Preventing Myocardial Infarction and Stroke With a Simplified Bundle of Cardioprotective Medications

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Objective: To assess the effect of promoting a bundle of fixed doses of a generic statin and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), delivered with minimal outpatient visits, laboratory testing, and dosage titration, to people with diabetes, coronary artery disease (CAD), or both in a large integrated healthcare system.

Study Design: Three-year observational study of 170,024 Kaiser Permanente members with diabetes, CAD, or both.

Methods: Using instrumental variable analysis, we assessed the impact of promoting the cardioprotective bundle on hospitalization rates for stroke and myocardial infarction (MI).

Results: In 2004 and 2005, 47,268 of 170,024 individuals received "low exposure" (medication possession on 1 to 365 days). Their risk of hospitalization for MI or stroke in 2006 was lowered by 15 events per 1000 person-years (95% confidence interval [CI] = 1, 30), preventing events in 726 people. Furthermore, 21,292 of 170,024 individuals received "high exposure" (medication possession on 366 to 730 days). Their risk of hospitalization for MI or stroke was reduced by 26 events per 1000 person-years (95% CI = 17, 34), preventing events in 545 people.

Conclusion: A simplified method for bundling fixed doses of a generic statin and an ACEI/ARB was successfully implemented in a large, diverse population in an integrated healthcare delivery system, reducing the risk of hospitalization for MI and stroke.

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For author information and disclosures, see end of text.

Seminal clinical trials established that statins and angiotensin-converting enzyme inhibitors (ACEIs) individually reduce the rate of fatal and nonfatal cardiovascular events among people with diabetes and/or cardiovascular disease. In patients with diabetes, coronary artery disease (CAD), or other occlusive arterial disease, simvastatin 40 mg/day reduces by about one-quarter the risk of myocardial infarction (MI), stroke, revascularization procedures, and coronary deaths.[1,2] Among individuals with known vascular disease or diabetes and another risk factor, ACEIs reduce the rate of MIs by 18% and the rate of stroke by 23%.[3,4]

More recently, researchers have investigated the impact of combination pharmacotherapy. In a very small study, the vascular and metabolic effects of combined therapy with simvastatin and ramipril in patients with type 2 diabetes were more beneficial than those of either drug alone.[5] In patients with diabetes, evidence-based pharmacotherapy combined with dietary and exercise interventions reduced the risk of cardiovascular events by approximately 50%.[6] In a pilot study of patients undergoing peripheral vascular interventions, evidence-based use of statins, ACEIs, beta-blockers, and antiplatelet therapy reduced death, MI, and stroke at 6 months; in a later study of patients with acute coronary syndrome, this evidence-based drug therapy was associated with a greatly reduced risk of death at 6 months.[7,8] In adults without known cardiovascular disease, a "polypill" containing low doses of thiazide, atenolol, ramipril, simvastatin, and aspirin reduced blood pressure, low-density lipoprotein cholesterol (LDL-C), and urinary 11-dehydrothromboxane B2 levels.[9]

Individual drug trials and subsequent studies raised 2 questions. First, could a simple process be developed to deliver combination pharmacotherapy to large numbers of people with diabetes or CAD in realistic settings across an entire delivery system? Second, how would implementing such a process affect hospitalizations for cardiovascular events?

In 2002, Kaiser Permanente used the Archimedes Model to project the effects of combined pharmacotherapy and to develop a simple, inexpensive method for delivering it.[10-12] The Archimedes Model realistically simulates the pathophysiology, treatments, and outcomes of disease and its complications at the level of individuals and aggregates the results to project population-

In this article
Take-Away Points / e89
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level effects that correlate well with clinical trial results.[13] Using evidence from available clinical trials, the model forecasted that a "bundle" of a statin and an ACEI would, beginning in the first year, reduce by 71% the risk of MI and stroke in a high-risk population of individuals with diabetes. Subsequent trials and meta-analyses enriched our understanding of the benefits of these medications, but were not available at the time of modeling.[14,15]

Take-Away Points

Statins and angiotensin-converting enzyme inhibitors individually reduce cardiovascular events, but their combined effectiveness in large populations is undocumented.

- We promoted the use of a cardioprotective bundle delivered via a simplified regimen—fixed doses of generic medications and minimal outpatient visits, laboratory testing, and dosage titration—to a high-risk population.
- Exposure to the bundle over 2 years reduced the risk of hospitalization for myocardial infarction or stroke in the following year.
- Our approach can be applied in many settings to reduce cardiovascular events in populations at risk.

The modeling also determined that using generic formulations and offering a fixed dose to every person, regardless of baseline blood pressure or LDL-C level, would achieve these results with the most efficient use of clinical resources. The model also predicted that population-level clinical benefits could be achieved without patient-by-patient titration to physiologic target, which has since been confirmed elsewhere.[16]

As a result, Kaiser Permanente's clinical leaders launched an initiative to make bundled cardioprotective therapy rapidly and widely available to all Kaiser Permanente members with diabetes over the age of 55 years and all members with CAD. Individuals were offered a medication bundle consisting of a statin (typically lovastatin 40 mg/day) and an ACEI (typically lisinopril 20 mg/day). Physicians were advised to use a single initiation visit to rule out contraindications, eliminate patients at high risk for complications (eg, those with serum creatinine >1.5 mg/dL, underlying liver disease, or prior rhabdomyolysis or angioedema), and adjust downward the lisinopril dosage in hypotension-prone patients. Physicians exercised clinical judgment about whether it was appropriate to titrate the dosage for safety purposes or to meet a target. An angiotensin II receptor blocker was substituted for the ACEI when clinically indicated; for convenience, we refer to both here as ACEIs. Laboratory tests consisting of total cholesterol and LDL-C, triglycerides, high-density lipoprotein cholesterol, serum creatinine, potassium, and alanine aminotransferase were advised before starting therapy and at 3 weeks to 3 months. The medication bundle also included low-dose aspirin, but aspirin was not part of our study because we could not consistently measure its use.

A variety of programwide strategies supported rapid implementation. Each Kaiser Permanente region determined how best to meet the guidelines of the initiative under local conditions, but key elements across all regions included extensive use of clinical champions, patient education, outreach strategies, and point-of-service reminders. In addition, electronic clinical decision support tools at the point of care identified members in the target population who were not yet receiving statins and ACEIs. As the initiative rolled out across the regions, a national network of clinical champions teleconferenced quarterly to share regional performance reports on bundle use and learnings about how to facilitate rapid implementation.

Bundle use grew rapidly. Between 2002 and 2005, the percentage of eligible members in the regions we studied who consistently used the medication bundle increased from 33% to 52% of the target population. We report here the clinical impact of the initiative.

METHODS

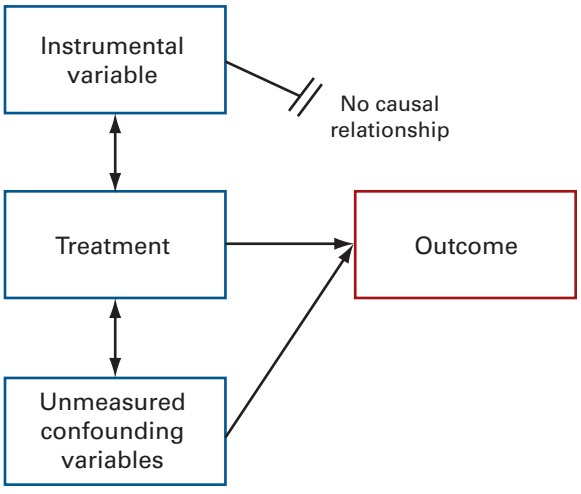
Setting, Subjects, and Data Sources

Kaiser Permanente is the largest not-for-profit integrated health delivery system in the United States, serving 8.7 million members in 8 regions spanning 9 states and the District of Columbia. Kaiser Permanente provides and coordinates the entire scope of members' care, including preventive care, well-baby and prenatal care, immunizations, emergency care, hospital and medical services, and ancillary services such as pharmacy, laboratory, and radiology.

We studied the bundle's impact in Kaiser Permanente's 2 largest regions: Northern and Southern California. Our study population consisted of 170,024 members who were (1) diagnosed with CAD and/or over the age of 55 years and diagnosed with diabetes, (2) not already taking both bundle medications as of 2003, and (3) continuously enrolled between January 1, 2001, and December 31, 2006. Members were included in the study if they received either statins or ACEIs in 2003 but were excluded if they received both. The study population was part of the much larger, programwide Kaiser Permanente population receiving the medication bundle.

We obtained baseline characteristics for the study population dating from 2001. Widespread use of the medication bundle rose most rapidly during 2003. We measured bundle use in 2004 and 2005 and adverse events in 2006. Data on diagnoses, medication use, and event rates before and after the initiative were derived from inpatient and outpatient encounter records

Figure. Instrumental Variables Analysis



and pharmacy and laboratory databases. Data on hospitalization rates for MI and stroke were extracted from hospital discharge and billing claims databases. The appropriate institutional review boards approved the evaluation protocol.

Measures

To measure exposure to the medication bundle, we first examined statins and ACEIs independently. We calculated exposure as the total number of days for which each drug was dispensed between January 1, 2004, and December 31, 2005 ("dispensed days"). We assumed that exposure to the medication bundle ("bundle days") was equal to the lower of the dispensed days for individual medications.

We classified members with zero bundle days dispensed during 2004 and 2005 as "no exposure," those with 1 to 365 bundle days dispensed as "low exposure," and members with 366 to 730 bundle days dispensed as "high exposure." The main outcome measure was hospitalization due to MI or stroke between January 1 and December 31, 2006.

Statistical Analysis

As is commonly the case when estimating clinical effects from observational studies, patient selection represented a significant source of potential bias.[17] Patients at highest risk may be more apt to take prescribed medications, and clinicians may be more likely to prescribe cardioprotective medications for patients at highest risk, although some evidence suggests a paradoxical risk-treatment relationship.[18] The possibility of selection bias is most acute when the analysis cannot incorporate some risk factors, as was the case in our study because we could not consistently obtain data on factors such as body mass index or smoking status.

Instrumental variable analysis can effectively address patient-level selection biases caused by unmeasured confounding variables.[19-21] It does so by introducing into the analytic model 1 or more variables, the "instruments," that are correlated with the treatment but not causally related to outcomes except through the treatment (**Figure**). Instrumental variable analysis yields unbiased estimates of individual-level treatment effectiveness if the underlying assumption about absent causal relationships between instruments and outcome is valid.

We used facility-level use rates as instruments, making use of variations across facilities in promoting bundle use. Facility-level use rates make good instrumental variables for this purpose because they are strongly associated with individual bundle exposure; by definition, patients at high-use facilities are more likely to have statins and ACEIs dispensed. We reasoned that facility-level use rates would be related to the outcomes only through individual exposure. The reasoning underlying our use of instrumental variable analysis is that patients can be viewed as randomly assigned to high- or low-use facilities. The resulting estimate of treatment effectiveness is based on patients who would have been treated at high-use facilities but not treated at low-use facilities.

Instrumental Variable. A total of 58 facilities, with 74 to 11,600 members of the study population per facility, were included; for each, we calculated the percentage of members of the target population who had any exposure to the bundle. Facility-level use rates ranged from 32.2% in the lowest-using quintile of facilities to 49.1% in the highest-using quintile. Unadjusted annual rates of hospitalization for MI or stroke in 2006 ranged from 22.8 per 1000 members in the lowest-using quintile of facilities to 17.7 per 1000 in the highest-using quintile.

Covariates. We adjusted for covariates for which we were able to obtain reliable and consistent observational data: age, sex, comorbidities (diabetes, heart failure, depression, CAD), and geographic region. We also adjusted for glycemic control in 2003; the number of previous hospitalizations due to MI, stroke, and all other causes in 2001-2004; and the number of previous coronary artery bypass graft and percutaneous transluminal coronary angioplasty procedures in 2001-2004. We also adjusted for history of hyperlipidemia through 2003, using a proxy variable based on documented LDL-C control and use of lipid-lowering medications during 2001-2003.

Risk Estimation. We examined patterns of bundle use across patient risk categories by first estimating a model of patients' risk of MI or stroke in 2006 using all the covariates listed above except bundle use and the instrumental variable. We then categorized patients according to their underlying risk of

MI or stroke and calculated the bundle use rate by quintile of individual risk and by facility use rate.

We performed analyses with Stata version 10 (StataCorp LP, College Station, TX) and considered a 2-sided *P* value of less than .05 to be significant. We calculated the number of avoided events by multiplying the rate reduction per 1000 members by the number of individuals in each exposure group.

RESULTS

Medication Bundle Exposure

The study population consisted of 170,024 individuals without prior bundle exposure, 77.8% of whom had diabetes with or without CAD and 31.7% of whom had CAD (Table 1). Of the study population, 47,268 (27.8%) had low exposure in 2004 and 2005 with a median exposure duration of 157 days; 21,292 (12.5%) had high exposure with a median exposure duration of 500 days; and 101,464 (59.7%) had no exposure.

We noted an unplanned pattern of bundle use involving facility-level use rates and patients' underlying risk of MI or stroke. At low-use facilities, bundle exposure was greater among members with the lowest underlying risk than among higher-risk members. The pattern was reversed at high-use facilities, where high-risk patients had greater bundle exposure. The risk of MI or stroke, irrespective of medication exposure or facility-level use rates, ranged from 5 to 9 events per 1000 individuals per year in the lowest-risk quintile to 27 to 38 events per 1000 in the highest-risk quintile.

Adverse Event Rates

In 2006, the rate of hospitalization for MI and stroke in the entire study population was 21 per 1000 members, reflecting 3570 adverse cardiovascular events. Among members with low 2-year bundle exposure, the hospitalization rate for MI and stroke was lower by 15 per 1000 members in the following year compared with members who had no exposure. Among members with high 2-year bundle exposure, the MI and stroke hospitalization rate in the following year was lower by 26 per 1000 members compared with members who had no exposure (Table 2).

Although our goal was to study decreased incidence of MI and stroke, we also assessed the relationship between bundle exposure and all-cause mortality, neither expecting nor finding any statistically significant differences. We also examined the rate of coronary artery bypass graft and percutaneous transluminal coronary angioplasty procedures. Among members with low bundle exposure, where MI hospitalization rates were not significantly reduced, the rate of percutaneous transluminal coronary angioplasty was lower by 15 per 1000 members (95% confidence interval [CI] = 6, 24) compared with members who had no exposure. The procedure rate remained unchanged among members with high exposure, where we observed a reduction in MIs.

Table 1. Characteristics of the Study Population

Characteristic	No. (%) (N = 170,024)
Median age, y	68
Sex	
Male	93,629 (55.1)
Female	76,395 (44.9)
Diagnosis	
Diabetes	132,286 (77.8)
Cardiovascular disease	53,883 (31.7)
Heart failure	11,584 (6.8)
Depression	19,416 (11.4)
2003 use of lipid-lowering medication[a]	57,084 (33.6)
2003 use of ACEI medication	43,556 (25.6)
History	
>1 hospitalization due to MI	263 (0.2)
>1 hospitalization due to stroke	106 (0.1)
>1 hospitalization due to any cause	17,167 (10.1)

ACEI indicates angiotensin-converting enzyme inhibitor; MI, myocardial infarction.
[a]Lipid-lowering medication includes statin, cholestyramine, fibric acid, derivative, and niacin.

After querying the Kaiser Permanente risk management database for the years 2004-2006, we found 5 reports of events potentially related to exposure to the bundle medications. Four resulted from drug–drug interactions, and all events were resolved.

DISCUSSION

A bundle consisting of fixed doses of generic statins and ACEIs reduced the MI and stroke hospitalization rate in a high-risk population. Higher exposure was associated with a greater reduction. Our finding is consistent with the well-documented cardioprotective effects of these medications and demonstrates that they can be obtained on a large scale with a simplified regimen, allowing for rapid implementation in populations at risk.

Strengths of our study include a large heterogeneous population treated in dozens of natural clinical settings and an analytical model that minimized the impact of selection bias. Limitations of our study include our inability to test the assumption that facility use rates were not causally related

Table 2. Impact of 2-Year Exposure to a Cardioprotective Medication Bundle on Rates of MI and Stroke, Compared With No Exposure

Event	Change in No. of Events per 1000 Members (95% CI)	Change in No. of Events (95% CI)
Low Exposure		
MI	1 (–13, 15)	60 (–607, 726)
Stroke	–15 (–25, –6)[a]	–727 (292, 1162)[a]
MI and stroke	–15 (–30, –1)[a]	–726 (38, 1414)[a]
High Exposure		
MI	–10 (–19, –1)[a]	–209 (21, 397)[a]
Stroke	–14 (–20, –9)[a]	–305 (181, 428)[a]
MI and stroke	–26 (–34, –17)[a]	–545 (361, 728)[a]

CI indicates confidence interval; MI, myocardial infarction.
[a] $P < .05$.

to outcomes and to measure a few potentially confounding variables, such as ejection fraction and serum creatinine. Although using facility-level use rates as the instrumental variable addressed the risk of individual-level confounding, it raised the possibility of facility-level confounding.

Facility use rates may be associated with unmeasured confounding variables such as high use rates for other medications. In a separate survey, we found that 75% of Kaiser Permanente members in the target population also were taking aspirin (R. J. Dudl, MD, unpublished data, October 2008). Thus, a conservative interpretation of the observed decreases in MI and stroke is that they also include any cardioprotective effects of aspirin, although these effects are uncertain among patients with diabetes but without cardiovascular disease or symptomatic peripheral arterial disease.[22,23] We found that beta-blocker use was weakly and negatively correlated with facility-level bundle use, suggesting it was not responsible for the observed effects. We did not measure use rates for other cardioprotective medications such as calcium channel blockers and aldosterone antagonists.

Behavioral interventions, such as smoking cessation or weight management, also could have affected our findings. Kaiser Permanente has long advocated lifestyle changes, but neither region engaged in enhanced promotion of behavioral interventions during the study period.

We observed the effect of the medication bundle on MI and stroke hospitalization rates in 1 calendar year. Based on results of the Archimedes Model, we anticipate that continued bundle use would result in ongoing reductions. Further study would confirm this. Our results do imply reductions in the rate of MI and stroke consistent with those predicted by the Archimedes Model; compared with no exposure, the low-exposure group experienced a 60% (95% CI = 1%, 96%) reduction in hospitalizations for MI and stroke.

We note that the estimated rate reduction in the high-exposure group, 26 events per 1000 members, exceeds the overall rate of 21 events per 1000 in the study population as a whole. This finding likely arises from the instrumental variable analysis estimates being inherently based on individuals who would have been treated in high-use facilities but not in low-use facilities; they include a disproportionate share of individuals with the highest underlying risk at 27 to 38 adverse events per 1000 members.

Although we did not observe a reduction in mortality in this study, longer-term follow-up may accentuate the benefits. An important direction for future research is to quantify 3- to 5-year outcomes, including both cardiovascular and all-cause mortality.

The scale of the initiative and competition for scarce organizational resources and constrained clinician time impeded the speed of implementation. Use of the bundle in the 2 regions continued to rise after the observation period; by 2008, approximately 65% of patients with CAD or with diabetes and over the age of 55 years were taking the medication bundle.

Although we lack data on population characteristics needed to precisely estimate the impact of widely implementing the A.L.L. (aspirin, lisinopril, lipid lowering therapy) bundle across the US healthcare delivery system, extrapolating from our results provides insight into its potential magnitude. Conservatively assuming that 20% of the 5.8 million Americans over the age of 65 years who are predicted to have diabetes by the year 2010 are exposed to the bundle for 1 to 365 days over 24 months, more than 17,000 MIs and strokes would be avoided the following year.[24] More boldly, assuming an additional 10% of this population has 366 to 720 days of exposure to the bundle over 2 years, a total of more than 32,000 MIs and strokes would be avoided in the following single calendar year.

Preventing adverse cardiovascular events among populations at risk is a pressing, ongoing need, and developing next-generation statins and ACEIs consumes substantial resources. However, improving treatment rates with generic formulations of older medications may yield improvements that exceed those of pursuing new medications with relatively small increases in efficacy. Forgoing the development of rosuvastatin and instead improving performance of and compliance with older, generic statins have been estimated to potentially save 7 times as many lives over 5 years.[25]

The initiative we describe is broadly applicable to other health plans and delivery systems. It already has been applied in community health centers in an underserved population with varying levels of health literacy, where the number of patients taking the bundle increased fourfold within a 12-month period.[26]

Translating evidence from clinical trials into practices resulting in large-scale benefits requires attention to scalability and efficiency. We designed, implemented, and evaluated a simplified formulation and process for delivering generic cardioprotective medications with minimal titration, testing, and outpatient visits. The strategy we describe here can be replicated in a wide variety of additional settings.

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