Clinical Outcomes and Medication Adherence in Acute Coronary Syndrome Patients With and Without Type 2 Diabetes Mellitus: A Longitudinal Analysis 2006-2011

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ABSTRACT

BACKGROUND: The presence of type 2 diabetes mellitus magnifies the risks associated with acute coronary syndrome (ACS), increasing the risk of recurrent cardiovascular events (CVEs) and doubling the risk of death. Managing cardiovascular risk factors has little effect on lowering the mortality risk in patients with type 2 diabetes.

OBJECTIVE: To evaluate the relationship between type 2 diabetes mellitus and subsequent CVEs and medication adherence following ACS hospitalization.

METHODS: Patients with ACS were identified using ICD-9-CM codes for acute myocardial infarction or unstable angina. The risk of subsequent CVEs was assessed at 1 and 3 years after the index ACS event based on type 2 diabetes status, adjusting for baseline demographic characteristics, comorbidities, medication use, and index ACS characteristics.

RESULTS: Of 140,903 patients with ACS (mean age 66.8 years, 58.6% male), 27.4% had type 2 diabetes. During follow-up, 22.0% had subsequent CVEs (26.2% type 2 diabetes, 19.0% nondiabetes). After adjusting for other covariates, type 2 diabetes was associated with increased risk of subsequent CVEs by 9.7% at 1 year and 10.2% at 3 years (both $P < 0.001$). Most patients were not revascularized at first recurrence after index ACS discharge (79.2% type 2 diabetes, 77.5% nondiabetes). Patients with type 2 diabetes had statistically significant higher adherence rates for antiplatelet agents at 1 year and antihypertensives at 1 and 3 years versus nondiabetes patients. Persistence was higher in the type 2 diabetes group for antihypertensives and in the nondiabetes group for antiplatelet agents and statins.

CONCLUSIONS: This analysis demonstrates that patients with type 2 diabetes have a higher risk of subsequent CVEs following an initial event versus those without diabetes, despite evidence of higher treatment persistence for certain medications. Adherence rates remained suboptimal, suggesting a continuing need for patient education.

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- After acute coronary syndrome (ACS), patients with type 2 diabetes remain at high risk for subsequent cardiovascular events (CVEs), despite intensive management with standard-of-care therapies.

What this study adds

- In this real-world analysis of patients who had been hospitalized with an ACS event, patients with type 2 diabetes had a higher rate of subsequent CVEs than those without diabetes.
- The majority of patients in the type 2 diabetes and nondiabetes cohorts did not undergo revascularization at the time of the initial ACS event.
- In general, adherence rates were not statistically different between patients with and without type 2 diabetes, but persistence was higher among patients with type 2 diabetes.
- Our findings show that there is opportunity to increase the use of, and adherence with, guideline-recommended treatment by encouraging and monitoring treatment of patients with type 2 diabetes following ACS.

Acute coronary syndrome (ACS) contributes to an estimated 1.3 million hospitalizations in the United States annually.^{1,2} ACS presents short- and long-term risks, with 20% of patients having a subsequent major cardiovascular event (CVE) within 3 years of the initial ACS diagnosis, even with successful treatment of that first event.³

The risks associated with ACS are magnified in the presence of type 2 diabetes mellitus.^{4,5} Patients with type 2 diabetes not only have more extensive cardiovascular disease (CVD), but they also have a higher prevalence of hypertension, heart failure, peripheral vascular disease, and neuropathy.⁶ Type 2 diabetes is an independent risk factor for all types of CVDs, as well as long-term mortality and need for revascularization.⁶ For patients with type 2 diabetes, the risk of death is approximately double that for those without diabetes; the risk of death specifically from CVD is tripled.⁷ Optimal management of cardiovascular risk factors does not appear to lower mortality risk in patients with type 2 diabetes.⁷

Patients surviving an ACS event are at increased risk of recurrent CVEs, and this risk is further increased in patients

What is already known about this subject

- Patients with type 2 diabetes have more extensive cardiovascular disease (CVD) and a higher prevalence of hypertension, heart failure, peripheral vascular disease, and neuropathy.
- Type 2 diabetes is an independent risk factor for all types of CVDs, as well as long-term mortality and need for revascularization.

with type 2 diabetes.⁸ Clinical studies indicate effective management of post-ACS patients with type 2 diabetes requires aggressive multidisciplinary efforts that include revascularization and intensive management of low-density lipoprotein cholesterol, blood pressure, and thrombotic risk.⁸ However, after an ACS event, patients with type 2 diabetes remain at high risk for subsequent CVEs despite intensive management with standard-of-care therapies,⁹ raising the question of whether patients are nonadherent with prescribed treatment regimens or the treatment regimens are less effective in these patients. Additional longitudinal, real-world data are needed to support the evidence base.

Currently, there is limited published literature regarding the relationship between type 2 diabetes and subsequent CVEs, quantifying long-term medication adherence and persistence following ACS. The increasing prevalence of type 2 diabetes drives the need for studies addressing the management of ACS in type 2 diabetes in routine clinical practice. To fill this knowledge gap, the relationship between type 2 diabetes and subsequent CVEs in patients following hospitalization for an ACS event was assessed using administrative claims data representing a real-world cohort. The objective was to evaluate the long-term impact of type 2 diabetes and associated medication management of ACS on outcomes in patients with ACS in a large, commercially insured U.S. population.

Methods

Study Design and Setting

This observational cohort study used administrative claims to evaluate longitudinal outcomes and adherence to guideline-recommended and nonguideline-recommended medications. The HealthCore Integrated Research Environment database was utilized, consisting of an integrated dataset containing medical, pharmacy, and eligibility claims of insured patients from 14 major commercial health plans across the United States.

This retrospective claims analysis was conducted in compliance with state and federal laws, including the Health Insurance Portability and Accountability Act of 1996. All claims data were from a limited dataset with de-identified patient information. No patients were directly involved in the study; therefore, review by an institutional review board was unnecessary.

Selection of Subjects

Patients were included in the analysis if they were at least aged 18 years, with at least 1 claim for acute myocardial infarction (MI; *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 410.xx) or unstable angina (UA; ICD-9-CM code 411.1x) during a hospitalization between January 1, 2006, and September 30, 2011 (identification period). The index date was defined as the date of the first hospitalization for ACS during the identification period.

All patients had at least 12 months of continuous health plan eligibility prior to the index date. Patients with a previous diagnosis of acute MI or UA/ACS within 1 year before the index date were excluded.

Patients were included in the type 2 diabetes cohort if they had 2 or more claims for type 2 diabetes at least 30 days apart, or if they had at least 1 claim for type 2 diabetes plus at least 1 claim for oral or injectable antidiabetic medications, or 2 or more claims for oral antidiabetic agents or glucagon-like peptide 1 medications. Patients with type 1 diabetes were excluded. Patients with no evidence of a diabetes diagnosis (type 1 or type 2) were included in the nondiabetes cohort.

Study Endpoints

Study endpoints included patient demographic characteristics, geographic region, health plan type, baseline comorbidities (cardiovascular and noncardiovascular), baseline medications, index event, and index procedure. Other endpoints included all-cause mortality, hospitalization for UA, resuscitated arrest, revascularization, and other CVEs (including heart failure, peripheral vascular disease, or hemorrhagic stroke). All endpoint measures were compared between the type 2 diabetes and nondiabetes cohorts. Post-index CVE (stroke, MI, or coronary heart disease [CHD]-related mortality) was evaluated by the number and type of events and time to event recurrence. CVE coding was identified as follows: nonfatal MI (ICD-9-CM codes 410.0x-410.8x), nonfatal stroke (ICD-9-CM codes 430.xx, 431, 432.0-432.9, 434.01, 434.11, 434.91), or CHD (ICD-9-CM codes 410.xx, 411.xx, 414.xx, 441.xx, ICD-9-CM Procedure codes 36.01-36.09, 36.1x, 36.2x, and Current Procedural Terminology codes 33510-33516, 33517-33545, 33572, 92975, 92980-92981, 92982-92984, 92995-92996). CHD-related mortality was defined as death within 7 days following the CHD event. Recurrence was reported by length of follow-up and stratified by diabetes status and whether patients received standard treatment at discharge (i.e., prescription for antiplatelet, anti-ischemic, antihypertensive, or antidiyslipidemic medications and other commonly used treatments, such as anticoagulants, plus medications for glycemic control for patients with diabetes).

To measure adherence to medication, postdischarge use of cardiovascular medications was evaluated longitudinally at 1 and 3 years. The medication possession rate (MPR) was calculated for patients who initiated therapy at any time between the index ACS event and 90 days following discharge from that admission. MPR was defined as the percentage of total number of days' supply of the ACS treatment prescription fill divided by the duration of the follow-up period (i.e., 365 and 1,095 days).

Adherence was measured by the MPR at 1 and 3 years and stratified by length of follow-up. The total length of therapy was described as the lengths of follow-up (i.e., patients with at least 1 year of follow-up, those with 2 years of follow-up, and those with 3 years of follow-up). Treatment

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TABLE 1 Baseline Patient Characteristics

	All Patients ^a	Patients With Type 2 Diabetes ^b			Patients Without Diabetes				
	Total (N = 140,903)	Total (n = 38,553)	With Recurrence ^c (n = 10,096)	Without Recurrence (n = 28,457)	Total (n = 81,845)	With Recurrence ^c (n = 15,574)	Without Recurrence (n = 66,271)		P Value ^d
Age, years, mean (SD)	66.8 (14.6)	68.2 (12.9)	72.2 (12.2)	66.8 (12.8)	65.6 (15.4)	72.5 (15.1)	64.0 (15.1)		<0.001
Gender, n (%)									
Male	82,517 (58.6)	22,689 (58.9)	5,642 (55.9)	17,047 (59.9)	48,026 (58.7)	8,595 (55.2)	39,431 (59.5)		0.571
Mortality, n (%)									
All-cause	12,798 (9.1)	4,238 (11.0)	1,289 (12.8)	2,949 (10.4)	6,502 (7.9)	1,575 (10.1)	4,927 (7.4)		
CHD-related	8,482 (6.0)	2,929 (7.6)	2,929 (29.0)	—	4,435 (5.4)	4,435 (28.5)	—		
Major baseline comorbidities, n (%)									
Hypertension	85,164 (60.4)	28,809 (74.7)	7,851 (77.8)	20,958 (73.7)	42,949 (52.5)	9,499 (61.0)	33,450 (50.5)		<0.001
Dyslipidemia	65,283 (46.3)	22,172 (57.5)	5,597 (55.4)	16,575 (58.3)	33,295 (40.7)	6,138 (39.4)	27,157 (41.0)		<0.001
Coronary artery disease	49,212 (34.9)	17,891 (46.4)	5,330 (52.8)	12,561 (44.1)	23,481 (28.7)	5,623 (36.1)	17,858 (27.0)		<0.001
Dyspnea	35,734 (25.4)	12,166 (31.6)	3,701 (36.7)	8,465 (29.8)	17,729 (21.7)	4,090 (26.3)	13,639 (20.6)		<0.001
Heart failure	22,428 (15.9)	9,361 (24.3)	3,426 (33.9)	5,935 (20.9)	9,387 (11.5)	2,926 (18.8)	6,461 (9.8)		<0.001
Anemia	22,485 (16.0)	8,793 (22.8)	2,988 (29.6)	5,805 (20.4)	10,012 (12.2)	2,825 (18.1)	7,187 (10.8)		<0.001
Renal disease	15,032 (10.7)	7,456 (19.3)	2,699 (26.7)	4,757 (16.7)	5,321 (6.5)	1,707 (11.0)	3,614 (5.5)		<0.001
Length of stay, index event, mean days (SD)	6.2 (11.8)	7.6 (13.7)	8.9 (14.4)	7.2 (13.4)	5.2 (9.3)	6.3 (9.3)	4.9 (9.3)		<0.001
Admitting diagnosis, n (%)									
Unstable angina	60,152 (42.7)	16,753 (43.5)	2,791 (27.6)	13,962 (49.1)	34,530 (42.2)	3,495 (22.4)	31,035 (46.8)		<0.001
STEMI	58,103 (41.2)	15,124 (39.2)	5,116 (50.7)	10,008 (35.2)	34,578 (42.3)	9,082 (58.3)	25,496 (38.5)		<0.001
NSTEMI	22,648 (16.1)	6,676 (17.3)	2,189 (21.7)	4,487 (15.8)	12,737 (15.6)	2,997 (19.2)	9,740 (14.7)		<0.001
Services during index hospitalization, n (%)									
PCI only	43,329 (30.8)	10,970 (28.5)	2,731 (27.1)	8,239 (29.0)	26,200 (32.0)	5,110 (32.8)	21,090 (31.8)		<0.001
CABG only	12,478 (8.9)	4,203 (10.9)	737 (7.3)	3,466 (12.2)	6,321 (7.7)	845 (5.4)	5,476 (8.3)		<0.001
PCI and CABG	1,003 (0.7)	274 (0.7)	63 (0.6)	211 (0.7)	570 (0.7)	128 (0.8)	442 (0.7)		<0.001

^aTotal includes 20,505 patients who were classified as "Other"; that is, they did not meet the strict inclusion criteria for patients with type 2 diabetes and did not meet the criterion of no claim for type 1 or type 2 diabetes. These patients were not included in the analyses.

^bPatients with type 2 diabetes were defined as having ≥ 2 claims of type 2 diabetes ≥ 30 days apart; ≥ 1 claim of type 2 diabetes and ≥ 1 claim for an antidiabetic medication; or ≥ 2 prescriptions of antidiabetic medications.

^cRecurrence is defined as occurrence of nonfatal myocardial infarction, nonfatal stroke, or CHD-related mortality after the index ACS event.

^dStatistical comparison between patients with type 2 diabetes and patients without type 2 diabetes.

ACS=acute coronary syndrome; CABG=coronary artery bypass graft; CHD=coronary heart disease; NSTEMI=non-ST segment elevation myocardial infarction; PCI=percutaneous coronary intervention; SD=standard deviation; STEMI=ST segment elevation myocardial infarction.

discontinuation was defined as a gap in treatment of 45 days or longer in each medication based on days of supply. Rates of adherence to medications were compared across medications and by the presence or absence of recurrent CVEs.

Medication classes included guideline-recommended cardiovascular treatments (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, antiplatelet agents, and statins) and other commonly used therapies such as antihypertensives, anticoagulants, antidiabetic medications (oral and parenteral). Treatment to clinical standard was defined as postdischarge fill within 30 days of an antiplatelet, anticoagulant, anti-ischemic (beta-blocker or calcium channel blocker), antihypertensive, or antidiabetic medication. For patients with type 2 diabetes, minimum treatment included medications targeted at glycemic control.

Persistence was measured as the length of treatment from the start of therapy to either the end of therapy (according to the minimum time recommended in the American College of Cardiology/American Heart Association [ACC/AHA] guidelines)¹⁰ or to a gap of 45 days, whichever occurred sooner. The total length of therapy was described as the lengths of follow-up (i.e., patients with at least 1 year and 3 years of follow-up). Treatment discontinuation was defined as a gap in treatment of 45 days or longer in each medication class based on days of supply. Rates of adherence and persistence with each medication were compared across medications and by the presence or absence of subsequent CVEs.

Statistical Analysis

Descriptive statistics included means (standard deviations) and relative frequencies for continuous and categorical data,

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TABLE 2 Cardiovascular Event Recurrence

	Patients With Type 2 Diabetes ^a			Patients Without Diabetes		
	Total	Treatment to Clinical Standard ^b	Treatment Not to Clinical Standard	Total	Treatment to Clinical Standard ^b	Treatment Not to Clinical Standard
Patients with recurrence during follow up, n (%)	10,096 (26.2)	4,660 (22.4)	5,436 (30.7)	15,574 (19.0)	8,893 (16.3)	6,681 (34.6)
Time to first recurrence, years, mean (SD)	0.8 (1.1)	1.0 (1.1)	0.7 (1.0)	0.7 (1.1)	0.9 (1.1)	0.5 (1.0)
First recurrent event type, n (%)						
Myocardial infarction	6,589 (65.3)	3,627 (77.8)	2,962 (54.5)	10,354 (66.5)	7,368 (82.9)	2,986 (44.7)
CHD-related mortality ^c	2,029 (20.1)	277 (5.9)	1,752 (32.2)	3,562 (22.9)	492 (5.5)	3,070 (46.0)
Nonfatal stroke	1,478 (14.6)	756 (16.2)	722 (13.2)	1,658 (10.7)	1,033 (11.6)	625 (9.4)
Intervention at first recurrence, n (%)						
No intervention	8,000 (79.2)	3,349 (71.9)	4,651 (85.6)	12,067 (77.5)	6,063 (68.2)	6,004 (89.9)
Coronary stent	1,972 (19.5)	1,272 (27.3)	700 (12.9)	3,601 (23.1)	2,963 (33.3)	638 (9.5)
Catheter	1,639 (16.2)	1,016 (21.8)	623 (11.5)	2,781 (17.9)	2,239 (25.2)	542 (8.1)
Primary angioplasty without stent	888 (8.8)	602 (12.9)	286 (5.3)	1,689 (10.8)	1,447 (16.3)	242 (3.6)
CABG	380 (3.8)	238 (5.1)	142 (2.6)	507 (3.3)	411 (4.6)	96 (1.4)
Patients with at least 12 months of eligibility, n	22,588	13,640	8,948	48,358	34,871	13,487
Patients with subsequent event during follow-up, n (%)	6,106 (27.0)	3,462 (25.4)	2,644 (29.6)	9,069 (18.8)	6,520 (18.7)	2,549 (18.9)
Cardiovascular rehospitalizations, n, mean (SD)						
Within 30 days	0.3 (0.6)	0.3 (0.6)	0.3 (0.6)	0.3 (0.6)	0.3 (0.6)	0.3 (0.6)
Within 182 days	1 (1.2)	1.0 (1.2)	1.0 (1.3)	0.8 (1.0)	0.8 (1.0)	0.8 (1.1)
Within 365 days	1.7 (1.8)	1.6 (1.7)	1.8 (1.9)	1.3 (1.3)	1.2 (1.3)	1.3 (1.4)
Time to first recurrence, years, mean (SD)	1.2 (1.2)	1.2 (1.2)	1.2 (1.2)	1.2 (1.2)	1.1 (1.2)	1.3 (1.2)
Patients with at least 36 months of eligibility, n	9,160	5,683	3,477	19,753	14,316	5,437
Patients with subsequent event during follow-up, n (%)	2,706 (29.5)	1,615 (28.4)	1,091 (31.4)	4,264 (21.6)	3,106 (21.7)	1,158 (21.3)
Cardiovascular rehospitalizations, n, mean (SD)						
Within 1 year	1.3 (1.6)	1.3 (1.5)	1.3 (1.7)	1.0 (1.1)	1.0 (1.1)	1.0 (1.1)
Within 2 years	2.3 (2.4)	2.2 (2.3)	2.4 (2.5)	1.6 (1.6)	1.6 (1.6)	1.7 (1.7)
Within 3 years	3.4 (3.7)	3.3 (3.5)	3.6 (4.0)	2.4 (2.3)	2.3 (2.3)	2.7 (2.4)
Time to first recurrence, years, mean (SD)	1.8 (1.4)	1.7 (1.4)	1.8 (1.4)	1.6 (1.4)	1.6 (1.4)	1.8 (1.4)

^aPatients with type 2 diabetes were defined as having ≥ 2 claims of type 2 diabetes ≥ 30 days apart; ≥ 1 claim of type 2 diabetes and ≥ 1 claim for an antidiabetic medication; or ≥ 2 prescriptions of antidiabetic medications.

^bTreatment to clinical standard is defined as postdischarge prescription fill within 30 days of an antiplatelet, anticoagulant, anti-ischemic (beta blocker or calcium channel blocker), antihypertensive, or antidyslipidemia medication. For patients with diabetes, minimum treatment also includes medications required for glycemic control.

^cCHD-related mortality is defined as presence of a diagnosis code for coronary heart disease 7 days prior to date of death.

CABG=coronary artery bypass graft; CHD=coronary heart disease; SD=standard deviation.

respectively. Descriptive analysis was performed for all variables in the study. Univariate statistics were calculated, and bivariate analyses were used to explore the relationships between ACS and medication use and clinically significant covariates.¹¹⁻¹³ Subgroup comparisons were performed using t-tests for continuous data and χ^2 tests for categorical data. The association between preventive medications and subsequent CVEs were assessed using χ^2 tests and multiple comparisons ANOVA adjusted for relevant cofactors. A Cox proportional hazards regression model was used to predict the time to recurrence.

Results

Baseline Patient Characteristics

A total of 140,903 ACS patients were included in the study (Table 1). Of these, 38,553 (27.4%) had type 2 diabetes. The mean age of the total population was 66.8 years (68.2 years

type 2 diabetes cohort, 65.6 years nondiabetes cohort). The mean length of follow-up was 1.9 years overall (1.8 years in the type 2 diabetes and nondiabetes cohorts).

At baseline, the most common comorbidities in the overall population were hypertension (60.4%), dyslipidemia (46.3%), coronary artery disease (34.9%), dyspnea (25.4%), and heart failure (15.9%). These baseline comorbidities were statistically significantly higher among patients in the type 2 diabetes group compared with the nondiabetes group (hypertension 74.7% vs. 52.5%; dyslipidemia 57.5% vs. 40.7%; coronary artery disease 46.4% vs. 28.7%; and heart failure 24.3% vs. 11.5%, respectively; $P < 0.001$ for all comparisons; Table 1).

Index ACS Characteristics

During the index hospitalization for ACS, 42.7% of patients overall had UA, and 40.4% had coronary artery bypass graft

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TABLE 3 Medication Adherence at 1 and 3 Years of Follow-up

	All Patients	Patients With Type 2 Diabetes ^a				Patients Without Diabetes			P Value ⁱ
	Total ^b n (%)	Total ^c n (%)	With Recurrence ^d n (%)	Without Recurrence ^e n (%)	Total ^f n (%)	With Recurrence ^g n (%)	Without Recurrence ^h n (%)		
Antihypertensives									
1 year	56,575 (66.5)	16,059 (71.1)	4,200 (68.8)	11,859 (72.0)	31,260 (64.6)	6,055 (66.8)	25,205 (64.2)		<0.001
3 years	23,808 (67.0)	6,614 (72.2)	1,882 (69.6)	4,732 (73.3)	12,807 (64.8)	2,857 (67.0)	9,950 (64.2)		<0.001
ACE/ARB									
1 year	26,479 (31.1)	7,874 (34.9)	2,050 (33.6)	5,824 (35.4)	14,442 (29.9)	3,181 (35.1)	11,261 (28.7)		<0.001
3 years	11,229 (13.2)	3,305 (36.1)	935 (34.6)	2,370 (36.7)	5,940 (30.1)	1,498 (35.1)	4,442 (28.7)		<0.001
Beta-blocker									
1 year	45,779 (53.8)	12,746 (56.4)	3,442 (56.4)	9,304 (56.5)	25,589 (52.9)	5,142 (56.7)	20,447 (52.0)		<0.001
3 years	19,339 (54.4)	5,217 (57.0)	1,550 (57.3)	3,667 (56.8)	10,564 (53.5)	2,455 (57.6)	8,109 (52.3)		<0.001
Statins									
1 year	42,787 (50.3)	11,735 (52.0)	2,931 (48.0)	8,804 (53.4)	24,289 (50.2)	4,620 (50.9)	19,669 (50.1)		0.039
3 years	17,705 (49.8)	4,712 (51.4)	1,300 (48.0)	3,412 (52.9)	9,863 (49.9)	2,162 (50.7)	7,701 (49.7)		0.876
Antiplatelets									
1 year	33,973 (39.9)	9,263 (41.0)	2,634 (43.1)	6,629 (40.2)	19,332 (40.0)	4,242 (46.8)	15,090 (38.4)		<0.001
3 years	14,572 (41.0)	3,891 (42.5)	1,227 (45.3)	2,664 (41.3)	8,039 (40.7)	2,054 (48.2)	5,985 (38.6)		0.298
Oral antidiabetics									
1 year	11,959 (14.1)	11,452 (50.7)	2,640 (43.2)	8,812 (53.5)	—	—	—		<0.001
3 years	5,097 (14.3)	4,873 (53.2)	1,273 (47.0)	3,600 (55.8)	—	—	—		<0.001
Other antidyslipidemics^j									
1 year	11,379 (13.4)	4,011 (17.8)	973 (15.9)	3,038 (18.4)	5,428 (11.2)	987 (10.9)	4,441 (11.3)		0.186
3 years	5,325 (15.0)	1,803 (19.7)	490 (18.1)	1,313 (20.3)	2,536 (12.8)	548 (12.9)	1,988 (12.8)		0.122
Other antihypertensives									
1 year	26,368 (31.0)	9,380 (41.5)	2,754 (45.1)	6,626 (40.2)	12,413 (25.7)	2,691 (29.7)	9,722 (24.7)		<0.001
3 years	11,007 (31.0)	3,826 (41.8)	1,230 (45.6)	2,596 (40.2)	5,061 (25.6)	1,220 (28.6)	3,841 (24.8)		<0.001
Anticoagulants									
1 year	7,453 (8.8)	2,259 (10.0)	695 (11.4)	1,564 (9.5)	3,704 (7.7)	957 (10.6)	2,747 (7.0)		0.010
3 years	3,089 (8.7)	888 (9.7)	286 (10.6)	602 (9.3)	1,507 (7.6)	389 (9.1)	1,118 (7.2)		0.170
Insulin									
1 year	5,297 (6.2)	5,111 (22.6)	1,567 (25.7)	3,544 (21.5)	—	—	—		<0.001
3 years	2,008 (5.7)	1,929 (21.1)	665 (24.6)	1,264 (19.6)	—	—	—		<0.001

^aPatients with type 2 diabetes were defined as having ≥ 2 claims of type 2 diabetes ≥ 30 days apart; ≥ 1 claim of type 2 diabetes and ≥ 1 claim for an antidiabetic medication; or ≥ 2 prescriptions of antidiabetic medications.

^b1 year: n=85,097; 3 years: n=35,540.

^c1 year: n=22,588; 3 years: n=9,160.

^d1 year: n=6,106; 3 years: n=2,706. Recurrence is defined as occurrence of nonfatal myocardial infarction, nonfatal stroke, or CHD-related mortality after the index ACS event.

^e1 year: n=16,482; 3 years: n=6,454.

^f1 year: n=48,358; 3 years: n=19,753.

^g1 year: n=9,069; 3 years: n=4,264. Recurrence is defined as occurrence of nonfatal myocardial infarction, nonfatal stroke, or CHD-related mortality after the index ACS event.

^h1 year: n=39,289; 3 years: n=15,489.

ⁱStatistical comparison between patients with type 2 diabetes and patients without type 2 diabetes.

^jOther antidyslipidemics included fibrates, niacin (nicotinic acid derivatives), bile acid sequestrants, cholesterol absorption inhibitors, fish oil (Lovaza), and statin combinations (any fixed-dose statin combination).

ACE/ARB=angiotensin-converting enzyme/angiotensin II receptor blocker; ACS=acute coronary syndrome; CHD=coronary heart disease.

(CABG) and/or percutaneous coronary intervention (PCI). A larger proportion of patients in the type 2 diabetes group had UA compared with the nondiabetes group (43.5% vs. 42.2%, $P<0.001$). A slightly smaller but statistically significant proportion of patients in the type 2 diabetes group had CABG and/or PCI compared with the nondiabetes group (40.1% vs. 40.4%, $P<0.001$) at the index hospitalization (Table 1).

Subsequent Cardiovascular Events

During the follow-up period, 10,096 patients (26.2%) in the type 2 diabetes group had a subsequent CVE, compared with 15,574 patients (19.0%) in the nondiabetes group (Table 2). The mean time to first CVE was 0.8 years for the type 2 diabetes group and 0.7 years for the nondiabetes group. In both cohorts, MI was the first subsequent CVE for the majority of

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TABLE 4 Treatment Persistence Days at 1 and 3 Years of Follow-up^a

	All Patients	Patients With Type 2 Diabetes ^b			Patients Without Diabetes			P Value ^d
	Total Mean (SD, Median)	Total Mean (SD, Median)	With Recurrence; ^c Mean (SD, Median)	Without Recurrence, Mean (SD, Median)	Total Mean (SD, Median)	With Recurrence, ^c Mean (SD, Median)	Without Recurrence, Mean (SD, Median)	
Antihypertensives								
1 year	0.76 (0.76, 0.76)	0.77 (0.77, 0.77)	0.77 (0.77, 0.77)	0.77 (0.77, 0.77)	0.75 (0.75, 0.75)	0.77 (0.77, 0.77)	0.75 (0.75, 0.75)	<0.001
3 years	1.84 (1.13, 2.15)	1.91 (1.11, 2.40)	1.94 (1.11, 2.47)	1.90 (1.12, 2.34)	1.79 (1.14, 1.98)	1.84 (1.13, 2.13)	1.77 (1.15, 1.94)	<0.001
Antiplatelets								
1 year	0.73 (0.35, 0.94)	0.70 (0.35, 0.91)	0.66 (0.35, 0.84)	0.71 (0.35, 0.93)	0.74 (0.35, 0.96)	0.73 (0.35, 0.95)	0.74 (0.35, 0.97)	<0.001
3 years	1.52 (1.12, 1.27)	1.45 (1.12, 1.17)	1.37 (1.10, 1.02)	1.49 (1.12, 1.24)	1.56 (1.12, 1.33)	1.53 (1.12, 1.31)	1.56 (1.12, 1.33)	0.002
Oral antidiabetics								
1 year	0.70 (0.33, 0.88)	0.71 (0.33, 0.89)	0.66 (0.34, 0.85)	0.72 (0.32, 0.90)	0.28 (0.28, 0.16)	0.32 (0.36, 0.14)	0.27 (0.26, 0.16)	<0.001
3 years	1.63 (1.13, 1.56)	1.66 (1.13, 1.61)	1.55 (1.13, 1.45)	1.69 (1.12, 1.69)	0.27 (0.36, 0.08)	0.11 (0.04, 0.11)	0.29 (0.38, 0.08)	0.001
Statins								
1 year	0.68 (0.34, 0.86)	0.66 (0.34, 0.83)	0.63 (0.34, 0.78)	0.68 (0.33, 0.84)	0.69 (0.34, 0.88)	0.68 (0.34, 0.86)	0.69 (0.34, 0.88)	<0.001
3 years	1.43 (1.13, 1.11)	1.38 (1.11, 1.04)	1.29 (1.09, 0.93)	1.41 (1.11, 1.09)	1.45 (1.13, 1.15)	1.42 (1.13, 1.07)	1.46 (1.14, 1.17)	0.004
Other antidyslipidemics								
1 year	0.64 (0.34, 0.80)	0.65 (0.34, 0.81)	0.61 (0.35, 0.77)	0.66 (0.34, 0.82)	0.64 (0.34, 0.80)	0.63 (0.34, 0.79)	0.64 (0.34, 0.80)	0.957
3 years	1.34 (1.10, 1.00)	1.35 (1.11, 1.01)	1.27 (1.11, 0.81)	1.39 (1.11, 1.07)	1.32 (1.10, 0.99)	1.31 (1.10, 0.94)	1.32 (1.10, 1.00)	0.226
Anticoagulants								
1 year	0.52 (0.35, 0.50)	0.53 (0.35, 0.50)	0.53 (0.35, 0.52)	0.52 (0.35, 0.49)	0.51 (0.35, 0.48)	0.51 (0.35, 0.50)	0.51 (0.36, 0.47)	0.024
3 years	0.96 (0.99, 0.51)	1.00 (1.00, 0.58)	1.02 (1.00, 0.58)	0.99 (1.01, 0.56)	0.94 (0.99, 0.49)	0.92 (0.99, 0.41)	0.95 (0.99, 0.50)	0.737
Insulin								
1 year	0.53 (0.37, 0.50)	0.53 (0.37, 0.53)	0.51 (0.37, 0.47)	0.54 (0.37, 0.56)	0.13 (0.18, 0.08)	0.19 (0.36, 0.08)	0.11 (0.12, 0.08)	<0.001
3 years	1.10 (1.13, 0.54)	1.12 (1.13, 0.56)	1.10 (1.12, 0.56)	1.12 (1.13, 0.56)	0.08 (0.03, 0.08)	0.08 (0.01, 0.08)	0.08 (0.04, 0.08)	0.132

^aPersistence days are defined as length of therapy from the start of therapy to either the end of therapy or a 45-day gap in treatment, whichever occurs first.

^bPatients with type 2 diabetes were defined as having ≥ 2 claims of type 2 diabetes ≥ 30 days apart; ≥ 1 claim of type 2 diabetes and ≥ 1 claim for an antidiabetic medication; or ≥ 2 prescriptions of antidiabetic medications.

^cRecurrence is defined as occurrence of nonfatal myocardial infarction, nonfatal stroke, or CHD-related mortality after the index ACS event.

^dStatistical comparison between patients with type 2 diabetes and patients without type 2 diabetes.

ACS=acute coronary syndrome; CHD=coronary heart disease; SD=standard deviation.

patients (65.3% type 2 diabetes group vs. 66.5% nondiabetes group). The majority of patients in both cohorts received no revascularization at the first recurrence following index ACS discharge (79.2% type 2 diabetes group vs. 77.5% nondiabetes group). Among those who underwent revascularization at first recurrence following index ACS discharge, coronary stenting was the most common procedure (19.5% in the type 2 diabetes group vs. 23.1 in the nondiabetes group).

Cardiovascular Event Recurrence

Patients with diabetes who received treatment to clinical standard had a lower rate of CVE recurrence compared with patients who did not receive treatment to clinical standard (Table 2). This was consistent for patients in the nondiabetes cohort overall and for 1 year of follow-up. Mean time to recurrence did not differ between the type 2 diabetes and nondiabetes cohorts or between patients who received treatment to clinical standard and those who did not receive treatment to clinical standard.

Adherence and Persistence

Adherence rates, as measured by MPR, were not statistically different between patients with and without type 2 diabetes for anticoagulants, statins, or other antidiyslipidemics at 1 or 3 years of follow-up or for antiplatelet agents at 3 years of follow-up. However, patients with type 2 diabetes had statistically higher adherence rates for antiplatelet agents at 1 year of follow-up and for antihypertensives at 1 and 3 years of follow-up, compared with patients without diabetes (Table 3).

Patients with type 2 diabetes were more persistent with antihypertensive therapy, as measured by duration of therapy, compared with patients without diabetes (Table 4). At 1 and 3 years of follow-up, for antihypertensive medications, patients with type 2 diabetes had significantly more days of persistence than those without diabetes. However, patients without diabetes had greater persistence for antiplatelet agents and statins at 1 and 3 years of follow-up. Persistence rates for antidiyslipidemics and anticoagulants were not significantly different between the 2 groups at 3 years of follow-up, although persistence with anticoagulants was significantly different at 1 year of follow-up.

Discussion

In this real-world analysis of patients who had been hospitalized with an ACS event, patients with type 2 diabetes had a higher rate of subsequent CVEs than those without diabetes. These findings are consistent with previous research in smaller cohorts and are plausible given the increased prevalence of other cardiovascular risk factors in patients with type 2 diabetes.¹⁴⁻¹⁶

The majority of patients in the type 2 diabetes and non-diabetes cohorts did not undergo revascularization (PCI or CABG) at the time of the initial ACS event. Intensive secondary preventive measures are recommended for patients with type 2 diabetes, so our results may suggest underutilization of revascularization for these patients.¹⁷ However, it is worth noting that a sizeable proportion of the study population (42.7%) had UA, for whom medication and noninvasive testing are recommended before catheterization or revascularization procedures unless the patients are at high risk for clinical events.¹⁸ Following ACS hospitalization, the patients who received standard clinical therapy according to ACC/AHA¹⁰ and American Diabetes Association guidelines¹⁹ (for patients with type 2 diabetes) had lower rates of CVE recurrence and a longer time to recurrence compared with those who did not receive treatment, which is consistent with previous studies.^{16,20}

In general, adherence rates were not statistically different between patients with and without type 2 diabetes, but persistence was higher among patients with type 2 diabetes. Our results indicate that adherence and persistence rates show room for improvement. The lack of a difference in adherence rates between the type 2 diabetes and nondiabetes cohorts differs from previous studies that reported type 2 diabetes was associated with lower adherence rates in patients with ACS.^{21,22} A possible explanation for the difference in adherence rates between the current and prior studies is that in the current study, patients were stratified based on their type 2 diabetes status. In contrast, earlier studies stratified patients according to ACS treatment and assessed the effect of type 2 diabetes as a subanalysis.^{21,22} Furthermore, the current study is unique in that a large patient population was followed for an extended period, unlike prior studies, which used smaller populations with follow-up periods of 12 months or less.^{21,22} Interestingly, insulin adherence was higher among patients in the type 2 diabetes cohort who had recurrent ACS events compared with those without recurrence. Insulin use may be a marker of a longer duration of disease—that is, patients taking insulin typically have more advanced or severe disease than those who are not receiving insulin therapy who are able to manage their condition with oral agents alone.

Although guidelines such as those for the management of ACS are based on clinical trial data, the applicability of guidelines may be reduced substantially by factors not present in a clinical trial situation, for example, nonadherence. In contrast, the findings of the current study are based on real-world

experience and reflect how precisely patients follow treatment regimens outside of a tightly controlled research environment. Treatment adherence is an important consideration when evaluating outcomes. For example, patients with type 2 diabetes remain at increased risk for subsequent CVEs following ACS even when they receive intensive standard-of-care treatment.⁹ The question is whether the increased risk is due to an inadequate standard of care or to poor treatment adherence. Treatment recommendations could be strengthened by focusing not only on what medications to prescribe but also on how to address noncompliance and improve adherence.

Limitations

The limitations of this study must be considered in interpreting its results. The data for the study were obtained from medical and pharmacy claims, which lack information pertaining to severity of type 2 diabetes and the degree to which type 2 diabetes was successfully managed. Furthermore, although the presence or absence of some other cardiovascular risk factors can be determined from claims analysis, it is not possible to measure the degree of risk or the success of management of these conditions (e.g., hypertension and hypercholesterolemia). Some other important cardiovascular risk factors, such as tobacco use, cannot be adequately addressed from claims analysis. Information on patients' weight and body mass index are also absent from claims. Patients with type 2 diabetes were defined as those who had 2 or more claims of type 2 diabetes at least 30 days apart; 1 or more claims of type 2 diabetes plus 1 or more claims for an antidiabetic medication; or 2 or more prescriptions for antidiabetic medications. This definition did not capture patients who had ICD-9-CM codes for type 1 diabetes or those with ICD-9-CM codes for type 2 diabetes but who did not satisfy other aspects of the definition of type 2 diabetes used for this study. Thus, some patients with type 2 diabetes may have inadvertently been placed into the nondiabetes cohort. Additionally, administrative claims may have contained undetected coding errors or omissions. All patients included in this study were members of large commercial health plans in the United States, and as such, findings may not be generalizable to patients with other types of insurance or to those living outside of the United States. The data regarding medication adherence and persistence may be inaccurate for patients who were treated with sample medications or through other programs that do not generate pharmacy claims. Furthermore, adherence and persistence with nonprescription medications (most notably aspirin) could not be addressed. Lastly, medications may have been prescribed for different durations for patients with and without diabetes. Differences in persistence and adherence rates may be a reflection of these different dosing regimens rather than an indication of adherence.

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Conclusions

This study provides contemporary, long-term data on the impact of type 2 diabetes on cardiovascular risk in a large population. Although patients with type 2 diabetes had a higher risk of subsequent CVEs following an initial ACS event compared with patients without diabetes, the rate of CVE recurrence was lower for patients who received standard-of-care treatment. Despite observed treatment persistence among patients with diabetes, medication adherence rates remained suboptimal in this group, indicating a continuing need for patient education. Focusing attention on guideline and medication adherence, particularly for patients at high risk, may be as important a strategy for reducing the burden of care as advancing the science that informs the practice guidelines.

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Study concept and design were contributed by Cziraky, Xu, and Fisher, along with the other authors. Data were collected primarily by Luthra and Fisher, assisted by the other authors, and analysed by Cziraky, Wilhelm, Power, and Reddy, with assistance from Xu, Fisher, and Luthra. The manuscript was written by Cziraky, Reddy, Luthra, Power, and Fisher, with assistance from Xu and Wilhelm, and revised by Power, Cziraky, Xu, Wilhelm, and Fisher, assisted by Reddy and Luthra.

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