Independent Contribution of A1C, Systolic Blood Pressure, and LDL Cholesterol Control to Risk of Cardiovascular Disease Hospitalizations in Type 2 Diabetes: An Observational Cohort Study

Gregory A. Nichols, PhD[1,4], Sandra Joshua-Gotlib, MSPH, MBA[2], and Shreekant Parasuraman, PhD[3]

[1]Kaiser Permanente Center for Health Research, Portland, OR, USA; [2]Formerly AstraZeneca LP, Wilmington, DE, USA; [3]AstraZeneca LP, Wilmington, DE, USA; [4]Center for Health Research, Portland, OR, USA.

BACKGROUND: Cardiovascular disease (CVD) prevention in diabetes requires broad-based treatment of dyslipidemia, hypertension, and hyperglycemia. The independent contribution of all combinations of risk factor control to CVD risk has not been evaluated.

OBJECTIVE: To estimate the independent association of control of glycosylated hemoglobin (A1C), systolic blood pressure (SBP), and low-density lipoprotein cholesterol (LDL-C) with risk of cardiovascular disease hospitalization.

DESIGN: Non-concurrent longitudinal cohort study.

PATIENTS: The study included 26,636 patients with type 2 diabetes who were members of an integrated group model HMO with multiple A1C, SBP, and LDL-C measurements.

MAIN MEASURES: Patients were followed for a mean (SD) of 5.6 (2.5) years until they died or disenrolled, or until 31 December 2010. The outcome was a first-observed CVD hospitalization. Using the mean of all A1C, SBP, and LDL-C measures during follow-up, we created dichotomous categories of A1C control (< 7 %), SBP control (< 130 mmHg), and LDL-C control (< 100 mg/dL) to estimate the incidence rate of CVD hospitalization associated with all combinations of risk factor control adjusting for demographic and clinical characteristics.

KEY RESULTS: Patients with no controlled risk factors (18.2/1,000 person-years, 95 % CI 16.5–20.2) or with only A1C in control (16.9, 15.0–19.0) had the highest rate of CVD hospitalization, whereas those with all three risk factors controlled (7.2, 6.2–8.4) or with SBP and LDL-C in control (6.1, 5.1–7.2) had the lowest rates. Those with only SBP or LDL-C in control, A1C and SBP controlled, or A1C and LDL-C controlled had statistically similar incidence between the highest and lowest rates.

CONCLUSIONS: Maintaining SBP < 130 mmHg or LDL-C < 100 mg/dL was significantly associated with reduced CVD hospitalization risk, especially when both risk factors were well controlled. Maintaining A1C < 7 % was not independently associated with reduced CVD hospitalization risk.

KEY WORDS: glycemic control; blood pressure control; cholesterol control; CVD risk factors.

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INTRODUCTION

Management of type 2 diabetes requires a multifaceted approach to optimize control of metabolic risk factors.[1] Despite recent evidence that tight glycemic control does not appear to reduce cardiovascular disease (CVD) risk,[2–4] epidemiologic analyses have consistently shown an association between higher glycosylated hemoglobin (A1C) and poor CVD outcomes.[5–7] In addition, evidence-based guidelines recommend more aggressive therapeutic targets for the treatment of blood pressure and lipids in patients with diabetes than are suggested for the general population.[8,9] Evidence behind these recommendations comes from clinical trials that studied treatment of specific risk factors without simultaneously intervening on other risk factors. One exception was the Steno-2 Study, which found that intensive intervention with multiple drug combinations was associated with significantly lower risk of CVD events, although no attempt was made to ascertain the *independent* contribution of each treated risk factor to CVD risk reduction.[10]

Preventing CVD in diabetes requires broad-based treatment of dyslipidemia, hypertension, and hyperglycemia.[11,12] Other observational studies have examined the additive effects of glycemia and blood pressure and glycemia and dyslipidemia.[13,14] To our knowledge, however, no study has simultaneously evaluated the independent contribution of all three of these risk factors to CVD risk. Therefore, our objective was to study the CVD benefits of

control of A1C, systolic blood pressure (SBP), and low-density lipoprotein cholesterol (LDL-C), alone and in all combinations, as predictors of CVD hospitalization in a large cohort of patients with type 2 diabetes.

METHODS

Kaiser Permanente Northwest (KPNW) is an integrated healthcare delivery system that provides comprehensive medical services to approximately 480,000 individuals in a 75-mile radius around Portland, Oregon. An electronic medical record has been in use since 1996 that links encounter diagnoses, laboratory results, and pharmaceutical dispensings. The present non-concurrent longitudinal cohort study was approved by the KPNW Institutional Review Board with a waiver of informed consent.

Sample Selection

Since 1989, KPNW has maintained a diabetes registry that identifies members with diabetes from pharmacy, laboratory and encounter databases. Patients enter the registry on the basis of anti-hyperglycemic dispenses, diagnostic-level fasting glucose or A1C values, and inpatient or outpatient diagnoses (ICD-9-CM 250.xx). Clinicians remove patients from the registry who they believe have been entered erroneously. We identified all patients who entered the registry in 2007 or earlier and who had an eligibility period between 2002 and 2010 (n=53,250). To ensure we were studying patients with type 2 diabetes, we excluded 5,514 individuals with an insulin dispense within the first year of diabetes recognition. Patients under age 18 years (n=378) were also excluded. All patients were required to have A1C, LDL-C, and SBP measured after diabetes diagnosis but no more than 6 months apart, resulting in the exclusion of 12,681 patients. The first occurrence of the three-test combination was used as the baseline set of measurements, and the latest date that one of the baseline measurements was recorded was defined as the index date. We excluded 4,042 individuals who had a CVD hospitalization prior to the index date. Last, all subjects were required to have at least one additional A1C, SBP and LDL-C measurement during follow-up, resulting in a final sample size of 26,636 patients.

Outcome, Observation Period, and Exposure Variables

Using the electronic medical record, we followed patients from the index date until a hospital admission was recorded with a primary diagnosis of coronary heart disease (ICD-9-CM codes 410.x, 411.x, 413.x, 414.x) or stroke (430.x, 431.x, 432.x, 434.x, 435.x, 436.x, 437.1), defining the composite as CVD. Patients were followed from index date until they first experienced the outcome, died or left the health plan, or until 31 December 2010.

We used the mean of all available measures of A1C, SBP, and LDL-C during the observation period to examine the association between these risk factors and CVD hospitalizations. We analyzed each risk factor continuously and as dichotomous variables, using guideline-recommended levels of control (A1C < 7 %, SBP < 130 mmHg, LDL-C < 100 mg/dL). In addition, we created eight categories representing all possible combinations of risk factor control: 1) none of the three risk factors controlled; 2) only A1C controlled; 3) only SBP controlled; 4) only LDL-C controlled; 5) A1C and SBP controlled, but not LDL-C; 6) A1C and LDL-C controlled, but not SBP; 7) SBP and LDL-C controlled, but not A1C; and 8) A1C, SBP, and LDL-C all controlled.

Covariates

Covariates included baseline age sex, race, and duration of diabetes (defined as the time between entry into the diabetes registry and the index date). Although we excluded patients with a previous CVD hospitalization, some patients had CVD diagnosed in the outpatient setting during observation. Therefore, we included a covariate for outpatient-diagnosed CVD (same ICD-9 codes as for the outcome), as well as the following comorbidities: heart failure (ICD-9 428.x), retinopathy (250.5, 369.x, 362.01-362.07), neuropathy (250.6, 358.1, 713.5, 337.1, 357.2), depression (296.2, 296.3, 400.4, 309.1, 311), and chronic kidney disease (GFR <60 mL/min/1.73 m^2, estimated from serum creatinine using the Modification of Diet in Renal Disease (MDRD) equation[15]). We also controlled for use of specific anti-hyperglycemic agents (metformin, sulphonylureas, thiazolidinediones, insulin, other agents), antihypertensive agents (angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs], β-blockers, other agents), antilipidemic agents (statins, fibrates, other agents), and antidepressants used within 100 days of the event (or the end of observation).

Statistical Analyses

We compared demographic and clinical characteristics, comorbidities, and pharmacotherapies among patients who did and did not experience a CVD event using t-tests for continuous variables and χ^2 tests for categorical variables. P values<0.05 were considered significant. We also compared A1C, SBP, and LDL-C among patients who did and did not experience a CVD event using t-tests for the continuous values and χ^2 tests for the dichotomous indicators of risk factor control and for the distribution of all possible combinations of risk factor control.

We calculated incidence rates for CVD hospitalizations per 1,000 person-years for each of the possible combinations of risk factor control adjusted for age, sex and diabetes duration, using generalized linear regression with Poisson errors and the natural log of person-years as an adjustment for unequal follow-up using Proc Genmod in SAS v9.2 (SAS Institute, Cary, NC). A p value of 0.05 was used to calculate 95 % confidence intervals. We used Cox proportional hazards regression analysis to further adjust for clinical characteristics, comorbidities, and pharmacotherapy variables described above. The first Cox model used continuous measures of A1C, SBP, and LDL-C, a second used non-mutually exclusive dichotomous variables of risk factor control, and the final regression model included all possible combinations of risk factor control, using "All Three Risk Factors in Control" as the reference group. We tested the proportional hazards assumption by including time-dependent variables for all combinations of risk factor control in a Cox model; none were significant at $p<0.05$, satisfying the assumption.

Sensitivity Analyses

We conducted three sensitivity analyses to confirm our findings. First, we used baseline measures of A1C, SBP, and LDL-C to analyze their association with risk of CVD hospitalization. Second, we substituted the last A1C, SBP, or LDL-C measurement prior to the event (or end of follow-up) for mean values and re-estimated the Cox models. Third, we repeated our analysis using mean values excluding individuals with mean A1C values < 6 %.

RESULTS

Of the 26,636 study patients, 1,943 (7.3 %) experienced a CVD hospitalization during the observation period (Table 1). Patients who experienced the outcome were older, more likely to be men, and had longer diabetes duration compared with those who remained event-free. All comorbidities except depression were more common among patients who experienced a CVD hospitalization as were use of several medications.

Mean A1C during follow-up did not differ between those who did and did not experience a CVD hospitalization (Table 2). However, mean SBP and LDL-C were significantly greater among those who experienced an event. Similarly, the proportion of patients with A1C in control was not significantly different, but the proportion with SBP control and LDL-C control was significantly lower among those who experienced an event.

Figure 1 displays CVD hospitalization incidence rates per 1,000 person-years for each of the eight mutually exclusive categories of A1C, SBP, and LDL-C control, adjusted for age, sex, and duration of diabetes. Patients with no controlled risk factors or with only A1C controlled had the highest CVD hospitalization rates, whereas those with all three risk factors controlled or with SBP and LDL-C controlled had the lowest rates. Patients with only SBP controlled, only LDL-C controlled, A1C and SBP controlled, or A1C and LDL-C controlled had statistically similar incidence rates that were significantly lower than those with no risk factors or only A1C controlled, and significantly higher than those with SBP and LDL-C or all three risk factors controlled.

After adjustment for demographic and clinical characteristics, comorbidities and pharmacotherapies, an increase of

Table 1. Study Sample Characteristics

	No CVD Hospitalization	Had CVD Hospitalization	*p* value
n (%)	24,693 (92.7)	1,943 (7.3)	–
Baseline age, years	58.6 (12.0)	65.5 (11.1)	< 0.001
Men	49.7	56.4	< 0.001
African-American	3.2	2.9	0.475
Smoker	13.1	13.6	0.558
Duration of diabetes (at baseline), years	3.4 (4.2)	5.2 (5.1)	< 0.001
Baseline BMI (kg/m^2)	33.7 (7.9)	32.0 (6.7)	< 0.001
Baseline eGFR (ml/min/1.73 m^2)	92 (30)	81 (28)	< 0.001
Baseline HDL-C (mg/dL)	48 (11)	47 (11)	0.010
Baseline triglycerides (mg/dL)	224 (218)	227 (190)	0.567
Total years of follow-up	5.5 (2.5)	6.4 (2.2)	< 0.001
Years to event	n/a	3.9 (2.2)	–
Comorbidities*			
Cardiovascular disease	28.0	67.1	< 0.001
Cerebrovascular disease	10.2	23.3	< 0.001
Heart failure	13.4	25.9	< 0.001
Chronic kidney disease	21.0	34.6	< 0.001
Neuropathy	35.0	43.8	< 0.001
Retinopathy	24.7	34.3	< 0.001
Depression	34.6	32.5	0.059
Pharmacotherapy†			
ACE inhibitors or ARBs	58.0	63.4	< 0.001
Beta-blockers	29.7	53.1	< 0.001
Other antihypertensives	40.7	53.2	< 0.001
Metformin	42.7	37.5	< 0.001
Sulfonylureas	31.3	37.6	< 0.001
TZDs	1.8	1.9	0.785
Other antihyperglycemics	0.6	0.9	0.142
Insulin	22.0	27.0	< 0.001
Statins	55.4	59.0	0.002
Fibrates	3.1	4.1	0.029
Other antihyperlipidemics	1.3	2.6	0.001
Antidepressants	24.6	25.5	0.348

Data are mean (standard deviation) or percent
**Comorbidities assessed from diagnoses occurring anytime prior to CVD hospitalization or end of observation if no hospitalization*
†Pharmacotherapy based on receipt of a dispense within 100 days prior to CVD hospitalization or last 100 days of observation if no hospitalization
ACE angiotensin-converting enzyme; ARB angiotensin receptor blocker; BMI body mass index; CVD cardiovascular disease; eGFR estimated glomerular filtration rate; HDL-C high-density lipoprotein cholesterol; TZD thiazolidinediones

Table 2. Unadjusted Mean A1C, Systolic Blood Pressure, and LDL-C Over Entire Observation Period, Proportion of Patients with A1C in Control, Systolic Blood Pressure in Control, LDL-C in Control, and Distribution of All Possible Combinations of Control Categories

	No CVD Hospitalization (n=24,693)	Had CVD Hospitalization (n=1,943)	p value
Continuous Measures			
Mean (SD) A1C (%)	7.3 % (1.2)	7.3 % (1.2)	0.581
Mean (SD) SBP (mm Hg)	132 (11)	137 (13)	< 0.001
Mean (SD) LDL-C (mg/dL)	97 (26)	102 (29)	< 0.001
Non–Mutually Exclusive Categories			
% A1C in control (< 7 %)	45.6	47.2	0.174
% SBP in control (< 130 mmHg)	44.1	27.9	< 0.001
% LDL-C in control (< 100 mg/dL)	59.5	51.9	< 0.001
Mutually Exclusive Categories			
% None in control	13.7	21.0	< 0.001
% Only A1C in control	10.1	15.4	
% Only SBP in control	9.2	6.5	
% Only LDL-C in control	18.0	18.3	
% A1C/SBP in control	7.6	5.2	
% A1C/LDL-C in control	14.2	17.4	
% SBP/LDL-C in control	13.6	7.1	
% All three in control	13.8	9.2	

Data are mean (standard deviation) or percent
A1C hemoglobin A1c; CVD cardiovascular disease; LDL-C low-density lipoprotein cholesterol; SBP systolic blood pressure

one standard deviation of SBP was associated with a 40 % increased risk of CVD hospitalization, as was one standard deviation increase of LDL-C (Table 3). Mean A1C was not associated with CVD risk. When A1C control, SBP control, and LDL-C control were included in models as non-mutually exclusive variables, SBP and LDL-C control were protective while A1C control was associated with a 14 % increased risk of CVD hospitalization. In adjusted models using all possible combinations of risk factor control, all categories, except having both SBP and LDL-C controlled, produced statistically significant adjusted hazard ratios relative to those with all three risk factors controlled.

Results of the sensitivity analyses are shown in the online appendix, supplementary Table 1. Associations between baseline measures of A1C, SBP, and LDL-C and CVD hospitalization were substantially weaker than mean values during observation. Substituting last values observed during follow-up produced results similar to those obtained using mean values. Exclusion of patients with mean A1C < 6 % attenuated the risk associated with A1C control, but did not change the results. Supplementary Table 2 in the online appendix shows the mean risk factor levels for the eight mutually exclusive categories. Similar values were seen among categories that indicated a specific risk factor was controlled and also among categories that indicated a specific risk factor was not controlled.

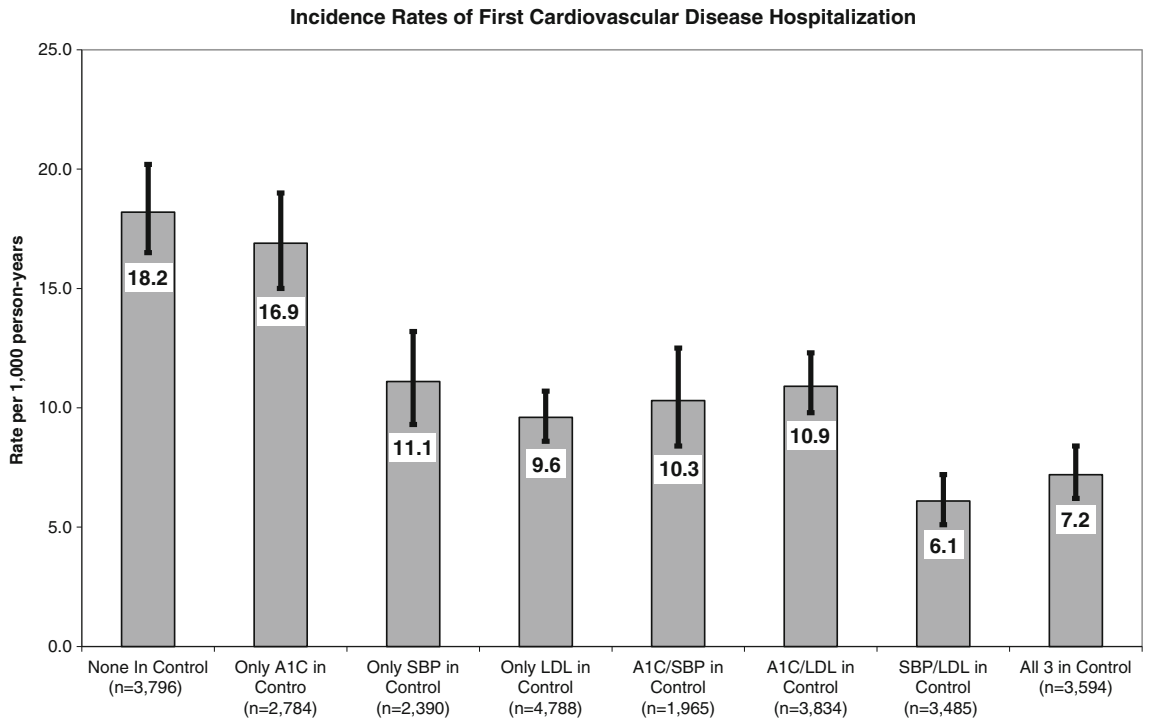

Figure 1. Incident rate per 1,000 person-years of first cardiovascular disease hospitalization, adjusted for age, sex, and duration of diabetes. The error bars represent 95 % confidence intervals for the incidence rates. *A1C* hemoglobin A1c; *LDL* LDL cholesterol; *SBP* systolic blood pressure.

Table 3. Adjusted Hazard Ratios for Continuous Measures of Risk Factors, Dichotomous Measures of Risk Factor Control, and All Possible Combinations of Risk Factor Control

	Adjusted Hazard Ratios* (95 % CI)	*p* value
Continuous Measures		
A1C (per SD)	1.01 (0.95−1.08)	0.661
SBP (per SD)	1.40 (1.33−1.47)	< 0.001
LDL-C (per SD)	1.40 (1.33−1.47)	< 0.001
Non-Mutually Exclusive Categories		
A1C in control (< 7 %)	1.14 (1.02−1.27)	0.024
SBP in control (< 130 mmHg)	0.63 (0.56−0.71)	< 0.001
LDL-C in control (< 100 mg/dL)	0.52 (0.47−0.57)	< 0.001
Mutually Exclusive Categories		
None in control	2.75 (2.25−3.37)	< 0.001
Only A1C in control	2.76 (2.25−3.40)	< 0.001
Only SBP in control	1.76 (1.36−2.26)	< 0.001
Only LDL-C in control	1.31 (1.07−1.62)	0.011
A1C/SBP in control	1.90 (1.46−2.48)	< 0.001
A1C/LDL-C in control	1.63 (1.33−1.99)	< 0.001
SBP/LDL-C in control	0.78 (0.60−1.00)	0.054
All three in control	ref	–

A1C hemoglobin A1c; CI confidence interval; CVD cardiovascular disease; LDL-C low-density lipoprotein cholesterol; SBP systolic blood pressure

**Adjusted for age, sex, race, diabetes duration, body mass index, HDL cholesterol, triglycerides, smoking, and presence of cardiovascular disease, heart failure, retinopathy, neuropathy, depression, chronic kidney disease, and use of metformin, sulphonylureas, thiazolidinediones, insulin, ACE inhibitors or angiotensin receptor blockers, β-blockers, other anti-hypertensive agents, statins, fibrates, and anti-depressants*

DISCUSSION

Clinical management of type 2 diabetes includes control of glycemia, blood pressure, and LDL-C to reduce the risk of CVD and other complications.[1] In the current observational study of 26,636 patients with type 2 diabetes followed over a mean of approximately 6 years, we found that controlling all three risk factors was associated with an incidence rate of CVD hospitalization that was approximately 2.5 times lower than if none of the risk factors was below guideline-recommended levels.

Despite guidelines recommending multi-factorial treatment of cardiometabolic risk factors, there are surprisingly few studies that have examined the simultaneous benefits of risk factor control. The ADVANCE study reported that combined treatment of A1C and SBP (compared with no active intervention) had no effect on the incidence of macrovascular events, but lipid control was not included.[16] A large observational study found that tight control of A1C and SBP reduced CVD risk by 33 %, but did not attempt to disentangle the relative benefits of the two risk factors, nor did it include lipid control as an analysis variable.[17] The UKPDS explored the additive effects of glycemia and blood pressure,[13] and a report from the Swedish National Diabetes Register analyzed the additive effects of glycemia and dyslipidemia.[14] To our knowledge, the only study to evaluate all three cardiometabolic risk factors simultaneously was the Steno-2 study, which demonstrated that intensive treatment of A1C, SBP, and lipids reduced the risk of cardiovascular events by 53 %[10]; an effect that was sustained well after the intervention ceased.[18] The Steno-2 sample size (n=160) was too small to determine which risk factor or combination of risk factors accounted for the effect. To our knowledge, the current study is the first to simultaneously evaluate the contribution of all possible combinations of A1C, SBP, and LDL-C control to CVD risk reduction.

Maintaining A1C control below 7 % was not associated with reduced CVD hospitalization risk below that obtained with SBP and LDL-C control. CVD hospitalization incidence per 1,000 person-years among those with A1C in control but neither of the other risk factors in control was statistically similar to incidence found among those with no risk factors in control; incidence among those with A1C in control in addition to either SBP or LDL-C was statistically similar to the rate among those with only SBP or LDL-C in control, respectively; and control of both SBP and LDL-C, but not A1C, produced a statistically similar rate to that of patients who had all three risk factors controlled. Our findings will likely contribute to the emerging controversy over optimal A1C levels. Glycemic control remains a cornerstone of good diabetes care. Despite clinical trials that found no CVD benefit and possible harm with tight control,[2–4] an A1C level < 7 % is still considered optimal for most patients,[12] although a less stringent patient-centered approach has recently been recommended.[19] The recommendation to achieve A1C < 7 % was initially due to UKPDS evidence that intensive control substantially reduced microvascular complications,[20] and more recent clinical trials re-affirm the microvascular benefit of low A1C levels.[3,21] The nature of the relationship between A1C and CVD risk, however, remains unclear. Over a decade ago, the UKPDS found that each 1 % reduction in A1C was associated with a 14 % reduced risk of myocardial infarction, with no threshold below which risk reduction could not be obtained.[5] More recent observational studies conducted on large samples in Sweden and New Zealand reported similar findings.[22,23] However, two other studies found a U-shaped relationship, with levels of A1C < 6%–6.5 % and > 8.5 % conferring risk of cardiovascular outcomes or death.[6,24] A post-hoc analysis from the ADVANCE trial found evidence of a threshold such that A1C < 7 % did not reduce macrovascular events.[25] The current study did not find an association between mean A1C < 7 % and reduced CVD risk after controlling for other risk factors. One possible explanation is that 90 % of patients had mean A1C levels < 9 %; the benefits of additional glycemic control in a relatively well-controlled sample may be difficult to detect. Our A1C results may also be confounded by non-random use of anti-hyperglycemic agents, specifically metformin and sulfonylureas, that are known to have differential CVD effects.[26,27]

All categories of risk factor control that included SBP were associated with lower CVD hospitalization incidence

than similar categories that did not. For example, CVD hospitalization incidence among those with only SBP in control was lower than among those with no risk factors in control, and incidence among those with SBP and LDL-C in control was lower than among those with only LDL-C in control. Our definition of SBP control (< 130 mmHg) was based on the American Diabetes Association guidelines that were in place during the observation period.[1] However, this level of SBP control is somewhat controversial. The American College of Cardiology/American Heart Association, for example, holds that < 140 mmHg is sufficient,[28] a level supported by recent trials. The ACCORD trial found that targeting SBP < 120 mmHg, as compared with < 140 mmHg, did not reduce the rate of major cardiovascular events.[29] Another recent study also suggested that tight SBP control (< 130 mmHg) was not associated with improved CVD outcomes relative to usual control of 130−139 mmHg, but did provide substantial benefit compared with SBP ≥ 140 mmHg.[30] The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) found no benefit in fatal or nonfatal cardiovascular outcomes by reducing SBP below 130 mmHg.[31] Nevertheless, our results suggest that achieving and maintaining SBP at that level is associated with CVD risk reduction.

Similar to SBP control, we found that all categories of risk factor control that included LDL-C were associated with lower CVD hospitalization incidence than similar categories that did not. CVD hospitalization incidence among those with only LDL-C in control was lower than among those with no risk factors in control, and CVD hospitalization incidence among those with SBP and LDL-C in control was lower than among those with only SBP in control. Because diabetes may be a cardiovascular risk equivalent,[32] current guidelines recommend an LDL-C target of < 100 mg/dL,[8] or perhaps as low as < 70 mg/dL, for patients with diabetes.[33] We did not test categories of control other than < 100 mg/dL, so we cannot determine whether a "floor" for LDL-C control exists.

Strengths of the study include its large sample size and the designed intent to study all possible combinations of control of three key cardiometabolic risk factors. There are several limitations. We required all three risk factors to be measured within 6 months of each other, resulting in the exclusion of 27 % of the eligible sample. However, excluded patients did not differ demographically from the study sample. As an observational study, we cannot conclude that the reported associations between risk factor control and CVD hospitalization risk are causal. Although we controlled for characteristics and risk factors that might affect CVD, residual confounding may exist. We included covariates for medications and duration of diabetes, but did not explore the myriad interactions between specific medications, dosages, and duration of therapy. We used death as a censoring event and some deaths could have occurred from cardiovascular causes outside the hospital, resulting in an underestimate of CVD rates. Moreover, A1C control may affect mortality differently than CVD hospitalizations.[2,24] We did not attempt to adjudicate CVD hospitalizations, relying on the accuracy of coding of inpatient diagnoses.

In summary, we found that maintaining SBP < 130 mmHg or LDL-C < 100 mg/dL over a mean follow-up of approximately 6 years was significantly associated with reduced risk of CVD hospitalization. The effect was especially strong when both of these risk factors were well controlled. Maintaining A1C < 7 % in an already well-controlled population was not associated with CVD hospitalization risk reduction.

Conflicts of Interest: *Funding for this research was provided by AstraZeneca LP and Bristol Myers-Squibb, and two of the coauthors are employees and shareholders of AstraZeneca. As coauthors, they contributed to the design and reporting of the study. By contract, however, the lead author (GAN), who is not affiliated with AstraZeneca or Bristol Myers-Squibb, had control of the data and retained final authority over design, content, and interpretation of the analyses. These data were presented in poster form at the 72nd Scientific Sessions of the American Diabetes Association in June, 2012.*

Corresponding Author: *Gregory A. Nichols, PhD; Center for Health Research, 3800 N. Interstate Avenue, Portland, OR 97227-1098, USA (e-mail: greg.nichols@kpchr.org).*

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