Quantifying Risk of Adverse Clinical Events With One Set of Vital Signs Among Primary Care Patients with Hypertension

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ABSTRACT

BACKGROUND Hypertension is often uncontrolled. One reason might be physicians’ reticence to modify therapy in response to single office measurements of vital signs.

METHODS Using electronic records from an inner-city primary care practice, we extracted information about vital signs, diagnoses, test results, and drug therapy available on the first primary care visit in 1993 for patients with hypertension. We then identified multivariable predictors of subsequent vascular complications in the ensuing 5 years.

RESULTS Of 5,825 patients (mean age 57 years) previously treated for hypertension for 5.6 years, 7% developed myocardial infarctions, 17% had strokes, 24% developed ischemic heart disease, 22% had heart failure, 12% developed renal insufficiency, and 13% died in 5 years. Controlling for other clinical data, a 10-mmHg increase in systolic blood pressure was associated with 13% increased risk (95% confidence interval [CI], 6%–21%) of renal insufficiency, 9% (95% CI, 3%–15%) increased risk of ischemic heart disease, 7% (95% CI, 3%–11%) increased risk of stroke, and 6% (95% CI, 2%–9%) increased risk of first stroke or myocardial infarction. A 10-mmHg elevation in mean blood pressure predicted a 12% (95% CI, 5%–20%) increased risk of heart failure. An increase in heart rate of 10 beats per minute predicted a 16% (95% CI, 2%–5%) increased risk of death. Diastolic blood pressure predicted only a 13% (95% CI, 4%–23%) increased risk of first stroke.

CONCLUSIONS Vital signs—especially systolic blood pressure—recorded routinely during a single primary care visit had significant prognostic value for multiple adverse clinical events among patients treated for hypertension and should not be ignored by clinicians.

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INTRODUCTION

Adverse cardiovascular events are the leading cause of death in developed nations. Their prevention and treatment consume a large proportion of national health care expenditures. Hypertension, a well-known modifiable risk factor for adverse cardiovascular events, is among the most common conditions treated in primary care. Yet, hypertension is often inadequately controlled,1,4 which adds to dramatic costs in terms of dollars and lost years of life as a result of preventable cardiovascular events.5 One possible reason for inadequate control is physicians’ ignoring elevated blood pressure readings. Blood pressure can vary substantially throughout the day,6,7 and office pressures correlate poorly with and confer less cardiovascular risk than ambulatory blood pressure readings.8,9 Indeed, guidelines for detecting and treating hypertension require multiple blood pressure elevations,1 reinforcing the notion that single measurements of blood pressure may not require a physician’s response.
There is also controversy concerning which vital signs (specifically blood pressure and heart rate), or their combinations, were prognostic. For example, systolic pressure has been shown to predict myocardial infarctions, strokes, renal insufficiency, and sudden death.\textsuperscript{11-17} Diastolic blood pressure correlates with developing ischemic heart disease,\textsuperscript{15,17-26} sometimes with a J-shaped distribution.\textsuperscript{15,20,21} Heart rate predicts cardiovascular death,\textsuperscript{22,21} while increased pulse pressure predicts heart failure.\textsuperscript{13,24-26} Moreover, these studies may have little relevance to everyday primary care because most occurred in tertiary care settings, with unusual physicians and patients, using protocols in which vital signs are usually measured multiple times by highly trained technicians with special equipment.

We undertook this study to help primary care clinicians answer the question, “What should I do with today’s vital signs?” We used an electronic medical record system serving the urban network of primary care practices\textsuperscript{27-29} to assess how well a single outpatient measurement of vital signs predicted the 5-year risk of myocardial infarction, stroke, ischemic heart disease, heart failure, renal insufficiency, and death from any cause.

**METHODS**

**Setting**

This study was approved by the Indiana University (IU) Institutional Review Board and used data collected during the routine delivery of primary care in IU Medical Group–Primary Care (IUMG–PC) sites.\textsuperscript{30} IUMG–PC is a single-practice organization that contains IUMG–ResNet, an urban primary care academic practice-based research network. ResNet practices include general internists, pediatrics, obstetricians-gynecologists, and family physicians who deliver care to 120,000 patients in more than 330,000 annual visits to 17 health centers in central Indiana. Of these 17 centers, 11 are affiliated with Wishard Memorial Hospital, an Indianapolis public teaching hospital where most patients are of an ethnic minority and indigent, the others being commercial managed care practices serving 60,000 adults who are mainly white and employed.

The Regenstrief Medical Record System (RMRS)\textsuperscript{29} stores clinical data for all IUMG–PC practices and their affiliated hospitals, routinely capturing all inpatient and outpatient diagnoses, diagnostic test results, drugs, and vital signs. Systolic blood pressure, diastolic blood pressure, and heart rate are measured routinely at all primary care visits, scheduled and unscheduled.

**Study Design**

This retrospective cohort study\textsuperscript{32} used only RMRS data. We identified the first scheduled visit to any IUMG–PC site in 1993 (the index date) for all new and established patients at least 18 years old who had both the diagnosis of hypertension in their active problem list recorded during that visit and at least one visit before and after their index date to any inpatient or outpatient venue using the RMRS: all IUMG–PC sites and Wishard Hospital’s inpatient service, emergency department, and more than 70 specialty and subspecialty clinics. If there were no vital signs recorded at the index visit, we then chose the next scheduled IUMG–PC visit in 1993 as the index visit. At the time of this study, 1999 was the latest year for which the Indiana State Department of Health had provided death certificate information (which captures >90% of deaths).\textsuperscript{33} We therefore chose 1993 as the index year, which gave us 5 years of mortality data for each patient.

Nursing assistants obtained blood pressure and heart rate on the index date using a manual or automated sphygmomanometer. The method for measuring vital signs was at the discretion of the nurses and site manager at each IUMG–PC practice and varied between practices and with time within individual practices. Physicians could also measure vital signs, which, if done, became the official vital signs for that visit. Vital signs were recorded on visit encounter forms and hand-entered into the RMRS by data entry technicians.\textsuperscript{29}

**Outcome Events**

The dependent (outcome) variables in this study were established a priori as the first occurrence after the index date of the following events:

1. Myocardial infarction, defined as (1) a hospital discharge diagnosis of myocardial infarction, (2) definitively abnormal cardiac enzyme studies, (3) an acute or old infarction read on an electrocardiogram or cardiac scintigram, or (4) new segmental wall motion abnormalities read on any echocardiogram

2. Stroke, occurring as an inpatient or outpatient diagnosis or read on any head computed tomogram or magnetic resonance imaging scan

3. Myocardial infarction or stroke, defined as the first appearance of either diagnosis (defined above) after the index date. We planned to assess this outcome a priori because both are acute ischemic events sharing similar cardiovascular risk factors.

4. Ischemic heart disease, defined as a myocardial infarction (defined above) or ischemic heart disease or angina recorded on any inpatient or outpatient problem list

5. Heart failure, defined as (1) that diagnosis recorded on any inpatient or outpatient problem list, (2) a cardiac scintigram with reduced left ventricular ejection fraction, or (3) an echocardiogram showing left ventricular dys-
function, global left ventricular wall motion abnormalities, or marked left ventricular dilatation.

6. Chronic renal insufficiency, defined as 2 serum creatinine values greater than 1.5 mg/dL more than 6 months apart.

7. Death from any cause recorded at hospital discharge or listed in the death certificate files linked to RMRS records using a validated algorithm. We did not assess cause of death because such information on death certificates is notoriously inaccurate.

The independent (predictor) variables came exclusively from patients' electronic records in the RMRS and included the following:

1. Vital signs (blood pressure, heart rate) recorded only on the index date.

2. Duration of hypertension treatment, the time between the first outpatient diagnosis of hypertension and the index date.

3. Existing comorbid diagnoses either (1) recorded by a physician (using terms from the RMRS clinical dictionary) from any inpatient or outpatient site on or before the index date, or (2) inferred by treatments or diagnostic test results (eg, inferring diabetes mellitus from glycated hemoglobin or antidiabetic medications).

4. Selected blood test results from the Wishard Hospital inpatient or outpatient laboratory.

5. Outpatient drugs dispensed from the Wishard Hospital inpatient pharmacy at the time of hospital discharge or the outpatient pharmacy, where 95% of primary care patients receive their prescriptions.

For each predictor variable, we used the last value recorded on or before each patient's index date in 1993. A patient was considered to be actively taking a drug on the index date if a new prescription had been filled within the previous 6 months. Diagnoses and drug use were coded “1” if present and “0” if absent. Missing variables occurred for only blood test results: if a result was missing for more than 15% of study patients, we excluded that variable from analysis. If a result was missing less than 15% of the time, we substituted mean results for all study patients, which we have shown to result in stable, unbiased predictive models.

Statistical Analyses
Using a SAS randomization scheme (SAS Institute, Cary, NC), we randomly created 2 equal cohorts of subjects: a derivation cohort upon which to create the predictive models, and a validation cohort in which we assessed their predictive power. This approach prevented us from overfitting the models to the patients upon whom they were derived.

We used subjects' clinical data to predict the time from the index date to the first evidence of each outcome event in the derivation cohort, using univariable proportional hazards (Cox) regression. We assessed various representations of vital signs: systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), pulse pressure (SBP minus DBP), mean blood pressure (DBP + [SBP - DBP] / 3), heart rate-blood pressure index (HR × SBP), and heart rate-pulse pressure index (HR × PP).

To adjust for subjects' demographic and clinical characteristics, we performed multivariable Cox regression by including all significant univariable predictors of the outcome being analyzed (P < .10 by univariable Cox regression). We limited the number of candidate predictor variables to avoid false-positive associations. To produce parsimonious models (ie, the smallest number of variables with significant predictive power), we used backwards stepwise selection, which first enters all variables into the Cox model and then, one-by-one, eliminates them until no variable can be removed without significantly lowering the model's ability to predict the time to the event. We analyzed all manifestations of vital signs listed above, and when 2 of them were highly correlated with each other and were predictive of the adverse event being analyzed, we excluded from analysis the variable with the weaker univariable predictive power.

We assessed the predictive power of each model in the validation cohort with the C-statistic which is numerically equivalent to the area under the receiver operating characteristics (ROC) curve. The ROC curve area is the frequency that a randomly selected patient with an outcome event has a higher predicted probability of that event than a randomly selected patient who did not experience that outcome event. A priori, we defined an ROC curve area of 0.70 or greater as significantly predictive.

To assess the additional risk associated with each vital sign with significant multivariable predictive power, we used the partial likelihood ratio test based on the partial log-likelihood for a Cox model. This statistic compares the predictive ability of the model containing both the vital sign variable and the other significant predictors with the model containing only the other predictors. This partial likelihood ratio test follows a chi-square distribution with one degree of freedom for large sample sizes.

RESULTS

Study Cohort
We used the RMRS data extraction utility to select 5,825 adult patients with hypertension and who had all their vital signs recorded during their index IUIMG–PC visit in 1993. The mean duration of hypertension before to the index date was 5.6 years, (SD 5.6 years,
range <1–18 years). As shown in Tables 1 and 2, the study patients were predominantly middle-aged, African American, and female. Their hypertension was being treated with diuretics (43%), calcium channel blockers (32%), angiotensin-converting enzyme inhibitors (29%), β-adrenergic blockers (12%), and α-adrenergic blockers (3%). On their index date, 1,761 patients (30%) had no prescriptions for antihypertensive drugs, 1,927 (33%) had 1 antihypertensive drug prescribed, and 2,137 (37%) had 2 or more antihypertensive drugs prescribed. During the 5 years after the index visit, 1,385 (24%) of these patients developed ischemic heart disease, 1,309 (22%) developed heart failure, 1,017 (17%) had a stroke, 433 (7%) had a myocardial infarction, 1,292 (22%) had either a stroke or a myocardial infarction, 718 (12%) developed chronic renal insufficiency, and 766 (13%) died.

### Univariable and Multivariable Predictors
Tables 1 and 2 also show the univariable and multivariable predictors of each cardiovascular outcome among the 2,913 patients (50%) in the model derivation cohort. Because of to the size of the study cohort, many variables had univariable significance at the $P < .10$ level. Although this outcome occasionally violated the rule that one investigate no more than 1 independent predictor variable for every 10 patients with the outcome being modeled, the models were not overfitted.
because we assessed only their discriminating power in the validation cohort.

Table 3 shows the multivariable results. Systolic blood pressure was a significant independent predictor of first myocardial infarction (among patients with no previous evidence of myocardial infarction), any stroke (first or recurrent), first myocardial infarction or stroke (among all patients and those with no previous myocardial infarction or stroke), ischemic heart disease, and chronic renal insufficiency. Using the risk ratios shown in Table 3, we calculated that each elevation of 10 mmHg in systolic blood pressure at the index visit carried a 10% (95% confidence interval [CI], 2%–18%) increase in the 5-year risk of having a first myocardial infarction, 7% (95% CI, 3%–11%) increased risk of any stroke (first or recurrent), 7% (95% CI, 2%–12%) increased risk of first myocardial infarction or stroke, 6% (95% CI, 2%–9%) increased risk for combined any myocardial infarction or stroke (first or recurrent), 9% (95% CI, 3%–15%) increased risk of ischemic heart disease, and 13% (95% CI, 6%–21%) increased risk of developing renal insufficiency.

Diastolic blood pressure was a significant independent predictor of first stroke: each increase of 10 mmHg was associated with a 13% (95% CI, 4%–23%) increase in 5-year risk. Mean blood pressure was a significant multivariable predictor of heart failure, where an increase of 10 mmHg was associated with a 12%
Vital Sign

Other Significant Multivariable Predictors*

adverse cardiovascular events.11-26 Our results extend equipment and protocols are important risk factors for signs measured by trained personnel with specialized Many studies have shown that abnormal results of vital DISCUSSION

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mented mortality risk by 16% (95% CI, 5%–26%). Table 4 shows the predictive power of each of the above models in the validation cohort. Five of the 10 models had acceptable predictive power (C-statistics >0.70). Table 5 contains the partial likelihood ratio test based on the partial log-likelihood for each multivariate Cox model. In each of the 9 models in which a vital sign added statistically significant predictive power to the model.

(95% CI, 5%–20%) increase in 5-year risk. Finally, heart rate was independently predictive of all-cause mortality: an increase of 10 beats per minute augmented mortality risk by 16% (95% CI, 5%–26%).

Table 4 shows the predictive power of each of the above models in the validation cohort. Five of the 10 models had acceptable predictive power (C-statistics >0.70). Table 5 contains the partial likelihood ratio test based on the partial log-likelihood for each multivariate Cox model. In each of the 9 models in which a vital sign was a significant independent predictor, that vital sign added statistically significant predictive power to the model.

DISCUSSION

Many studies have shown that abnormal results of vital signs measured by trained personnel with specialized equipment and protocols are important risk factors for adverse cardiovascular events.11-26 Our results extend these findings to a single set of routine vital signs, especially systolic blood pressure, obtained by regular office personnel using regular office equipment and procedures. Too often in practice a physician may be tempted to ignore a single elevated blood pressure reading, as in, for example, noncompliant patients or those in pain or under stress,27,28 opting to wait and reassess the patient during the next visit. Yet, hypertension is a well-recognized cardiovascular risk factor, and elevations should generally be treated unless there are compelling reasons not to treat. Despite the inherent variability in vital signs, which would mitigate against their predicting bad outcomes, we found a single set of abnormal vital sign readings to be a significant predictor of several adverse clinical events. This finding suggests that physicians should consider making adjustments in antihypertensive therapy to lower cardiovascular risk whenever they encounter elevated blood pressures. The strength of vital signs in predicting these events among our validation cohort remained after adjusting for

| Outcome Predicted (Subjects) | Vital Sign  | P Value | Risk Ratio (95% CI) | Other Significant Multivariable Predictors* |
|------------------------------|-------------|---------|--------------------|-------------------------------------------|
| Myocardial infarction (all patients) | None        |         | ⬠0.16 1.010 (1.002–1.018) | Previous myocardial infarction, smoker, nitrates, warfarin, diabetes, time treated for hypertension, renal insufficiency, aspirin Calcium channel blocker, diabetes, uric acid, African American |
| First myocardial infarction (patients with no previous infarction) | Systolic blood pressure | ⬠0.01 1.007 (1.003–1.011) | Prior stroke, age, weight, aspirin, chronic obstructive pulmonary disease, uric acid, diabetes, renal insufficiency, glucose, previous myocardial infarction or stroke, creatinine clearance (calculated) |
| Stroke (all patients) | Systolic blood pressure | ⬠0.005 1.013 (1.004–1.023) | Age, weight, aspirin, chronic obstructive pulmonary disease, diabetes, heart failure, uric acid, creatinine, creatinine clearance (calculated), glucose, renal insufficiency |
| First stroke (patients with no previous stroke) | Diastolic blood pressure | ⬠0.005 1.006 (1.002–1.009) | Previous stroke, previous stroke or myocardial infarction, age, aspirin, renal insufficiency, diabetes, smoker, weight, time treated for hypertension, nitrates, chronic obstructive pulmonary disease, glucose |
| Myocardial infarction or stroke (all patients) | Systolic blood pressure | ⬠0.0015 1.007 (1.002–1.012) | Age, smoker, chronic obstructive pulmonary disease, diabetes, uric acid, body mass index, renal insufficiency, glucose, warfarin |
| First myocardial infarction or stroke (patients with no previous myocardial infarction or stroke) | Systolic blood pressure | ⬠0.005 1.009 (1.003–1.015) | Insulin, heart failure, age, oral hypoglycemic drug, African American, peripheral arterial disease |
| Ischemic heart disease (patients with no previous ischemic heart disease) | Systolic blood pressure | ⬠0.005 1.012 (1.005–1.020) | Age, albumin, insulin, uric acid, chronic obstructive pulmonary disease, previous myocardial infarction, oral hypoglycemic drug, cholesterol, obesity, calcium channel blocker |
| Heart failure (patients with no prior heart failure) | Mean blood pressure | ⬠0.001 1.013 (1.006–1.021) | Creatinine, insulin, albumin, oral hypoglycemic drug, heart failure, glucose, acute renal failure, alcoholism, calcium channel blocker, hemoglobin, peripheral arterial disease |
| Chronic renal Insufficiency (patients with no prior chronic renal insufficiency) | Systolic blood pressure | ⬠0.001 <1.016 (1.005–1.026) | Age, albumin, heart failure, alcoholism glucose, peripheral arterial disease, renal insufficiency, creatinine, smoker, time treated for hypertension, chronic obstructive pulmonary disease, renal insufficiency, aspirin |
| All-cause mortality | Heart rate | ⬠0.003 1.016 (1.005–1.026) |Peripheral arterial disease |

CI = 95% confidence interval.

* From information available on or before index visit. See text for definitions. Variables are listed in decreasing order of predictive power. Those variables underlined were negatively correlated with risk of the outcome event.
a substantial number of multivariably significant clinical variables. As expected, the strongest predictors of the adverse events we modeled were previous events of the same type or evidence of other cardiovascular disease. Yet a single measurement of blood pressure and pulse rate was often as strong as, or stronger than, many other well-accepted clinical risk factors. This finding reinforces the notion that the blood pressure and heart rate are truly vital signs and should be taken seriously in the everyday practice of primary care.

The most consistent vital sign found to predict adverse clinical events was the systolic blood pressure. This finding is consistent with growing evidence from the medical literature that the systolic blood pressure is replacing the diastolic pressure as the most important vital sign in assessing risk of cardiovascular events, especially in an aging population. The strength of the association varied among outcome events we modeled, but overall an elevation of 10 mmHg in blood pressure was associated with an increase in risk ranging from 6% for stroke or myocardial infarction (first or recurrent) to 13% for chronic renal insufficiency. Changes in systolic pressures of this magnitude are common among primary care patients treated for hypertension, and reductions of 6% to 13% in the 5-year incidence of such morbid events would be clinically meaningful.

A perusal of the other important predictors in the models is consistent with previous studies but raises some questions. For example, it is reasonable that having had a myocardial infarction, greater age, smoking, and having diabetes were multivariable predictors of myocardial infarction (Table 3). Treatment with nitrates and aspirin, however, also seemed to place patients at higher risk. This apparent relationship can be explained by "confounding by indication." Patients whose providers believe them to be at higher risk of an outcome are more likely to be placed on risk-lowering drugs. Even if effective, these drugs might not lower risk sufficiently to overcome the selection bias.

Treatment with a calcium channel blocker was associated with increased risk of first myocardial infarction, stroke, heart failure, and renal insufficiency. Although this finding might be another example of confounding by indication, β-blockers have the same indications, yet they appeared in none of the predictive models in Table 3. Our study was not designed to answer this question but to adjust for any risk (or reduction of risk) engendered by drugs being taken at the time of the index visit. Nonetheless, these results are consistent with other studies and support current hypertension treatment guidelines.

Our study has limitations. We studied primary care patients under treatment for hypertension in an urban primary care practice with a substantial number of women and African Americans who experienced a relatively high incidence of cardiovascular events. Our results are thus applicable only to patients being

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### Table 4. Model Performance in the Validation Cohort

| Outcome Predicted (Subjects) | Number of Patients | Patient With Outcome No. (%) | C-Statistic |
|------------------------------|--------------------|-------------------------------|-------------|
| Myocardial infarction (all patients) | 2,912 | 198 (6.8) | 0.76* |
| First myocardial infarction (patients with no previous myocardial infarction) | 2,522 | 112 (4.4) | 0.62 |
| Stroke (all patients) | 2,912 | 514 (18) | 0.79* |
| First stroke (patients with no previous stroke) | 2,612 | 317 (12) | 0.67 |
| Myocardial infarction or stroke (all patients) | 2,912 | 640 (22) | 0.78* |
| First myocardial infarction or stroke (patients with no previous myocardial infarction or stroke) | 2,326 | 334 (14) | 0.65 |
| First ischemic heart disease (patients with no previous ischemic heart disease) | 1,811 | 194 (11) | 0.63 |
| First heart failure (patients with no previous heart failure) | 2,481 | 332 (13) | 0.68 |
| First chronic renal insufficiency (patients with no previous renal insufficiency) | 2,281 | 151 (6.6) | 0.81* |
| All-cause mortality (all patients) | 2,912 | 378 (13) | 0.78* |

* Good predictive model (defined a priori as having a C-statistic > 0.70).

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### Table 5. Marginal Predictive Power of the Significant Vital Sign

| Outcome Predicted | Partial Likelihood Ratio Statistic | P Value |
|-------------------|-----------------------------------|---------|
| First myocardial infarction (patients with no previous myocardial infarction) | 5.55 | .0180 |
| Stroke (all patients) | 10.32 | .0013 |
| First stroke (patients with no previous stroke) | 7.78 | .0053 |
| Myocardial infarction or stroke (all patients) | 6.28 | .0120 |
| First myocardial infarction or stroke (patients with no previous myocardial infarction or stroke) | 7.66 | .0065 |
| First ischemic heart disease (patients with no previous ischemic heart disease) | 7.76 | .0053 |
| First heart failure (patients with no previous heart failure) | 9.99 | .0016 |
| First chronic renal insufficiency (patients with no previous renal insufficiency) | 13.38 | .0002 |
| All-cause mortality (all patients) | 8.65 | .0033 |
actively treated for hypertension, and may not be generalizable to men or persons of other races and socioeconomic status. Our results, however, are relevant to inner-city practices that include many African Americans who are at increased cardiovascular risk.\textsuperscript{1,14} It is possible that the evidence of incident adverse events might have existed (but not been recognized) before the subjects’ index date. For example, a patient with a dizzy spell after her index date and could have a computed tomographic scan showing evidence of a previous stroke. In our study, such a stroke would have been considered an adverse outcome, yet it could have been extant on the index date. We minimized the chance of this occurring by eliminating from the analysis of new strokes and myocardial infarctions any evidence of previous events (by diagnosis, laboratory tests, and imaging studies). Yet, if a few of the outcome adverse events had actually occurred before the index date, they would likely have reduced the models’ predictive ability. Moreover, our analysis mirrored real life: if evidence of these conditions were not found in patients’ records, it is very likely that patients’ primary care physicians were also unaware of them.

We conclude that a single set of vital signs, especially elevated systolic blood pressure, recorded as part of ongoing primary care carries important prognostic information and should motivate primary care physicians to intervene to lower patient risk of morbid clinical events. Future research should assess the degree to which intervening lowers risk and which changes in care among patients treated for hypertension are most effective (and cost-effective) in lowering patient risk.

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