Insulin-Sensitizing Antihyperglycemic Drugs and Mortality After Acute Myocardial Infarction

Insights from the National Heart Care Project

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OBJECTIVE — Thiazolidinediones (TZDs) and metformin are insulin-sensitizing antihyperglycemic agents with reported benefits on atherosclerosis. Despite extensive use in patients with diabetes and cardiovascular disease, there is a paucity of outcomes data with metformin and none yet with TZDs. We sought to determine the impact of these insulin sensitizers on outcomes in diabetic patients after hospitalization with acute myocardial infarction (AMI).

RESEARCH DESIGN AND METHODS — We conducted a retrospective cohort study of 24,953 Medicare beneficiaries with diabetes discharged after hospitalization with AMI between April 1998 and March 1999 or July 2000 and June 2001. The independent association between discharge prescription for metformin, TZD, or both agents and outcomes at 1 year was assessed in multivariable Cox proportional hazards models, adjusting for patient, physician, and hospital variables. The primary outcome was time to death within 1 year of discharge; secondary outcomes were time to first rehospitalization within 1 year of discharge for AMI, heart failure, and all causes.

RESULTS — There were 8,872 patients discharged on an antihyperglycemic agent, of which 819 were prescribed a TZD, 1,273 metformin, and 139 both drugs. After multivariable analysis, compared with patients prescribed an antihyperglycemic regimen that included no insulin sensitizer, mortality rates were not significantly different in patients treated with either metformin (hazard ratio [HR] 0.92 [95% CI 0.81–1.06]) or a TZD (0.92 [0.80–1.05]) but were lower in those prescribed both drugs (0.52 [0.34–0.82]). The results were similar among patients with heart failure. The prescription of a TZD was associated with a borderline higher risk of all-cause readmission (1.09[1.00–1.20]), predominately due to a higher risk for heart failure readmission (1.17 [1.05–1.30]).

CONCLUSIONS — Individually, prescription of insulin-sensitizing drugs is not associated with a significantly different risk of death in older diabetic patients within 1 year following AMI compared with other antihyperglycemic agents. Combined, however, metformin and TZDs may exert benefit. TZD prescription is associated with a higher risk of readmission for heart failure after myocardial infarction.

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Ischemic heart disease (IHD) is the leading cause of mortality in patients with type 2 diabetes (1), an association that may relate, in part, to insulin resistance (2). To date, the benefit of antihyperglycemic therapies that target insulin deficiency (e.g., sulfonylureas or insulin) on IHD outcomes has not been shown (3). In contrast, metformin, which has insulin-sensitizing properties, may reduce myocardial infarction rates in newly diagnosed type 2 diabetic patients (4). Recently, the thiazolidinediones (TZDs), which specifically target insulin resistance and improve metabolic and vascular markers of the metabolic syndrome, have become increasingly popular (5). Although the TZDs are no more effective in lowering glucose than conventional agents, several experts have proposed that they reduce cardiovascular risk due to their pleiotropic effects (5–9). Despite a large and growing body of evidence demonstrating benefit on cardiovascular disease surrogates, however, there are no data proving a benefit of TZDs on IHD outcomes. Moreover, according to the Food and Drug Administration, both metformin and TZDs are contraindicated in many patients with heart failure, which frequently complicates AMI, due to concerns of lactic acidosis and increased fluid retention, respectively.

Ideally, the effect of metformin or TZDs on IHD outcomes would be ad-

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Abbreviations: AMI, acute myocardial infarction; IHD, ischemic heart disease; TZD, thiazolidinedione.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

dressed by randomized clinical trials. Although some are now underway, full results are not expected for several more years. In addition, many randomized trials of therapy in cardiovascular diseases do not include adequate numbers of elderly patients with significant comorbidity. It is therefore informative to investigate the effect of metformin and TZDs on IHD outcomes in population-based observational studies, which have the advantage of including a broad spectrum of patients typically seen in clinical practice. We therefore evaluated the relationship between the prescription of insulin-sensitizing agents and the outcomes of death and readmission among elderly diabetic patients after hospitalization for AMI.

RESEARCH DESIGN AND METHODS

Data sources

The National Heart Care Project. The National Heart Care Project is a Centers for Medicare & Medicaid Services initiative designed to assess and improve the quality of care for Medicare beneficiaries with AMI. The data for the project consist of two longitudinal national cohorts of fee-for-service Medicare beneficiaries hospitalized with a principal discharge diagnosis of AMI. The first sample included hospitalizations with discharge dates between April 1998 and March 1999, inclusive, and the second between July 2000 and June 2001, inclusive. All admissions in each of the 50 states, Washington DC, and Puerto Rico identified within these time frames were sorted by age, sex, race, and hospital. Detailed demographic and clinical data were abstracted from these records by trained medical record reviewers. Data quality was enhanced through the use of medical record abstraction software and random record reabstraction.

Additional data sources. The sample cohort was linked with the American Medical Association Physician Masterfile (10) and with the American Hospital Association Annual Surveys to ascertain the characteristics of the attending physicians and hospitals, respectively (11). Dates of death were assessed through linkage with the Medicare Enrollment Database (12). Linkage with part A Medicare data provided the dates and diagnoses for rehospitalizations occurring within a year of the index hospitalization.

Patients

The cohort consisted of 35,713 records in 1998–1999 and 35,407 in 2000–2001, for a total of 71,120 records. A clinical diagnosis of AMI was confirmed using standard clinical electrocardiogram and laboratory criteria (13).

Candidates for this study were those patients with a diagnosis of diabetes (n = 24,953) established by documentation in the hospital record or the prescription of an antihyperglycemic medication either at hospital admission or discharge. Because this study focused on the effects of diabetes drug therapy, only those patients that received an antihyperglycemic agent (metformin, TZDs, sulfonylurea, nonsulfonylurea insulin secretagogues, α-glucosidase inhibitors, or insulin) upon discharge were included (n = 14,786). Those patients in whom a diagnosis of AMI could not be confirmed were excluded (n = 2,829). Patients receiving long-term hemodialysis and those <65 years of age (n = 2,888) were also excluded because such Medicare beneficiaries may not be representative of older patients with cardiac disease. Finally, those patients who died during their hospitalizations (n = 3,070), were with unknown dates of death (n = 185) or unknown readmission data (n = 1,079), were discharged to hospice, were transferred to another hospital, or left against medical advice (n = 4,250) were also excluded. After the exclusion of those patients meeting one or more of the above criteria, a total sample size of 8,872 records were then analyzed.

Measurements

Variables. The main independent variable was the prescription of metformin or a TZD at hospital discharge. A complete list of discharge medications was abstracted from the records of all patients surviving hospitalization. The only TZD available in the U.S. during the 1998–1999 sampling period was troglitazone (Rezulin; Parke-Davis), which was withdrawn in March 2000 (between sampling periods). By the beginning of the 2000–2001 sampling period, both rosiglitazone (Avandia; Glaxo-SmithKline; approved May 1999) and pioglitazone (Actos; Takeda; approved July 1999) were available for use in the U.S. Thus, a variable accounting for the sampling frame was included in all models.

Outcomes. The primary outcome variable was time from hospital discharge to death from any cause censored at 1 year of discharge. Secondary outcomes included time to first readmission for myocardial infarction, first readmission for heart failure, and first readmission for any cause censored at 1 year of discharge.

Statistical analysis

Primary analysis. Patients were categorized into four mutually exclusive groups by their antihyperglycemic drug prescription: patients who were prescribed an antihyperglycemic regimen that included neither metformin nor a TZD, patients prescribed metformin (but not a TZD), patients prescribed a TZD (but not metformin), and patients discharged on both metformin and a TZD. Differences in the characteristics of patient, physician, and hospital were compared pairwise using χ^2 tests for categorical variables and t tests for continuous variables among these four groups, with the group of patients who were prescribed neither insulin-sensitizing drug as the referent group. The relationships between metformin or TZD prescription and outcomes were first compared with χ^2 tests pairwise among the four groups, and the independent relationships were evaluated with multivariable Cox proportional hazards models. The multivariable models were adjusted for the following factors: demographics (age, sex, and race); cardiac history (history of heart failure, myocardial infarction, hypertension, and revascularization); noncardiovascular history (admission source, mobility, cerebral vascular accident, chronic pulmonary disease, urinary incontinence, and dementia); clinical characteristics at hospital admission (systolic blood pressure, respiratory rate, heart failure, sodium, glucose, blood urea nitrogen, creatinine, white blood cell count, and hematocrit); hospital course (atrial fibrillation, heart failure/pulmonary edema on admission chest radiograph, cardiac catheterization, percutaneous coronary intervention, coronary artery bypass grafting, and diabetes complications); other discharge prescriptions, including the prescription of other antihyperglycemic agents (sulfonylureas and nonsulfonylurea insulin secretagogues, α-glucosidase inhibitors, and insulin) and agents commonly used to reduce cardiovascular risk in post-AMI patients (aspirin, ACE inhibitors, β-ad-

renergic receptor blockers, calcium channel blockers, statins, and fibrates); and the sample frame in which the index hospitalization occurred. Covariates reflecting diabetes severity included the admission blood glucose level, prescription of other antihyperglycemic drugs at hospital discharge, and the presence of the ICD-9 code for a diabetes complication in the discharge abstract for the index hospitalization or in any part A record during the year before the admission. Complications included diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, and peripheral vascular disease. Attending physician (specialty and board certification) and the treating hospital (bed size, geographic location, ownership, level of cardiac care facilities, and teaching status) were also included in the model. These factors were chosen based on both clinical significance and statistical significance ($P < 0.05$) using the stepwise method in the multivariate models. The models also adjusted for clustering of patients by hospitals.

Secondary analyses. Because both TZDs and metformin are contraindicated in patients with advanced heart failure, analyses were stratified by the presence or absence of heart failure/pulmonary edema by admission chest radiograph and by the degree of left ventricular systolic dysfunction. Because edema occurs more frequently in TZD patients also treated with insulin, results were stratified by concomitant prescription of insulin at discharge.

Statistical analyses were performed with SAS 8.20 (SAS, Cary, NC) and Stata 7.0 (Stata, College Station, TX). The use of the National Heart Care Project database was approved by the Yale University Human Investigation Committee.

RESULTS — The mean age of the cohort was 76.4 ± 7.1 years, and the majority were Caucasian (88.2%) and were women (52.4%). Heart failure/pulmonary edema were present on admission chest radiograph in 30.1% of patients. A total of 1,273 (14.3%) were discharged on metformin, 819 (9.2%) on a TZD, and 139 (1.6%) on both insulin sensitizers (Table 1). A total of 6,641 (74.9%) patients were discharged on an antihyperglycemic drug regimen with neither insulin sensitizer, including 3,515 on a sulfonylurea and 3,509 on insulin. Compared with patients discharged on neither sensitizer, TZD-treated patients were younger but more likely to have a prior history of myocardial infarction, percutaneous coronary intervention, heart failure, or a documented diabetes-related complication. Patients treated with metformin were younger, more likely Caucasian, and less likely female. Proportionately fewer metformin patients had chronic illnesses, including heart failure, and were less likely to have diabetes-associated complications, including renal insufficiency. Metformin-treated patients also more often had preserved left ventricular systolic function and were more likely to have undergone invasive cardiac procedures during the index hospitalization. Finally, they were more often discharged on β-blockers, ACE inhibitors, or sulfonylureas but less often concomitantly treated with insulin. Patients prescribed both insulin sensitizers shared many but not all of the characteristics of metformin-only patients.

Mortality

Overall mortality in the cohort was 6.5% at 30 days, 20.0% at 6 months, and 28.3% at 1 year. In our fully adjusted model, 31 clinical factors were independently associated with mortality (12 with hazard ratio [HR] <1.0 and 19 with >1.0.) The six variables with the greatest positive association with mortality were prior coronary artery bypass grafting (HR 0.47 [95% CI 0.37–0.59]), prior percutaneous transluminal coronary angioplasty (0.72 [0.60–0.86]), cardiac catheterization (0.77 [0.68–0.88]) during the hospitalization, and discharged on a fibrate (0.71 [0.52–0.96]), statin (0.80 [0.73–0.88]), or β-blocker (0.85 [0.78–0.92]). The six variables with the greatest negative association with mortality were documented diabetes complications (1.47 [1.33–1.64]), left ventricular systolic dysfunction (1.46 [1.31–1.62]), age ≥85 years (1.46 [1.28–1.66]), admission from a skilled nursing, intermediate care, or extended care facility (1.44 [1.26–1.64]), a white blood cell count ≥11 mm^3 on admission (1.44 [1.31–1.59]), and dementia (1.33 [1.18–1.51]).

Compared with patients not discharged on an insulin sensitizer, patients treated with metformin had significantly lower unadjusted mortality rates at all time points (5.1 vs. 6.8% at 30 days [$P = 0.02$], 13.0 vs. 21.6% at 6 months [$P < 0.0001$], and 19.3 vs. 30.3% at 1 year [$P < 0.0001$]) (Table 2). However, a similar trend was not observed for patients treated with a TZD (6.6, 19.8, and 28.9% [P = NS for all]). After adjustment for patient, provider, and hospital characteristics, sampling period, and differences in other medical treatments at discharge, both metformin-prescribed (HR 0.92 [95% CI 0.81–1.06]) and TZD-prescribed (0.92 [0.80–1.05]) patients (Table 3, Fig. 1*A*) had a mortality risk that was not significantly different from patients discharged without an insulin sensitizer. Because patients treated with sulfonylureas have different characteristics than patients treated with insulin, we conducted a second analysis in which the patients not treated with an insulin sensitizer were divided into two groups, those discharged on a sulfonylurea and those on insulin. Adjusted analysis showed no difference in mortality or readmissions between these two nonsensitizer groups. Our results were also unchanged by comparison of both groups to either the metformin or TZD patients (data not shown.)

Readmissions

At 1 year, 63.9% of patients had at least one readmission for any cause, with 18.4% being readmitted for myocardial infarction and 42.3% being readmitted for heart failure. Compared with patients not discharged on an insulin sensitizer, those discharged on metformin had significantly lower crude rates of readmission for all causes at 6 and 12 months, for heart failure at all time points, and there was a trend toward lower crude rates of readmission for myocardial infarction at the later time points (Table 2). In contrast, patients treated with a TZD had a higher risk of all-cause readmission of borderline statistical significance at 1 year and higher risks for readmission for heart failure at all time points, while readmission for myocardial infarction was similar.

After multivariable adjustment, the risk for readmission from all causes was no different among patients discharged on metformin than among those not discharged on an insulin sensitizer but was borderline higher among TZD-treated patients (HR 1.09 [95% CI 1.00–1.20]) (Table 3, Fig. 1*B*), predominately due to a higher risk of heart failure readmission (1.17 [1.05–1.30]). Readmission for

Table 1—*The patient population*

	No insulin sensitizer	Metformin		Thiazolidinedione		Both	
	n = 6,641	*n* = 1,273	*P**	*n* = 819	*P**	*n* = 139	*P**
Demographics							
Age (years)	76.8 ± 7.1	75.2 ± 7.0	<0.001	75.8 ± 6.9	<0.001	73.6 ± 6.8	<0.001
Female (%)*	53.2%†	48.2%*	0.001	53%*	0.904	46.8%*	0.131
Nonwhite	12.5	8.6	<0.001	10.7	0.143	11.5	0.720
Cardiac history							
Congestive heart failure	41.6	28.1	<0.001	46.6	0.006	30.9	0.012
Myocardial infarction	44.5	39.1	<0.001	52.0	<0.001	50.4	0.172
Hypertension	80.3	77.6	0.031	80.7	0.760	76.3	0.242
Coronary artery bypass graft	22.7	21.1	0.195	23.9	0.431	31.7	0.013
Percutaneous coronary intervention	16.0	17.1	0.328	19.2	0.022	20.9	0.124
Noncardiac history							
Cerebrovascular accident	24.1	18.7	<0.001	25.6	0.339	19.4	0.199
Chronic obstructive pulmonary disease	22.8	19.2	0.004	21.1	0.276	19.4	0.346
Dementia/Alzheimer's disease	9.2	5.8	<0.001	7.7	0.159	9.4	0.946
Diabetes complications (12 months prior to admission)	13.7	6.0	<0.001	17.2	0.006	5.0	0.003
Diabetic coma (250.1, 250.2, 250.3)	0.6	0.2	0.114	0.6	0.935	0.0	0.365
Renal complications (250.4)	4.9	0.5	<0.001	6.0	0.165	0.7	0.023
Ophthalmic manifestation (250.5)	2.5	1.0	0.001	3.3	0.166	2.2	0.807
Neurological manifestations (250.6)	5.1	3.3	0.006	7.2	0.012	2.9	0.233
Peripheral circulatory disorders (250.7)	2.2	1.0	0.007	1.8	0.529	0.0	0.079
Other complications/ manifestations (250.8, 250.9)	4.1	1.8	<0.001	4.5	0.525	0.7	0.047
Presenting features							
ST elevation on electrocardiogram	23.9	24.7	0.517	20.6	0.038	19.4	0.220
Congestive heart failure/pulmonary edema	31.4	22.2	<0.001	33.7	0.175	21.6	0.014
Anterior AMI	31.4	31.7	0.837	31.0	0.837	27.3	0.311
Admission laboratory values							
Glucose			0.064		0.758		0.529
<136 mg/dl	14.1	12.2		14.7		11.5	
136–185 mg/dl	19.7	21.2		19.5		16.5	
186–250 mg/dl	28.5	30.9		29.8		29.5	
>250 mg/dl	37.7	35.7		36.0		42.4	
Creatinine			<0.001		<0.001		<0.001
<1.5 mg/dl	50.2	72.9		41.6		66.9	
1.5–2.5 mg/dl	31.7	22.5		38.0		29.5	
>2.5 mg/dl	18.1	4.6		20.4		3.6	
In-hospital events							
Atrial fibrillation	17.9	15.6	0.040	16.8	0.438	11.5	0.050
Ventricular tachycardia	0.6	0.5	0.498	0.9	0.458	0.7	0.898
Congestive heart failure/pulmonary edema on chest radiograph	35.5	28.5	<0.001	38.1	0.145	20.9	<0.001
Left ventricular systolic function			<0.001		0.290		0.003
Preserved (normal or mild)	40.4	46.4		43.2		54.0	
Impaired (moderate or severe)	32.9	31.9		31.1		21.6	
Not measured	26.7	21.7		25.6		24.5	
Cardiac catheterization	41.4	53.8	<0.001	43.5	0.263	55.4	0.001
Primary reperfusion							
Early thrombolytic therapy	2.4	2.7	0.515	1.7	0.194	2.9	0.741
Early percutaneous coronary intervention	1.4	1.4	0.931	0.9	0.172	3.6	0.038

Continued on following page

Table 1—*Continued*

	No insulin sensitizer	Metformin		Thiazolidinedione		Both	
	n = 6,641	*n* = 1,273	*P**	*n* = 819	*P**	*n* = 139	*P**
Percutaneous coronary intervention beyond 12 h of admission	17.2	26.2	<0.001	20.0	0.048	21.6	
Coronary artery bypass graft	10.0	11.9	0.043	8.4	0.157	10.1	0.181
Diabetes complications	24.4	13.5	<0.001	29.1	0.004	20.1	0.248
Discharge medications							
ACE inhibitor	54.8	59.9	0.001	54.5	0.848	71.9	<0.001
β-Blocker	63.2	68.8	<0.001	66.4	0.074	74.1	0.009
Calcium channel blocker	25.8	23.6	0.095	27.6	0.268	18.0	0.037
Aspirin	76.0	79.7	0.005	75.7	0.844	77.0	0.792
Lipid-lowering agents							
Statin	32.1	42.3	<0.001	48.0	<0.001	57.6	<0.001
Fibrates	2.3	2.9	0.211	3.2	0.132	4.3	0.125
Other anticoagulants	0.4	0.5	0.743	1.3	<0.001	2.2	0.002
Antihyperglycemic agents							
Sulfonylureas	52.9	58.9	<0.001	39.3	<0.001	54.0	0.810
Nonsulfonylurea secretagogues	1.0	1.3	0.298	1.6	0.129	3.6	0.003
α-Glucosidase inhibitors	0.6	0.5	0.731	0.9	0.458	2.2	0.028
Insulin	52.8	14.5	<0.001	47.1	0.002	23.7	<0.001
Attending physican specialty			<0.001		<0.001		<0.001
Cardiologist	27.3	33.2		29.5		42.4	
Noncardiologist	38.2	38.7		45.1		41.0	
Unknown	34.6	28.0		25.4		16.5	
Hospital characteristics							
Rural location	25.9	28.4	0.063	27.2	0.398	30.2	0.246
Ownership			0.002		0.858		0.022
Public	10.7	10.8		10.3		9.4	
Not for profit	76.9	73.4		76.7		69.8	
For profit	9.2	10.8		10.0		16.5	
Teaching status			0.002		0.215		0.745
COTH (Council of Teaching Hospitals) member	17.3	14.6		14.8		18.7	
Residency affiliated	28.5	28.6		28.0		25.2	
Nonteaching	50.9	51.8		54.2		51.8	
Cardiac care facilities			<0.001		0.132		0.033
Cardiac surgery suite	50.4	54.8		53.1		59.7	
Cardiac catheterization lab	15.5	13.0		16.7		15.8	
No invasive facilities	26.7	22.8		23.0		15.8	
Sampling period			<0.001		<0.001		<0.001
1998–1999	52.0	40.5		31.6		14.4	
2000–2001	48.0	59.5		68.4		85.6	

Data are means ± SE and %. **P* for comparison with the "no insulin sensitizer" group.

myocardial infarction was not significantly different in either group.

Combination therapy and outcomes

After multivariable analysis, adjusted mortality in the small subset of patients treated with both metformin and a TZD (*n* = 139) was significantly lower (HR 0.52 [95% CI 0.34–0.82]) compared with those patients receiving no insulin sensitizer. The relationship between the two insulin sensitizers and mortality was greater in combination than individually (*P* = 0.045 for interaction between metformin and TZD) (Table 3, Fig. 1*A*). There were no differences in readmission rates in the combination treatment group (Table 3, Fig. 1*B*). The metformin-TZD combination group also had significantly lower mortality compared with either the sulfonylurea-treated (0.51 [0.32–0.81]) or the insulin-treated (0.54 [0.34–0.86]) patients.

Stratified analyses

In those patients with impaired left ventricular systolic function, mortality was not significantly higher in either insulin sensitizer group after multivariable analysis compared with the referent group

Table 2—*Crude outcomes*

Outcome	No insulin sensitizer		Metformin			Thiazolidinedione			Both		
	n	%	*n*	%	*P*	*n*	%	*P*	*n*	%	*P*
Mortality											
within 30 days of discharge	453	6.8	65	5.1	0.023	54	6.6	0.807	3	2.2	0.030
within 3 months of discharge	954	14.4	113	8.9	0.000	117	14.3	0.951	7	5.0	0.002
within 6 months of discharge	1,431	21.5	165	13.0	<0.001	162	19.8	0.244	12	8.6	<0.001
within 1 year of discharge	2,014	30.3	246	19.3	<0.001	237	28.9	0.414	17	12.2	<0.001
Readmission											
Myocardial infarction											
within 30 days of discharge	331	5.0	63	4.9	0.958	46	5.6	0.436	4	2.9	0.257
within 3 months of discharge	664	10.0	118	9.3	0.425	78	9.5	0.668	11	7.9	0.417
within 6 months of discharge	953	14.4	155	12.2	0.041	107	13.1	0.320	18	12.9	0.641
within 1 year of discharge	1,247	18.8	210	16.5	0.054	154	18.8	0.986	21	15.1	0.272
Heart failure											
within 30 days of discharge	1,046	15.8	162	12.7	0.006	159	19.4	0.007	17	12.2	0.259
within 3 months of discharge	1,808	27.2	280	22.0	<0.001	260	31.7	0.006	38	27.3	0.976
within 6 months of discharge	2342	35.3	354	27.8	<0.001	313	38.2	0.096	50	36.0	0.863
within 1 year of discharge	2859	43.1	435	34.2	<0.001	402	49.1	0.001	54	38.8	0.322
All cause											
within 30 days of discharge	1669	25.1	309	24.3	0.517	235	28.7	0.027	29	20.9	0.250
within 3 months of discharge	2829	42.6	489	38.4	0.006	385	47.0	0.016	54	38.8	0.376
within 6 months of discharge	3596	54.1	610	47.9	<0.001	465	56.8	0.154	70	50.4	0.375
within 1 year of discharge	4268	64.3	759	59.6	0.002	555	67.8	0.048	88	63.3	0.816

(metformin [*n* = 406]: HR 0.92 [95% CI 0.72–1.18]; TZD [*n* = 255]: 1.04 [0.83–1.31]). Similarly, in those patients with heart failure/pulmonary edema on admission chest radiograph, mortality was also not increased with either insulin sensitizer (metformin [*n* = 312]: 0.96 [0.78–1.19]; TZD [*n* = 363]: 0.92 [0.75–1.13]).

The magnitude of the relationship between TZD therapy and heart failure readmissions was not substantively different from the referent group among patients additionally prescribed insulin on discharge (*n* = 386; HR 1.16 [95% CI 1.01–1.34]) versus those not on insulin (*n* = 433; 1.14 [0.96–1.36]) nor in those with impaired left ventricular function (*n* = 255; 1.15 [0.97–1.38]) versus those with preserved ventricular function (*n* = 354; 1.14 [0.95–1.38]) (*P* for interaction >0.05 for both comparisons). Also, in those patients who were readmitted for heart failure, mortality was not increased in those treated with metformin (*n* = 435; 0.87 [0.73–1.04]) or TZDs (*n* = 402; 0.92 [0.77–1.10]).

CONCLUSIONS — Our observational study of a large nationally representative sample of older patients with AMI demonstrates no large apparent short-term mortality benefit nor any mortality risk associated with the prescription of metformin or TZDs. TZD prescription was associated with a borderline relative increased risk of all cause readmission, predominately due to a 17% relative increased risk of readmission for heart failure. One conclusion that may be drawn from our data is that despite a host of prognostic factors that appear worse in TZD-prescribed patients, these drugs are not associated with any higher mortality, even in the unadjusted analyses. Conclusions regarding metformin are less clear. Patients prescribed metformin had significantly better risk profiles, as reflected by their lower crude mortality rates. Adjustments increase the HRs closer to 1. These data appear to indicate that metformin therapy post-AMI may offer little vascular benefit in the short term.

The modestly increased risk of heart failure readmission associated with TZDs is likely the result of the propensity for these drugs to cause fluid retention, usually manifested as peripheral edema alone (14). It should be noted, however, that the accuracy of the readmission diagnoses

Table 3—*Adjusted outcomes*

	Metformin	*P*	Thiazolidinediones	*P*	Both	*P*
Mortality	0.92 (0.81–1.06)	0.255	0.92 (0.80–1.05)	0.221	0.52 (0.34–0.82)	0.004
Myocardial infarction readmission	1.02 (0.86–1.20)	0.831	0.92 (0.77–1.10)	0.355	0.88 (0.56–1.37)	0.568
Heart failure readmission	1.06 (0.95–1.18)	0.334	1.17 (1.05–1.30)	0.004	1.24 (0.94–1.63)	0.122
All cause Readmission	1.04 (0.96–1.13)	0.368	1.09 (1.00–1.20)	0.052	1.06 (0.87–1.30)	0.543

Data are HR (95% CI).

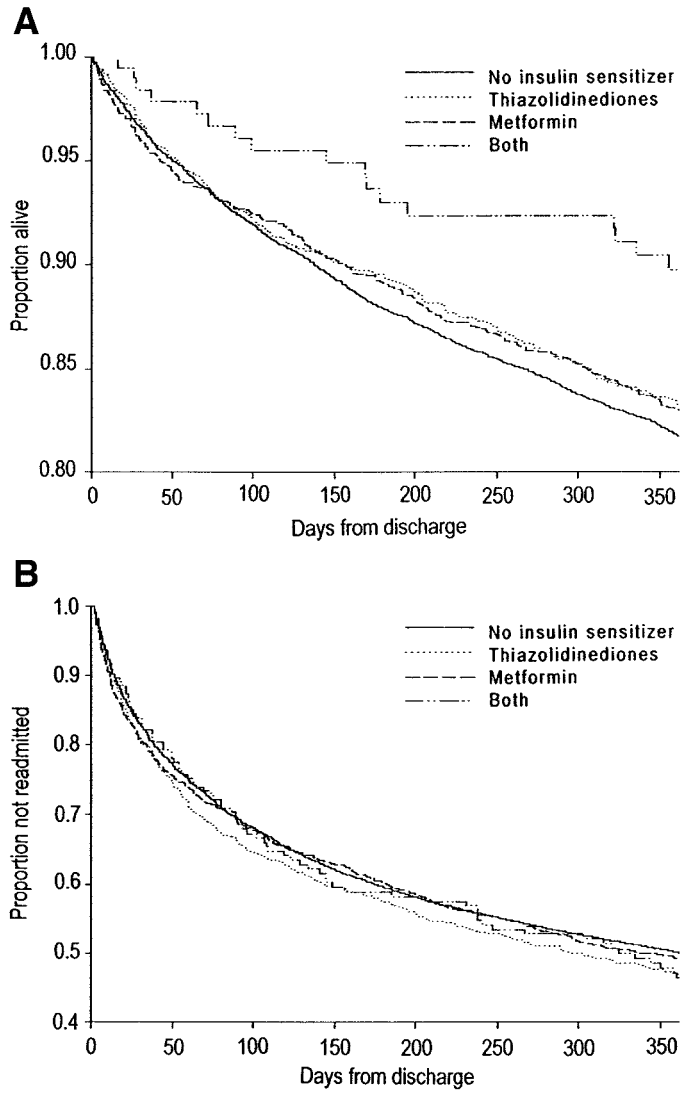

Figure 1—*Adjusted Kaplan-Meier curves for mortality* (A) *and all-cause readmission* (B) *for the four treatment groups: patients discharged on an antihyperglycemic regimen that included neither a TZD nor metformin (solid line); patients with a discharge prescription for a TZD (but not metformin) (dotted line); patients with a discharge prescription for metformin (but not a TZD) (dashed line); patients with discharge prescriptions for both a TZD and metformin (dotted and dashed line).*

of heart failure cannot be assessed from these data. Interestingly, heart failure readmission rates were not any greater in those insulin-treated patients also prescribed a TZD (a combination known to increase the risk of edema) versus a non-insulin sensitizer. They were also not greater in TZD-treated patients with left ventricular systolic dysfunction. This might be an indirect reflection of some benefit on cardiac metabolism/ventricular function in patients with preexisting heart failure. The increased heart failure readmission risk was also not associated with any increased mortality. It is interesting to note that, in a different database recently analyzed by our group, Medicare patients discharged with a diagnosis of heart failure and treated with either metformin or a TZD had a 13% lower 1-year mortality, despite a borderline significant 6% increased risk of heart failure readmission in the TZD group (15). Thus, while the prescription of a TZD, compared with non–insulin sensitizer drugs, appears to confer no clear beneficial or adverse effect on mortality over the 1st year following AMI in older diabetic patients, their use is associated with a mildly increased risk of heart failure readmission. Close monitoring for fluid retention in these patients is clearly advisable (16).

When both metformin and TZDs were used in combination, a prominent relationship with lower mortality was demonstrated, with a risk reduction approaching 50%. Although the number of patients in this combination group was small (only 1.5% of the entire cohort), this relationship was consistent at all measured time points and persisted after multivariable analysis that accounted for a large number and variety of patient, physician, and hospital characteristics. There are few trials examining the combined use of these insulin sensitizer classes, with the majority assessing solely glycemic effects (17–20). In one study, additive benefits on lipids were demonstrated (21). Conceptually, combined insulin sensitization could have significant cardiovascular benefits, but this finding needs to be confirmed by others and should not affect clinical decision-making at this point.

Insulin resistance, the primary metabolic defect in type 2 diabetes, has been associated with cardiovascular disease (22), although there is yet no compelling evidence from prospective studies to suggest that improving insulin sensitivity decreases cardiovascular event rates. The pharmacological agents that increase insulin sensitivity, metformin and the TZDs, appear to exert their insulin-sensitizing effects by different mechanisms (17), but both are associated with improvements in cardiovascular risk factors (5,6,23,24). Metformin decreases triglyceride and LDL cholesterol concentrations and the antifibrinolytic factor plasminogen activator inhibitor-1 and improves vasoreactivity (24). TZDs increase HDL cholesterol and reduce triglycerides, free fatty acids, plasminogen activator inhibitor-1, and the inflammatory markers C-reactive protein, matrix metalloproteinase-9, and CD40 ligand (5,6,23,25). In addition, TZDs improve endothelial function and markedly increase circulating concentrations of the adipocytokine adiponectin (26), which may have antiatherogenic properties (27). Studies in humans are limited to several investigations (28–30) suggesting a benefit on carotid intimal-medial thickness, a surrogate for atherosclerosis, and two small studies (31,32) showing a reduction in restenosis rates after coronary angioplasty. In contrast to these studies that suggest benefit, metformin is known to

increase homocysteine levels (33), an emerging cardiovascular disease risk factor, and some TZDs increase LDL cholesterol concentrations (although this may relate to these drugs' effect on LDL particle size and not LDL particle number) (5,6). Also, both drugs are contraindicated in many patients with heart failure, which frequently accompanies or soon follows the diagnosis of AMI (16).

To date, no beneficial effect has been consistently demonstrated with any insulin sensitizer on IHD outcomes. Metformin monotherapy reduced AMI rates in a small subset of overweight, newly diagnosed type 2 diabetic patients within the UKPDS (U.K. Prospective Diabetes Study) (4). When used in combination with sulfonylureas in the same study, however, an increase in mortality was observed. TZDs have only been available since 1997, and it was not until 2001 that randomized, controlled clinical trials examining cardiovascular outcomes studies were initiated, data from which are not yet available.

Recently, small observational studies have suggested benefit from insulin sensitizers on IHD outcomes in patients with diabetes (34–37). Each of these reports have had methodological limitations, including small sample sizes, retrospective design, failure to control for other potential confounders (34–37), and relatively low exposure frequency to TZDs (36,37). Current studies underway to test the effect of insulin sensitizer therapy on cardiovascular outcomes in patients with diabetes include BARI-2D (personal communication, Dr. M.M. Brooks, 16 July 2004), PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) (38), and RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) (39). Their results are anticipated to shed further light on this important area.

Our study is the first large investigation into outcomes with insulin-sensitizing medications in diabetic patients following a major cardiovascular event. Yet, there are several issues to consider when interpreting our data. Our database is only able to measure outcomes up to 1 year following AMI, a time interval that may not be optimal to assess for the progression of already established, advanced atherosclerosis. Mortality at this time may indeed be driven primarily by the degree of myocardial damage, pump dysfunction, arrhythmic events, and embolic complications. It is possible that the benefits (and/or risks) of treatment with insulin sensitizers would be apparent over a longer time frame, such as after 3–5 years, as is conventionally used in cardiovascular trials. In addition, our database captures medications prescribed to the patients upon discharge, but it was not possible to determine compliance or changes in drug regimens in the follow-up period. Such misclassification would tend to bias the study toward the null. Because of the observational design, unmeasured confounding factors could influence the observed associations (or lack thereof). For example, we were not able to determine metabolic control after hospital discharge, specifically the quality of glucose (i.e., HbA_{1c}), lipid, or blood pressure management, which has been, of course, associated with poorer cardiovascular outcomes by others. On the other hand, other retrospective "real world" studies of this type have replicated the results from subsequent randomized controlled trials (13,40). We were also not able to exclude patients with type 1 diabetes, although in this older Medicare population, it is unlikely that patients with type 1 diabetes represented more than a small minority of the cohort. Finally, since this study only analyzed data from older Medicare beneficiaries discharged from hospitals after AMI, the results may not apply to other patient populations, such as younger individuals or those with chronic, stable coronary artery disease.

In conclusion, this study suggests no clear mortality benefit or risk from the prescription of individual insulin-sensitizing drugs to older type 2 diabetic patients with AMI over the 1st year following hospital discharge compared with patients given other antihyperglycemic agents. However, the prescription of a TZD was associated with a mildly increased risk of rehospitalization for a diagnosis of heart failure. Current antihyperglycemic therapy guidelines, which do not favor one drug over another in patients with type 2 diabetes and cardiovascular disease, therefore appear appropriate until further information becomes available (41). In contrast, the suggestion of a marked mortality benefit from the combined metformin-TZD prescription is provocative in this setting but requires further confirmation. Adequately powered randomized, controlled clinical trials will be instrumental in determining rational antihyperglycemic regimens for the growing population of older patients with both type 2 diabetes and coronary artery disease.

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