Published in final edited form as:
Diabet Med. 2005 August ; 22(8): 986–993. doi:10.1111/j.1464-5491.2005.01704.x.

Pioglitazone Initiation and Subsequent Hospitalisation for Congestive Heart Failure

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Abstract

Aims—Thiazolidinediones (TZD) have been associated with an expansion in plasma volume and the development of peripheral oedema. A recent study reported an association between the use of TZDs and development of congestive heart failure (CHF). The objective of this study was to determine if short-term use of pioglitazone, a TZD, is associated with increased risk of CHF hospitalisation in a well-characterised, community-based cohort of type 2 diabetic patients without prevalent CHF.

Methods—A cohort study of all patients in the Kaiser Permanente Medical Care Program with type 2 diabetes (Kaiser Permanente Northern California Diabetes Registry) who initiated any diabetes pharmacotherapy (n=23,440) between October, 1999 and November, 2001. Only patients initiating single new therapies ("new users") were included to reduce confounding and create mutually-exclusive exposure groups. We constructed Cox proportional hazards models (with sulfonylureas initiators specified as the reference group) to evaluate the impact of initiating new diabetes therapies on time to incident CHF hospitalisation, defined by primary hospital discharge diagnosis.

Results—Patients initiated pioglitazone (15.2%), sulfonylureas (25.3%), metformin (50.9%), and insulin (8.6%) alone or as additions to pre-existing or maintained therapies. Three hundred and twenty CHF hospitalisations were observed during the follow-up (10.2 months on average) after initiation. Relative to sulfonylurea initiators, there were no significant increases in the incidence of CHF hospitalisation among those initiating pioglitazone (hazard ratio (HR) = 1.28; 95% confidence interval (CI): 0.85 – 1.92) after adjusting for demographic, behavioural, and clinical factors. There was a significantly higher incidence among those initiating insulin (HR = 1.56; 95% CI: 1.00 – 2.45) and lower incidence among those initiating metformin, (HR = 0.70; 95% CI: 0.49 – 0.99).

Conclusions—This study of patients with type 2 diabetes failed to find evidence that short-term pioglitazone use was associated with an elevated risk of CHF hospitalisation relative to the standard, first line diabetes therapy.

Keywords

diabetes mellitus; congestive heart failure; thiazolidinediones; pioglitazone; hypoglycaemic agents; pharmacoepidemiology; new user design

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INTRODUCTION

There is increasing awareness and concern about the potential risks associated with the use of the thiazolidinedione (TZD) class of diabetes medications,(1) particularly the risks of fluid retention and congestive heart failure (CHF). The Federal Drug Administration (FDA) approved the first TZD, troglitazone, in 1997, and TZDs have since become widely utilised. (2) TZDs are recognised as effective diabetes medications which improve glucose control by decreasing insulin resistance in skeletal muscle and hepatocytes, thereby increasing glucose uptake and decreasing hepatic glucose production, and inducing a compensatory decrease in plasma insulin levels.(3) TZDs also have beneficial effects on newer markers of cardiovascular disease risk, e.g., inflammatory markers,(4) pulse wave velocity(5) and visceral adiposity(6). An adverse effect of TZDs is an expansion in plasma volume, which may be associated with development of oedema in a dose-dependent fashion.(7) It has been suggested that these hemodynamic changes may increase the risk of developing or exacerbating congestive heart failure (CHF). Subsequently, product monographs for the two currently licensed TZDs (rosiglitazone/Avandia(8) and pioglitazone/Actos(9)) list CHF as a contraindication.

Typically, randomised controlled trials evaluating the efficacy and safety of unapproved, novel therapies are insufficiently powered to evaluate relatively rare, adverse drug effects such as CHF(10). Instead, carefully designed, population-based, post-market observational studies are the most reliable method for quantifying the frequency of such effects(10;11). A recent retrospective cohort study(12) compared new users of TZD to all other diabetic patients being treated with oral hypoglycaemic agents (OHA) and reported that TZD use was associated with increased risk of CHF. We conducted a similar study but limited our analysis to initiators of new diabetes therapies and employed a “new user” design(10). We assessed the relationship between any newly initiated diabetes therapy and the incidence of CHF hospitalisation in a large, group-model managed care population of 23,440 patients with type 2 diabetes mellitus (Kaiser Permanente Northern California Diabetes Registry).

PATIENTS AND METHODS

Study Population

Kaiser Permanente Medical Care Program (“Kaiser Permanente”), a fully-integrated, non-profit, group practice, prepaid health plan, provides comprehensive medical services to over 2.9 million members (as of January, 2000) throughout Northern California (including the San Francisco Bay and Sacramento metropolitan areas), or ~30% of the surrounding population. The Kaiser Permanente membership closely approximates the general population ethnically and socioeconomically except for the extreme tails of the income distribution,(13-15) but is comparable to the characteristics of other insured populations in Northern California.

In 1993, Kaiser Permanente established the *Kaiser Permanente Northern California Diabetes Registry*. The *Registry* is updated annually by identifying all health plan members with diabetes and has been the basis for extensive epidemiologic and health services research. (16-27) Registry sensitivity was estimated to be 99% in 2001 based on the inclusion of patients in the registry who self-report diabetes in a general membership health survey. Each registry member was linked via medical record identification number to detailed clinical data available from electronic records of pharmacy utilisation, laboratory findings, hospitalisations and outpatient diagnoses.

Cohort eligibility, baseline definition and follow-up

To most accurately assess the possible iatrogenic risk of CHF associated with the use of pioglitazone relative to the use of other hypoglycaemic agents, we restricted the cohort to members initiating any single diabetes pharmacotherapy, defined as the "index therapy," with follow-up from the date of initiation ("baseline"). This pharmacoepidemiologic approach is called the "new-user" design(10) in which the cohort is restricted to patients initiating therapy. Comparisons that synchronise patients at the time of therapy initiation (i.e., "new users" only), particularly those initiating single therapies, provide a less biased assessment of drug effect than comparisons of drug initiators to others in a cohort which includes patients who are stable, ongoing users of therapy and which excludes patients who may have already discontinued therapy because they experienced an adverse effect. Also, while patients may switch therapies due to adverse effects, most patients initiate intensified therapy because they have failed to maintain adequate glycaemic control with their previous regimens(2). Thus, patients who initiate a new diabetes therapy, particularly a therapy not considered to be first-line, may be more likely to have poorer glycaemic control and more advanced disease, and thus greater risk for adverse effects, than those who maintain previous therapy. However, even this design has the potential for bias, albeit a conservative one, since strategies of diabetes therapy intensification likely lead physicians to use TZDs later among patients who are sicker.

We included only health plan members who met all of the following eligibility conditions: a) maintained continuous health plan membership for one year prior to baseline (i.e., date of initiation); b) diagnosed with type 2 diabetes prior to 1999; c) initiated a single index therapy after the introduction of pioglitazone onto the Kaiser Permanente drug formulary (October 1999) and before one month prior to the end of the study (November, 2001); d) refilled the index therapy prescription at least once after initiation and before one month prior to the end of follow-up; and e) maintained adequate pill supply (i.e., ≥ 80% adherence during follow-up based on pharmacy records for refill frequency and days supply). We excluded patients with any utilisation of the index therapy in the 12 months previous to baseline. In order to simplify analytic assessment of effect, we excluded the 2% of new users that initiated multiple index therapies. Thus, our cohort could be divided into mutually exclusive exposure groups defined by a single index therapy. Prospective follow-up from baseline to study end resulted in roughly comparable length of exposure to each therapy. We defined "maintained therapies" as those diabetes medications that were used 1) prior to the initiation of the index therapy and 2) throughout the period from baseline to the end of the period of observation. Thus if a patient was on insulin and added pioglitazone during our observation window (i.e., is switched from insulin monotherapy to insulin-pioglitazone combination therapy at baseline), then we would classify pioglitazone as the "index therapy", while insulin would be classified as the "maintained therapy". We excluded patients with prevalent CHF, defined as an outpatient, emergency room, or hospital discharge diagnosis of congestive heart failure recorded within 5 years prior to baseline. Patients with type 1 diabetes were excluded by default since they do not switch therapeutic class. Members not covered by a pharmacy benefit (4.2%) were excluded to minimise under-ascertainment of pharmacy utilisation. Patients without this benefit have been shown to be more likely to fill their prescriptions at non-Kaiser Permanente pharmacies, for which we have no records (Karter, unpublished report). Study subjects were followed from baseline until incident CHF hospitalisation, and were censored at the time of discontinuation of the index therapy or the addition of a new diabetic medication, loss to follow-up, or the end of the study on December 31, 2001. All laboratory tests were performed at Kaiser Permanente regional laboratories, and test results were obtained from the regional laboratory database.

Exposure Categorisation

To ascertain exposure to diabetes medications, we used a computerised pharmacy database (Pharmacy Information Management System) which is used for all Kaiser Permanente pharmacy operations. Pharmacy personnel enter data in real time on each outpatient and inpatient prescription before the medication can be dispensed. Because the data are used to prepare the prescription label, they are considered complete and accurate. Exposure to each index diabetes medication was categorised specifically as pioglitazone, sulfonylurea, metformin, or insulin. Acarbose, repaglinide, miglitol and the non-formulary TZD (rosiglitazone) were rarely used during the study period, and their exposure data were excluded due to insufficient sample size to support statistical analysis.

Outcome of Interest

All CHF hospitalisations occurring in Kaiser Permanente hospitals were captured via Kaiser Permanente's hospital discharge automated records. Any events occurring in non-Kaiser Permanente hospitals were captured through a claims database for all outside medical services. The *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes for primary discharge diagnosis were used to identify CHF (ICD-9-CM codes 401.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.93, 428.0, 428.1, 428.9, 4251, 4254, 4255, 4257). In a previous chart review validation study,(28) 97% of CHF cases identified by automated records met either the major or minor Framingham criteria for heart failure.(29) As Kaiser Permanente Northern California clinical guidelines recommend hospitalisation for patients with no prior CHF who develop a first episode of moderate or severe CHF, who are unstable, or who have uncontrolled diabetes mellitus, it is likely that by using CHF hospitalisations as our endpoint, we captured nearly all episodes of CHF. To minimise misclassification, we excluded outpatient diagnoses of CHF because these often represent clinical suspicion or "rule-out CHF" work-up, rather than actual CHF events.

Statistical Methods

The demographic and clinical characteristics of patients taking each index therapy were described with simple (unadjusted) summary statistics. Age- and sex-adjusted incidence densities of CHF hospitalisation were estimated for users of each index therapy. Cox proportional hazards models were specified to examine the effect of index therapy on the time from baseline to first hospitalisation for CHF. Because our design dictated that use of any of the four index therapies was mutually exclusive, we specified three dummy variables (one each for initiation of pioglitazone, metformin and insulin), with sulfonylurea initiators serving as the reference group. Sulfonylurea initiators were chosen as the reference group because 1) sulfonylureas are the first-line therapy for diabetes; and 2) sulfonylureas are not suspected to increase the risk of CHF. Fifty-eight percent of patients starting these index therapies were also taking additional, maintained therapies as part of a combination regimen. Because use of the maintained therapies were not mutually exclusive, we parameterised the model with indicator flags for each maintained therapy, allowing us to statistically adjust for the unique combinations of therapies these new users were exposed to.

First, a multivariate model was specified using each index therapy (or exposure of interest) and potential confounders including patient age and sex, and indicators for the maintained therapies that are used in combination with the index therapies (Model 1). Next, this model enhanced by including prevalent ischemic heart disease, haemoglobin A_{1c} (HbA_{1c}), serum creatinine, non-HDL cholesterol, diagnoses of hypertension, microalbuminuria, and proteinuria; dispensing of lipid-lowering medication, beta blockers, diuretics, angiotensin converting enzyme-(ACE) inhibitors or angiotensin II receptor blockers (ARB); diabetes medication refill adherence (using standard pharmacoepidemiologic methods(30;31)), and a

validated comorbidity weighting score(32) based on total healthcare utilisation (Model 2). Pharmacy utilisation was assessed during the year prior to baseline. Laboratory values were assessed within one year prior to baseline. There were no missing data in models 1. For model 2, missing indicators were specified for patients who had missing administrative data. To assess whether the potential effect of pioglitazone on CHF may differ between subgroups at higher risk for CHF, we assessed interactions between known CHF risk factors and diabetes therapy by testing the statistical significance of cross-product terms (e.g., prevalent IHD × diabetes therapy) and specifying stratified analyses. These stratifying factors included: prevalent IHD versus no prevalent IHD; elevated serum creatinine (>176.8 μmol/L) versus normal levels; and poor glycaemic control (HbA_{1c} >9.5) versus HbA_{1c} ≤9.5. All continuous variables were coded categorically. We verified that our data were consistent with Cox model's proportional hazards assumption.

RESULTS

We identified 23,440 Kaiser Permanente members who initiated a single diabetes therapy, did not have prevalent CHF and met our other inclusion criteria during the observation period. Study subjects were followed for a mean of 10.2 months after baseline. The distribution of index therapies and characteristics of patients initiating each of these therapies is shown in Table 1.

Compared to those initiating other therapies, pioglitazone initiators had a higher prevalence of many CHF risk factors, including the greatest prevalence of ischemic heart disease, hypertension, elevated serum creatinine, microalbuminuria, and the poorest glycaemic control; and the lowest mean HDL. Pioglitazone initiators were far more likely to be taking other diabetes mediation in combination with pioglitazone. Pioglitazone initiators were the most likely to be prescribed medications for dyslipidemia and hypertension, and had the greatest outpatient and inpatient utilisation. Thus, pioglitazone was initiated more frequently in diabetic patients with more advanced disease and longer duration of diagnosed diabetes.

Three hundred and twenty of the 23,440 study subjects without prevalent CHF were hospitalised for CHF for the first time during the period of study. The age and sex-adjusted incidence density was 21.5 incident cases per 1000 person-years (95% CI: 18.7-24.6). The rate was not significantly different for men (22.6 cases per 1000 p-yrs; 95% CI: 18.6-27.1) and women (20.4 cases per 1000 p-yrs; 95% CI: 16.6-24.7). The age and sex-adjusted incidence rate of CHF hospitalisation was highest among patients initiating insulin (56.3 cases per 1000 p-yrs; 95% CI: 33.9-86.1), followed by pioglitazone initiators (32.9 cases per 1000 p-yrs; 95% CI: 23.9-43.8), sulfonylurea initiators (25.4 cases per 1000 p-yrs; 95% CI: 20.3-31.2), and metformin initiators (12.9 cases per 1000 p-yrs; 95% CI: 9.9-16.3). The median time (unadjusted) from drug initiation to incident CHF hospitalisation for those who developed heart failure was 5.9 months overall and 5.3 months for initiation of pioglitazone, 1.5 months for initiation of insulin, 6.0 months for initiation of sulfonylureas and 7.5 months for initiation of metformin.

Relative to sulfonylurea initiation, use of pioglitazone was not associated with a significant increase in risk of CHF hospitalisation in models adjusted for age and sex and the use of maintained therapies (Model 1). This lack of effect remained despite further adjustment for a wide range of clinical factors including prevalent ischemic heart disease, hypertension diagnosis, HbA_{1c}, serum creatinine, lipid levels; dispensing of lipid-lowering medication, beta blockers, diuretics, ACE inhibitors or ARB; diabetes medication refill adherence, and an inpatient and outpatient risk adjuster (Model 2). Moreover, the relationship between pioglitazone use and incidence of CHF hospitalisation was not significantly different for those with versus without conditions that elevate CHF risk including prevalent IHD, poor

glycaemic control (HbA_{1c} >9.5%), or elevated serum creatinine (data not shown). This suggests that initiation of pioglitazone did not introduce a short-term increase in risk of CHF over that incurred when initiating sulfonylureas.

Initiating insulin, on the other hand, was associated with a significantly increased risk of incident CHF hospitalisation relative to initiating sulfonylureas. This increase was significant in the model (Model 1) adjusting for age, sex, and maintained therapy use (HR = 2.23; 95% CI: 1.44 – 3.46; p = 0.0003), but was attenuated after adjusting for clinical factors in the fully adjusted model (Model 2) (HR = 1.56; 95% CI: 1.00 – 2.45; p = 0.05). Metformin initiation was significantly protective; associated with a 40% lower CHF hospitalisation incidence than sulfonylurea initiation in the fully adjusted model (HR = 0.70; 95% CI: 0.49 – 0.99; p = 0.05),

DISCUSSION

In this cohort study of 23,440 diabetic patients who initiated a new diabetes therapy and had no prior history of CHF, initiation of pioglitazone was not associated with a significantly increased risk of CHF hospitalisation relative to those initiating the first line therapy, sulfonylureas. The lack of an association between pioglitazone and CHF hospitalisation was consistent across subgroups with differing risk of CHF. In particular, we found no statistical difference in the pioglitazone-CHF hospitalisation relationship among those with and without prevalent IHD, poor glycaemic control, and elevated serum creatinine, each of which are known risk factors for CHF among patients with diabetes.(28;33). Our findings of elevated risk of CHF hospitalisation associated with insulin and decreased risk associated with metformin initiation was consistent with previous research.(34)

Observational studies are particularly vulnerable to bias because there may be substantial imbalance in risk of events or disease severity between therapy exposure groups (confounding by indication(35)). Pharmacoepidemiologic studies comparing therapy initiators to ongoing users encounter bias (case-mix imbalance) because patients who initiate new therapies are often sicker than ongoing users.(10) In our study of patients initiating new diabetes medications, we observed substantially elevated prevalence of several markers of disease severity, particularly poor glycaemic control, relative to ongoing users.(22)

Another potential source of bias is called “chronology bias”(36). If the risk of an adverse event and therapy discontinuation is greatest soon after drug initiation, then higher risk individuals are eliminated and the ongoing users who remain are at relatively lower risk. The comparison of drug initiators to ongoing drug users may be biased, in addition to an increased likelihood of case mix imbalances.(10) Thus the association between TZDs and CHF recently reported by Delea et al.(12) (comparing TZD new users to ongoing users of all other therapies) may be attributable in part to residual biases mentioned above, rather than to any causal association between TZDs and CHF. The “new user” design avoids both chronology bias and imbalances in disease risk between therapy initiators and ongoing users by restricting analysis to comparisons among initiators, i.e., “new users”. In some cases clinical disparities between pioglitazone initiators and the rest of the diabetes registry were large; 43.6% of pioglitazone initiators had HbA_{1c} >9.5% (vs. 21.1% in the rest of the registry), 20.3% had prevalent ischemic heart disease (vs. 15.0%), 17.6% had elevated serum creatinine (vs. 11.3%), 44.3% had diagnosed hypertension (vs. 33.0%), and 39.6% were treated for dyslipidemia (versus 21.8%). Even when restricting to new users, however, we found that pioglitazone initiators were sicker than patients who initiated other diabetes therapies. Compared to patients initiating other therapies, pioglitazone initiators had the greatest prevalence of ischemic heart disease (20.3% in pioglitazone initiators vs. 15.9% in initiators of other therapies), hypertension (44.3% vs. 37.1%), microalbuminuria (37.6% vs.

32.6%), proteinuria (6.9% vs. 3.2%), use of antilipemic therapy (39.6% vs. 28.5%), morbid (class 2) obesity (24.0% vs. 21.6%), and highest comorbidity weighting score for inpatient (1.78 vs. 1.41) and outpatient (2.13 vs. 1.77) utilisation score.

Because metformin was contraindicated for patients with CHF at the time of the study, physicians would likely have discontinued this therapy at the first sign of fluid retention, before reaching the point of a CHF hospitalisation. This would make metformin appear protective, since patient follow-up was censored in the analysis at the point of discontinuation of initiated therapy. It is possible that physicians were also more vigilant for CHF symptoms among the patients they treated with pioglitazone than among other patients, although warnings about this potential adverse effect did not appear until 2001. It is unlikely, however, that a physician would miss the diagnosis of CHF severe enough to warrant hospitalisation.

These study findings are limited by reliance on observational, non-randomised data. We have adjusted for a wide range of clinically relevant covariates; however as in all observational studies, there remains the chance that our estimate of risk is biased due to omitted variables. The mean follow-up period of 10.2 months was relatively short, thus limiting statistical power and our ability to detect pioglitazone-associated CHF that might occur only after longer-term exposure to therapy. Future ascertainment of outcomes during a longer period of follow-up is needed. We did not have the clinical information necessary to classify the severity of heart failure in terms of functional status (New York Heart Association class), left ventricular function, atrial fibrillation or systolic function (ejection fraction). While we are unaware of any evidence suggesting that differing etiologies (e.g., systolic vs. diastolic dysfunction vs. myocardial ischemia) of CHF modify the relationship between type of diabetes therapy and CHF risk, this possibility can not be ruled out. Due to incomplete data on some of the clinical indicators (23% of the subjects in Model 3 lacked at least one of the model covariates), we needed to rely on missing indicators. However, study findings based on these models with less complete data were consistent with models based on complete data (Model 2).

Our model specification precluded certain comparisons because, for a given subject, any therapy that was initiated (the index therapy) could not also be a maintained therapy. For example, subjects who started insulin as an index therapy could not simultaneously have insulin as a maintained therapy. Thus CHF rates, adjusted for (conditioned on) maintained therapy, could only be compared between subsets of new users of two index therapies if they 1) did not use additional (maintained) therapies, or 2) used the same maintained therapy (which must differ from the two index therapies being compared). Maintained therapies may play a role in the development of CHF, and thus we felt it was important to make comparisons for subjects that were adjusted for maintained therapy despite this inherent limitation. When we removed “maintained therapy” from Model 2 and thus excluded no subjects, the hazard ratios associated with CHF changed minimally: from 1.28 (95% CI: 0.85 -1.92) to 1.11 (95% CI: 0.80 -1.55) for pioglitazone; from 0.70 (95% CI: 0.49 – 0.99) to 0.62 (95% CI: 0.47 - 0.82) for metformin, and from 1.56 (95% CI: 1.00 -2.45) to 1.42 (95% CI: 0.92 -2.19) for insulin. Thus point estimates and overall interpretation were quite similar between models with and without adjustment for maintained therapy, suggesting that this issue should be of limited concern.

We also did not investigate the effects of pioglitazone on weight gain or oedema, which are known effects of TZDs. However, Tang et al. have shown that the peripheral oedema caused by TZDs is not necessarily related to the development of CHF(37). By limiting our outcome to inpatient diagnoses of CHF, it is possible that we did not capture those mild cases of CHF that were treated exclusively in outpatient clinics. However, our outcome of inpatient CHF

has been validated for our study population(28). Inclusion of outpatient diagnoses would have limited our ability to draw accurate conclusions, as such diagnoses may represent an ongoing work-up for possible CHF, and are not as specific as those made during hospitalisation. Moreover, outpatient diagnoses would be substantially more vulnerable to detection bias associated with heightened vigilance for CHF symptoms among TZD users. Additionally, our findings are limited to the effect of pioglitazone only, and it is unclear as to whether these findings are generalisable to the other TZD, rosiglitazone.

The major strengths of this study is the “new-user” design, and thereby its avoidance of chronology bias introduced when new users of drugs are compared to ongoing users of drugs(10;36). Our ability to collect and control for a wide range of relevant medical conditions, behaviours and intermediate markers of clinical control afford a unique ability to assess differences in case mix across exposure groups.

In addition to its antihyperglycaemic properties(7;38;39), there is emerging evidence that TZDs have other important benefits,(3) including favorable decreases in triglycerides,(40) blood pressure,(38) intimal wall thickness,(41) changes in inflammatory markers(4) and favorable redistribution of visceral adiposity.(6) However, given the association between TZD use and fluid retention and case reports of CHF onset, it is important to assess the impact of longer-term exposures to TZD on CHF incidence. This impact, if any, must be weighed against the known benefits of improved glycaemic control in reducing risk of microvascular and macrovascular complications.

Even the largest well-designed clinical trials conducted to gain pre-market approval may fail to undercover serious adverse effects that surface in widely used therapies.(42) Spontaneous adverse drug reaction reports from post-marketing surveillance are subject to over-interpretation given the often atypical clinical characteristics of cases (confounding), unawareness of the population background rate, and exaggerating effect of media focus, (43;44) underscoring the importance of large epidemiologic studies to estimate the risk of adverse events associated with drug use.(43) Physicians are faced with difficult decisions regarding how to balance competing risks and benefits when deciding upon the best therapy for their diabetic patients.

We conclude from our data that short-term exposure to pioglitazone treatment, relative to other diabetes therapies, does not confer excess risk of CHF hospitalisation among patients with diabetes without prevalent CHF. Although in stark contrast to the findings of one early study by Delea et al., our findings are consistent with another study which provides an even more rigorous and conservative assessment of risk. Masoudi et al. studied 16,156 diabetic patients hospitalised with a primary discharge diagnosis of CHF and discharged on TZDs and metformin (despite both being contraindicated for patients with CHF).(45) These authors reported a 30% and 25% lower mortality rate among those discharged on TZD and metformin, respectively, but no lowering in mortality among those discharged on sulfonylureas or insulin. Their and our findings suggest that, despite existing recommendations against such use, insulin sensitisers may have important benefits in this high risk population which need to be reexamined in further studies.

There is the potential for harm to the public’s health when effective treatments are discontinued due to perceived risks in the absence of complete or unbiased data. At the same time, given TZD’s association with oedema, there is no doubt that clinical vigilance is vital. We await the publication of randomised controlled clinical trials of TZDs (e.g., the *Action to Control Cardiovascular Risk in Diabetes or ACCORD Trial*) in comparison with other therapies, in order to most reliably determine the effect of this class of medication upon CHF incidence.

Acknowledgments

This study was funded by a clinical research grant through the American Diabetes Association. We would like to thank Drs. Joe Selby, Assiamira Ferrara, Jonathan Brown, Gregg Nichols, Alan Go, and Carlos Irribaren for comments on earlier drafts, and the American Diabetes Association and American Heart Association's Working Group on Glitazones and Congestive Heart Failure for thought-provoking discussions on this topic.

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Abbreviations

CHF	Congestive heart failure
TZD	thiazolidinedione
HbA_{1c}	haemoglobin A_{1c}
ACE	angiotensin converting enzyme
ARB	angiotensin receptor blocker
BMI	body mass index
IHD	ischemic heart disease
HDL	high density lipoprotein
HR	hazard ratio
UKPDS	United Kingdom Prospective Diabetes Study

Diabet Med. Author manuscript; available in PMC 2013 January 29.

Table 1

Baseline characteristics* of the study sample by index therapy.

	All therapy initiators N (%)	**PIO N (%)**	**SU N (%)**	**MET N (%)**	**INS N (%)**
N (%)	23,440 (100%)	3,556 (15.2)	5,921 (25.3)	11,937 (50.9)	2,026 (8.6)
Mean age (SD)	58.9 (12.3)	60.2 (11.3)	59.9 (12.7)	58.5 (11.6)	56.1 (15.3)
Female (%)	11,150 (47.6)	1735 (48.8)	2677 (45.2)	5671 (47.5)	1067 (52.7)
Number of maintained diabetes therapies used in combination with index therapy (%)					
No additional drug (i.e., index therapy is used as monotherapy)	9841 (42.0)	348 (9.8)	5,098 (86.1)	3,296 (27.6)	1,099 (54.2)
1 additional drug	11,488 (49.0)	1,672 (47.0)	784 (13.2)	8,440 (70.7)	592 (29.2)
2 additional drugs	2,071 (8.8)	1,497 (42.0)	39 (0.7)	201 (1.7)	334 (16.5)
3 additional drugs	40 (0.2)	39 (1.1)	0 (0)	0 (0)	1 (0.1)
Maintained diabetes therapies used in combination with each index therapy‡					
Sulfonylureas	10,514 (44.9)	2352 (66.1)	NA	7459 (62.5)	703 (43.7)
Metformin	2867 (12.2)	1690 (47.5)	623 (10.5)	NA	554 (27.3)
Insulin	2358 (10.1)	741 (20.8)	237 (4.0)	1380 (11.6)	NA
HbA_{1c}					
Mean (SD)	9.4 (2.0)	9.6 (1.7)	8.9 (2.1)	9.6 (1.9)	9.8 (2.4)
≤7%	1867 (9.1)	146 (4.4)	854 (17.7)	674 (6.2)	202 (12.0)
7-8%	3542 (17.2)	457 (13.8)	1152 (24.1)	1708 (15.8)	225 (13.3)
8-9.5%	6647 (32.3)	1271 (38.5)	1325 (27.7)	3634 (33.6)	417 (24.7)
>9.5%	8525 (41.4)	1427 (43.2)	1462 (30.6)	4790 (44.3)	846 (50.1)
Hypertension					
Antihypertensive prescription within 1 year prior to baseline	15,482 (66.0)	2812 (79.1)	3397 (57.4)	7969 (66.8)	1304 (64.4)
Hypertension diagnosis	8719 (37.2)	1585 (44.6)	1966 (33.2)	4460 (37.4)	708 (35.0)
Prevalent Ischemic Heart Disease	3735 (15.9)	736 (20.7)	901 (15.2)	1742 (14.6)	356 (17.6)
History of myocardial infarction	1531 (41.0)	269 (36.6)	407 (45.2)	708 (40.6)	147 (41.3)
History of revascularisation procedures (i.e., CABG and PTCA)	1376 (36.8)	262 (35.6)	307 (34.1)	675 (38.8)	132 (37.1)
Renal function					
Mean serum Creatinine, μmol/L (SD)	79.6 (44.2)	88.4 (53.0)	88.4 (44.2)	79.6 (17.7)	97.2 (97.2)

	All therapy initiators N (%)	PIO N (%)	SU N (%)	MET N (%)	INS N (%)
Elevated Cr (>176.8 μmol/L)	1811 (9.4)	562 (17.7)	493 (11.1)	491 (4.9)	265 (15.5)
Normoalbuminuria	6104 (63.6)	1053 (55.6)	1299 (68.2)	3268 (65.7)	484 (58.5)
Microalbuminuria	3120 (32.5)	708 (37.4)	540 (28.3)	1603 (32.2)	269 (32.5)
Proteinuria	381 (4.0)	134 (7.1)	67 (3.5)	106 (2.1)	74 (9.0)
Dyslipidemia					
Prescription for cholesterol-lowering medication within 1 year of baseline	6743 (28.8)	1433 (40.3)	1351 (22.8)	3457 (29.0)	502 (24.8)
Mean total cholesterol, (SD)mmol/L	5.48 (1.17)	5.37 (1.13)	5.61 (1.24)	5.48 (1.13)	5.33 (1.23)
Mean LDL Cholesterol, (SD)mmol/L	3.15 (0.95)	3.01 (0.93)	3.24 (0.98)	3.17 (0.92)	3.01 (0.99)
Mean HDL Cholesterol, (SD)mmol/L	1.17 (1.31)	1.16 (0.30)	1.19 (0.31)	1.17 (0.29)	1.19 (0.35)
Mean Triglycerides, (SD)mmol/L	6.55 (7.91)	6.59 (6.25)	6.70 (7.44)	6.54 (8.62)	6.63 (7.34)
Comorbidity Weighting Score †					
Outpatient utilisation weighting (median)	1.78	2.14	1.63	1.72	1.95
Inpatient utilisation weighting (median)	1.41	1.79	1.32	1.34	1.65
Low medication refill adherence (patients filling less than half of prescribed oral agent supply)	404 (1.8)	43 (1.2)	110 (2.0)	173 (1.5)	78 (5.4)

PIO=pioglitazone; SU=any sulfonylureas; MET=metformin; INS=insulin; SD= Standard Deviation

*Characteristics are presented by treatment use; categories are mutually exclusive.

†Comorbidity Weight Score(32) based on outpatient and inpatient utilisation.

‡These are not mutually-exclusive categories because one or more of these maintained therapies may be used in combination with the index therapy. Additionally, pioglitazone is not represented among the maintained therapies because study follow-up starts when pioglitazone was first introduced onto the Kaiser formulary (precluding previous and ongoing utilisation).

Table 2

Hazard ratios (HR) for the effect of index therapy from Cox proportional hazard models of incident CHF hospitalisation. Sulfonylurea initiators were specified as the reference group.

Therapy	Model 1†		Model 2‡	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Pioglitazone initiation	1.41 (0.94 – 2.11)	0.1	1.28 (0.85 -1.92)	0.2
Insulininitiation	2.23 (1.44 – 3.46)	0.0003	1.56 (1.00 – 2.45)	0.05
Metformin initiation	0.56 (0.40 – 0.80)	0.001	0.70 (0.49 – 0.99)	0.05

*Model 1 adjusted for maintained therapies, age and sex.

†Model 2 adjusted for other maintained therapies, age, sex, outpatient and inpatient diagnoses of ischemic heart disease, non-HDL cholesterol levels, HbA_{1C}, urinary albumin excretion, serum creatinine, hypertension diagnosis, other medication use (beta adrenergic blocker, diuretic, angiotensin converting enzyme-inhibitors (ACE), angiotensin receptor blockers (ARB), calcium channel blocker, other antihypertensives or antilipemics), oral diabetes medication refill adherence, self-monitoring of blood glucose, inpatient and outpatient risk adjuster score. Missing indicators included for subjects lacking data on all covariates.