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Case-control study of second-line therapies for type 2 diabetes in combination with metformin and the comparative risks of myocardial infarction and stroke

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Abstract

We conducted a population-based case-control study to assess the myocardial infarction (MI) and stroke risks associated with sulfonylureas and insulin when used in combination with metformin. Cases had type 2 diabetes and used metformin + insulin or metformin + sulfonylureas at the time of a first MI or first stroke from 1995–2010; controls used the same treatment combinations and were randomly sampled from the same population. MI and stroke diagnoses and potential confounders were validated by medical record reviews. Compared with metformin + sulfonylurea, metformin + insulin was associated with similar risks of MI or stroke (OR 0.98 [95% CI, 0.63–1.52]). Meta-analysis with another observational study improved the precision of the risk estimate (RR 0.92 [95% CI, 0.69–1.24]). Current evidence suggests that there may not be large differences in cardiovascular risk associated with the use of insulin or sulfonylureas when used in combination with metformin.

Keywords

sulfonylureas; metformin; insulin; myocardial infarction; stroke; cardiovascular outcomes; case-control study; comparative safety

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CONTRIBUTIONS

JSF designed the study, conducted the analyses, drafted the manuscript, and had full access to the study data. JSF, NLS, SRH, and BMP obtained funding and were involved in data collection. All authors contributed to the interpretation of the results, critically revised the manuscript for important intellectual content, and approved the final version of the manuscript. JSF is the guarantor of this work.

CONFLICTS OF INTEREST

Psaty serves on the DSMB of a clinical trial of a device funded by the manufacturer (Zoll LifeCor) and on the Steering Committee of the Yale Open Data Access Project funded by Johnson & Johnson.

INTRODUCTION

American and European guidelines recommend metformin as the first-line treatment for type 2 diabetes mellitus (T2DM) [1]. Most patients will eventually require a second glucose-lowering therapy to reach glycemic targets, but the optimal second-line treatment is an open question because little is known about the comparative cardiovascular effects of these drugs when used in combination with metformin [2].

A recent observational study of male veterans found that the risk of cardiovascular events was similar for the combination of metformin + insulin and for metformin + sulfonylureas (HR 0.88 [95% CI, 0.59–1.30]) [3]. We assessed these treatment combinations in a population-based case-control study of myocardial infarction and stroke that included both men and women. We hypothesized that the combined results from these studies would exclude clinically important differences in cardiovascular risk, since neither second-line drug has been shown to prevent cardiovascular complications [4].

METHODS

Subjects were enrolled in case-control studies conducted at Group Health Cooperative (GHC) in Washington State [5]. Cases experienced a first MI or a first stroke from January 1995 through December 2010. Controls were randomly sampled during the same period, frequency matched to MI cases by age, sex, hypertension status, and calendar year. Trained abstractors who were blinded to study hypotheses reviewed the entire medical record of each subject to validate MI and stroke diagnoses, confirm eligibility criteria, and identify cardiovascular risk factors present at the time of case-control sampling, including smoking status and duration of diabetes.

Medication use was ascertained using information from computerized prescription records and medical record reviews. Subjects treated with metformin + sulfonylurea or metformin + insulin were eligible for analysis. Case identification, eligibility criteria, and drug exposure ascertainment are described further in Supporting Information (Appendix S1).

Logistic regression was used to estimate odds ratios (ORs) and confidence intervals (CIs) for MI and stroke separately, and for the composite of MI or stroke. Analyses were adjusted for matching variables (age, sex, hypertension status, calendar year), smoking status, prior cardiovascular disease, prior revascularization, atrial fibrillation, diastolic blood pressure, cholesterol, creatinine, and diabetes duration. Hemoglobin A1c (HbA_{1c}) was not adjusted for in primary analyses, because the degree of glycemic control could mediate potential cardiovascular effects. For variables with missing data in > 1% of subjects (HbA_{1c} 5% and diabetes duration 9%), multiple imputation was conducted, using all variables from primary analyses and 25 imputations [6]. Because of the risk set sampling of case and control subjects, odds ratios in this study are unbiased estimators of risk ratios and analogous to hazard ratios from Cox regression with time-varying assessments of drug exposures and confounding variables [7].

Secondary analyses tested various assumptions about inclusion criteria and adjustment variables. Results for the composite endpoint of MI or stroke were combined with results

from the veterans study in a fixed-effects inverse-variance weighted meta-analysis [8]. Analyses were conducted with STATA version 11.

RESULTS

There were 180 MI cases, 130 stroke cases, and 331 control subjects; 46% were female and the mean age was 65 years (Table 1). MI and stroke cases had higher blood pressure and cholesterol and used statins less often than controls. Among controls, subjects in the metformin + insulin group had more prior cardiovascular disease, had a longer duration of diabetes, and used statins more often than subjects in the metformin + sulfonylurea group, while HbA_{1c} levels were similar. In the metformin + insulin group, 97% used long-acting insulin and 47% used regular or rapid-acting insulin. In the metformin + sulfonylurea group, 97% used a second-generation sulfonylurea (76% glyburide, 21% glipizide).

Compared with metformin + sulfonylurea, the use of metformin + insulin was associated with similar risks of MI (OR 0.96 [95% CI, 0.60–1.56]), stroke (OR 0.85 [95% CI, 0.47–1.51]), and the composite outcome of MI or stroke (OR 0.98 [95% CI, 0.63–1.52]). Secondary analyses that excluded users of regular or rapid-acting insulin, excluded subjects who started metformin after sulfonylureas or insulin, adjusted for duration of sulfonylureas or insulin use, adjusted for HbA_{1c}, restricted to ischemic strokes, and evaluated women and men separately, yielded results that were similar to primary results (Table 2). Glyburide was associated with a similar risk of MI or stroke as glipizide (OR 0.97 [95% CI, 0.53–1.78]).

Combining results from our study (n = 276 events) with results from the veterans study (n = 270 events) doubled the total number of cardiovascular events (n = 546). There was little evidence of heterogeneity (Cochran's Q = 0.12, p = 0.73). The combined relative risk (RR) for cardiovascular events associated with metformin + insulin compared with metformin + sulfonylurea was 0.92 (95% CI, 0.69–1.24).

DISCUSSION

In this population-based study that included men and women, insulin and sulfonylureas were associated with similar cardiovascular risks when used in combination with metformin. A meta-analysis with the veterans study excluded large differences in cardiovascular risk: metformin + insulin was associated with no more than a 24% increased RR or a 31% decreased RR compared with metformin + sulfonylureas. These results are consistent with the UK Prospective Diabetes Study, which found that neither sulfonylureas nor insulin decreased the risk of cardiovascular complications when used as first-line treatments [4].

In the veterans study, metformin + insulin was associated with increased all-cause mortality, due to an increase in cancer deaths (HR 1.85 [95% CI, 1.21–2.84]) [3]. However, the limited ability of non-randomized studies to account for all factors that are related to the various diseases that contribute to all-cause mortality (e.g., cancer) can result in substantial confounding for this endpoint [10]. Such residual confounding may explain the cancer finding in the veterans study, which conflicts with evidence from a large randomized controlled trial (RCT) of insulin therapy [9]. In our study, we could not assess comparative all-cause mortality risks because of the case-control study design.

The “null” results from our study have important public health implications. Convincing evidence does not exist that any second-line treatment for T2DM prevents cardiovascular complications. Instead, there have been concerns that glucose-lowering drugs could have adverse cardiovascular effects since the University Group Diabetes Program trial concluded over forty years ago [11], and safety signals related to newer drugs have been identified recently [12]. Questions about cardiovascular drug safety helped to motivate an ongoing comparative effectiveness RCT that will evaluate several second-line drugs in combination with metformin, including the sulfonylurea glimepiride and insulin glargine [13]. However, this trial is powered to detect only a 50% or greater difference in the RR for cardiovascular disease between treatment groups, and will not conclude until 2020. In contrast, our meta-analysis excluded a 30% difference in the RR for cardiovascular events associated with insulin vs. sulfonylureas when these drugs are used with metformin.

One limitation of our study was the lack of power to detect smaller differences in cardiovascular risk (e.g., 10%–20%), which could be clinically important. Another important limitation was the potential for bias from residual confounding. For example, if insulin users were at greater risk for cardiovascular disease than sulfonylurea users in unmeasured ways, then a potential protective effect of insulin may have been obscured. To avoid this, we reviewed the entire medical record of each subject, spanning 20 years on average, which allowed us to accurately assess the duration of diabetes and the presence of cardiovascular risk factors, which can be poorly captured in studies that rely on administrative data. In addition, because we assessed drug use at the time of case-control sampling, our study would be sensitive to short-term adverse effects such as hypoglycemia, which has been hypothesized to mediate adverse cardiovascular harm [14].

RCTs provide the highest level of evidence about the cardiovascular effects of drug treatments. Until evidence from such trials is available, well-designed observational studies can help to address unanswered questions about the cardiovascular risks and benefits of therapies for T2DM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of case and control subjects.

	Myocardial infarction cases (n=180)	Stroke cases (n=130)	Controls	
			Metformin + Sulfonylurea (n=238)	Metformin + Insulin (n=93)
Age, years (mean, SD)	65 (9)	67 (8)	64 (9)	64 (8)
Female (n, %)	86 (48%)	70 (54%)	98 (41%)	40 (43%)
Race (n, %)				
White	147 (82%)	103 (79%)	186 (78%)	75 (81%)
Black	8 (4%)	10 (8%)	18 (8%)	9 (10%)
Other	24 (13%)	14 (11%)	34 (14%)	9 (10%)
Group Health enrollment, yrs (mean, SD)	19 (11)	19 (13)	21 (11)	23 (12)
Duration of diabetes, yrs (mean, SD)	10.8 (6.3)	11.1 (8.0)	8.3 (5.3)	12.0 (6.5)
Daily dose MET, g/d (mean, SD)	1.5 (0.7)	1.5 (0.7)	1.5 (0.6)	1.5 (0.6)
Tobacco use (n, %)	21 (12%)	14 (11%)	24 (10%)	11 (12%)
Treated hypertension (n, %)	162 (90%)	117 (90%)	219 (92%)	88 (95%)
Prior cardiovascular disease (n, %)	73 (41%)	38 (29%)	79 (33%)	39 (42%)
Atrial fibrillation (n, %)	15 (8%)	21 (16%)	11 (5%)	9 (10%)
Congestive heart failure (n, %)	13 (7%)	11 (8%)	7 (3%)	9 (10%)
Systolic blood pressure (mean, SD)	142 (22)	148 (23)	140 (19)	137 (15)
Diastolic blood pressure (mean, SD)	78 (12)	81 (13)	78 (11)	75 (9)
Body mass index (mean, SD)	33 (7)	33 (7)	33 (7)	35 (7)
Total cholesterol, mg/dL (mean, SD)	205 (50)	209 (49)	191 (46)	189 (50)
Serum creatinine, mg/dL (mean, SD)	1.0 (0.3)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)
HbA _{1c} , % (mean, SD)	8.2 (1.6)	8.5 (1.8)	8.1 (1.4)	8.3 (1.6)
Statin use (n, %)	73 (41%)	50 (38%)	116 (49%)	59 (63%)

Table 2

Associations between second-line diabetes therapies in combination with metformin and the risks of incident myocardial infarction and stroke.

	MI			Stroke			MI + Stroke		
	Cases/controls	OR	95% CI	Cases/controls	OR	95% CI	Cases/controls	OR	95% CI
Primary analysis									
Metformin + Sulfonylurea	124/211	1 (ref)		97/226	1 (ref)		195/201	1 (ref)	
Metformin + Insulin	56/81	0.96	0.60–1.56	33/82	0.85	0.47–1.51	81/71	0.98	0.63–1.52
Secondary analyses									
Restricted to long-acting INS									
Metformin + Sulfonylurea	124/211	1 (ref)		97/226	1 (ref)		195/201	1 (ref)	
Metformin + Insulin	29/43	0.92	0.51–1.66	18/45	0.98	0.49–1.97	45/39	1.03	0.61–1.76
SU/INS started after MET									
Metformin + Sulfonylurea	28/54	1 (ref)		22/61	1 (ref)		46/54	1 (ref)	
Metformin + Insulin	32/47	1.02	0.43–2.42	21/45	1.02	0.38–2.70	48/40	1.10	0.38–2.70
Restricted to ischemic stroke									
Metformin + Sulfonylurea				97/226	1 (ref)				
Metformin + Insulin				33/82	0.92	0.50–1.69			
Adjusted for duration SU/INS									
Metformin + Sulfonylurea	124/211	1 (ref)		97/226	1 (ref)		195/201	1 (ref)	
Metformin + Insulin	56/81	1.05	0.62–1.75	33/82	0.73	0.38–1.40	81/71	0.94	0.60–1.51
Adjusted for A1c									
Metformin + Sulfonylurea	124/211	1 (ref)		97/226	1 (ref)		195/201	1 (ref)	
Metformin + Insulin	56/81	0.96	0.60–1.56	33/82	0.80	0.44–1.43	81/71	0.96	0.61–1.49
Men									
Metformin + Sulfonylurea	63/118	1 (ref)		45/133	1 (ref)		96/113	1 (ref)	
Metformin + Insulin	31/47	1.03	0.56–1.92	15/49	0.94	0.43–2.02	41/43	1.06	0.56–2.01
Women									
Metformin + Sulfonylurea	61/93	1 (ref)		52/93	1 (ref)		99/88	1 (ref)	
Metformin + Insulin	25/34	0.88	0.44–1.76	18/33	0.85	0.40–1.80	40/28	0.92	0.52–1.62

INS = insulin, MI = myocardial infarction, SU = sulfonylurea.