

Clinical and Economic Benefits Associated With the Achievement of Both HbA_{1c} and LDL Cholesterol Goals in Veterans With Type 2 Diabetes

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OBJECTIVE—This study compared the clinical and economic benefits associated with dual-goal achievement, glycated hemoglobin (HbA_{1c}) <7% (53 mmol/mol) and LDL cholesterol (LDL-C) <100 mg/dL, with achievement of only the LDL-C goal or only the HbA_{1c} goal in veterans with type 2 diabetes mellitus (T2DM).

RESEARCH DESIGN AND METHODS—This retrospective cohort analysis evaluated electronic medical records (Veterans Integrated Service Network 16) in adult T2DM patients with two or more measurements of LDL-C and HbA_{1c} between 1 January 2004 and 30 June 2010 (N = 75,646). Cox proportional hazards models were used to compare microvascular and cardiovascular outcomes by goal achievement status; generalized linear regression models were used to assess diabetes-related resource utilization (hospitalization days and number of outpatient visits) and medical service costs.

RESULTS—Relative to achievement of only the LDL-C goal, dual-goal achievement was associated with lower risk of microvascular complications (adjusted hazard ratio [aHR] 0.79), acute coronary syndrome (0.88), percutaneous coronary intervention (0.78), and coronary artery bypass graft (CABG) (0.74); it was also associated with fewer hospitalization days (adjusted incidence rate ratio [aIRR] 0.93) and outpatient visits (0.88), as well as lower diabetes-related annual medical costs (−\$130.89). Compared with achievement of only the HbA_{1c} goal, dual-goal achievement was associated with lower risk of the composite cardiovascular-related end point (aHR 0.87) and CABG (aHR 0.62), as well as fewer outpatient visits (aIRR 0.98).

CONCLUSIONS—Achieving both HbA_{1c} and LDL-C goals in diabetes care is associated with additional clinical and economic benefits, as compared with the achievement of either goal alone.

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The American Diabetes Association recommends that patients with type 2 diabetes mellitus (T2DM) maintain levels of glycated hemoglobin (HbA_{1c}) <7% (53 mmol/mol) and LDL cholesterol (LDL-C) <100 mg/dL (1). The level of HbA_{1c}, an indicator of average glycemia over several months, is a strong predictor of diabetes-related complications (1). Intensive treatments aimed at decreasing HbA_{1c} levels have been

associated with a reduced risk of microvascular complications (e.g., nephropathy and retinopathy) in patients with T2DM (1–4). The beneficial effects of decreasing HbA_{1c} levels on the rate of cardiovascular events is less evident, with recent data showing that cardiovascular benefits of tight glycemic control are predominantly observed in patients who are newly diagnosed with diabetes and have minimal comorbidities (5). Conversely,

treatments aimed at lowering LDL-C levels in patients with diabetes, especially in individuals with a high baseline cardiovascular risk, have been associated with significantly lower rates of cardiovascular events, including death (6–10). In addition, studies suggest that in diabetes, a condition estimated to incur direct annual costs (2007) of \$116 billion in the U.S. (11), treatments aimed at glycemic (12–15) and LDL-C control (16–18) are generally considered cost-effective.

Cardiovascular disease is the most frequent underlying cause of death in diabetic patients (19). Although the cardiovascular benefits of LDL-C control in patients with diabetes have been well established (1), the benefits of achieving the HbA_{1c} goal in addition to achieving the LDL-C goal are not clear. In diabetes, multifactorial interventions (i.e., targeting several risk factors simultaneously, including HbA_{1c}, LDL-C, blood pressure, and lifestyle) have been associated with significant reductions in microvascular and cardiovascular morbidity and mortality when compared with conventional treatments in several studies, including the Steno-2 Study (20,21), and appear to be cost-effective (22,23). However, existing research has not assessed the additional benefits associated with appropriate control of both HbA_{1c} and LDL-C levels versus the control of only one.

Since the cardiovascular benefits associated with HbA_{1c} goal achievement in addition to LDL-C goal achievement are not clear, the primary objective of our study was to assess the clinical and economic benefits associated with the achievement of both HbA_{1c} and LDL-C goals compared with achievement of only the LDL-C goal. Additional objectives included comparisons of clinical and economic outcomes in dual-goal achievers versus HbA_{1c}-only achievers, dual-goal achievers versus no-goal achievers, and each group of single-goal achievers versus no-goal achievers.

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RESEARCH DESIGN AND METHODS

Data source

This retrospective observational study was conducted using electronic medical records from the South Central Veterans Affairs Health Care Network (VISN 16), one of the largest of the 23 VISNs in the Veterans Health Administration (VHA). The VHA is a national integrated health care system providing a set of comprehensive services to veterans. As of 2010, ~23 million veterans were living in the U.S., a large majority (90.6%) of whom were male. About one-third of veterans were enrolled in the VHA.

The VISN 16 data warehouse is an integrated, de-identified, individual-level database representing ~7.8% of U.S. veterans and covers a geographic region of ~170,000 square miles, including the states of Arkansas, Louisiana, Mississippi, and Oklahoma, and parts of Alabama, Florida, Missouri, and Texas. It includes records for >445,000 veterans from 10 medical centers and 40 outpatient clinics, with information regarding demographics, vital signs, laboratory results, diagnoses, procedures, inpatient and outpatient services (e.g., admission date, length of stay, and emergency room visits), drug prescriptions, and database enrollment history. As in the national VHA population, patients in VISN 16 are predominantly male (90.1%). All data comply with the Health Insurance Portability and Accountability Act. The study protocol was approved by the institutional review board and research and development committee of the Southeast Louisiana Veterans Health Care Systems.

Sample selection

Adult patients (≥ 18 years of age) were included in the study if they had two or more diagnoses of T2DM between 1 January 2004 and 30 June 2010. Patients who had more than one diagnosis of T1DM were excluded. Patients had at least one measurement of HbA_{1c} and LDL-C within 30 days of each other (paired measurements) after the first diabetes diagnosis; the earlier date of the HbA_{1c} or LDL-C measurement was defined as the index date. All patients were further required to have at least one more measurement of HbA_{1c} and LDL-C within 1 year after the index date, irrespective of the gap between the measurements. The final sample included patients who were enrolled in the database for at least 12 months after the index date.

Data preparation

Longitudinal data were analyzed by 6-month cycles, starting from the index date. Average HbA_{1c} and LDL-C levels were estimated for each cycle using the area under the curve method (24,25). For each cycle, these estimated averages were used to stratify patients into one of four goal achievement categories: dual goal (average HbA_{1c} <7% [53 mmol/mol] and average LDL-C <100 mg/dL), HbA_{1c} only (average HbA_{1c} <7% [53 mmol/mol] and average LDL-C ≥ 100 mg/dL), LDL-C only (average LDL-C <100 mg/dL and average HbA_{1c} $\geq 7\%$ [53 mmol/mol]), or no goal (average HbA_{1c} $\geq 7\%$ [53 mmol/mol] and average LDL-C ≥ 100 mg/dL).

Patient characteristics

Patient characteristics as of the first cycle were summarized for the overall population, as well as stratified according to goal achievement status. Demographic information included age on index date, sex, race, BMI, and year of index date. The history of diabetes-related complications (microvascular, macrovascular, and other), comorbidities, and surgical procedures was identified as of the first cycle using ICD-9, Clinical Modification (ICD-9-CM) codes. Medication use during the first cycle was categorized by drug therapeutic class; health care resource utilization during the first cycle was categorized by hospitalization days and outpatient visits.

Characteristics were compared across the four groups according to goal achievement status using the ANOVA method for continuous variables and χ^2 tests for categorical variables.

Clinical outcomes

Clinical outcomes were selected a priori and comprised 1) a composite cardiovascular-related end point (cerebrovascular disease [stroke], acute myocardial infarction, or cardiovascular death [defined by a diagnosis of coronary artery disease or cerebrovascular disease on the day of death]), 2) a composite end point for microvascular complications (diabetic retinopathy, nephropathy, or neuropathy), 3) acute coronary syndromes (ACS; acute myocardial infarction or unstable angina), and 4) cardiovascular procedures (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]).

For each clinical outcome, goal achievement and patient characteristics were measured in a given cycle and outcomes were

assessed for the following cycle. The time to the first clinical event was evaluated using a Cox proportional hazards model, with goal achievement status as a time-dependent variable, controlling for patient demographics and other potential confounding factors such as cumulative comorbidity history, resource utilization, and medication use. All clinical outcomes were measured from the start of the second cycle until the first event, death, or end of data; for the analyses of specific clinical outcomes, patients were excluded from the analysis if any clinical event defining the particular outcome occurred before the end of the first cycle. Results are reported as adjusted hazard ratios with 95% CI.

Economic outcomes

The numbers of diabetes-related hospitalization days and outpatient visits were estimated for each 6-month cycle. Diabetes-related medical service costs were measured in each cycle using the average cost method (26). Costs were adjusted for inflation to 2011 U.S. dollars according to the medical care services component of the Consumer Price Index (27,28). Utilization and costs were considered diabetes related if they were associated with diagnoses of any of the following: diabetes, macrovascular complications, or microvascular complications.

The associations between goal achievement status in a given study cycle and utilization in the following cycle were assessed using generalized linear regression models (GLMs) with a Poisson distribution; results are reported as adjusted incidence rate ratios with 95% CIs. The associations between goal achievement status in a given cycle and costs in the following cycle were assessed using GLMs with a γ distribution, and adjusted results are reported as annualized incremental cost differences. All longitudinal GLMs accounted for within-patient correlation using a generalized estimating equation approach and controlled for demographics and time-dependent variables such as cumulative comorbidity history, resource utilization, and medication use. SAS software version 9.2 was used to conduct statistical analyses, and a two-tailed α level of 0.05 was used to determine statistical significance.

RESULTS

Patient characteristics

Of the 149,613 patients with at least two recorded diagnoses of T2DM between

1 January 2004 and 30 June 2010, a total of 75,646 patients met the selection criteria and were included in the analysis.

As shown in Table 1, as of the index date, most patients were older than 55 years (84.1%; mean age 64.7 years) and had an average BMI of 31.6 kg/m². Almost all patients were men (97.4%), and approximately two in three were white (67.4%). During the first cycle, 35.1% of patients achieved both goals (dual-goal achievers), whereas 21.6% achieved only the LDL-C goal (LDL-C achievers), 24.6% achieved only the HbA_{1c} goal (HbA_{1c} achievers), and 18.6% did not achieve either goal (no-goal achievers) (Table 1). Compared with all other groups, dual-goal achievers were older (67.1 vs. 61.4–64.4 years). Rates of microvascular complications were lower for dual-goal (24.1%) and HbA_{1c} achievers (22.4%) than for LDL-C (33.0%) and no-goal achievers (30.2%); similar differences were observed for the usage of insulin (10.4 and 7.5% vs. 34.6 and 30.1%, respectively) and oral antidiabetic drugs (67.4 and 64.0% vs. 82.2 and 82.7%, respectively). A higher rate of macrovascular complications was observed among dual-goal (47.4%) and LDL-C achievers (45.6%) than among HbA_{1c} (33.8%) and no-goal achievers (33.9%) (Table 1).

Clinical outcomes

The median duration of follow-up time was 4.5 years from the index date. After adjusting for demographics, diabetes-related complications, comorbidities, surgical procedures, diabetic medication use, and health care utilization, dual-goal achievement, when compared with achievement of LDL-C goal alone, was associated with a significantly reduced risk of microvascular complications (adjusted hazard ratio 0.79 [95% CI 0.76–0.82]), ACS (0.88 [0.81–0.96]), PCI (0.78 [0.67–0.90]), and CABG (0.74 [0.60–0.92]), but not of the composite cardiovascular-related end point (1.00 [0.94–1.06]) (Fig. 1). Compared with HbA_{1c} achievers, dual-goal achievement was associated with a lower risk of CABG (0.62 [0.49–0.79]) and the composite cardiovascular end point (0.87 [0.81–0.93]).

Compared with no-goal achievers, dual-goal achievers had a significant 19–30% lower hazard of the cardiovascular end point or diabetes-related microvascular or ACS-related events, and a 45–49% lower hazard of undergoing PCI or CABG. In addition, relative to no-goal achievers, both groups of single-goal achievers had

significant reductions in hazard for all categories of complications and surgical procedures, except microvascular complications among LDL-C achievers.

Resource utilization

After controlling for demographics, diabetes-related complications, comorbidities, surgical procedures, diabetic medication use, and health care utilization, dual-goal achievers generally used less health care resources compared with single- or no-goal achievers (Fig. 2). In particular, compared with LDL-C achievers, dual-goal achievers had significantly fewer hospitalization days (adjusted incidence rate ratio 0.93 [95% CI 0.87–1.00]) and outpatient visits (0.88 [0.87–0.89]). Compared with HbA_{1c} achievers, dual-goal achievers had significantly fewer outpatient visits (0.98 [0.97–1.00]), but there was no statistical difference in the number of hospitalization days (0.98 [0.89–1.07]). Compared with no-goal achievers, dual-goal achievers had significantly fewer hospitalization days (0.81 [0.72–0.90]) and outpatient visits (0.86 [0.85–0.87]). Similarly, both groups of single-goal achievers also had significantly fewer hospitalization days (LDL-C achievers, 0.87 [0.78–0.96]; HbA_{1c} achievers, 0.83 [0.73–0.94]) and outpatient visits (LDL-C achievers, 0.98 [0.96–0.99]; HbA_{1c} achievers, 0.87 [0.86–0.89]) than patients who did not achieve either goal.

Medical service costs

After adjusting for demographics, diabetes-related complications, comorbidities, surgical procedures, diabetic medication use, and health care utilization, dual-goal achievers incurred significantly lower annualized diabetes-related medical service costs compared with those who achieved only the LDL-C goal (–\$130.89; $P = 0.016$), but no statistically significant difference was observed between dual-goal achievers and HbA_{1c} goal achievers (–\$56.17; $P = 0.404$) (Fig. 3). Diabetes-related medical service costs were significantly lower for dual-goal (–\$376.50; $P < 0.001$), LDL-C (–\$245.61; $P < 0.001$), and HbA_{1c} achievers (–\$320.32; $P < 0.001$) compared with those who did not achieve either goal.

CONCLUSIONS—The study results showed that, compared with the achievement of only the LDL-C goal, achievement of both HbA_{1c} and LDL-C goals is associated with a lower risk of microvascular complications, ACS, and cardiovascular

surgeries (PCI or CABG), lower utilization of health care resources, and lower costs of care, but no additional effect was observed for the composite cardiovascular-related end point. In addition, dual-goal achievement relative to HbA_{1c} goal achievement is associated with a lower risk of the composite cardiovascular-related end point, CABG, and outpatient visits.

Clinical outcomes: dual- vs. single-goal achievement

To our knowledge, this is the first study that was designed to quantify the differences in clinical and economic outcomes between dual-goal and single-goal achievement in patients with T2DM. The results from our study are generally consistent with findings from previous studies designed to assess the benefits of treatment paradigms aimed at achieving more than one clinical goal in diabetes. In Steno-2, a Danish open-label, randomized, parallel-group study of patients with established T2DM, patients assigned to receive an intensive treatment targeting tighter goals for blood pressure (systolic <130–140 mmHg; diastolic <80–85 mmHg), HbA_{1c} (<6.5% [48 mmol/mol]), total cholesterol (<175–190 mg/dL), and triglycerides (<150 mg/dL) had a significantly lower risk of cardiovascular disease and microvascular complications over an average follow-up of 7.8 years, compared with patients assigned to antidiabetic treatment in accordance with national guidelines (21). A 5.5-year extension of that same study demonstrated that the multifactorial therapy was associated with sustained lower risk of cardiovascular events or death (20). In the Steno-2 Study, lipid-lowering treatments were suggested to have had the greatest contribution to cardiovascular risk reduction, whereas antihypertensive and antidiabetic treatments were considered to have accounted for the greatest reduction in microvascular complications (29). These results are in alignment with our findings that suggest that there are additional cardiovascular benefits associated with the achievement of both LDL-C and HbA_{1c} goals when compared with only HbA_{1c} goal achievement, while there are additional microvascular benefits associated with the achievement of both HbA_{1c} and LDL-C goals when compared with only LDL-C goal achievement.

In contrast to the Steno-2 Study (21), we did not assess the impact of multiple interventions or goal achievements other than HbA_{1c} and LDL-C. The blood pressure

Table 1—Patient baseline characteristics, demographics, comorbidities, complications, medications, and resource use

| Characteristics | Patient group* | | | | P value*, † | | | |
|--|----------------|---------------|---------------|-------------------|---------------|----------------------------|----------------|--------------------------------------|
| | All patients | Dual | LDL-C | HbA _{1c} | None vs. dual | HbA _{1c} vs. dual | LDL-C vs. dual | LDL-C vs. HbA _{1c} vs. none |
| Number of patients, n (%) | 75,646 | 26,587 (35.1) | 16,337 (21.6) | 18,643 (24.6) | 14,079 (18.6) | | | |
| Demographics | | | | | | | | |
| Age as of the index date, years, mean | 64.7 | 67.1 | 64.4 | 63.9 | 61.4 | <0.001 | <0.001 | <0.001 |
| Age-group, n (%) | | | | | | | | |
| 18–44 | 2,214 (2.9) | 384 (1.4) | 425 (2.6) | 672 (3.6) | 733 (5.2) | | | |
| 45–54 | 9,820 (13.0) | 2,300 (8.7) | 2,112 (12.9) | 2,732 (14.7) | 2,676 (19.0) | | | |
| 55–64 | 29,402 (38.9) | 9,288 (34.9) | 6,544 (40.1) | 7,466 (40.1) | 6,104 (43.4) | | | |
| 65–69 | 9,836 (13.0) | 3,787 (14.2) | 2,234 (13.7) | 2,238 (12.0) | 1,577 (11.2) | | | |
| 70–74 | 10,085 (13.3) | 4,298 (16.2) | 2,214 (13.6) | 2,244 (12.0) | 1,329 (9.4) | | | |
| 75–79 | 7,779 (10.3) | 3,537 (13.3) | 1,565 (9.6) | 1,763 (9.5) | 914 (6.5) | | | |
| 80+ | 6,510 (8.6) | 2,993 (11.3) | 1,243 (7.6) | 1,528 (8.2) | 746 (5.3) | | | |
| Male, n (%) | 73,695 (97.4) | 26,095 (98.2) | 16,072 (98.4) | 17,933 (96.2) | 13,595 (96.6) | 0.081 | <0.001 | <0.001 |
| White, n (%) | 51,015 (67.4) | 18,724 (70.4) | 11,159 (68.3) | 12,358 (66.3) | 8,774 (62.3) | <0.001 | <0.001 | <0.001 |
| BMI, kg/m ² , mean | 31.6 | 31.2 | 31.9 | 31.4 | 32.0 | <0.001 | <0.001 | 0.246 |
| Index year, n (%) | | | | | | <0.001 | <0.001 | <0.001 |
| 2004 | 13,157 (17.4) | 4,061 (15.3) | 3,245 (19.9) | 3,055 (16.4) | 2,796 (19.9) | | | |
| 2005 | 30,516 (40.3) | 10,323 (38.8) | 7,037 (43.1) | 7,126 (38.2) | 6,030 (42.8) | | | |
| 2006 | 11,830 (15.6) | 4,130 (15.5) | 2,205 (13.5) | 3,345 (17.9) | 2,150 (15.3) | | | |
| 2007 | 8,051 (10.6) | 3,188 (12.0) | 1,524 (9.3) | 2,095 (11.2) | 1,244 (8.8) | | | |
| 2008 | 8,065 (10.7) | 3,297 (12.4) | 1,497 (9.2) | 2,036 (10.9) | 1,235 (8.8) | | | |
| 2009 | 4,027 (5.3) | 1,588 (6.0) | 829 (5.1) | 986 (5.3) | 624 (4.4) | | | |
| Diabetes-related complications, n (%) | | | | | | | | |
| Microvascular complications | 20,233 (26.8) | 6,417 (24.1) | 5,389 (33.0) | 4,174 (22.4) | 4,253 (30.2) | <0.001 | <0.001 | <0.001 |
| Macrovascular complications | 31,120 (41.1) | 12,597 (47.4) | 7,452 (45.6) | 6,295 (33.8) | 4,776 (33.9) | <0.001 | <0.001 | 0.767 |
| Ocular problems§ | 25,176 (33.3) | 9,153 (34.4) | 5,515 (33.8) | 6,125 (32.9) | 4,383 (31.1) | 0.156 | <0.001 | <0.001 |
| Comorbidities, n (%) | | | | | | | | |
| Hypertension | 61,783 (81.7) | 22,287 (83.8) | 13,535 (82.9) | 14,852 (79.7) | 11,109 (78.9) | 0.008 | <0.001 | <0.001 |
| Hyperlipidemia | 54,096 (71.5) | 19,011 (71.5) | 11,338 (69.4) | 13,615 (73.0) | 10,132 (72.0) | <0.001 | <0.001 | 0.033 |
| Depression | 26,413 (34.9) | 8,742 (32.9) | 5,415 (33.2) | 7,116 (38.2) | 5,140 (36.5) | 0.571 | <0.001 | <0.001 |
| Surgical procedures, n (%) | | | | | | | | |
| Lower-extremity amputation | 295 (0.4) | 94 (0.4) | 81 (0.5) | 50 (0.3) | 70 (0.5) | 0.025 | 0.113 | 0.030 |
| CABG | 574 (0.8) | 242 (0.9) | 146 (0.9) | 107 (0.6) | 79 (0.6) | 0.860 | <0.001 | 0.001 |
| PCI | 1,061 (1.4) | 402 (1.5) | 303 (1.9) | 191 (1.0) | 165 (1.2) | 0.007 | <0.001 | 0.005 |
| Diabetic medications, n (%) | | | | | | | | |
| Oral antidiabetic | 54,916 (72.6) | 17,914 (67.4) | 13,427 (82.2) | 11,934 (64.0) | 11,641 (82.7) | <0.001 | <0.001 | 0.257 |
| Insulin | 14,057 (18.6) | 2,776 (10.4) | 5,651 (34.6) | 1,396 (7.5) | 4,234 (30.1) | <0.001 | <0.001 | <0.001 |
| Antihypertensive | 57,941 (76.6) | 20,409 (76.8) | 13,308 (81.5) | 13,405 (71.9) | 10,819 (76.8) | <0.001 | <0.001 | 0.852 |
| Lipid lowering | 56,164 (74.3) | 20,102 (75.6) | 12,792 (78.3) | 12,822 (68.8) | 10,448 (74.2) | <0.001 | <0.001 | <0.001 |

Continued on p. 3301

Table 1—Continued

| Characteristics | Patient group* | | | | P value*, † | | |
|-----------------------------|----------------|---------------|---------------|-------------------|----------------|----------------------------|--------------------------------------|
| | All patients | Dual | LDL-C | HbA _{1c} | LDL-C vs. dual | HbA _{1c} vs. dual | LDL-C vs. HbA _{1c} vs. none |
| Resource utilization, n (%) | 5,712 (7.6) | 2,058 (7.7) | 1,484 (9.1) | 1,143 (6.1) | <0.001 | 1,027 (7.3) | <0.001 |
| Inpatient visit | 1,788 (2.4) | 629 (2.4) | 392 (2.4) | 465 (2.5) | 0.824 | 302 (2.2) | 0.138 |
| Emergency room visit | 74,474 (98.5) | 26,192 (98.5) | 16,057 (98.3) | 18,354 (98.5) | 0.065 | 13,871 (98.5) | 0.102 |
| Outpatient visit | | | | | | | 0.594 |

Demographic information is from the index date; all other characteristics were measured in the first 6-month cycle. *Dual, patients achieving both LDL-C and HbA_{1c} goals; HbA_{1c}, patients achieving only the HbA_{1c} goal; LDL-C, patients achieving only the LDL-C goal; none, patients achieving neither goal (see text for details). †P values for categorical variables were obtained using χ^2 tests; P values for continuous variables were obtained using ANOVA tests. ‡Includes glaucoma, macular edema, retinal edema, vitreous hemorrhage, and blindness.

level cutoff recommended by major national and international guidelines for patients with diabetes (<130/80 mmHg) may be difficult to achieve, and the benefits of achieving this blood pressure goal are unclear (30). We decided to await final consensus on the optimal blood pressure goal for patients with diabetes before creating appropriate models to account for blood pressure goal achievements. Current lipid and glycemic goals, however, are relatively easy to achieve, as can be seen from our study, and their effects are therefore easier to take into consideration.

Clinical outcomes: single- vs. no-goal achievement

Our results are also consistent with findings from large randomized trials that evaluated situations analogous to the achievement of single metabolic goals. The 10-year UK Prospective Diabetes Study found that intensive glycemic control reduces the risk of microvascular complications but does not affect the risk of macrovascular disease (31). This lack of association between intensive glycemic control and macrovascular benefits has been observed in other large trials, such as Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled

Evaluation (ADVANCE) (4), Action to Control Cardiovascular Risk in Diabetes (ACCORD) (2,3), and Veterans Affairs Diabetes Trial (VADT) (32), except in the case of patients with newly diagnosed diabetes (5,33). Our study showed a 6% lower hazard of cardiovascular-related end point for HbA_{1c} achievers compared with no-goal achievers. Our findings are in agreement with the results from several large randomized trials that found that the treatments aimed at lowering LDL-C were associated with a reduced risk of cardiovascular events in patients with diabetes (6–10).

In our study, achievement of the HbA_{1c} goal alone and the LDL-C goal alone were each associated with a lower risk of cardiovascular surgeries, which is consistent with other research in patients with diabetes which has shown that patients who undergo CABG (34–36) and PCI (37,38) often have elevated HbA_{1c} levels, and that lowering LDL-C levels is also associated with lower risks of coronary events (6,7,39).

Economic outcomes

This is the first study to examine the differences between dual- and single-goal achievement in terms of health care resource

Hazard Ratio (95% CI)

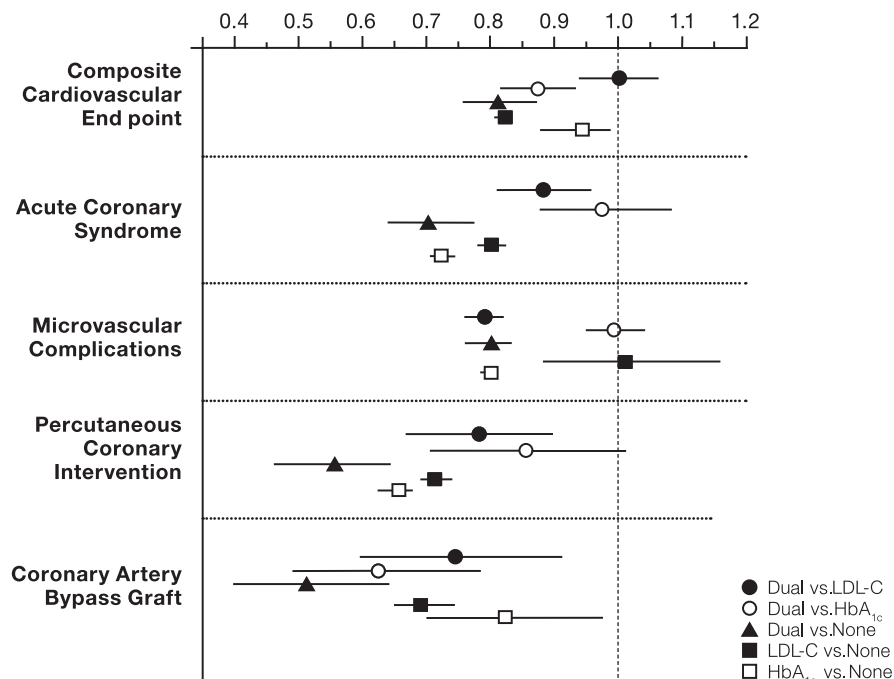


Figure 1—Goal achievement and clinical outcomes. Dual, patients achieving both LDL-C and HbA_{1c} goals; HbA_{1c}, patients achieving only the HbA_{1c} goal; LDL-C, patients achieving only the LDL-C goal; none, patients achieving neither goal (see text for details).

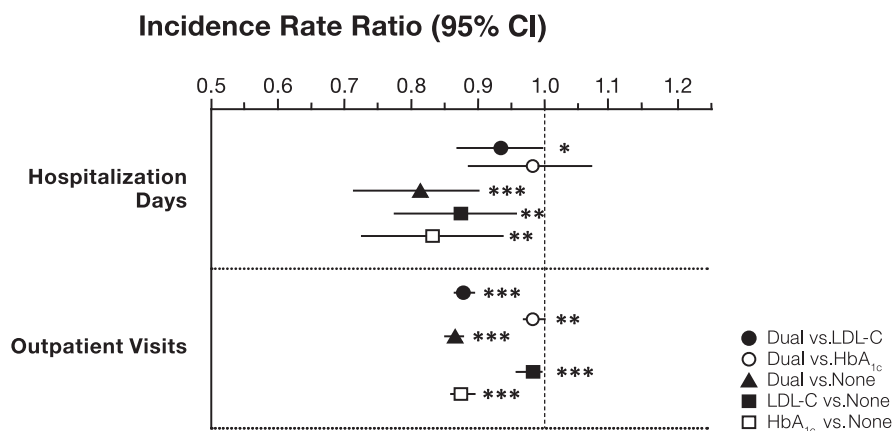


Figure 2—Goal achievement and health care utilization. Dual, patients achieving both LDL-C and HbA_{1c} goals; HbA_{1c}, patients achieving only the HbA_{1c} goal; LDL-C, patients achieving only the LDL-C goal; none, patients achieving neither goal. *P < 0.05; **P < 0.01; ***P < 0.001.

utilization and costs in patients with diabetes. Our results suggest that dual-goal achievement provides additional economic benefits, over LDL-C goal alone, but not over HbA_{1c} goal alone. Our results are consistent with previous studies that show that control of either LDL-C (40) or HbA_{1c} (15) is associated with cost savings. For example, a 2003 study designed to assess cost of statin therapy for the primary prevention of major coronary events

in U.S. patients with diabetes and LDL-C levels >100 mg/dL found that among individuals with LDL-C levels of 100–129 mg/dL and ≥130 mg/dL, the annual cost difference between patients with major coronary events with statin treatment versus without statin treatment was \$480–950 and \$590–1,920, respectively (16). A 2005 analysis conducted to predict costs and outcomes for patients with uncontrolled T1DM and T2DM, compared with

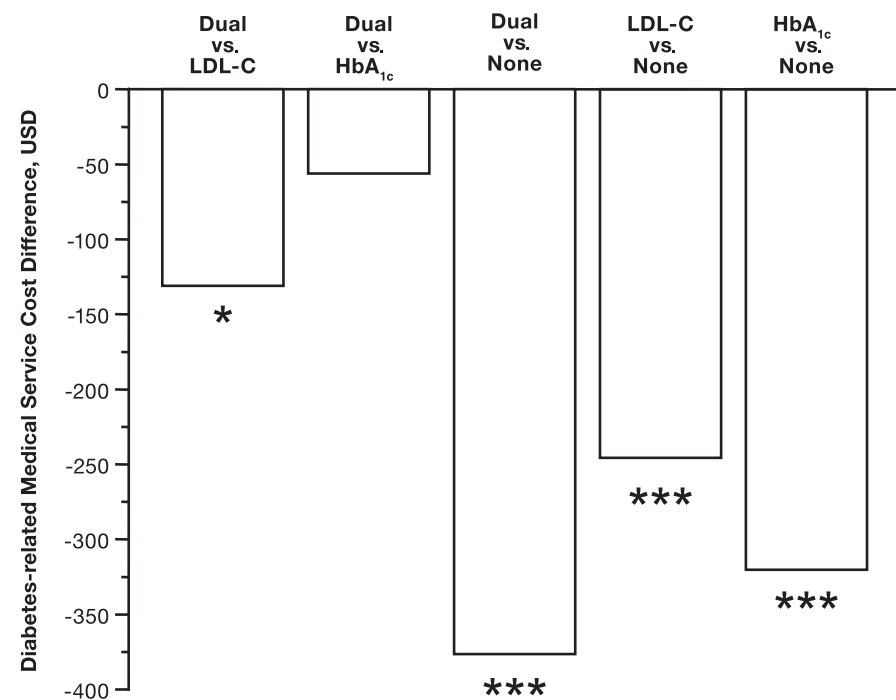


Figure 3—Goal achievement and diabetes-related medical service cost difference. Dual, patients achieving both LDL-C and HbA_{1c} goals; HbA_{1c}, patients achieving only the HbA_{1c} goal; LDL-C, patients achieving only the LDL-C goal; none, patients achieving neither goal. *P < 0.05; ***P < 0.001.

patients who remained at HbA_{1c} levels of 7% (53 mmol/mol) or 6.5% (48 mmol/mol), found that efficient targeting of financial resources toward achievement of HbA_{1c} goals in the U.S. would result in \$35–72 billion savings over the subsequent 10 years (15).

The design and methods of this study had several strengths. First, the data used for this study include laboratory measurements for patients over time. Second, this study used a longitudinal design that was able to capture the time-varying nature of laboratory measurements. This allowed for better estimation of the association between goal achievement and risk of complications over time, compared with a simple cross-sectional design, which would use baseline laboratory values in regression models. The limitations of the study include the usual caveats associated with retrospective studies. First, due to the retrospective observational design, the analysis may have been affected by unobserved factors that were not taken into account in the model. Second, the electronic medical records did not include information on disease severity, disease duration, lifestyle modifications, or other interventions. Third, although patients enrolled in the VHA do not typically use services outside of the system, any health care services that were administered by a provider outside of the VHA were not included in the electronic records. Fourth, because we used VHA data, the patients in our study were predominantly male. Although our sample was representative of the VHA population, gender imbalance may limit the generalization of our findings. As the VHA population may have characteristics that are distinct from those in the general population, similar studies in the general population should be performed. Finally, studies on the clinical and economic benefits associated with triple goal achievement of HbA_{1c}, LDL-C, and blood pressure goals may shed additional light on the appropriate management of patients with T2DM.

In conclusion, this retrospective study among U.S. veterans suggests that the achievement of both LDL-C and HbA_{1c} goals is associated with additional clinical and economic benefits, compared with the achievement of either goal alone. These findings may facilitate decision making when considering the health and pharmacoeconomic benefits of various treatment strategies to target multiple treatment goals for individuals with diabetes.

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L.S., M.L., E.Q.W., and H.S. conceived and designed the study, analyzed and interpreted data, and reviewed and edited the manuscript for important intellectual content. X.Y. conceived and designed the study and reviewed and edited the manuscript for important intellectual content. D.T. analyzed and interpreted data and reviewed and edited the manuscript for important intellectual content. V.A.F. conceived and designed the study, reviewed and edited the manuscript for important intellectual content, and supervised the study. L.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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References

- American Diabetes Association. Standards of medical care in diabetes—2012. *Diabetes Care* 2012;35(Suppl. 1):S11–S63
- Chew EY, Ambrosius WT, Davis MD, et al.; ACCORD Study Group; ACCORD Eye Study Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med* 2010;363:233–244
- Ismail-Beigi F, Craven T, Banerji MA, et al.; ACCORD trial group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 2010;376:419–430
- Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560–2572
- Skyler JS, Bergenstal R, Bonow RO, et al.; American Diabetes Association; American College of Cardiology Foundation; American Heart Association. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Diabetes Care* 2009;32:187–192
- Colhoun HM, Betteridge DJ, Durrington PN, et al.; CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685–696
- Collins R, Armitage J, Parish S, Sleight P, Peto R; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003;361:2005–2016
- Goldberg RB, Mellies MJ, Sacks FM, et al.; The Care Investigators. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the Cholesterol and Recurrent Events (CARE) trial. *Circulation* 1998;98:2513–2519
- Sever PS, Poulter NR, Dahlöf B, et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA). *Diabetes Care* 2005;28:1151–1157
- Shepherd J, Barter P, Carmena R, et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. *Diabetes Care* 2006;29:1220–1226
- Centers for Disease Control and Prevention. *National Diabetes Fact Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States*. Atlanta, GA, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011
- Diabetes Prevention Program Research Group. The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS. *Diabetes Care* 2012;35:723–730
- Gilmer TP, O'Connor PJ, Manning WG, Rush WA. The cost to health plans of poor glycemic control. *Diabetes Care* 1997;20:1847–1853
- Klarinbach S, Cameron C, Singh S, Ur E. Cost-effectiveness of second-line anti-hyperglycemic therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin. *CMAJ* 2011;183:E1213–E1220
- Minshall ME, Roze S, Palmer AJ, et al. Treating diabetes to accepted standards of care: a 10-year projection of the estimated economic and health impact in patients with type 1 and type 2 diabetes mellitus in the United States. *Clin Ther* 2005;27:940–950
- Brandle M, Davidson MB, Schriger DL, Lorber B, Herman WH. Cost effectiveness of statin therapy for the primary prevention of major coronary events in individuals with type 2 diabetes. *Diabetes Care* 2003;26:1796–1801
- Grover SA, Coupal L, Zowall H, Dorais M. Cost-effectiveness of treating hyperlipidemia in the presence of diabetes: who should be treated? *Circulation* 2000;102:722–727
- Sorensen SV, Frick KD, Wade A, Simko R, Burge R. Model-based simulation to explore the cost-effectiveness of following practice guidelines for triglyceride and low-density lipoprotein cholesterol control among patients with diabetes mellitus and mixed dyslipidemia. *Clin Ther* 2009;31:862–879
- Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia* 2001;44(Suppl. 2):S14–S21
- Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008;358:580–591
- Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;348:383–393
- Gozzoli V, Palmer AJ, Brandt A, Spinaz GA. Economic and clinical impact of alternative disease management strategies for secondary prevention in type 2 diabetes in the Swiss setting. *Swiss Med Wkly* 2001;131:303–310
- Gaede P, Valentine WJ, Palmer AJ, et al. Cost-effectiveness of intensified versus conventional multifactorial intervention in type 2 diabetes: results and projections from the Steno-2 study. *Diabetes Care* 2008;31:1510–1515
- Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA(1c): analysis of glucose profiles and HbA(1c) in the Diabetes Control and Complications Trial. *Diabetes Care* 2002;25:275–278
- Tai MM. A mathematical model for the determination of total area under glucose tolerance and other metabolic curves. *Diabetes Care* 1994;17:152–154
- Barnett PG. Determination of VA health care costs. *Med Care Res Rev* 2003;60(Suppl.):124S–141S

27. U.S. Bureau of Labor Statistics. Chapter 17: The Consumer Price Index. In *Bureau of Labor Statistics Handbook of Methods*. Washington, DC, U.S. Bureau of Labor Statistics, 2007
28. U.S. Bureau of Labor Statistics. *Consumer Price Index Annual Average Indexes*. Washington, DC, U.S. Bureau of Labor Statistics, 2011
29. Gaede P, Pedersen O. Intensive integrated therapy of type 2 diabetes: implications for long-term prognosis. *Diabetes* 2004; 53(Suppl. 3):S39–S47
30. Bangalore S, Kumar S, Lobach I, Messerli FH. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: observations from traditional and bayesian random-effects meta-analyses of randomized trials. *Circulation* 2011;123:2799–2810
31. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352: 837–853
32. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;360: 129–139
33. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. *BMJ* 2011;343:d4169
34. Engoren M, Habib RH, Zacharias A, et al. The prevalence of elevated hemoglobin A1c in patients undergoing coronary artery bypass surgery. *J Cardiothorac Surg* 2008;3:63
35. Kosuge K, Sasaki H, Ikarashi T, et al. Risk factors for severe coronary artery disease - a case-control study of patients who have undergone coronary artery bypass grafting. *J Atheroscler Thromb* 2006;13: 62–67
36. McGinn JT Jr, Shariff MA, Bhat TM, et al. Prevalence of dysglycemia among coronary artery bypass surgery patients with no previous diabetic history. *J Cardiothorac Surg* 2011;6:104
37. Corpus RA, George PB, House JA, et al. Optimal glycemic control is associated with a lower rate of target vessel revascularization in treated type II diabetic patients undergoing elective percutaneous coronary intervention. *J Am Coll Cardiol* 2004;43:8–14
38. Corpus RA, O'Neill WW, Dixon SR, Timmis GC, Devlin WH. Relation of hemoglobin A1c to rate of major adverse cardiac events in nondiabetic patients undergoing percutaneous coronary revascularization. *Am J Cardiol* 2003;92: 1282–1286
39. Pyörälä K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 1997; 20:614–620
40. Mihaylova B, Briggs A, Armitage J, Parish S, Gray A, Collins R; Heart Protection Study Collaborative. Lifetime cost effectiveness of simvastatin in a range of risk groups and age groups derived from a randomised trial of 20,536 people. *BMJ* 2006;333:1145