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A Cluster-randomized Trial of a Centralized Clinical Pharmacy Cardiovascular Risk Service to Improve Guideline Adherence

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Abstract

Background—Numerous studies have demonstrated the value of including pharmacists in team-based care to improve adherence to cardiovascular (CV) guidelines, medication adherence and risk factor control but there is limited information on whether these models can be successfully implemented more widely in diverse settings and populations. The purpose of this study is to evaluate whether a centralized, web-based CV risk service (CVRS) managed by clinical pharmacists will improve guideline adherence in multiple primary care medical offices with diverse geographic and patient characteristics.

Methods—This study is a prospective trial in 20 primary care offices stratified by the percent of under-represented minorities and then randomized to either the CVRS intervention or usual care. The intervention will last for 12 months and all subjects will have research visits at baseline and 12 months. The primary outcome is the difference in guideline adherence between groups. Data will also be abstracted from the medical record at 24 months to determine if the intervention effect is sustained after it is discontinued.

Conclusions—This study expects to enroll subjects through 2016 with results expected in 2019. This study will provide information on whether a distant, centralized CV risk service can be

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implemented in large numbers of medical offices, if it is effective in diverse populations, and if the effect can be sustained long-term.

Keywords

cardiovascular disease; diabetes; clinical trial; pharmacist management; guideline adherence

Introduction

An American Heart Association (AHA) report stated that “On the basis of 2007 mortality rate data, more than 2,200 Americans die of cardiovascular disease (CVD) every day...1 death every 39 seconds.”¹ The cost was \$286 billion, or 15% of total healthcare expenditures.² When considering only stroke, it is the third leading cause of death with one death every 4 minutes in 2007¹ and it will cost over a trillion dollars from 2005-2020.³ Adherence to guidelines for CVD treatment and prevention is low and there are regional and age variations in the use of guideline concordant therapy.⁴⁻⁸ The primary barrier is suboptimal medication use leading to poor disease control, often because busy providers must address acute non-CVD complaints.^{9, 10} The Institute of Medicine (IOM), Centers for Disease Control and Cochrane center call for more research to evaluate the use of pharmacists for CVD management.¹¹⁻¹⁴ Managed care organizations and other settings are increasingly hiring clinical pharmacists to improve management of CVD.

The **MEDication Focused Outpatient Care for Underutilization of Secondary Prevention** (MEDFOCUS) trial will evaluate a centralized, web-based CVRS. All MEDFOCUS medical offices have clinical pharmacists located in the office. However, the typical office has one clinical pharmacist for 20 or more physicians. The pharmacists' are far too busy to provide the frequent contact for adherence and medication management for patients with multiple medical conditions. The MEDFOCUS intervention is designed to support onsite clinical pharmacists and primary care providers to improve the management of CVD and achieve key performance measures.¹⁵ The intervention was designed from a CVRS managed by clinical pharmacists at Kaiser Permanente Colorado.^{16, 17} A retrospective study at Kaiser (N=4896) found that any exposure to the CVRS was associated with lower mortality compared with no exposure ($p<0.001$). Kaiser provides this service for over 14,000 patients in the Denver region indicating they have a viable business model.

We are conducting a second trial of the CVRS in private physician offices in Iowa that lack clinical pharmacists.¹⁸ These two trials will give us the opportunity to evaluate different facilitators and barriers to implementation of the same intervention in two very different types of medical offices and patient populations. The purpose of this paper is to describe the methods for the MEDFOCUS trial.

Methods

This is a 5-year, prospective, cluster-randomized multi-center clinical trial in 20 medical offices from 11 states in the US. All clinics employ clinical pharmacists. Clinics were stratified on the percentage of racial minorities (high $\geq 40\%$, low $<40\%$) and then randomized to a: 1) 12-month CVRS intervention, or 2) control group. A study coordinator

(SC) in each office will enroll approximately 20-25 subjects who meet inclusion criteria. Subjects will provide written informed consent and be followed prospectively for 12 months. In addition, chart-audited data will be collected on all subjects at 24 months to determine the effect of the intervention once it is discontinued.

The primary aim of this study is to determine if a distant, centralized, web-based CVRS managed by clinical pharmacists will be implemented within diverse primary care offices as measured by adherence to guidelines (below). Secondary aims are to evaluate barriers and facilitators to implementation and dissemination of the intervention and to demonstrate if the CVRS is cost-effective.

A SC (RN, LPN or MA) employed in each medical office will enroll subjects, collect study data and abstract data from medical records. All coordinators completed human subjects education and were trained in Iowa City in December 2014 or February 2015 on the web-based case report forms that will be used on the secure website operated by the Data Coordinating Center (DCC). One investigator (BLC) provided training and certification on proper BP measurement technique using an automated Omron HEM 907-XL device.¹⁹

Subject Population and Recruitment

Subject recruitment was initiated in early 2015. Our previous study in these offices enrolled 56% of subjects from minority groups.²⁰ In that study, many subjects had annual incomes $\leq$ \$25,000 (49%), had Medicaid (14%) or free care/self-pay (11%) and 50% had diabetes or chronic kidney disease (CKD). We expect similar subject characteristics in the present study.

We will enroll 400 subjects, of which 180 are expected to be Blacks and 40 Hispanics. Inclusion criteria will include: 1) English speaking males or females, ≥ 55 years of age who utilize the physician office and who have a history of at least one of the following: 2) coronary artery disease, 3) myocardial infarction (MI), 4) stroke, 5) transient ischemic attack (TIA), 6) atrial fibrillation, 7) systolic heart failure or the following coronary artery disease (CAD) risk equivalents: 8) peripheral vascular disease/ Claudication, 9) carotid artery disease or 10) diabetes mellitus with co-existing uncontrolled hypertension and/or hyperlipidemia. Exclusion criteria (at baseline) will include: 1) signs of acute angina, stroke, heart failure or renal failure; 2) systolic BP > 200 or diastolic BP > 114 mm Hg; 3) significant hepatic disease, including cirrhosis, hepatitis B or C infection, or laboratory abnormalities (serum alanine transaminase (ALT) or aspartate transaminase (AST) > 3 times control or total bilirubin > 2.0 mg/dl); 4) pulmonary hypertension; 5) inability to give informed consent or impaired cognitive function; 6) nursing home residence, or 7) those who refuse to at least consider attempting to obtain access to the internet at home, library, community center or the clinic office.

The study will be approved by the local IRBs for each medical office and the University of Iowa IRB. Potential subjects will be identified from billing record lists, physician referral or identified while in the office. Subjects identified by lists will be sent a standardized letter, signed by the lead study physician or study coordinator from their office. Once the subject provides informed consent, the SC employed by each office will collect data from the

subject and medical record including, but not limited to, demographics (age, sex, race, ethnicity), height, weight, tobacco use, alcohol use, problem list and current medications. Specific data elements and timing are displayed in Table 1. The SC will measure BP using an automated Omron device with a standardized technique.^{21, 22} Blood will be drawn for lipid profile and hemoglobin A1c (HA1c) for all subjects, with additional chemistries drawn for intervention subjects, and BP will be measured at baseline and 12 months. The chemistries in the intervention group will include serum creatinine, sodium and potassium and liver function tests to assist with evaluating BP and lipid therapy.

The SC will administer baseline questionnaires on barriers to medication adherence including instruments validated by Svarstad²³ and colleagues and Krantz et al.²⁴ We will use a method developed by Doherty et al to evaluate readiness to change health behaviors at baseline and 12 months in both control and intervention subjects.²⁵ The SC will administer the survey for these health behaviors and the results will be available to the intervention pharmacist (intervention group only) at baseline to allow for tailoring their interactions to best motivate patient behavior change. In addition, the pharmacist will continue to assess readiness to change behaviors as they implement the behavioral interventions for lifestyle modification and medication adherence to better inform their intervention strategies. All data collected by the SC will be uploaded via the web to the database housed in the Data Coordinating Center (DCC: see section below). Subjects will be reimbursed \$75 for the baseline visit and \$75 for the follow-up visit for completing blood draws and data collection procedures.

DCC Database

The NIH requires a study of this size to include an experienced DCC. This study will utilize the Clinical Trials Statistical and Data Management Center (CTSDMC or “DCC”) at the University of Iowa. This DCC was previously used for another clinical trial of a physician-pharmacist collaborative model for hypertension.^{20, 22} The DCC developed comprehensive Standard Operating Procedures (SOPs) that guide the development and maintenance of the data collection systems. The online data entry systems have been designed and implemented using Microsoft technologies and development tools. In order to maintain strict security for study data entered via the internet, all data are encrypted using the Secure Sockets Layer (SSL) protocol. Primary and secondary servers are backed up regularly.

Data Entry System Design, Development, and Access Rights—A web-based data entry system has been developed, tested, and implemented for this trial. Data entry screens for electronic case report forms (eCRFs) were modeled on paper CRFs that were developed as design prototypes. Checks will also be performed for valid values, missing values, and logical consistency between items on the same form (intra-form checks) or between items from different forms (inter-form checks). The database has undergone multi-phase testing to ensure that it is operating according to user specifications. After the database was validated, the software was moved into the ‘Production’ environment.

A key feature of the DCC database collection system is connectivity to a subject portal database, the Patient Health Record (PHR) record, so that the intervention pharmacists have

the medical record data needed to assess study subjects. The PHR is described in the accompanying paper on the Improved Cardiovascular Risk Reduction to Enhance Rural Primary Care (ICARE) study.¹⁸ This connectivity was completed and tested in January 2015 and is operating successfully.

All data entry systems were developed in compliance with FDA regulations outlined in 21 CFR Part 11, and in accordance with Good Clinical Practices (GCP). The DCC trained and certified all SCs in the data entry process before they were granted permission to enter the data into the database.

Pharmacist Intervention

All offices employ clinical pharmacists to provide onsite patient management and education. However, the purpose of the MEDFOCUS trial is to determine if the centralized CVRS pharmacists can assist busy providers (both onsite physicians and clinical pharmacists) with the extensive communication and management needed for patients with complex medical issues. The CVRS pharmacists will not make independent care decisions but will make recommendations for implementation to the onsite clinical pharmacists. We chose this method of communication because we did not want to usurp the role of the onsite clinical pharmacists who have established relationships with physicians.

The intervention will be directed at both patients and physicians. Interventions for patients will primarily be devoted to improving medication adherence, education when medication regimens are revised and obtaining important preventative healthcare services within the Guideline Advantage (GA) metrics. Interventions for physicians will be directed at improving guideline adherence for reducing CV risk and preventive care. Specific guidelines that are incorporated into the GA metrics include: CV guidelines based on the AHA,² the diabetes guidelines,²⁶ the 2013 ACC/AHA cholesterol guidelines,²⁷ the 2014 hypertension guidelines²⁸ and AHA/ASA guidelines on secondary prevention.^{2, 29-31} The CVRS pharmacists will provide the intervention (Table 2) and recommendations for changes based on these guidelines.^{2, 29-32} The CVRS pharmacist will use the clinician interface with the patients' Personal Health Record (PHR) to view patients' self-monitoring data (e.g. BP, blood glucose, lipids), reconcile and update medications and provide frequent education, alerts, text messages and reminders. Subjects will not be required to log on to the PHR.

The CVRS pharmacists are not located in the physician offices. They will be introduced to the lead physician and onsite clinical pharmacist in Skype sessions that will discuss preferred methods of communication with onsite providers. The CVRS pharmacists will need a method to obtain key subject data such as medical history, laboratory and other data to provide the comprehensive assessments needed for the intervention. We have developed the PHR system to house these data for the intervention pharmacists as well as provide subjects with the opportunity to enter self-monitored data (e.g. blood pressure or blood sugar) and communicate with the CVRS pharmacists. Because we want to be able to isolate the intervention effect, both control and intervention subjects will be instructed by the SCs about how to use the PHR. If a given subject does not use the PHR, the CVRS pharmacist will identify alternate avenues the patient prefers such as telephone, text messages or email.

The design features and uses of the PHR are described in the supplement and accompanying paper.¹⁸

The intervention will provide patient-centered recommendations for ongoing support and patient education to improve medication adherence, lifestyle modifications and/or smoking cessation. The CVRS pharmacists provide the physicians and on-site clinical pharmacists with quarterly action plans to suggest changes in drug therapy which should markedly reduce the gaps in guideline-concordant therapy that place patients at risk for CVD events. The on-site clinical pharmacists will receive the recommendation and, in consultation with the primary care physician, accept, reject or modify the plan. The CVRS pharmacists will not make therapy changes independently. The frequency of web and telephone communication was developed by consultants for MEDFOCUS and one other telemedicine study using team-based care.³³⁻³⁵

Table 3 lists examples of recommendations that might be made by the CVRS pharmacists to patients and/or physicians, tailored to co-existing conditions or functional status. We will capture whether or not the physician accepted the recommendation when reconciled against the medication lists and progress notes for lifestyle or prevention recommendations. The CVRS pharmacist will complete an encounter form and upload it into the DCC database. This form will be used to track the recommendations made by the CVRS pharmacist in the care plan sent to the on-site physicians and pharmacists. The encounter form will also include a complete accounting of time required to perform the intervention for a cost-effectiveness analysis.

Subjects in control offices will receive usual care with the exception that they will be offered the opportunity to use the PHR. Pharmacists located within control offices will not provide any unique services for study subjects but will continue to provide “curbside consultations” if physicians specifically ask questions about subjects in the study.

Primary Outcome

Prospective data will be collected at baseline, and 12 months and data will be abstracted from medical records at 24 months to evaluate sustainability (12 months after the intervention is discontinued). The primary outcome will be adherence to the guidelines adapted from the Guideline Advantage criteria, measured as a percentage of applicable criteria met for each subject and used as a surrogate for quality of care. [<http://www.guidelineadvantage.org/TGA/>] We selected these guidelines as the primary outcome since subjects may, or may not, have various chronic conditions or risk factors. An algorithm has been developed to score whether applicable criteria have been achieved at baseline, 12 months, and 24 months. The two co-primary hypotheses (Primary hypothesis 1a & 1b) are that: “Adherence to guidelines for secondary prevention of CVD will be significantly greater in patients from clinics randomized to the centralized CVRS group compared to the control group” for all subjects and in the subset of under-represented minorities, respectively.

Sample size and power—Power and sample size calculations were determined from several sources. We previously found 40% adherence to applicable criteria at baseline for

hypertension.²¹ Another study found combined guideline concordance of approximately 30% for LDL, HA1c and systolic BP.³⁶ Therefore, we expect baseline guideline scores to be 30-35% $\pm$ 20 but we have conservatively assumed they will be 40% $\pm$ 20 for sample size calculations. We expect these scores to increase to 50% $\pm$ 20 in the control group and 60% $\pm$ 20 in the intervention group at 12 months. Since we expect the intervention to be equally effective among racial and ethnic minorities, the study is powered to detect effects in both the overall population and the subset of under-represented minority subjects. Finally, based on an examination of our previous study, we assumed an intra-class correlation coefficient of 0.004 and a 15% lost-to-follow-up rate.³⁷ Because there are two primary hypotheses of interest, we will apply a Bonferonni correction and test each primary hypothesis at the $0.05/2 = 0.025$ significance level.

Based on these assumptions, a sample size of 400 subjects provides greater than 99% power to detect the effect of interest in the overall population, and 83% power to detect these same effects in the under-represented minority population.

Secondary Outcomes

Since we do not know the precise number of Black subjects who will be enrolled in the study, we will explore whether “Adherence to the guidelines are significantly greater in Black subjects from intervention clinics compared to the control group.” This analysis will be a secondary outcome.

The other key secondary outcome is to determine the effect on guideline adherence after the intervention is discontinued as measured 12 months later. This hypothesis is that “Adherence to guidelines will deteriorate after the intervention is discontinued but still remain higher in the intervention group compared to the control group.” Additional secondary outcomes evaluating implementation and dissemination of the intervention can be found in the supplement.

Handling Missing Data

The primary analysis will follow the intent-to-treat principle. As such, it will be critically important to minimize the occurrence of missing data. We will make every effort to obtain complete data during the conduct of the study using a variety of methods in order to minimize the percentage of missing data in this trial. Nevertheless, there is likely to be a small percentage of missing data. For subjects who drop out of the study before their 12 month data can be obtained, we propose to use a multiple imputation method to impute their outcome. This multiple imputation will be implemented using a model based on guideline adherence at baseline and the 12 month guideline adherence values for all subjects with observed data. We will use five separate imputations, and will average the parameters across all five imputations for the final analysis.

Interim Monitoring

One formal futility analysis will be conducted when half of the planned active participants have completed their twelve month follow-up. The futility assessment will be based on a

determination of the predictive power. If this predictive power is below 5% at the time the interim analysis is conducted, then we propose that the trial should stop for futility.

Data Analysis

The data analyses for both primary outcomes, and the secondary outcome related to Blacks, will utilize the same methods. For each subject, the primary outcome will involve a determination of the percentage of applicable GA criteria met at each time period. All three hypotheses will be assessed using a mixed model, adjusted for adherence at baseline and the minority status grouping. This model will also use an exchangeable correlation structure to adjust for the correlation among subjects treated in the same clinic. For example, the following model will be fit to these data:

$$Y_{ij} = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3ij} + \gamma_i + \varepsilon_{ij}$$

where Y_{ij} represents the adherence at twelve months for the j^{th} subject in the i^{th} cluster, X_{1i} is an indicator variable for the minority status of the i^{th} cluster ($=0$ if $< 40\%$, $=1$ if $\geq 40\%$), X_{2i} is an indicator variable for whether the i^{th} cluster was randomized to the CVRS or usual care group, X_{3ij} is the baseline adherence score for the j^{th} subject in the i^{th} cluster, γ_i is the cluster i 'random effect' with variance σ_c^2 and ε_{ij} is the usual random measurement error term with variance σ^2 . Hence, this model corresponds to the 'compound symmetry' assumption that implies that all members of a cluster are equally correlated with each other – and that members in different clusters are independent of each other. We believe this is a reasonable assumption since physicians and pharmacists only practice in one study location. Correspondingly, the hypothesis of interest can be assessed by performing the following hypothesis test:

$$H_0: \beta_2 = 0 \quad \text{vs.} \quad H_A: \beta_2 \neq 0$$

This test will be implemented using an appropriate contrast statement with the model specified above.

Because randomization was performed at the site level, it is possible that some other important subject-level covariates (age, gender, family history, co-morbidities, number of CV medications at baseline, baseline medication adherence, smoking status, education level, insurance status, economic status, or marital status) may be imbalanced in this study. Thus, we will carefully monitor the ongoing study for imbalances among important covariates. Should important imbalances occur, we will control for these additional covariates in the linear regression model above. We will also assess the normality assumption involved in the model. If this assumption is violated, an appropriate transformation will be employed, or a nonparametric model will be fit.

The secondary outcomes include the effect of the intervention after it is discontinued, provider attitudes about implementation of the intervention and a cost-effectiveness analysis. The analyses for each of these secondary analyses are briefly described below. Additional details for each analysis can be found in the online supplement.

Effect of Intervention After Discontinuation—This secondary hypothesis will examine whether “Adherence to guidelines will deteriorate after the intervention is discontinued but still remain higher in the intervention group compared to the control group.” This hypothesis will be assessed in the same manner as the primary hypotheses, except adherence to guidelines at 24 months will be used in place of the 12 month adherence outcome variable.

Predictors of implementation—This study will evaluate barriers and facilitators to implementation of the intervention. To predict intent to use the intervention we need to know attitudes (do they favor it), social pressure (subjective norm) and control of the action (perceived control).³⁸⁻⁴¹ All potential study physicians and on-site pharmacists will receive a questionnaire using the Theory of Planned Behavior (TPB) that was created using the developmental manual for that instrument.^{39, 41, 42} The purpose of this sub-study is to test for potential mediators of behavior change so that underlying mechanisms for the final results can be identified. The online supplement provides detail on data collection for this aim.

Cost-effectiveness Analysis—To complete this objective we will test the working hypothesis that “There will be significantly greater costs associated with the CVRS but costs will be outweighed by the major reductions in risk.” We will examine all the costs associated with the CVRS intervention, communication and overhead using previous procedures.⁴³

Physician consulting time and costs for pharmacist's time will be estimated using wage rates from the Occupational Employment Statistics Survey, Bureau of Labor Statistics.⁴⁴ All CVRS pharmacist time including record review, patient assessment, email time and telephone follow-up will be collected. Clinic visits, emergency department visits, hospitalizations and laboratory procedures will have costs assigned.^{45, 46} Differences in guideline adherence between groups will be calculated at 12 months and 24 months and expressed as dollars per incremental improvement using our previous methods.⁴³

Discussion

The MEDFOCUS trial will be the second study of a centralized cardiovascular risk service designed to provide more intensive communication and management of patients at high risk for CV disease in medical offices. The study was designed to replicate a model that has been found to be effective in one managed care organization that employs clinical pharmacists in all of their medical offices in the Denver/Boulder region.¹⁶ The study will address several aspects of the Medical Home including improved access for patients, self-management, improved technology and the use of team-based care.⁴⁷⁻⁴⁹ The ICARE study uses a similar intervention but unlike the present study, ICARE involves private physician offices that lack clinical pharmacists.¹⁸ By conducting studies in these very different environments, we will be able to evaluate barriers and facilitators to implementation in unique settings. These two studies should help improve the generalizability of the intervention model.

The need for the CVRS might be questioned since the on-site clinical pharmacist could perform these activities. However, we have found in other studies that busy on-site clinical pharmacists do not have time for the frequent email and telephone interaction required to achieve good guideline adherence as there are just too many patients in the office (there is an average of only one onsite clinical pharmacist for every 28 physicians in the office).²⁰ Thus, there are far too many patients with chronic health conditions for pharmacists to help manage the population. Our intervention is designed to provide a more efficient method to deliver the intense counseling and follow-up support that is needed to provide population-based management.

Conclusions

The MEDFOCUS study is expected to complete patient enrollment in 2016. The results of this study are expected to be available in 2019 and should provide information on barriers and facilitators to implementing this physician/pharmacist collaborative model to improve adherence to key CV guidelines and whether the intervention is effective in under-represented minorities.

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Table 1
Data Sources and Timing

Data Element	Source of Information	Baseline	12 Months	24 Months*
Primary & Secondary Endpoints				
• Aim 1a: Adherence to Guideline Advantage criteria	Direct measurement and Medical Records	X	X	X
• Aim 1b & 1c: Adherence to Guidelines in minorities and in Blacks	Direct measurement and Medical Records	X	X	X
Other Secondary Endpoints				
• BP control, mean BP, LDL cholesterol, HA1c	Direct measurement and Medical Records	X	X	X
• Stages of Change	Patient interviews	X	X	
• Medication intensity	Interview/Medical records	X	X	X
• Medical Home Index	Physicians	X		X
• Provider barriers and facilitators to implementation	Physician, pharmacist surveys, formative evaluations	X		X
Control Variables and Process Measures				
• Socio-demographics	Interview / Medical records	X		X
• Weight and BMI	Measurement/medical records	X	X	X
• Comorbidity	Medical records	X	X	X
• Number of clinic visits	Medical records, encounter forms	X	X	X
• Number of CV and diabetes medications	Patient interview	X	X	X
• Medication adherence	Patient interview	X	X	X
• Smoking status	Patient interview	X	X	X

* All data at 24 months will be collected from a retrospective medical record review.

Table 2
CVRS clinical pharmacist activities

Send email, telephone or text messages every two weeks $\times$ 2 months then at least monthly to engage patient and obtain self-monitoring data;
Use motivational interviewing to conduct monthly follow-up assessment and counseling for medication adherence, side effects, exercise, CHD knowledge, weight, diet, tobacco use and alcohol use;
Assess stages of change for exercise, diet, weight management and tobacco use;
Provide frequent email or telephone contact with the patient if necessary to resolve medication problems;
Address problems with medication adherence or persistence;
Develop an action plan that addresses gaps in guideline-concordant therapy, update medication list and FAX recommendations for medication changes to the primary physician and on-site clinical pharmacist as needed;;
Document all patient and provider encounters and time for each activity (to determine intervention fidelity and cost-effectiveness); and

Table 3
Selected Examples of CVRS Pharmacist's Recommendations*

Patient Circumstances	Typical CVRS Pharmacist Recommendation
Condition not controlled and patient not adhering to regimen	Address reasons for non-adherence, stages of change, adjust regimen, monitor.
Patient continues to smoke	Address readiness to quit, refer to tobacco quit line.
Patients with Type II diabetes not taking aspirin, ACEI (or ARB), statin, metformin	Add aspirin 75-162mg, add ACEI (or ARB if adverse effects to ACEI), add statin, add/or metformin if no contraindications and adjust to proper dose
CAD, MI and not taking aspirin, beta blocker or ACE inhibitor	Begin aspirin 75-162 mg and/or beta blocker if no contraindications. ACEI (or ARB) if no contraindications
Elevated cholesterol risk	Start statin or increase dose. Add additional agents to treat specific lipid disorder and to achieve goal.
DM with HA1c $\geq$ 7%	Optimize therapy as necessary.
SBP or DBP above goal and adhering to lifestyle and/or medications	Add thiazide-like diuretic if not part of regimen, otherwise add synergistic second-line drug, reinforce lifestyle modification
Important drug interactions or adverse drug events	Adjust medication regimen to eliminate or minimize drug problems

* Note, examples are not all inclusive. ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker, CAD- coronary artery disease; MI – myocardial infarction, DM – diabetes mellitus, HA1c – hemoglobin A1c, SBP – systolic blood pressure, DBP, diastolic blood pressure.