 4.4 mEq/dL, respectively. At follow-up, 8.2% (n = 37;  $P < .001$ ) were on no ACE inhibitor therapy and 68.7% (n = 311;  $P < .001$ ) of patients had achieved the target dose. From baseline to follow-up, mean systolic blood pressure decreased 4.4 mm Hg ( $P < .001$ ). Changes in serum potassium or creatinine were not clinically significant. Of the 142 subjects unable to achieve the target dose, 31 experienced hypotension, 29 did not have the dose increased because of the potential for hypotension, and 23 experienced cough.

**Conclusion:** A population management approach to increasing the proportion of patients with CAD and diabetes who receive target-dose ACE inhibitor therapy was effective and safe.

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For author information and disclosures, see end of text.

Three recently published meta-analyses found a 17% to 19% relative risk reduction in cardiovascular death and a 12% to 14% relative risk reduction in all-cause mortality in patients with stable coronary artery disease (CAD) without evidence of heart failure who received angiotensin-converting enzyme (ACE) inhibitors.<sup>1-3</sup> Trials that have shown cardiovascular benefit and a slowing of atherosclerotic processes<sup>4-6</sup> used comparatively higher doses of ACE inhibitor than those that did not show these benefits.<sup>7</sup> Achievement of an adequate ACE inhibitor dose is likely an important factor to ensure that the benefits observed in trials such as MICRO-HOPE and PERSUADE are translated to clinical practice.<sup>1,8,9</sup>

The American Heart Association/American College of Cardiology Guidelines for Secondary Prevention for Patients with Coronary and Other Atherosclerotic Vascular Disease provide a level 1A recommendation that ACE inhibitors be used in all patients with concurrent diabetes.<sup>10</sup> Despite this recommendation, a treatment gap with secondary-prevention strategies such as aspirin,  $\beta$ -blockers, statins, and ACE inhibitors has been well recognized, specifically in patients with diabetes.<sup>11</sup>

Population-based strategies aimed at increasing the proportion of patients who receive adequate ACE inhibitor doses can potentially decrease the morbidity and mortality associated with CAD and diabetes. The purpose of this study was to increase the proportion of patients with both CAD and diabetes who received target-dose ACE inhibitor therapy. Secondary goals of this study were to determine the safety and tolerability of initiation and different methods of titration of ACE inhibitor therapy to achieve target doses.

## METHODS

This prospective cohort study was performed in collaboration with physicians from the Colorado Permanente Medical Group and was approved by the Kaiser Permanente Colorado (KPCO) institutional review board.

### Participants

KPCO is a not-for-profit health maintenance organization that provides care for approximately 430 000

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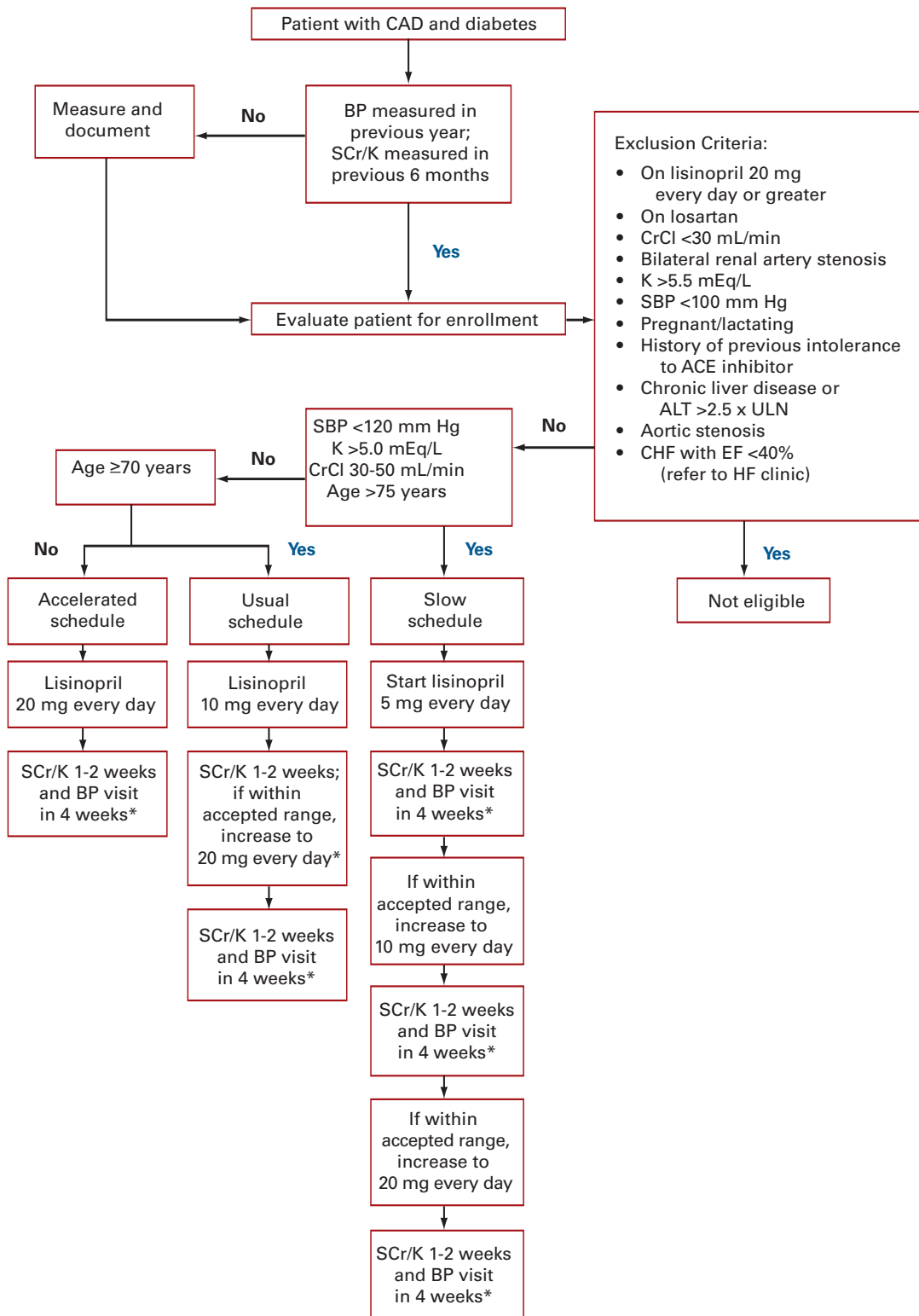
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Appendix Tables A and B

## ACE Inhibitor Therapy for Coronary Artery Disease and Diabetes Mellitus

■ **Figure 1.** Implementation of ACE Inhibitor Therapy in Patients With CAD and Diabetes Mellitus



\*If SCr increases by >30%, reevaluate in 1 week. If SCr increases by >50%, stop ACE inhibitor and refer patient to primary care physician. Titration may be stopped at any time (at patient's highest tolerated dose or discontinued if necessary.)  
ACE indicates angiotensin-converting enzyme; CAD, coronary artery disease; BP, blood pressure; SCr, serum creatinine; K, potassium; CrCl, creatinine clearance (estimated by Cockcroft-Gault equation); SBP, systolic blood pressure; ALT, alanine aminotransferase; ULN, upper limit of normal; CHF, congestive heart failure; EF, ejection fraction; HF, heart failure.

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patients at 18 medical offices in the Denver/Boulder metropolitan area. The Clinical Pharmacy Cardiac Risk Service (CPCRS) is a clinical pharmacy specialist–managed, physician-supervised service that currently coordinates care for approximately 11 000 patients with established CAD (defined as myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention with or without stent placement, unstable angina, or CAD diagnosed by catheterization).<sup>12,13</sup> The 18 CPCRS specialists have advanced training (Doctor of Pharmacy degree and postgraduate residency training). The goal of CPCRS is to reduce CAD-related morbidity and mortality. The clinical pharmacy specialists evaluate lipids, blood pressure, and smoking status, and assist with initiation, titration, and monitoring of evidence-based secondary-prevention medications (ie, statins, antiplatelet agents,  $\beta$ -blockers).<sup>12,14</sup> A Web-based tracking database (HealthTRAC<sup>®</sup>) containing membership and other administrative data for all patients enrolled in CPCRS is used for ongoing clinical and population management, patient tracking, and quality improvement activities.

Patients were identified administratively through a HealthTRAC query on March 1, 2004. The study population included all patients older than 18 years of age diagnosed with diabetes and CAD. Eligible patients were active KPCO members and alive for the entire study duration. Patients were excluded for the following reasons: currently taking the target ACE inhibitor dose ( $\geq 20$  mg of lisinopril daily); currently taking an angiotensin receptor blocker (ARB) or another ACE inhibitor; a previous documented history of ACE inhibitor intolerance; an ejection fraction of  $< 40\%$  (referred to the heart failure clinic); renal disease (creatinine clearance  $< 30$  mL/min); hyperkalemia ( $> 5.5$  mEq/L); hypotension (systolic blood pressure [SBP]  $< 100$  mm Hg); pregnancy or lactation; abnormal hepatic function (alanine aminotransferase  $> 2.5$  times the upper limit of normal); aortic stenosis; bilateral renal artery stenosis; or noncompliance with CPCRS laboratory follow-up (Figure 1). Patients had the option to decline starting or increasing lisinopril therapy.

### Interventions

Patients from the cohort were screened by clinical pharmacy specialists for appropriateness of lisinopril therapy during their usual clinical activities between March 1, 2004, and May 31, 2005. Baseline serum creatinine, potassium, and blood pressure(s) were evaluated for all patients. Existing creatinine and potassium levels were used as baseline levels if the tests had been done within the previous 6 months. Blood pressure readings were utilized as baseline levels if they had been taken within the previous 12 months. If these values

were not available, a clinical pharmacy specialist would facilitate obtaining the missing data. Blood pressure measurements may have been obtained by a clinical pharmacy specialist, nurse, or physician.

To most closely mimic the MICRO-HOPE study, a daily dose of lisinopril 20 mg (our preferred formulary ACE inhibitor) was targeted as approximately the therapeutic equivalent of ramipril 10 mg daily.<sup>15</sup> Eligible patients were assessed and assigned to a lisinopril titration schedule. Titration schedules (slow, usual, or accelerated) were determined based on data from a prior study conducted at KPCO (Figure 1).<sup>15</sup> Patients at an increased risk of adverse drug events were assigned to the slow titration schedule.

Lisinopril dose titration was stopped when the patient reached the target dose unless the patient's blood pressure remained above 130/80 mm Hg. If a patient developed hyperkalemia or hypotension, the primary care physician was consulted. Lisinopril was discontinued if the patient developed any serious reactions (eg, angioedema). Patients unable to tolerate lisinopril because of cough were considered for losartan 50 mg daily if they had microalbuminuria, hypertension, or left ventricular hypertrophy.<sup>16-19</sup> Adverse effects and medication changes were communicated to the primary care physician via the electronic medical record or telephone.

The primary study outcome was the proportion of patients with CAD and diabetes taking the target ACE inhibitor dose of  $\geq 20$  mg of lisinopril daily at baseline versus study completion. The secondary outcome was the proportion of patients with CAD and diabetes taking any dose of lisinopril or ARB at baseline versus study completion. Safety and tolerability of each titration schedule also were evaluated. Changes in creatinine, potassium, and blood pressure as well as reasons the target dose was not achieved were collected and evaluated.

### Statistical Methods/Analysis

ACE inhibitor and ARB utilization was considered confirmed if an administrative claim for that medication was recorded in the baseline (within 90 days before enrollment) and follow-up (within 90 days after study completion) periods. Age was calculated as of the date of enrollment. Changes in blood pressure, serum potassium, and creatinine were calculated by subtracting the baseline value from the follow-up value. Data are displayed as mean  $\pm$  standard deviation or proportions as appropriate. Distributions of interval-level data (eg, blood pressure) were assessed for normality, and all were found to approximate normal distributions. McNemar's test and the 1-sample *t* test were utilized to test differences in proportions and means, respectively, within the groups

between the baseline and follow-up periods. Two-tailed probability values of less than .05 were considered statistically significant.

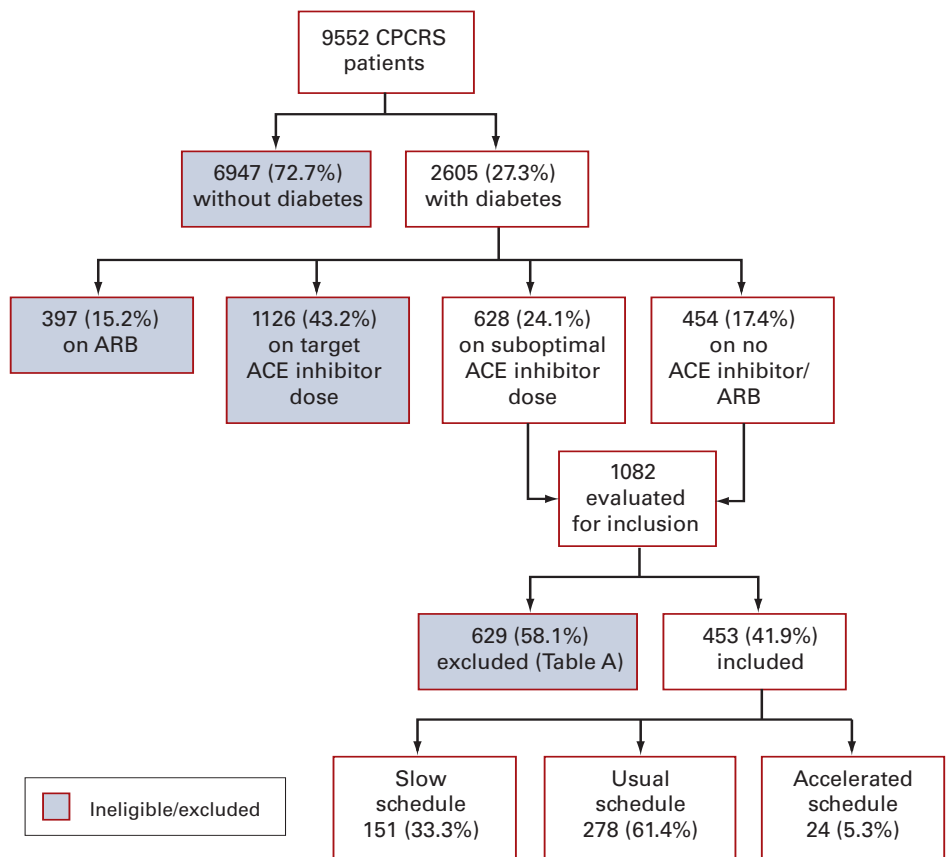
## RESULTS

**Figure 2** describes the origin of the study population. Exclusions are listed in **Appendix Table A** (available at [www.ajmc.com](http://www.ajmc.com)). There were 151 (33.3%) patients whose doses were titrated via the slow schedule, 278 (61.4%) patients via the usual schedule, and 24 (5.3%) patients via the accelerated schedule. The **Table** shows baseline patient characteristics by titration schedule. At the onset of the study, 31% ( $n = 140$ ) and 69% ( $n = 313$ ) were on no or suboptimal ACE inhibitor therapy, respectively.

At the conclusion of the study, 68.7% ( $n = 311$ ) of the participants were receiving the target ACE inhibitor dose (Table). More than 80% of the patients in the accelerated titration schedule reached target lisinopril dose, and more than 50% of patients achieved this dose using the slow titration schedule. Nearly 92% ( $n = 416$ ) of participants were on some dose of ACE inhibitor or ARB, an increase of 22.8% over baseline. Of the 453 enrolled patients, 37 (8.2%) patients were on neither an ACE inhibitor nor an ARB at the conclusion of the study. The slow titration schedule had the largest proportion of patients on neither an ACE inhibitor nor an ARB (12.6%,  $n = 19$ ) at study completion.

**Appendix Table B** (available at [www.ajmc.com](http://www.ajmc.com)) lists the reasons patients ( $n = 142$ ) were unable to achieve the target dose. The most common reason was hypotension ( $n = 31$ ), followed by concern about hypotension should the dose be increased ( $n = 29$ ). Twenty-three patients were unable to tolerate lisinopril because of cough, and 20 patients refused to either start ACE inhibitor/ARB therapy or to advance their dose.

■ **Figure 2.** Patient Disposition



CPCRS indicates Clinical Pharmacy Cardiac Risk Service; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

## DISCUSSION

Preventive medications (eg, ACE inhibitors) are important tools to help stave off the cardiovascular complications that plague patients with CAD and diabetes. This study applied evidence and guidelines to clinical practice by clinical pharmacy specialists. We undertook a population-based initiative to increase the proportion of patients with stable CAD and diabetes who receive target-dose ACE inhibitor therapy. To our knowledge, results of this type of initiative have not been previously published for patients without heart failure. The proportion of patients receiving target-dose ACE inhibitor ( $\geq 20$  mg of lisinopril daily) was increased from 0% in the predefined population to 68.7%. An additional 103 patients were on some dose of ACE inhibitor or ARB (91.8% of eligible patients) at study completion. By the end of this study, the entire CAD and diabetes population evaluated was either on the therapy or, if not, had a clearly documented reason in the medical record. Based

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■ **Table.** Baseline Characteristics and Follow-up Outcomes by Titration Schedule

Characteristic	Overall		Slow		Usual		Accelerated	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
<b>Mean age, y (SD)</b>	67.9 (9.6)		70.7 (9.6)		66.9 (9.1)		57.9 (6.8)	
<b>Male, %</b>	77.0		82.9		74.5		70.8	
<b>Mean SBP (SD)</b>	128.0 (14.1)	124.3 (16.2)*	125.6 (16.3)	121.6 (15.6) <sup>†</sup>	129.4 (13.1)	126.2 (16.5)*	127.3 (6.1)	118.5 (12.3) <sup>†</sup>
<b>Mean DBP (SD)</b>	73.1 (9.3)	69.9 (9.4)*	71.4 (8.8)	67.7 (9.9)*	73.5 (9.3)	70.8 (9.1)*	78.4 (10.1)	73.1 (7.6)
<b>Mean SCr level (SD)</b>	1.04 (0.27)	1.06 (0.24)*	1.01 (0.32)	1.10 (0.22)*	1.04 (0.24)	1.05 (0.25)	0.84 (0.16)	0.90 (0.21) <sup>†</sup>
<b>Mean K level (SD)</b>	4.39 (0.37)	4.43 (0.36)	4.33 (0.38)	4.44 (0.39)*	4.43 (0.37)	4.43 (0.35)	4.33 (0.31)	4.42 (0.32)
<b>Lisinopril dose, %</b>								
≥20 mg	0.0	68.7*	0.0	55.6*	0.0	74.5*	0.0	83.3*
10 mg to <20 mg	39.7	13.9	6.6	13.3	60.4	14.8	8.3	8.3
5 mg to <10 mg	24.9	4.9	37.8	11.3	16.9	1.8	37.5	0.0
>0 mg to <5 mg	4.4	1.3	9.3	3.3	1.8	0.4	4.2	0.0
<b>ARB use only, %</b>	0.0	4.9*	0.0	6.0 <sup>‡</sup>	0.0	4.0 <sup>‡</sup>	0.0	8.3
<b>No ACE inhibitor or ARB use, %</b>	30.9	8.2*	46.4	12.6*	20.9	6.5*	50.0	0.0*

\**P* < .001.  
<sup>†</sup>*P* < .050.  
<sup>‡</sup>*P* < .010.  
 SBP indicates systolic blood pressure; DBP, diastolic blood pressure; SCr, serum creatinine; K, potassium; ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme.

on the prior clinical studies, our results may translate into morbidity or mortality benefits. Although the methods were specific to our organization, we believe this study has practical applicability for many healthcare systems and showed that population-based initiatives can successfully implement proven secondary-prevention therapies.

Implementation of ACE inhibitor therapy was safe and well tolerated, even in a population largely at goal blood pressure (<130/80 mm Hg). The prevalence of side effects such as cough was similar to that commonly found in practice.<sup>20</sup> Hypotension was the most common reason the target dose was not achieved (likely because most patients were not hypertensive), but remained low (<7% of the enrolled population). Titration of the ACE inhibitor was stopped if concern for causing hypotension existed. No adverse events due to hypotension occurred. Elevated serum creatinine and potassium levels were encountered rarely and were reversible. We believe the monitoring strategies used in this initiative helped prevent any serious adverse events.

This study also explored alternative dosing strategies for achieving target doses that may be useful in clinical practice. Practitioners typically start with a low or moderate ACE inhibitor dose and increase the dose periodically based on seri-

al laboratory and blood pressure measurements. For uncomplicated cases, we used an accelerated dosing schedule of 20 mg of lisinopril (ie, the target dose) as the starting dose. More than 83% of patients selected for this group were on the target dose at follow-up, and more than 91% were on some dose of ACE inhibitor. Although a small number of patients qualified for this approach (n = 24), it appeared to be safe and reasonable for this subset of patients. Accelerated titration may help with patient willingness and adherence because it reduces the number of blood pressure measurements and laboratory tests. We also attempted to initiate and titrate ACE inhibitor therapy in a population that generally may be “passed over” for fear of complications or adverse drug events. This population included patients with borderline low blood pressure, renal impairment, or advanced age. With a careful approach to titration and monitoring, more than 50% of these patients achieved the target ACE inhibitor dose and more than 87% were able to take some dose without complications. Because a wide variety of patients were included in this study, the results should be widely applicable for most patients with stable CAD and diabetes who are eligible for ACE inhibitor therapy. Overall, fewer than 5% of patients refused initiation or titration of an ACE inhibitor.



Our study has limitations. The study, by design, was not randomized, as 3 different dosing approaches were used in subgroups with slightly different patient characteristics. We also had no control group, because this was a population-based initiative to increase ACE inhibitor utilization. Although protocols were used, we cannot rule out slight differences in practice and clinical judgment among clinical pharmacy specialists. Inter- and intrarater variability was likely inherent in the blood pressure measurements. Finally, in our organization, lisinopril is the preferred formulary ACE inhibitor. To date, there have been no cardiovascular outcomes studies using lisinopril in stable CAD patients without heart failure or compromised ventricular function. Optimal dose and specific ACE inhibitor for cardio-protection continue to spur debate.

Healthcare systems can use a population-based approach to apply evidence-based medicine. In this study, a systematic, organized approach to increasing the proportion of patients with CAD and diabetes on target (or any) dose of ACE inhibitor was successful and safe. As part of a comprehensive cardiac risk reduction service, our clinical pharmacy specialists continue to pursue target-dose ACE inhibitor therapy for patients with CAD and diabetes in an effort to improve cardiovascular outcomes. Future studies in our population will investigate the morbidity and mortality implications of such an approach.

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**Authorship Information:** Concept and design (KJM, EBZ, AMD, SLK, KAH, CRK, JAM); acquisition of data (KJM, EBZ, AMD, SLK, KAH, CRK); analysis and interpretation of data (KJM, EBZ, KAH); drafting of the manu-

#### Take-away Points

A systematic, organized approach to increasing the proportion of patients with coronary artery disease (CAD) and diabetes who receive target-dose angiotensin-converting enzyme (ACE) inhibitor therapy was effective and safe.

- Utilization of ACE inhibitor therapy for patients with CAD and diabetes remains suboptimal despite national guideline recommendations.
- Population-based initiatives can successfully implement proven secondary-prevention therapies.
- Based on clinical trials, our results may translate into morbidity or mortality benefits.
- Although the methods were specific to our organization, we believe this study has practical applicability to many healthcare systems.

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