Original Investigation

Association Between Intensification of Metformin Treatment With Insulin vs Sulfonylureas and Cardiovascular Events and All-Cause Mortality Among Patients With Diabetes

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IMPORTANCE Preferred second-line medication for diabetes treatment after metformin failure remains uncertain.

OBJECTIVE To compare time to acute myocardial infarction (AMI), stroke, or death in a cohort of metformin initiators who added insulin or a sulfonylurea.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort constructed with national Veterans Health Administration, Medicare, and National Death Index databases. The study population comprised veterans initially treated with metformin from 2001 through 2008 who subsequently added either insulin or sulfonylurea. Propensity score matching on characteristics was performed, matching each participant who added insulin to 5 who added a sulfonylurea. Patients were followed through September 2011 for primary analyses or September 2009 for cause-of-death analyses.

MAIN OUTCOMES AND MEASURES Risk of a composite outcome of AMI, stroke hospitalization, or all-cause death was compared between therapies with marginal structural Cox proportional hazard models adjusting for baseline and time-varying demographics, medications, cholesterol level, hemoglobin A_{1c} level, creatinine level, blood pressure, body mass index, and comorbidities.

RESULTS Among 178 341 metformin monotherapy patients, 2948 added insulin and 39 990 added a sulfonylurea. Propensity score matching yielded 2436 metformin + insulin and 12 180 metformin + sulfonylurea patients. At intensification, patients had received metformin for a median of 14 months (IQR, 5-30), and hemoglobin A_{1c} level was 8.1% (IQR, 7.2%-9.9%). Median follow-up after intensification was 14 months (IQR, 6-29 months). There were 172 vs 634 events for the primary outcome among patients who added insulin vs sulfonylureas, respectively (42.7 vs 32.8 events per 1000 person-years; adjusted hazard ratio [aHR], 1.30; 95% CI, 1.07-1.58; $P = .009$). Acute myocardial infarction and stroke rates were statistically similar, 41 vs 229 events (10.2 and 11.9 events per 1000 person-years; aHR, 0.88; 95% CI, 0.59-1.30; $P = .52$), whereas all-cause death rates were 137 vs 444 events, respectively (33.7 and 22.7 events per 1000 person-years; aHR, 1.44; 95% CI, 1.15-1.79; $P = .001$). There were 54 vs 258 secondary outcomes: AMI, stroke hospitalizations, or cardiovascular deaths (22.8 vs 22.5 events per 1000 person-years; aHR, 0.98; 95% CI, 0.71-1.34; $P = .87$).

CONCLUSIONS AND RELEVANCE Among patients with diabetes who were receiving metformin, the addition of insulin vs a sulfonylurea was associated with an increased risk of a composite of nonfatal cardiovascular outcomes and all-cause mortality. These findings require further investigation to understand risks associated with insulin use in these patients.

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Diabetes mellitus and its complications represent an enormous health care burden and result in nearly 200 000 deaths annually. The American Diabetes Association and the European Association for the Study of Diabetes recommend that, for patients with preserved renal function, treatment begin with metformin and lifestyle changes to achieve a glycated hemoglobin (HbA_{1c}) level of less than or equal to 7%. Often patients will require a second agent to reach this goal, but there is no consensus regarding which medication to choose: insulin, sulfonylureas, thiazolidinediones, glucagon-like peptide 1 receptor agonists, or dipeptidyl peptidase 4 inhibitors.[1] Evidence to inform treatment choices after metformin monotherapy remains limited.

Clinicians begin administration of insulin to attain fast and flexible control of blood glucose levels. In addition, a few trials have suggested that early insulin initiation is effective in preserving beta cell function.[2-4] Accordingly, there has been an increase in early initiation of insulin and its use as add-on therapy to metformin.[5-7] However, patients often want to delay insulin initiation because of fears of difficulty with administration, weight gain, and hypoglycemia.

We sought to compare time to cardiovascular disease (CVD) or death among patients who intensified their diabetes treatment with addition of insulin vs a sulfonylurea. We hypothesized that intensification with insulin would be associated with a lower risk of CVD or death compared with sulfonylurea, according to the superiority of insulin in achieving glycemic control.[8]

Methods

Study Design and Data Sources

We assembled a retrospective cohort of Veterans Health Administration (VHA) patients.[9] Veterans Health Administration data identified dispensed prescriptions, including medication, date filled, days supplied, pill number, and dosage[10]; VHA demographic data and *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) coded diagnostic and procedure information identified inpatient and outpatient encounters.[11] We collected laboratory results from standard clinical sources. Vital signs data included all outpatient height, weight, and blood pressure measurements. For enrollees in Medicare or Medicaid, we obtained encounter, prescription (Part D), and self-reported race/ethnicity data (coded as white, black, Hispanic, American Indian, Asian/Pacific Islander, other) from the Centers for Medicare & Medicaid Services through VHA's interagency exchange agreement.[12,13] We obtained dates of death from VHA vital status files and cause of death from National Death Index data from VHA National Death Index agreements.[14] The institutional review boards of Vanderbilt University and the VHA Tennessee Valley Healthcare System approved this study with waiver of informed consent.

Study Population

The study population comprised veterans aged 18 years or older who received regular VHA care (encounter or a prescription fill at least once every 180 days) for at least 2 years. Incident users of metformin from October 2001 through September 2008 with at least 365 days of baseline data preceding their first prescription fill who had not filled any diabetic drug prescription within 180 days were identified. These metformin initiators were eligible for the treatment intensification cohort on the date that they subsequently filled either insulin or a sulfonylurea prescription. We selected patients who were adherent to metformin by excluding those with no metformin available on the date of their insulin or sulfonylurea prescription or the previous 180 days. Follow-up began 180 days after the intensified prescription to distinguish patients who continued intensified therapy from those who switched to either insulin or sulfonylurea monotherapy. We excluded patients receiving hospice care or dialysis at intensification.

Exposures

The exposures of interest were insulin (long-acting, premixed, or short/fast-acting insulin) and sulfonylurea (glyburide, glipizide, or glimepiride) as metformin cotherapies. Follow-up continued through a study outcome or the study end. The study end was September 30, 2011, for all analyses except those that included cause of death as an outcome, for which the study end was September 30, 2009. Patients were censored for loss of follow-up, defined as the 181st day of no contact with any VHA facility (inpatient, outpatient, or pharmacy use); nonpersistence, defined as 90 days without metformin; or prescription for a third antidiabetic drug. In our population, allowing 90 days to refill medications approximates 80% adherence.[15]

Primary Outcome: CVD and All-Cause Death

The primary composite outcome was acute myocardial infarction, stroke hospitalization, or all-cause death. We defined acute myocardial infarction by a 410.x *ICD-9-CM* primary discharge diagnosis (positive predictive value 90% vs VHA medical record review). Stroke hospitalizations encompassed patients with a primary discharge diagnosis for ischemic stroke (433.x1, 434 [excluding 434.x0], or 436), intracerebral hemorrhage (431), and subarachnoid hemorrhage (430) and excluded traumatic brain injury (800-804 and 850-854) (positive predictive value 81%).[16]

We determined all-cause death by using the Vital Status file, which combines information from Medicare, VHA, Social Security, and VHA compensation and pension benefits to determine date of death (sensitivity 98.3%; specificity 99.8% relative to that of the National Death Index).[17] When the date of death in the VHA vital status file conflicted with the National Death Index date of death (<3%), we used the latter.

Secondary outcomes included CVD events (acute myocardial infarction and stroke combined), all-cause deaths, and a composite of acute myocardial infarction, stroke, and cardiovascular death (through September 30, 2009). Cardiovascular deaths were identified from death certificates with an *International Classification of Diseases, 10th Revision* cause of death including I00-I78 (cardiovascular deaths) or R98, R99, R960, and R961 (unattended deaths), excluding I30.X (diseases of the pericardium). This definition included the Centers for Disease Control and Prevention's broad definition of

cardiac death and a validated strategy for identification of sudden cardiac deaths.[18]

Covariates

Study covariates were collected in the 730 days before intensification and as time-varying covariates and included age, sex, race (white, black, other), fiscal year, indicators of health care use (hospitalization, months from hospitalization to intensification, nursing home use, number of outpatient visits, and Medicare or Medicaid use in past year), physiologic variables (blood pressure, creatinine level, HbA_{1c} level, low-density lipoprotein levels, presence of proteinuria, and body mass index), duration of metformin monotherapy before intensifying diabetes regimen (diabetes duration), selected medications, smoking, and presence of comorbidities (eTable 1 in the Supplement). Because race can influence study outcome, it was included in all models.[19]

For patients missing covariates, we conducted multiple imputation with the Markov chain Monte Carlo method and a noninformative Jeffreys prior.[20] All covariates from the primary analysis, survival time, and a censoring indicator were included in 20 imputation models and used to compute the final estimates.

Statistical Analyses

The primary analysis was time to the composite: acute myocardial infarction, stroke, or all-cause death in a propensity score–matched cohort. The propensity score modeled the probability of metformin + insulin use, given covariates and Veterans Integrated Service Network of care. Because of size differences between the 2 groups, metformin + insulin observations were propensity score matched to metformin + sulfonylurea observations with a 1:5 optimal matching algorithm[21,22] (eTables 2 and 3 and eFigure 1 in the Supplement).

Marginal structural Cox proportional hazards models were used to compare outcomes for metformin + insulin vs metformin + sulfonylurea (referent) while controlling for baseline and time-varying covariates in the matched cohort (eTables 2-4 in the Supplement). Because these model estimates can be unstable in the presence of disproportionately large inverse probability treatment weights,[23,24] the primary analysis used stabilized inverse probability treatment weights and truncated weights at 5, the 99th percentile. Thus, the models included the main effects of metformin + insulin vs metformin + sulfonylurea weighting by inverse probability treatment weight. The proportional hazards assumptions were verified through examination of log-log plots. Statistical significance was considered a 2-sided $P < .05$.

Sensitivity and Subgroup Analyses

First, in an approach similar to that used in intention-to-treat analyses, we used the intensification regimen to define drug exposure and ignored subsequent changes (persistent exposure not required). Because patients were not censored for nonpersistence, this method increases follow-up and events. Second, we changed the stabilized inverse probability treatment weights threshold (untruncated, truncated at 100, and 10). Third, we conducted subgroup analyses, stratifying by CVD history and age (<65 and ≥65 years), to assess effect modification. Among the subgroup with death certificates, we analyzed specific causes of death to identify cardiovascular, cancer, and all other deaths. Finally, we estimated the absolute prevalence difference of a hypothetical unmeasured binary confounder that would be required to yield a statistically nonsignificant association between exposure and outcome.[25] We assumed a confounder-outcome association similar to our observed covariates (hazard ratio = 1.25) and considered a broad range of confounder prevalences in both exposures.

Analyses were conducted with R (http://www.r-project.org; modules optmatch[26] and RI tools[27]) and SAS version 9.2 (modules Proc MI, ProcPHREG for marginal structural Cox proportional hazards models, and Proc Lifetest).

Results

Study Cohort and Patient Characteristics

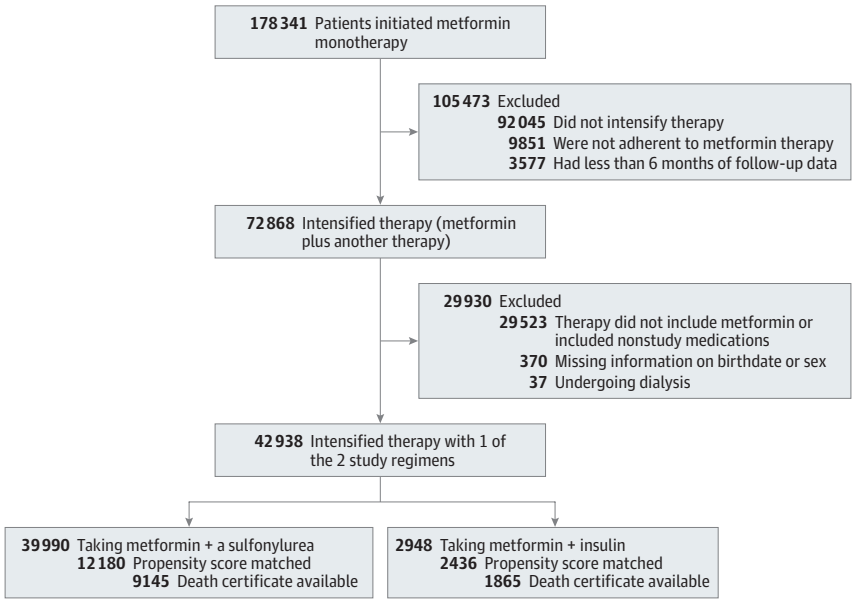
There were 178 341 patients who initiated metformin during 2001-2008. Fifty-two percent (n = 92 045) never intensified therapy (median follow-up, 50 months [IQR, 19-67 months]), 6% (n = 9851) stopped filling metformin prescriptions, and 2% (n = 3577) had fewer than 6 months of follow-up. Among the remaining 41% (n = 72 868) of metformin initiators who started receiving another therapy, 40% (n = 29 523) were excluded because their regimen excluded metformin or included nonstudy medications.

Fifty-nine percent (43 345/72 868) of metformin patients intensified with 1 of the 2 study regimens. We excluded less than 1% (n = 407) of patients with data errors (n = 370), hospice (n = 0), or dialysis (n = 37). The cohort included 2948 patients (7%) who added insulin (47% long-acting, 22% both long- and short-acting, 17% premixed, and 11% short-acting) and 39 990 patients (92%) who added a sulfonylurea (55% glipizide, 43% glyburide, and 2% glimepiride). Seventy-six percent of matched patients who died had a death certificate available (**Figure 1**).

Patients were 95% men and 70% white. Compared with patients who added a sulfonylurea, patients who added insulin to metformin intensified therapy earlier (14 months vs 18 months), had higher median HbA_{1c} levels (8.5% vs 7.5%), and had a higher prevalence of comorbidities. The proportion of patients prescribed metformin + insulin increased over time, with the odds increasing by an average of 17% (IQR, 14%-20%) per year ($P < .001$). After propensity score matching, we included 14 616 patients: 2436 metformin + insulin and 12 180 metformin + sulfonylurea. Baseline characteristics were not statistically different (**Table 1**).

The most common reasons for censoring were therapy change (58.7% metformin + insulin vs 61.7% metformin + sulfonylurea), leaving the VHA (1.3% vs 2.5%), or reaching the study end (32.9% vs 30.6%). The median number of years before censoring or the outcome was 1.15 (IQR, 0.5-2.4) among metformin + insulin patients and 1.15 (IQR, 0.5-2.2) among metformin + sulfonylurea patients. At 1 year, median HbA_{1c} level declined to 7% (IQR, 6.3%-8.0%) among metformin + insulin users and 6.9% (IQR, 6.4%-7.7%) among met-

Figure 1. Flow of Eligible Patients



formin + sulfonylurea users. Patient characteristics at 1 year were not statistically different (eTable 5 in the Supplement).

Absolute and Relative Hazards of Cardiovascular Events and Deaths

There were 172 vs 634 events for the primary outcome among patients who added insulin vs sulfonylureas, respectively (42.7 vs 32.8 events per 1000 person-years; adjusted hazard ratio [aHR], 1.30; 95% CI, 1.07-1.58; $P = .009$) (**Table 2**, **Figure 2**A). Cardiovascular disease (acute myocardial infarction and stroke) events were 41 and 229 among patients who added insulin or sulfonylurea, respectively (10.2 and 11.9 per 1000 person-years; aHR, 0.88; 95% CI, 0.59-1.30; $P = .52$). All-cause deaths were 137 vs 444, respectively (33.7 and 22.7 per 1000 person-years; aHR, 1.44; 95% CI, 1.15-1.79; $P = .001$).

For the secondary outcome, fatal and nonfatal cardiovascular events, there were 54 vs 258 events (22.8 vs 22.5 per 1000 person-years; aHR, 0.98; 95% CI, 0.71-1.34; $P = .87$) (Table 2, Figure 2B).

Sensitivity and Subgroup Analyses

In sensitivity analysis in which persistent exposure was not required, there were 394 events for the primary outcome among those who added insulin (7456 person-years) and 1553 events among those who added a sulfonylurea (37 237 person-years), yielding 52.8 (IQR, 48.0-58.2) and 41.7 (IQR, 39.7-43.8) events per 1000 person-years, respectively (aHR, 1.29; 95% CI, 1.15-1.46; $P < .001$). Results of the stabilized nontruncated weights in the analysis of persistent exposure not required yielded comparable results (aHR, 1.30; 95% CI, 1.15-1.46; $P < .001$). Marginal structural Cox proportional hazards models analyses, which varied the threshold of the maximal stabilized weight, yielded consistent results (eFigure 2 in the Supplement). No interaction between exposure and CVD history was detected ($P = .78$). Subgroup analyses stratifying by CVD or age were consistent with the primary analysis, but CIs were wide (eFigure 3 in the Supplement). In separate analyses that evaluated cause of death, the aHRs for metformin + insulin vs metformin + sulfonylureas were increased for all groups, but statistically significant only for cancer death (**Table 3**). Assuming an association comparable to our measured covariates (ie, hazard ratio, 1.25), an unmeasured binary confounder would need to be 30% higher among metformin + insulin users compared with metformin + sulfonylurea users to yield nonsignificant results in the main findings and 70% higher to yield statistical nonsignificance in the outcome of all-cause mortality (eTables 6 and 7 in the Supplement).

Discussion

Among patients with diabetes who were receiving metformin, the addition of insulin compared with a sulfonylurea was associated with an increased hazard of a composite of nonfatal cardiovascular outcomes and all-cause mortality. There is consensus that metformin is first-line diabetes treatment; however, uncertainty remains regarding additional therapy after inadequate control with metformin. Among the options, intensification with either insulin or a sulfonylurea is considered a high-efficacy strategy with reasonable costs.[1]

Although sulfonylurea use predominated as add-on therapy, we observed increasing use of insulin intensification during the study. Reasons may include increasing prevalence of obesity and insulin resistance, emphasis on metrics such as glycemic targets,[28,29] increasing comfort with newer analog insulins, and benefit in microvascular outcome prevention.[30]

Table 1. Characteristics of Patients at Treatment Intensification

Characteristics	Cohort					
	Full			Propensity Matched		
	Metformin + Sulfonylurea (n = 39 990)	Metformin + Insulin (n = 2948)	Standardized Differences[a]	Metformin + Sulfonylurea (n = 12 180)	Metformin + Insulin (n = 2436)	Standardized Differences[a]
Age, median (IQR), y	61 (56 to 69)	60 (54 to 67)	−0.13	60 (54 to 68)	60 (55 to 68)	0.02
Male, No. (%)	38 345 (96)	2787 (95)	−0.07	11 521 (95)	2315 (95)	0.02
Race/ethnicity, No. (%)						
White	29 458 (74)	2023 (69)	−0.11	8612 (71)	1726 (71)	0
Black	5161 (13)	571 (19)	0.19	2028 (17)	400 (16)	−0.01
Hispanic/other	1832 (5)	124 (4)	−0.02	512 (4)	111 (5)	0.02
Missing data	3539 (9)	230 (8)	−0.04	1028 (8)	199 (8)	−0.01
Time to intensification, median (IQR), mo[b]	18 (7 to 34)	14 (5 to 30)	−0.13	14 (6 to 31)	14 (5 to 30)	−0.01
Clinical Measures						
HbA_{1c}, median (IQR), %	7.6 (7.0 to 8.6)	8.5 (7.0 to 10.7)	0.54	8.1 (7.2 to 9.9)	8.1 (6.9 to 9.9)	−0.07
Missing measurement, No. (%)	5470 (14)	573 (19)	0.17	2315 (19)	470 (19)	0.01
Low-density lipoprotein, median (IQR), mg/dL	87 (70 to 110)	87 (67 to 113)	−0.02	86 (67 to 110)	87 (67 to 113)	0.02
Missing measurement, No. (%)	8492 (21)	851 (29)	0.19	3408 (28)	694 (28)	0.01
Creatinine, median (IQR), mg/dL	1.0 (0.9 to 1.1)	1.0 (0.9 to 1.2)	0.04	1.0 (0.9 to 1.1)	1.0 (0.9 to 1.2)	0
Glomerular filtration rate, median (IQR), mL/min	81 (70 to 95)	82 (69 to 100)	0.06	82 (70 to 98)	82 (70 to 98)	0.01
Missing measurement, No. (%)	5978 (15)	555 (19)	0.11	2372 (19)	468 (19)	−0.01
Proteinuria, No. (%) negative	20 909 (52)	1489 (50)		6044 (50)	1214 (50)	
Trace through 4+, No. (%)	7468 (19)	615 (21)	0.01	2534 (20)	503 (20)	0
Missing measurement, No. (%)	11 613 (29)	844 (29)	0.01	3602 (30)	719 (30)	0
Blood pressure, median (IQR), mm Hg						
Systolic	132 (122 to 143)	131 (120 to 142)	−0.08	131 (120 to 143)	131 (120 to 142)	0.01
Diastolic	77 (70 to 84)	76 (68 to 83)	−0.07	76 (68 to 83)	76 (68 to 84)	−0.01
Missing measurement, No. (%)	1689 (4)	187 (6)	0.10	788 (6)	159 (7)	0
Body mass index, median (IQR)	32.5 (28.9 to 36.7)	32.4 (28.3 to 37.0)	−0.04	32.3 (28.6 to 37.0)	32.6 (28.4 to 37.1)	0
Missing measurement, No. (%)	2098 (5)	236 (8)	0.12	961 (8)	191 (8)	0
Baseline Comorbidities, No. (%)[c]						
Malignancy	3059 (8)	273 (9)	0.06	1115 (9)	223 (9)	0
Liver/respiratory failure	1156 (3)	213 (7)	0.25	668 (5)	117 (5)	−0.04
HIV	125 (0.3)	24 (0.8)	0.09	69 (0.6)	14 (0.6)	0
Congestive heart failure	2222 (6)	306 (10)	0.21	1053 (9)	209 (9)	0
Cardiovascular disease	11 849 (30)	1056 (36)	0.14	4125 (34)	825 (34)	0
Serious mental illness	11 162 (28)	1028 (35)	0.15	3878 (32)	768 (32)	−0.01
Smoking	7719 (19)	685 (23)	0.10	2581 (21)	528 (22)	0.01
Chronic obstructive pulmonary disease/asthma	6114 (15)	634 (22)	0.17	2378 (20)	481 (20)	0.01
Cardiac valve disease	766 (2)	84 (3)	0.07	296 (2)	62 (2)	0.01
Arrhythmia	3449 (9)	338 (11)	0.10	1274 (10)	255 (10)	0
Parkinson disease	192 (0.5)	36 (1)	0.10	107 (0.9)	21 (0.9)	0
Year, No. (%)			0.14			−0.03
2002-03	1354 (3)	104 (3)		474 (4)	93 (4)	
2004	3047 (8)	191 (6)		837 (7)	171 (7)	
2005	4698 (12)	282 (10)		1171 (10)	250 (10)	
2006	6737 (17)	450 (15)		1848 (15)	379 (16)	
2007	7659 (19)	451 (15)		1895 (16)	401 (16)	
2008	6544 (16)	546 (19)		2209 (18)	428 (18)	
2009	5162 (13)	475 (16)		1915 (16)	369 (15)	
2010	3691 (9)	353 (12)		1463 (12)	275 (11)	
2011	1098 (3)	96 (3)		368 (3)	70 (3)	

(continued)

Table 1. Characteristics of Patients at Treatment Intensification (continued)

Characteristics	Cohort					
	Full			Propensity Matched		
	Metformin + Sulfonylurea (n = 39 990)	Metformin + Insulin (n = 2948)	Standardized Differences[a]	Metformin + Sulfonylurea (n = 12 180)	Metformin + Insulin (n = 2436)	Standardized Differences[a]
Use of Medications, No. (%)						
ACE inhibitors or ARBs	28 685 (72)	2072 (70)	−0.03	8576 (70)	1727 (71)	0.01
Antihypertensive medications	28 945 (72)	2147 (73)	0.01	8894 (73)	1762 (72)	−0.02
Statin and nonstatin lipid-lowering agents	32 206 (81)	2210 (75)	−0.14	9250 (76)	1858 (76)	0.01
Antiarrhythmics, digoxin, and other inotropes	569 (1)	78 (3)	0.10	274 (2)	57 (2)	0.01
Anticoagulants, platelet inhibitors	4603 (12)	482 (16)	0.15	1849 (15)	363 (15)	−0.01
Nitrates	3821 (10)	376 (13)	0.11	1472 (12)	297 (12)	0
Aspirin	9441 (24)	872 (30)	0.14	3411 (28)	666 (27)	−0.02
Loop diuretics	4204 (11)	545 (18)	0.25	2022 (17)	395 (16)	−0.01
Antipsychotics	3254 (8)	405 (14)	0.20	1436 (12)	279 (11)	−0.01
Indicators of Health Care Use, No. (%)						
Hospitalized						
Past year	5692 (14)	1023 (35)	0.57	3274 (27)	631 (26)	−0.03
90 d before intensification	2286 (6)	679 (23)	0.06	1732 (14)	334 (14)	−0.02
Nursing home encounter in past year	38 (0.1)	11 (0.4)	0.08	24 (0.2)	4 (0.2)	−0.01
Outpatient visits in past year	6 (4 to 10)	7 (4 to 12)	0.15	7 (4 to 12)	7 (4 to 12)	−0.03
Medicare use in past year	11 349 (28)	1066 (36)	0.17	4191 (34)	843 (35)	0
Medicaid use in past year	1046 (3)	202 (7)	0.25	590 (5)	122 (5)	0.01

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; HbA_{1c}, hemoglobin A_{1c}; HIV, human immunodeficiency virus; IQR, interquartile range.

SI conversion factors: Body mass index is calculated as weight in kilograms divided by height in meters squared.

[a] Standardized differences are the absolute difference in means or percentage divided by an evenly weighted pooled standard deviation, or the difference between groups in number of standard deviations. All *P* values in the unmatched cohort demonstrated statistically significant differences at $P < .001$. In the matched cohort, all standardized differences were statistically insignificant except HbA_{1c} at $P = .05$.

[b] Time to treatment intensification represents the median number of months patients received metformin monotherapy. It is an approximation of the duration of diabetes because patients were free of all hypoglycemic medications for 180 d before initiation of metformin.

[c] Definitions of comorbidities are available in eTable 1 in the Supplement.

Two large randomized trials demonstrated that regimens including greater insulin use and tighter control did not reduce cardiovascular events compared with standard care. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, patients were randomized to intensive control (target HbA_{1c} level <6%) or standard care. Approximately 77% of patients in the intensive group received insulin compared with 55% in the standard group.[31] ACCORD was stopped when interim analyses found more all-cause deaths in the intensive vs standard group (5.0% vs 4.0%; hazard ratio, 1.22; 95% CI, 1.01-1.46). Most excess mortality was due to cardiovascular deaths (2.63% vs 1.83% during a mean 3.5 observation years; $P = .02$). Whether insulin itself or other effects of intense treatment such as hypoglycemia[32,33] contributed to the increased mortality remains unknown.

The Outcome Reduction With an Initial Glargine Intervention (ORIGIN) trial randomized 12 537 patients with CVD risk factors and prediabetes or diabetes to insulin glargine or standard care. Metformin (28%) and sulfonylurea (29%) use was similar in both groups, but insulin reached only 11% in the standard group by study end. After a median of 6 years, there was no difference in the incidence of cardiovascular death, myocardial infarction, or stroke between groups (2.94 vs 2.85 per 100 person-years, respectively; hazard ratio, 1.02; 95% CI, 0.94-1.11).[34] There was also no difference in the incidence of cancer or cancer death. However, patients in the insulin group had more weight gain and hypoglycemic events.

Several observational studies have also reported no cardiovascular benefit of insulin relative to noninsulin comparators, and some have suggested worse outcomes. A Canadian study[35] reported increased all-cause mortality among insulin users compared with nonusers in a dose-response manner. Similarly, a study of primary care patients in the UK General Practice Research database[36] determined that metformin + insulin was associated with an elevated risk of all-cause mortality and cardiovascular- and cancer-related outcomes compared with metformin monotherapy. However, these studies did not address confounding by disease severity adequately. The first did not control for HbA_{1c}, and the second compared more intensive therapies such as insulin (alone or in combination) with metformin monotherapy.

Our finding of a modestly increased risk of a composite of cardiovascular events and death in metformin users who add insulin compared with sulfonylurea is consistent with the available clinical trial and observational data. None of these studies found an advantage of insulin compared with oral agents

for cardiovascular risk, and several reported increased cardiovascular risk or weight gain and hypoglycemic episodes, which could result in poorer outcomes. Although insulin remains a reasonable option for patients who have very high glucose levels or who desire flexible and fast glucose reduction, most patients prefer to delay insulin initiation.[37] Our study suggests

Table 2. Rates and Adjusted Hazard of Primary and Secondary Outcomes Among Patients Who Intensified With Metformin + Insulin vs Metformin + Sulfonylurea Among a Propensity Score–Matched Cohort

Persistent Exposure Required[a]	Metformin + Sulfonylurea	Metformin + Insulin
Sample size, No.	12 180	2436
Person-years, No.	19 315	4025
Composite cardiovascular events or all-cause death (No. of events)	634	172
Unadjusted rate/1000 person-years (95% CI)	32.8 (30.4-35.4)	42.7 (36.9-49.4)
Adjusted hazard ratio (95% CI)[b]	1 [Reference]	1.30 (1.07-1.58)
AMI and stroke hospitalizations (No. of events)	229	41
Unadjusted rate/1000 person-years (95% CI)	11.9 (10.4-13.5)	10.2 (7.5-13.8)
Adjusted hazard ratio (95% CI)[b]	1 [Reference]	0.88 (0.59-1.30)
All-cause death (No. of events)[c]	444	137
Person-years	19 596	4071
Unadjusted rate/1000 person-years (95% CI)	22.7 (20.7-24.8)	33.7 (28.5-39.6)
Adjusted hazard ratio (95% CI)[b]	1 [Reference]	1.44 (1.15-1.79)
Composite cardiovascular events or cardiovascular death (No. of events)[d]	258	54
Sample size, No.	9145	1865
Person-years, No.	11 473	2364
Unadjusted rate/1000 person-years (95% CI)	22.5 (19.9-25.4)	22.8 (17.5-29.7)
Adjusted hazard ratio (95% CI)[b]	1 [Reference]	0.98 (0.71-1.34)

Abbreviation: AMI, acute myocardial infarction.

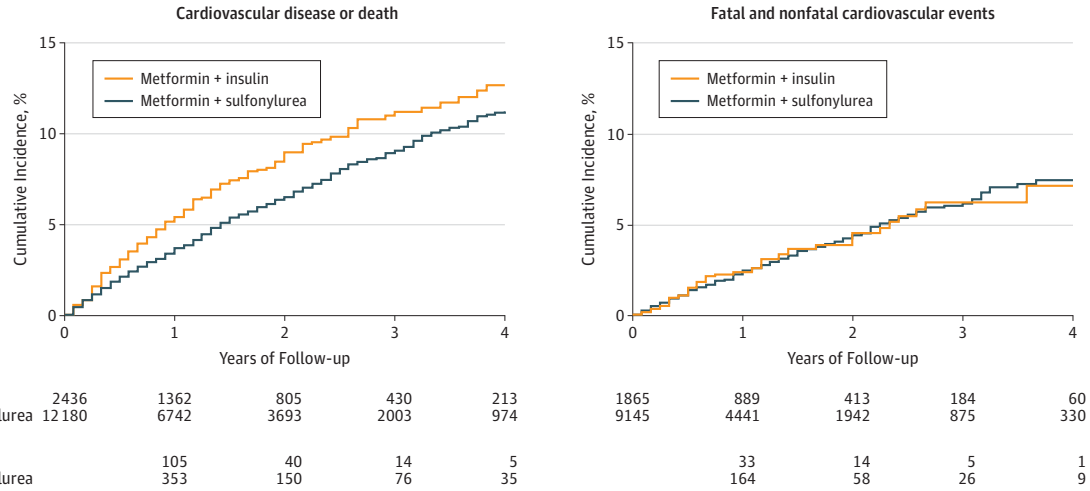
[a] Primary analysis required persistence in receiving metformin; patients were censored after 90 d without metformin.

[b] Adjusted hazard was derived from the Cox proportional hazards marginal structural model for time to outcome, truncating weights at 5. Refer to eTable 2 in the Supplement for the inverse probability treatment weights and eTables 3 and 4 in the Supplement for the models used to derive inverse probability treatment weights.

[c] For the outcome of all-cause death, patients were followed until death as an outcome, and AMI/stroke events were ignored. In the composite outcome, we considered the time to the first event (AMI, stroke, or death), which reduced the number of deaths in the composite outcome.

[d] Death certificates with cause of death were available through September 30, 2009, and only patients with a date of intensification before September 30, 2009, were included in analyses.

Figure 2. Cumulative Incidence of Cardiovascular Events and Mortality



No. at risk										
Metformin + insulin	2436	1362	805	430	213	1865	889	413	184	60
Metformin + sulfonylurea	12 180	6742	3693	2003	974	9145	4441	1942	875	330
No. of events										
Metformin + insulin		105	40	14	5		33	14	5	1
Metformin + sulfonylurea		353	150	76	35		164	58	26	9

A, Cumulative incidence of cardiovascular disease (acute myocardial infarction, stroke) or death among a propensity score–matched cohort of patients taking metformin + sulfonylurea vs patients taking metformin + insulin. All follow-up is through September 30, 2011. Events are the composite of cardiovascular disease or all-cause death that occurred in the 12 months between each point. B, Cumulative incidence of fatal and nonfatal cardiovascular events (acute myocardial infarction, stroke, or cardiovascular deaths) among a propensity score–matched cohort of patients taking metformin + sulfonylurea vs patients taking metformin + insulin. All follow-up is through September 30, 2009. Events are the composite of fatal and nonfatal cardiovascular events that occurred in the 12 months between each point.

Table 3. Comparison of Specific Causes of Death[a] Among a Propensity Score–Matched Cohort

Persistent Exposure Required[b]	Metformin + Sulfonylurea (n = 9145)	Metformin + Insulin (n = 1865)
Person-years, No.	11 622	2392
Cardiovascular death	91	24
Unadjusted rate/1000 person-years (95% CI)	7.8 (6.4-9.6)	10.0 (6.8-14.9)
Adjusted hazard ratio (95% CI)[c]	1 [Reference]	1.21 (0.74-2.00)
Cancer death	82	35
Unadjusted rate/1000 person-years (95% CI)	7.1 (5.7-8.7)	14.6 (10.5-20.3)
Adjusted hazard ratio (95% CI)[c]	1 [Reference]	1.85 (1.21-2.84)
All other deaths	123	41
Unadjusted rate/1000 person-years (95% CI)	10.6 (8.9-12.6)	17.1 (12.7-23.2)
Adjusted hazard ratio (95% CI)[c]	1 [Reference]	1.36 (0.90-2.04)

[a] Death certificates with cause of death were available through September 30, 2009, and only patients with a date of intensification before September 30, 2009, were included in analyses.

[b] Primary analysis required persistence in receiving metformin; patients were censored after 90 d without metformin. Cardiovascular outcomes such as acute myocardial infarction or stroke were ignored.

[c] Adjusted hazard was derived from the Cox proportional hazards marginal structural model for time to outcome, truncating weights at 5. Refer to eTable 2 in the Supplement for the inverse probability treatment weights and eTables 3 and 4 in the Supplement for the propensity score models and the model used to derive inverse probability treatment weight.

that intensification of metformin with insulin among patients who could add a sulfonylurea (HbA_{1c} level less than ≈10%) offers no advantage in regard to risk of cardiovascular events and is associated with some risk.

Our findings must be interpreted in light of limitations. Although we applied an extensive set of strategies to address confounding by indication, including rigorous selection criteria, propensity score matching, and marginal structural models, residual confounding from difficult-to-measure factors such as patient frailty or diabetes severity remains possible. Nevertheless, our sensitivity analyses estimated that a large confounding effect would be needed for an unmeasured confounder to explain our observations. Using similar methods in a VHA diabetes cohort, we previously demonstrated drug effects on lipids, HbA_{1c}, and body mass index that were concordant with that of clinical trials and meta-analyses.[9,38-40] Our results are consistent with UK Prospective Diabetes Study results, which demonstrated a reduction of cardiovascular events with metformin but not insulin or sulfonylurea.

There are several other limitations. We used refill data as a proxy for receipt of medication. Nevertheless, prescription fills are a good proxy for medication use. Veterans may not receive all their care or medications in VHA facilities,[12,13] resulting in missing events or medications, which we partially addressed through supplementation with Medicare and Medicaid information. Because we required patients to persist in receiving their medications, censoring was high. In addition, patients who added insulin composed only 7% of intensifiers, which resulted in a relatively small sample size and limited the precision of some estimates. The statistical significance of our primary outcome was driven by all-cause mortality, and a clinically significant cardiovascular benefit could not be excluded. Our primary analyses considered a matched population. Some patients who were prescribed metformin + insulin did not match metformin + sulfonylurea users. Excluded metformin + insulin users (N = 512) had a median HbA_{1c} level of 11.8% and 67% of these patients were hospitalized in the 90 days before insulin initiation (eTable 8 in the Supplement). Results can be generalized only to metformin patients who were eligible to add either medication. Finally, our patients reflect a typical veteran population, with most patients being white men.

Conclusions

Among patients with diabetes who are receiving metformin, the addition of insulin compared with sulfonylurea was associated with an increased risk of a composite of nonfatal cardiovascular outcomes and all-cause mortality. These findings require further investigation to understand risks associated with insulin use in these patients and call into question recommendations that insulin is equivalent to sulfonylureas for patients who may be able to receive an oral agent.

ARTICLE INFORMATION

Author Contributions: Drs Roumie and Greevy had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Roumie, Greevy, Grijalva, Hung, Elasy, Griffin.
Acquisition, analysis, or interpretation of data: Roumie, Greevy, Grijalva, Hung, Liu, Murff, Griffin.
Drafting of the manuscript: Roumie, Greevy.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Greevy, Liu.
Obtained funding: Roumie, Greevy, Griffin.
Administrative, technical, or material support: Murff, Elasy.
Study supervision: Greevy, Grijalva, Griffin.

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