Rapid identification of myocardial infarction risk associated with diabetic medications using electronic medical records

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Objective: To assess the ability to identify potential association(s) of diabetic medications with myocardial infarction (MI) using usual care clinical data obtained from the electronic medical record.

Research Design and Methods: We defined a retrospective cohort of patients (n=34,253) treated with a sulfonylurea, metformin, rosiglitazone, or pioglitazone in a single academic health care network. All patients were over 18 years of age with at least one prescription for one of the medications between January 1st, 2000 and December 31st, 2006. The study outcome was acute MI requiring hospitalization. We used a cumulative temporal approach to ascertain the calendar date for earliest identifiable risk associated with rosiglitazone compared to other therapies.

Results: 11,200, 12,490, 1,879, and 806 patients were prescribed sulfonylurea, metformin, rosiglitazone, or pioglitazone therapy, respectively. 1,343 MIs were identified. After adjustment for potential MI risk factors, relative risk for MI with rosiglitazone was 1.3 (95% CI, 1.1-1.6) compared to sulfonylurea, 2.2 (95% CI, 1.6-3.1) compared to metformin, and 2.2 (95% CI 1.5-3.4) compared to pioglitazone. Prospective surveillance using these data would have identified increased risk for MI with rosiglitazone compared to metformin within 18 months of its introduction with a risk ratio of 2.1 (95% CI 1.2-3.8).

Conclusions: Our results are consistent with a relative adverse cardiovascular risk profile for rosiglitazone. Our use of usual care electronic data sources from a large hospital network represents an innovative approach to rapid safety signal detection that may enable more effective post-marketing drug surveillance.
Adverse events that occur infrequently during pre-marketing randomized clinical trials or are under-reported with traditional post-marketing methods of drug surveillance underscore needs for additional methodologies and data sources to monitor drug safety. Critical insights may be realized by monitoring large clinical databases using automated data feeds in near real-time. Diabetes medications present an ideal paradigm to test new safety signal detection approaches as they are used frequently in large numbers of patients with type 2 diabetes, and new products have been recently launched while suitable drug comparators remain marketed. Existing concerns over adverse cardiovascular risk for diabetes therapies provide motivation for hypothesis-driven prospective surveillance. Rosiglitazone has been implicated to have adverse cardiovascular side effects. Although a recent non-inferiority clinical trial has provided some evidence exonerating risk for excess mortality, concern remains regarding possible adverse risk for myocardial infarction. We test an automated strategy analyzing clinical data in real-time to detect adverse drug-related events. Since pre-marketing clinical trials of diabetes therapies are currently designed primarily to evaluate efficacy for glycemic improvement, and have not previously been designed to assess relatively infrequent but clinically important adverse outcomes, active surveillance may play a valuable role in assessment of risk. Active surveillance could provide evidence of risk earlier than post-marketing outcome trials. Furthermore, it may be cost prohibitive to conduct randomized control trials for each drug product toward important hard safety outcomes. While such an analysis would not provide conclusive causal evidence, we determine whether prospective analysis of clinical data could have provided early evidence of cardiovascular risk associated with rosiglitazone that would warrant additional evaluation.

RESEARCH DESIGN AND METHODS
Study Setting and Population: We identified a cohort of patients newly prescribed diabetes medications within Partners Healthcare System, a large, non-profit academic health care network including Brigham and Women's and Massachusetts General Hospitals. The source of clinical data was the Research Patient Data Registry (RPDR), a centralized data warehouse including patient demographic information, dates of service, medications, diagnoses, laboratory results, and discharge summaries.

The retrospective cohort analysis included all patients aged over 18 years identified by an International Classification of Diseases, Ninth Revision (ICD 9) code for Diabetes Mellitus (250.XX) or an HbA1c of above 6.0 and at least one record of prescription of an oral diabetic medication as an outpatient or dispensation as an inpatient, between January 1st, 2000 and December 31st, 2006. Analyses focused on three classes of diabetic medications: sulfonylureas, the biguanide metformin, and the thiazolidinediones, rosiglitazone and pioglitazone. Evidence of insulin therapy did not exclude patients but was adjusted for in multivariate models and used for stratified analysis (described below). We excluded patients receiving metformin or either thiazolidinedione who carried diagnosis of polycystic ovaries but not diabetes. For each patient, all available

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associated data were extracted, including narrative notes and hospital discharge summaries. Narrative notes were used for validating coded medications and diagnoses found in medical records, permitting determination of sensitivity and specificity of events as recorded in the electronic medical record.

**Patient Enrollment, Observation, Drug Exposure and Event Identification:** The study population does not receive healthcare exclusively within the Partners system, and thus some patients within the surveillance database may have incomplete records. To address this issue, we used healthcare encounters (inpatient or outpatient) as a proxy for receipt of care at Partners over a specific observation period. We constructed 14 six-month observation periods, beginning on January 1\(^{st}\) or July 1\(^{st}\) between 2000 and 2006, during which a patient had a least one outpatient office visit, including psychotherapy or nutrition visits, or an inpatient encounter. Study entry was considered the first period meeting one of these criteria within the study dates.

For each patient, duration of exposure to individual diabetic medications was assessed in six month increments during which only one of the four medications was prescribed. Patients on multiple medications under consideration were excluded. The study endpoint for each evaluable patient was first hospitalization between January 1\(^{st}\) 2000 and December 31\(^{st}\), 2006 for myocardial infarction (MI) (ICD-9 code 410), death (all causes), a gap in care in which there were no patient encounters in subsequent observation periods, or end of study in 2006. The ICD-9 diagnostic code for acute MI has been previously validated.\(^{(7)}\) Events were associated with a particular medication only when the prescription or dispensation occurred within the six months before the documented MI. If a patient did not have any activity for a 6 month observation period but resumed activity in the following period, than the particular 6 month observation period with no activity was excluded from analysis. Analysis was repeated considering only patients having been prescribed one of the four medications, considered to be monotherapy. Finally, we also performed stratification of our data to analyze patients who had not received insulin as outpatient therapy.

We conducted a manual review of outpatient notes and inpatient discharge summaries on a random sample of 200 patients to validate use of electronic medical record data to identify both drug exposure and myocardial infarction events. Review included patients identified as exposed to rosiglitazone and with MI (n=50), or exposed and without event (n=50), as well as the comparator group of patients (on one of the other three oral diabetic medication but not exposed to rosiglitazone) and with (n=50) or without MI event (n=50). Institutional Review Board (IRB) approval was obtained for medical record review.

**Statistical Analysis:** Relative risk of MI associated with therapy was calculated for rosiglitazone compared to metformin, sulfonylureas, or pioglitazone. Both crude and adjusted rate ratios with 95% confidence intervals were estimated using generalized linear modeling, assuming a Poisson distribution for the response and set duration of time on a particular medication (as six month intervals) as the offset. To account for overdispersion in the count data, extra-Poisson variability was modeled and incorporated into estimates of standard errors. Parameter estimates were transformed to rate ratios.
Adjustments were made for potential risk factors including age, gender, cardiovascular disease prior to enrollment (defined by billing codes for coronary artery disease, myocardial infarction, angina, congestive heart failure, cerebrovascular accident, percutaneous coronary intervention, coronary artery bypass graft surgery), any use of hypertensive medications, lipid-lowering medications, and outpatient insulin use during study period. The model also included adjustment for underlying morbidity using an age-adjusted Charlson score. In an additional model, we evaluated potentially important factors for which we had less than complete data. These included race/ethnicity (with information available in 93% of patients), insurance coverage (Commercial, Medicare, Medicaid, Uninsured) (83%), HbA1c (60%), and creatinine (71%) levels. Overall mean HbA1c and creatinine levels (less than or greater than 2.0mg/dL) during the study period were considered indicators of diabetes severity. Differences in these characteristics between medication groups were identified with analysis of variance and Tukey’s post-hoc test. Finally, because previous MI imparts greater risk for recurrent cardiovascular events (8) and the need to consider new starts on medications to minimize potential prolonged effects of prior diabetes therapies on cardiovascular events, we tested a model where all patients who had ever had a recorded inpatient stay for MI or had been prescribed a diabetic medication in the year prior to entry were excluded.

**Signal detection analysis:** To construct a general surveillance approach to identify adverse events from clinical data, we repeated the above analysis using a cumulative temporal approach by the defined six-month intervals. All available data from the first time period (January 1\textsuperscript{st}, 2000 to May 31\textsuperscript{st}, 2000) were analyzed and data were iteratively added with each subsequent six-month period. Cumulative data were analyzed until the final period. Data were treated as cumulative with additional new patients and patient-year exposure providing increased power to the analyses. A significant risk ratio (where the lower bound of the 95% confidence interval was above 1.0) was considered to be a safety signal. All analyses were carried out using the SAS statistical software (version 9.0, SAS Institute Inc., Cary, NC). Numbers of prescriptions of pioglitazone were insufficient for comparison with rosiglitazone until January 1\textsuperscript{st}, 2002.

**RESULTS**

We identified 34,252 diabetic patients treated with at least one of the four diabetic medications between January 1\textsuperscript{st}, 2000 and December 31\textsuperscript{st}, 2006. Of the total 159,586 evaluable six-month intervals, there were 40,695 periods of sulfonylurea therapy (17,157 patients), 48,713 periods of metformin therapy (18,162 patients), 8,707 periods of rosiglitazone therapy (4,274 patients) and 3,591 periods of pioglitazone therapy (1,800 patients). When only one of the four diabetic medications was prescribed in a six-month period, we identified 7,152 patients on sulfonylureas, 8,798 patients on metformin, 1,028 patients on...
rosiglitazone and 418 patients on
pioglitazone. Given the large number of
patients in the different treatment groups,
there were statistically significant,
although generally small, differences in
many baseline variables. These were
adjusted for in analyses to control for
known baseline differences.
We identified 1,343 hospitalized MI
events, and an overall event rate of 16.8
per 1000 patient years. There were 768
events associated with sulfonylureas
(38.0. events per 1000 patient years), 406
with metformin (14.6 events per 1000
patient years), 133 with rosiglitazone
(46.9 events per 1000 patient years), and
36 with pioglitazone (27.9 events per
1000 patients years). Manual review of
235 randomly selected patient records
revealed a high level of confirmation for
drug exposure to individual medications,
with both sensitivity and specificity of
94%. Identification of MI events was
confirmed with a sensitivity of 93% and
specificity of 74%. Lower specificity was
primarily due to presence of previous and
“rule out” MIs noted in patient records.
Overall there were no differences
in specificity and sensitivity of MI by drug
type.
Rosiglitazone was associated with an
unadjusted rate ratio for increased MI of
1.2 (95 percent confidence interval (CI)
1.0-1.3) compared to sulfonylureas, 3.3
(95% CI, 2.9-3.6) compared to metformin,
and 1.7 (95% CI 1.3-2.1) compared to
pioglitazone. After adjustment for
identified risk factors (age, gender,
cardiovascular disease, hypertensive
medications, lipid-lowering medications,
age-adjusted Charlson score), individuals
treated with rosiglitazone had an
increased rate ratio for MI risk of 1.3
(95% CI, 1.0-1.6) compared to
sulfonylurea, 2.7 (95% CI, 2.2-3.4)
compared to metformin, and 1.7 (95% CI
1.1-2.6) compared to pioglitazone.
Additional adjustments for factors with
limited data in our patient population
(race/ethnicity, insurance coverage,
HbA1c and creatinine levels) resulted in
only small differences in adjusted relative
risk. In the model with additional factors
not available for the entire population,
rosiglitazone was associated with a
relative risk of MI compared to sulfonylurea, metformin, and pioglitazone
of 1.4 (95% CI 1.0-1.9), 2.4 (95% CI 1.0-
4.2), and 2.0 (95% CI 1.0-4.2),
respectively. Analyses restricted to
patients without prior MI (29,055 out of
34,252) and patients with no prior diabetic
medication in the 12 months before
enrollment (30,142 out of 34,252), had no
effect on model results.
Considering only patients on
monotherapy, rosiglitazone was
associated with an unadjusted rate ratio
for increased MI of 1.1 (95% CI 1.0-1.3)
compared to sulfonylureas, 3.5 (95% CI
3.1-3.9) compared to metformin, and 1.9
(95% CI 1.4-2.5) compared to
pioglitazone. After adjustment for
identified risk factors, individuals treated
with rosiglitazone had an increased rate
ratio for MI of 1.2 (95% CI, 1.0-1.4)
compared to sulfonylurea, 2.5 (95% CI,
2.0-3.2) compared to metformin, and 1.7
(95% CI 1.3-2.2) compared to
pioglitazone. In the model with additional
factors not available for the entire
population, rosiglitazone was associated
with a relative risk of MI compared to
sulfonylurea, metformin, and pioglitazone
of 1.3 (95% CI 1.1-1.6), 2.2 (95% CI 1.6-
3.1), and 2.2 (95% CI 1.5-3.4),
respectively.
After performing stratification of our data
to analyze patients who had not received
insulin as an outpatient therapy, we found
rosiglitazone was associated with an
unadjusted rate ratio for increased MI of
1.3 (95% CI 1.1-1.4) compared to sulfonylurea and 3.5 (95% CI 3.2-3.9) compared to metformin. After adjustment for identified risk factors, individuals treated with rosiglitazone had an increased rate ratio for MI risk of 1.3 (95% CI, 1.0-1.7) compared to sulfonylureas, and 3.0 (95% CI, 2.4-3.7) compared to metformin. In the model with additional factors not available for the entire population, rosiglitazone was associated with a relative risk of MI compared to sulfonylureas and metformin of 1.4 (95% CI 1.0-2.0) and 2.6 (95% CI 1.8-3.6), respectively. No MIs were identified among the 594 patients receiving pioglitazone without additional insulin outpatient therapy.

The iterative temporal analysis to define the earliest possible date a safety signal would have been detected (Figure 1) demonstrates a safety signal would have been identified for rosiglitazone compared to metformin after 18 months in July, 2001 with an adjusted risk ratio of 2.1 (95% CI 1.2-3.8). Compared to sulfonylurea or pioglitazone, rosiglitazone safety signals would have been identified by January 2005 with adjusted risk ratios of 1.2 (95% CI 1.1-1.8) and 1.8 (95% CI 1.0-3.4), respectively.

CONCLUSIONS
A recent meta-analysis of available case-control and cohort studies derived from the rosiglitazone phase III clinical data set suggested a 43% increase risk for cardiovascular events in patients receiving rosiglitazone.(3) Many factors contribute to uncertainty regarding these findings, including availability of only summary trial-level data rather than patient-level data, heterogeneity of trial design, and absence of uniform event adjudication.(9) However, review of patient level data by the FDA yielded similar relative risk findings.(10) Absolute risk was low as cardiovascular event rates were sparse in these studies and statistical methods to deal with infrequent event rates yield uncertainty regarding validity of the risk.(11) Likewise, phase IV studies in patients with type 2 diabetes have neither confirmed nor excluded an increased hazard ratio for rosiglitazone.(12; 13) and similarly large randomized multicenter trials in high risk diabetes patients with substantial use of rosiglitazone neither confirm nor exclude increased risk (14; 15). The recently completed phase IV RECORD study was designed as a non-inferiority study comparing rosiglitazone plus either sulfonylurea or metformin versus metformin and sulfonylurea. While it was underpowered and treatment crossover complicated interpretation of findings, relative risk for mortality was approximately 1.0; however risk for myocardial infarction with rosiglitazone was 1.14, leaving the risk of rosiglitazone for myocardial infarction uncertain.(5) In contrast, results of randomized phase IV clinical trials and meta-analyses have suggested pioglitazone to be neutral to favorable in cardiovascular risk profile.(16; 17)

The thiazolidenediones, rosiglitazone and pioglitazone, both gained FDA approval within a short time span, have similar indications for being prescribed, similar cost, and initially without apparent prescription bias. Comparison of these two products reduces likelihood of co-morbidities and unmeasured variables confounding findings, which might cause greater potential bias for drugs of different class, cost, or safety profiles. Thus, evaluating cardiovascular safety of approved oral diabetes therapies in a real-world setting provides context, internal model validation, and potentially
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valuable clinical information for health care providers. Our results are consistent with previously suggested protective effect for metformin (18), more neutral effect for pioglitazone (16; 17) and potential relative adverse cardiovascular safety profile for rosiglitazone (19; 3; 4; 20). In particular, our results comparing rosiglitazone with pioglitazone complement other recent findings (19; 20) and are not likely to be confounded by indication, given the similar prescribing patterns. Together, these findings demonstrate methods for medical record surveillance may provide useful adjunct methods to assess post-marketing drug safety.

It is interesting that the relative risk confidence limits boundary either touches or is near 1.0 in all analysis for rosiglitazone compared to sulfonylureas. Sulfonylureas are established agents used for the treatment of type 2 diabetes since approval in the 1950’s. Our findings are consistent with those in the meta-analysis performed by the FDA (10) which suggested no increase in risk for rosiglitazone compared to this established therapeutic class. Our results do differ somewhat from other recent studies. An analysis of potentially more robust data showed similar trends of decreased relative risk for cardiovascular disease with metformin, and increased relative risk for sulfonylureas, but they did not show significant increased relative risk for rosiglitazone compared to pioglitazone.(21) However, this finding contrasts other observational studies showing increased risk with rosiglitazone.(19; 22) Differences between patient populations, absolute event rates or in methodologies may underlie differences in magnitude of relative risks in such studies. Importantly, combined treatments for dyslipidemia, hypertension, anti-thrombotic agents, and glycemia have markedly reduced event rates in patients with type 2 diabetes, and these gains are realized using strategies that include rosiglitazone.(13; 14) Relative risk analysis may be used to inform a provider regarding priority for selecting among treatment options, but individual patient co-morbidities and tolerance must also be considered when choosing among specific therapeutic options, and absolute risk must be carefully considered before withholding a therapeutic option. Our analysis does have important limitations. We do not have complete longitudinal prescription data for all individual patients, and patients may not take medication that has been prescribed. Hence we cannot confirm for all patients whether they were on a medication at time of MI. Although we have derived an estimate of recent exposure, defining true exposure is currently not possible with usual clinical data. We may also have missed cases that did have exposure. Prescriptions for diabetic medications may have been obtained outside Partners system and might therefore not have been captured. However, this would underestimate rather than overestimate drug risk. Our use of other diabetic medications as comparator, however, should reduce or eliminate the majority of these potential biases although we cannot fully exclude biases introduced by physicians or patients leading to selection of specific drugs. Additionally, there may be increased cardiovascular risk with rosiglitazone for patients using insulin, which may also be a surrogate for duration of diabetes. In addition to adjusting for insulin in our models, we performed stratification, yielding very similar results. Notably, no patients
receiving pioglitazone without additional outpatient insulin were identified to have an MI. Future analyses should consider drug combinations as concomitant use of insulin and thiazolidinediones may be particularly unfavorable.\cite{10, 21} Furthermore, our low specificity for detection of MI events of 74% is of particular concern indicating a need for future analyses to incorporate laboratory data to verify the occurrence of MI more accurately. Composite end points of major adverse cardiovascular events (MACEs) are standard measures for comparing treatments in large cardiovascular outcome studies. Our analysis included only myocardial infarction while other cardiovascular events, such as sudden death and stroke, were not considered in this analysis. Finally, if there is increased health risk shortly after initiation of therapy that is abrogated with longer duration administration, then cumulative assessments including additional new patients and patient-year exposure would tend to bias towards early risk. The control of residual confounders in observational data is an important issue. Approaches addressing this issue medical record data include comparing risk in groups for the measured outcome before and after an exposure \cite{23} to test if a group was at prior higher risk, picking comparable exposures (medications in the same class) where heuristically there is no reasonable argument for differences in groups, and global, accepted measurements of acuity (such as the Charlson score) that may be used to detect differences in underlying health of groups. We selected the latter method as there was some suggestion of risk differences for the two marketed thiazolidendione products available for study. While the increased risk ratio for rosiglitazone compared to other diabetes medications has been demonstrated in more robust clinical datasets with adequate longitudinal records of patients\cite{21}, the current study provides two novel and important insights. First, with need to monitor numerous products and numerous potential events, it is increasingly difficult to develop randomized clinical trials adequately addressing all potential study bias and confounding factors. From a surveillance perspective, a real-time strategy detecting risk that may require further investigation is potentially more cost-effective than numerous long-term investigations into one drug-one event relationships. Moreover, designing studies to identify relatively infrequent, but medically important, adverse events that would likely be missed by phase III clinical trials and current post-marketing voluntary reporting mechanisms would likely be expensive and curtail or delay development of new treatments. Surveillance analysis should be guided by a priori evidence (such as non-statistically significant adverse events) from phase III clinical trials to limit potential for false positives. It is important to note surveillance methods work best when agents have adequate population uptake. For instance, time to identify signal comparing rosiglitazone and pioglitazone was delayed because of low samples sizes for both drugs. Methodologies that improve detection performance especially when drugs and events are rare, or permit all possible drug-event interactions are described elsewhere.\cite{24} Second, our study shows how relatively simple clinical surveillance methods can be implemented in real-time. With availability of electronic datasets such as the one used herein, it is possible to carry

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out analyses of drug-event combination prospectively on a quarterly, monthly or even weekly basis. In this study, we demonstrate that if these methods had been in use when thiazolidendiones were first introduced to market, a potential hazard would have been apparent approximately 18 months after launch, in 2001, well before concerns were raised publicly in 2007.(3) This time frame is also faster than would be realized in phase IV post-marketing trials, and may cause less delay than requiring cardiovascular outcome trials prior to FDA approval for diabetes medications that do not have adverse safety signal in aggregate phase II-III study analysis. While these methods would not provide the same degree of information as a prospective randomized control trial, they might provide caution to care providers faced with multiple newer medications options to prescribe, fulfilling clear needs for complimentary approaches (25)

Our study provides a framework for implementation of future post-marketing surveillance activities with semi-automated extraction of large clinical datasets. Despite inherent limitations, these data can provide robust real-time signals of adverse drug events in the post-marketing setting. How such systems will interact with activities at FDA requires thoughtful consideration.

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Figure Legend
Figure 1. Temporal analysis to ascertain the calendar date for earliest identifiable risk associated with rosiglitazone compared to other therapies is shown with each curve represents relative risk ratio of MI for patients on rosiglitazone compared to alternatively prescribed medications (sulfonylurea, metformin, pioglitazone).
REFERENCES


### Table 1. Characteristics of the population

<table>
<thead>
<tr>
<th></th>
<th>Rosiglitazone</th>
<th>Metformin</th>
<th>Sulfonylurea</th>
<th>Pioglitazone</th>
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<tr>
<td>Total Patients</td>
<td>1879</td>
<td>12490</td>
<td>11200</td>
<td>806</td>
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<tr>
<td>Age Mean (SD)</td>
<td>64.0 (11.4)</td>
<td>61.7 (12.2)</td>
<td>65.8 (12.1)</td>
<td>63.7 (11.5)</td>
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<td>Gender – female</td>
<td>908 (48.3)</td>
<td>6628 (53.1)</td>
<td>4760 (42.5)</td>
<td>384 (47.6)</td>
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<td>MI outcome</td>
<td>133 (7.1)</td>
<td>406 (3.3)</td>
<td>768 (6.9)</td>
<td>36 (4.5)</td>
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<td>Prior MI</td>
<td>234 (12.5)</td>
<td>1421 (11.4)</td>
<td>1945 (17.4)</td>
<td>94 (11.7)</td>
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<tr>
<td>Prior CVD</td>
<td>597 (31.8)</td>
<td>3369 (27.0)</td>
<td>4544 (40.6)</td>
<td>251 (31.1)</td>
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<td>Hypertension</td>
<td>1689 (89.9)</td>
<td>10454 (83.7)</td>
<td>(90.0)</td>
<td>709 (88.0)</td>
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<td>Hyperlipidemia</td>
<td>1466 (78.0)</td>
<td>8484 (67.9)</td>
<td>7545 (67.4)</td>
<td>602 (74.7)</td>
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<td>Chronic renal insufficiency (Cr &gt; 2 mg/dl)</td>
<td>338 (18.0)</td>
<td>936 (7.5)</td>
<td>2374 (21.2)</td>
<td>121 (15.0)</td>
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<td>Outpatient insulin use</td>
<td>446 (23.7)</td>
<td>2341 (18.7)</td>
<td>1425 (12.7)</td>
<td>263 (32.6)</td>
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<td>HbA1c (SD)</td>
<td>8.0 (1.7)</td>
<td>7.8 (1.7)</td>
<td>7.7 (1.7)</td>
<td>8.1 (1.8)</td>
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<td>Antihyperlipidemic medication use</td>
<td>1340 (71.3)</td>
<td>7721 (61.8)</td>
<td>6610 (59.0)</td>
<td>556 (69.0)</td>
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<td>Combination</td>
<td>35 (1.9)</td>
<td>90 (0.7)</td>
<td>80 (0.7)</td>
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<td>Fibrates</td>
<td>191 (10.2)</td>
<td>887 (7.1)</td>
<td>730 (6.5)</td>
<td>86 (10.7)</td>
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<td>6428 (57.4)</td>
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<td>9358 (74.9)</td>
<td>8620 (77.0)</td>
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<td>ACE Inhibitors</td>
<td>1096 (58.3)</td>
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<td>1697 (15.2)</td>
<td>170 (21.1)</td>
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<td>1315 (11.7)</td>
<td>123 (15.3)</td>
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<td>Alpha-Beta</td>
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<td>739 (5.9)</td>
<td>1068 (9.5)</td>
<td>47 (5.8)</td>
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<td>5 (0.3)</td>
<td>67 (0.5)</td>
<td>73 (0.7)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Unclassified Combinations</td>
<td>10 (0.5)</td>
<td>24 (0.2)</td>
<td>17 (0.2)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Age Adjusted Charlson Score Mean(SD)</td>
<td>7.9 (4.4)</td>
<td>7.1 (4.2)</td>
<td>8.5 (4.5)</td>
<td>7.5 (4.2)</td>
</tr>
</tbody>
</table>

* values are Number (%) unless otherwise noted.
# Age at index date
Myocardial infarction risk associated with diabetic medications