Changes in A1C Levels Are Significantly Associated With Changes in Levels of the Cardiovascular Risk Biomarker hs-CRP

Results from the SteP study

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OBJECTIVE—The effect of therapeutic strategies on cardiovascular (CV) disease can be evaluated by monitoring changes in CV risk biomarkers. This study investigated the effect of a structured self-monitoring of blood glucose (SMBG) protocol and the resulting improvements in glycemic control on changes in high-sensitivity C-reactive protein (hs-CRP) in insulin-naïve patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS—The Structured Testing Program (STeP) study was a prospective, cluster-randomized, multicenter trial in which 483 poorly controlled, insulin-naïve patients with type 2 diabetes were randomized to active control (ACG) or structured testing (STG) that included quarterly structured SMBG. Changes in A1C, hs-CRP, and glycemic variability (STG subjects only) were measured at baseline and quarterly.

RESULTS—Reductions in geometric mean hs-CRP values were significantly greater in the STG group at months 3 ($P = 0.005$), 6 ($P = 0.0003$), and 12 ($P = 0.04$) than in the ACG group. STG patients at high CV risk (>3 mg/L) showed significantly greater reductions in hs-CRP levels than ACG patients at high CV risk: −3.64 mg/dL (95% CI −4.21 to −3.06) versus −2.18 mg/dL (−2.93 to −1.43), respectively ($P = 0.002$). There was a strong correlation between reductions in hs-CRP and A1C in both groups: standardized coefficient (β) was 0.25 for the entire cohort ($P < 0.0001$), 0.31 for STG ($P < 0.0001$), and 0.16 for ACG ($P = 0.02$).

CONCLUSIONS—Reductions in hs-CRP level are associated with reductions in A1C but not reductions in lipids or glycemic variability. Comprehensive structured SMBG-based interventions that lower A1C may translate into improvements in CV risk, as evidenced by levels of the biomarker hs-CRP.

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It is widely acknowledged that early and intensive glycemic intervention reduces the risk of diabetes-associated complications, in particular, microvascular complications (1–4). However, there is still a need for further reductions in comorbidities, in particular, the risk of cardiovascular (CV) disease (CVD), which is the most common cause of death in patients with diabetes (5). Although the ultimate measure of CVD management is a reduction in morbidity and mortality, it may be possible to monitor the effectiveness of therapeutic strategies to reduce CVD using surrogate markers of CV risk such as high-sensitivity C-reactive protein (hs-CRP).

Several studies have linked high levels of hs-CRP to an increased risk of thrombotic events, including myocardial infarction (6–8), and have identified hs-CRP as a predictive biomarker of CV risk and CV mortality in various patient populations, including diabetic patients (9). In diabetic patients with an acute myocardial infarction and elevated hs-CRP levels, hospital outcome is poorer than in nondiabetic patients with an acute myocardial infarction (10).

The link between hs-CRP and poor glycemic control in diabetes still remains to be fully elucidated. An early study by King et al. (11) using cross-sectional data, found that a higher A1C is significantly associated with a greater likelihood of higher hs-CRP among adults with diabetes; however, there is a growing body of evidence to suggest that in patients with type 2 diabetes (T2DM), short-term glycemic excursions, such as postprandial hyperglycemia, are even more damaging than long-term high blood glucose levels, that their negative effect on diabetes-related complications is independent of A1C levels (12–14), and that medications targeting postprandial excursions are associated with reductions in hs-CRP levels (15). Further, although abnormal lipid levels have long been considered to be a significant risk factor and possible mechanism for CVD (16), prospective analyses of 12 recognized markers of inflammation (including inflammation, lipids, and lipoproteins), among healthy women, found hs-CRP was the strongest predictor of CV events (17).

To further explore the relationship between glycemic control and levels of hs-CRP, we examined data from the Structured Testing Program (STeP) study, a 12-month, cluster-randomized, multicenter clinical trial in primary care that evaluated whether 483 poorly controlled insulin-naïve T2DM patients would benefit from a comprehensive, integrated physician/patient intervention using a structured data collection form before each quarterly clinic visit (18). At 12 months,

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the intent-to-treat analysis showed significantly greater reductions in mean A1C in the structured testing group (STG) patients than in the active control group (ACG) patients ($P = 0.04$). Per protocol analysis showed even greater A1C reductions in STG patients ($P < 0.003$). STG patients also experienced significantly lower average preprandial and postprandial glucose levels at all meals and at bedtime ($P < 0.001$), with significant reductions in preprandial-to-postprandial glucose excursions at all meals ($P < 0.005$). There were also significant reductions in glycemic variability among STG patients as measured by mean amplitude of glucose excursions (MAGE) at month 12 ($P = 0.0003$). No significant changes were noted in lipid levels.

This report addresses three research questions. First, to explore further the relationship between glycemic control and hs-CRP, was there a relationship between change in glycemic control and change in hs-CRP over time in patients of the STG or the ACG group? Second, what additional effect, if any, did reduced glycemic variability have on the relationship between A1C and hs-CRP? Third, did lipids mediate the relationship between A1C and hs-CRP?

RESEARCH DESIGN AND METHODS

Details of the STeP study design have been reported previously (18–20). In brief, this was a 12-month, cluster-randomized clinical trial designed to assess the use of structured SMBG, as part of a comprehensive, collaborative intervention, on glycemic control compared with enhanced usual care in 483 patients with non–insulin-treated T2DM.

The study was conducted in 34 primary care practices across the eastern U.S. Patients were randomized to the structured SMBG group (STG) or to an active control group (ACG) for comparison. STG patients received enhanced usual care and used the Accu-Chek 360 View blood glucose analysis system (Roche Diagnostics, Indianapolis, IN) to record and plot a 7-point SMBG profile (preprandial/postprandial at each meal and at bedtime) on 3 consecutive days before a study visit. STG patients received training in the use of the analysis system and how to interpret their results and use their findings to make changes to their diet and physical activity. STG physicians also received training on interpreting the SMBG data from the device. Enhanced usual care comprised quarterly clinic visits focusing on diabetes management with office point-of-care glycated hemoglobin measurement. ACG patients received enhanced usual care. ACG patients and physicians received no additional training. Free blood glucose meters and test strips (Accu-Chek Aviva blood glucose meter system, Roche Diagnostics) were provided to patients in both study arms. Patient visits occurred at baseline and at months 1, 3, 6, 9, and 12.

The study protocol was approved by the Copernicus Group (Central Institutional Review Board) and is in compliance with the Declaration of Helsinki (21). Written informed consent was obtained from all patients.

Measurements

As reported previously (18), A1C analysis was conducted by a central laboratory (Covance, Indianapolis, IN) using the Variant II and Variant II Turbo hemoglobin testing systems (Bio-Rad Laboratories, Hercules, CA). Measurements of fasting glucose and postprandial excursions were based on STG patient-reported data from the quarterly 7-point glycemic profiles; accuracy of these data were confirmed using downloaded blood glucose meter data. The 7-point glycemic profiles were also used to assess glycemic variability, which was reported as the MAGE.

Measurements of LDL-cholesterol, HDL-cholesterol, triglycerides, and hs-CRP were taken at baseline and at months 3, 6, 9, and 12. The hs-CRP analysis was also conducted at a central laboratory (Covance). Cutoff points for CV risk were defined as low (mean hs-CRP levels <1.0 mg/L) elevated (mean hs-CRP levels 1.0 to 3 mg/L), and high (mean hs-CRP levels >3.0 mg/L) (22).

Table 1—*Baseline characteristics of patients with type 2 diabetes by study group*

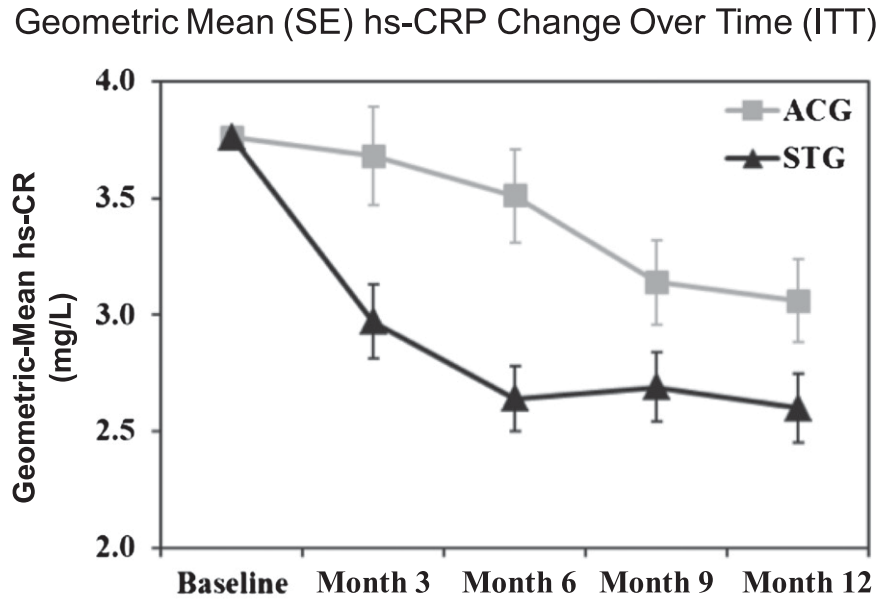
	All $N = 481$	ACG $n = 226$	STG $n = 255$	P value
Age (years), mean (SD)	55.8 (10.7)	57.0 (11.2)	54.7 (10.1)	0.02
Male, *n* (%)	256 (53.2)	121 (53.5)	135 (52.9)	0.90
Ethnicity, *n* (%)				0.0004
African American	148 (30.8)	71 (31.4)	77 (30.2)	
Caucasian	305 (63.4)	152 (67.3)	153 (60.0)	
Other	28 (5.8)	3 (1.3)	25 (9.8)	
Diabetes duration (years), mean (SD)	7.6 (6.1)	7.7 (6.1)	7.4 (6.1)	0.61
A1C (%), mean (SD)	8.9 (1.2)	8.9 (1.2)	8.9 (1.2)	0.91
BMI (kg/m^2), mean (SD)	35.1 (7.3)	35.1 (6.7)	35.0 (7.8)	0.87
All patients				
hs-CRP (mg/L), geometric mean (SD)	3.74 (2.89)	3.93 (2.97)	3.60 (2.86)	0.39
Low-CV-risk patients,† *n* (%)	56 (11.6)	28 (12.4)	28 (11.0)	0.63
hs-CRP (mg/L), geometric mean (SD)	0.61 (1.40)	0.63 (1.36)	0.59 (1.45)	0.41
Elevated-CV-risk patients,‡ *n* (%)	148 (30.8)	62 (27.4)	86 (33.7)	0.14
hs-CRP (mg/L), geometric mean (SD)	1.90 (1.38)	1.86 (1.39)	1.92 (1.36)	0.64
High-CV-risk patients,§ *n* (%)	277 (57.6)	136 (60.2)	141 (55.3)	0.28
hs-CRP (mg/L), geometric mean (SD)	7.85 (1.93)	8.00 (1.95)	7.61 (1.93)	0.54

†hs-CRP <1.0 mg/L. ‡hs-CRP between 1.0 and 3.0 mg/L. §hs-CRP >3.0 mg/L.

Statistical analyses

Details of the STeP study statistical analysis methodologies have been reported previously (18). Briefly, a cluster-randomization strategy was chosen, whereby all patients within a given practice were assigned to the same study arm. The analysis of change in A1C and other dependent variables was performed using linear mixed models (LMM) analysis with SAS PROC MIXED (23,24). Control variables in all analyses included baseline-dependent variables of patient age, sex, and race (white/nonwhite) as fixed effects; and practice site and subject as random effects. Missing data were estimated using maximum likelihood methods (25). Additional analyses of patient attrition at each step in the protocol also were undertaken.

The primary analysis methods used for this study were similar to those previously reported in the STeP study. LMM analysis was performed for the natural logarithm of hs-CRP at postbaseline visits, with group (ACG or STG), baseline $\log_e$ (hs-CRP), age, sex, and race (white/nonwhite) as fixed effects, and patient and site as random effects. The geometric mean estimates at postbaseline visits were derived from the LMM. Geometric mean estimates at baseline were calculated from raw data. The values reported for change from baseline in hs-CRP concentration (mg/L) are absolute differences from baseline in geometric means (95% CI, delta method) at postbaseline visits. Relationships between change in glycemic control, glycemic variability, and change in hs-CRP (log-scale) were examined with a general linear model, with patient demographics, diabetes duration, and BMI as controls. Tests of mediated models via lipids were assessed following the recommendations of Baron and Kenny (26).



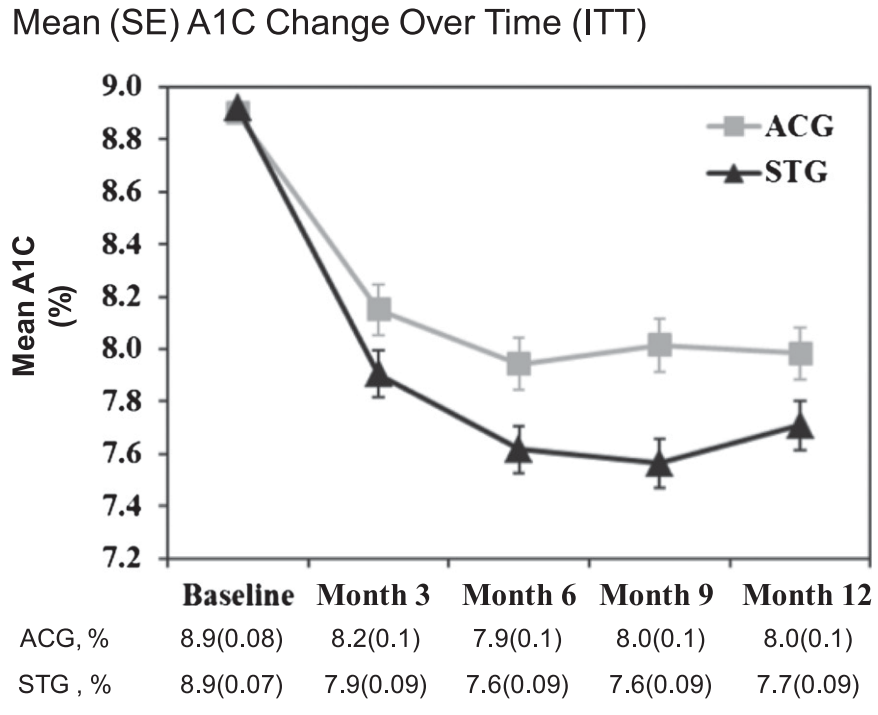


Figure 1—*Comparison of change in geometric mean (SE) levels of hs-CRP* (top) *with changes in mean (SE) A1C* (bottom) *during the 12-month study period in intent-to-treat cohorts.*

RESULTS—As reported previously (18), 13 primary care practices were randomized to the ACG and 21 to the STG. Patient demographic and disease-related characteristics at baseline between the two study groups differed only by age and ethnicity; these differences were controlled in all subsequent analyses (Table 1). Attrition was higher in the STG (n = 81, 28.6%) than in the ACG (n = 43, 18.1%) group. Characteristics of dropout patients did not differ between the two groups.

Geometric mean baseline hs-CRP levels were recorded for 481 patients (Table 1). At baseline, more than 30% of patients were classified as at an elevated CV risk; whereas, almost 60% were found to be at high CV risk, according to hs-CRP level. Patients at high CV risk tended to be younger, more likely to be female, less educated, have higher BMI, shorter diabetes duration, higher diastolic blood pressure, and higher cholesterol levels.

The number of study patients taking statin, β-blocker, and/or ACE-inhibitor medications at baseline was relatively equal among the groups (ACG, n = 157; STG, n = 182) and remained so throughout the study period. Geometric mean (SD) baseline hs-CRP values (mg/L) for these patients were 3.19 (2.76) for ACG

patients and 3.67 (2.93) for STG patients. Mean (SD) baseline lipids for the full intent-to-treat cohort were: LDL-cholesterol, 107.1 (42.1) mg/dL; HDL-cholesterol, 44.4 (11.9) mg/dL; and triglycerides, 238.6 (183.6) mg/dL, with no significant between-group differences.

Change in hs-CRP over time

In both study arms, there was a consistent decrease in geometric mean hs-CRP levels over the study duration, which was significantly associated with reductions in A1C observed throughout the study ($P < 0.0001$; Fig. 1). Reductions in mean hs-CRP values were significantly greater in the STG group at months 3 ($P = 0.005$), 6 ($P = 0.0003$), and 12 ($P = 0.04$) than in the ACG group (Table 2). However, LMM analysis of hs-CRP over time showed no significant difference in change in geometric mean hs-CRP between adherent and nonadherent STG patients: −0.86 vs. −1.01 mg/L, respectively ($P = 0.84$). STG patients at high CV risk (adherent and nonadherent) showed significantly greater reductions in hs-CRP levels than ACG patients at high CV risk, with the greatest between-group difference seen at month 6: −3.64 (95% CI −4.21 to −3.06) vs. −2.18 (−2.93 to −1.43) mg/dL, respectively ($P = 0.002$).

Among patients treated with statin, β-blocker, and/or ACE-inhibitors, the STG showed a significantly greater reduction in hs-CRP levels from baseline compared with the ACG: −1.08 (95% CI, −1.39 to −0.77) vs. 0.59 (−0.99 to −0.19) mg/L, respectively ($P = 0.049$). Although significantly more STG than ACG subjects received a thiazolidinedione (TZD) during the study, 22.7 vs. 12.3%, respectively ($P = 0.004$), which can influence hs-CRP levels, there was no significant association between use of these medications or change in these medications and change in hs-CRP (P = NS). This finding remained the same even after excluding patients who were receiving TZD therapy at baseline.

Relationship between change in A1C and change in hs-CRP over time

Our analysis showed that the reductions in A1C were significantly related to reductions in hs-CRP over time in the sample as a whole and in each of the two study groups: the standardized coefficient (β) was 0.25 for the entire cohort ($P < 0.0001$), 0.31 for STG ($P < 0.0001$), and 0.16 for ACG ($P = 0.002$). These associations were consistent across the study sample and did not vary by patient demographic or diabetes characteristics.

Effects of glycemic variability on the relationship between changes in A1C and changes in hs-CRP over time

In analyses that included A1C plus MAGE or MAGE alone, changes in MAGE were unrelated to changes in hs-CRP over time ($P = 0.82$ or $P = 0.37$). Similar results were recorded when changes in postprandial glucose excursions were included ($P = 0.20$ or $P = 0.99$). Hence, changes in glycemic variability, in combination with changes in A1C or alone, did not account for changes in hs-CRP.

Influence of changes in lipid levels

We assessed the potential role of changes in lipids as a mediator in the relationship between changes in A1C and changes in hs-CRP over time: there was no reduction in the relationship between changes in A1C and changes in hs-CRP when changes in LDL-cholesterol, HDL-cholesterol, and triglycerides were evaluated in the model individually or as a group, following Baron and Kenny (26). Thus, lipids did not mediate the relationship between changes in A1C and changes in hs-CRP over time.

CONCLUSIONS—Our study is the first to report a relationship between the significant glycemic outcomes of a structured SMBG intervention and changes in hs-CRP, a clinical marker of CV risk, with a demonstrated association between inflammation and atherosclerosis (27). A significant positive association was found in both study groups between the degree of reduction of A1C and the degree of reduction in hs-CRP; these improvements were especially significant among STG patients who were at the highest CV risk (hs-CRP >3 mg/L), and their A1C levels dropped the most. Although we were unable to identify the underlying mechanism(s) to explain the relationship

Table 2—*Geometric mean change from baseline in hs-CRP concentration (mg/L)*

	ACG			STG			
Month	*N*	Mean change (mg/L)	95% CI	*N*	Mean change (mg/L)	95% CI	*P* value*
Overall cohort (intent to treat)†							
3	203	−0.08	−0.49 to 0.33	210	−0.79	−1.11 to −0.48	0.005
6	193	−0.25	−0.64 to 0.15	199	−1.12	−1.40 to −0.83	0.0003
9	180	−0.62	−0.99 to −0.26	184	−1.07	−1.36 to −0.77	0.06
12	185	−0.70	−1.05 to −0.35	182	−1.16	−1.45 to −0.88	0.04
Patients classified by hs-CRP level at elevated CV risk at baseline‡							
3	57	0.34	−0.06 to 0.74	71	−0.10	−0.38 to 0.19	0.07
6	58	0.38	−0.02 to 0.79	67	−0.35	−0.59 to 0.10	0.001
9	51	−0.04	−0.38 to 0.31	63	−0.28	−0.54 to −0.01	0.26
12	51	−0.14	−0.47 to 0.19	58	−0.35	−0.61 to −0.09	0.31
Patients classified by hs-CRP level at high CV risk at baseline§							
3	122	−1.75	−2.54 to −0.96	115	−2.92	−3.59 to −2.26	0.02
6	115	−2.18	−2.93 to −1.43	108	−3.64	−4.21 to −3.06	0.002
9	109	−2.35	−3.09 to −1.61	97	−3.52	−4.13 to −2.90	0.01
12	113	−2.59	−3.28 to −1.89	102	−3.63	−4.22 to −3.04	0.02

*P value for treatment effect. †Intent-to-treat population. ‡Baseline hs-CRP between 1.0 and 3.0 mg/L. §Baseline hs-CRP >3.0 mg/L.

between reductions in A1C and hs-CRP, our analyses did rule out several commonly hypothesized mechanisms. For example, postprandial excursions and overall glycemic variability have been linked with oxidative stress (28) and other markers of vascular disease (e.g., carotid intima-media thickening) (29); however, our analyses found no relationship between reduced postprandial glucose excursions or glycemic variability (as measured by MAGE and the magnitude of postprandial glucose excursions) and changes in hs-CRP, nor did HDL-cholesterol, LDL-cholesterol, or triglycerides (individually or combined) mediate the relation between changes in A1C and changes in hs-CRP. Zero-order correlations among these variables also were not significant. Moreover, because the reductions in hs-CRP seen in both study groups were independent of treatment with statins, β-blockers, ACE-inhibitors, and/or TZDs, use of lipid-lowering and/or antihypertensive medications did not appear to be a factor in our findings. However, when one considers the effects of oxidative stress, which is commonly considered to be the link between hyperglycemia and diabetes complications and is believed to be one of the earliest pathophysiologic changes in the inflammatory process that triggers endothelial dysfunction (14), the effects of "metabolic memory" may partially explain the relationship between changes in A1C and changes in hs-CRP.

The concept of metabolic memory hypothesizes that diabetic vascular stresses persist after glycemia has been reduced and that early aggressive treatment aiming to "normalize" metabolic control, as seen in the STeP trial (20), in combination with the agents that reduce cellular reactive species and glycation, may minimize long-term diabetes complications (30). Given that both STeP study groups experienced significantly greater A1C reductions early in the study compared with ACG patients at month 3 and even greater reductions among STG subjects (adherent and nonadherent) at month 6, this early improvement in glycemia possibly conferred a long-term protective effect against oxidative stress that resulted in lower hs-CRP levels even though A1C levels in nonadherent STG patients deteriorated to the same level as in ACG patients at 12 months.

Regardless of the mechanism(s) involved, we showed that reductions in A1C are significantly linked with reductions in CV risk (as assessed by hs-CRP levels) in non–insulin-treated T2DM. Although there are several possible approaches to reducing A1C levels, there is a growing body of evidence demonstrating the effectiveness and practicality of structured SMBG-based interventions in lowering A1C and markers of metabolic risk in this population (31,32). Long-term follow-up, including assessment of compliance, would determine whether the results found in our analyses translate into clinical benefits such as long-term improvement of cardiovascular outcome.

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O.S., I.A.-Z., A.M., C.G.P., M.A.S., L.F., and W.H.P. contributed to analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, and final approval of the version to be published. Z.J. and J.L.B. performed the statistical analysis, contributed to analysis and interpretation of data, drafted the article, revised it critically for important intellectual content, and gave final approval of the version to be published. O.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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