# Beneficial Effects of Thiazolidinediones on Myocardial Infarction Risk in Patients with Type 2 Diabetes

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## Abstract

Type 2 diabetes is associated with increased cardiovascular risk. Thiazolidinediones (TZDs), effective antidiabetic agents, have been shown to improve insulin sensitivity, enhance endothelial function and reduce mediators of prothrombotic activity and inflammatory markers of cardiovascular risk. A case-control study was conducted to determine whether TZDs alter the risk of myocardial infarction (MI) compared to traditional antidiabetic agents.

Incident cases of MI hospitalizations among type 2 diabetic patients were identified from the Integrated Healthcare Information Services (IHCIS) managed care database from 1997 and 2002. Patients with prior MI were excluded. Six controls were matched to each case on age, gender and calendar year of MI diagnosis (index year). The odds of MI were modeled using conditional logistic regression, adjusting for age, gender, index-year, Nitrate use, ACE inhibitors, Beta-blockers, diuretics, hyperlipidemia and hypertension.

Two hundred and twenty nine incident cases of MI hospitalizations were matched to 1,374 controls. Compared to insulin monotherapy, TZD use was associated with 49% reduction in the risk of MI (95% CI = 0.27-0.95). Among specific TZDs, the adjusted odds ratio for rosiglitazone on MI risk was 0.43 (95% CI = 0.19-0.97) and that for pioglitazone was 0.61 (95% CI = 0.27-1.39).

TZD use is associated with a reduction in MI risk in type 2 diabetes. This potentially translates into economic benefit. Numerous outcomes studies are in progress to prospectively confirm these findings.

## Introduction

Type 2 diabetes is associated with increased cardiovascular risk. Thiazolidinediones (TZDs), effective antidiabetic agents, have been shown to improve insulin sensitivity, enhance endothelial function and reduce mediators of prothrombotic activity and inflammatory markers of cardiovascular risk. A case-control study was conducted to determine whether TZDs alter the risk of myocardial infarction (MI) compared to traditional antidiabetic agents.

## Aims

The primary objective of this study is to determine if the odds of myocardial infarction development differs in TZD exposed patients compared to other antidiabetic agents adjusting for differences in case mix and disease severity given the observational nature of the study.

## Methods

A nested case-control study design was used in which incident cases of MI hospitalizations among type 2 diabetic patients were identified from a cohort of type 2 diabetics in the Integrated Healthcare Information Services (IHCIS) managed care database from 1997 and 2002. Patients with prior MI were excluded. Six controls were matched to each case on age, gender and calendar year of MI diagnosis (index year). The odds of MI were modeled using conditional logistic regression, adjusting for age, gender, index-year, Nitrate use, ACE inhibitors, Beta-blockers, diuretics, hyperlipidemia and hypertension.

**Table 1: Descriptive statistics of the overall cohort and the cases and controls**

| | Overall Cohort | | Case Patients | | Control Patients | |
|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | N | (%) |
| Total | 213,143 | (100) | 229 | (100) | 1374 | (100) |
| Age category | | | | | | |
| <30 | 10,784 | (5.06) | 1 | (0.44) | 5 | (0.36) |
| 30-45 | 47,550 | (22.31) | 19 | (8.30) | 119 | (8.66) |
| 45-65 | 137,091 | (64.32) | 168 | (73.36) | 1022 | (74.38) |
| ≥65 | 17,718 | (8.31) | 41 | (17.90) | 228 | (16.59) |
| Mean age (SD) | 51.60 | (12.51) | 59.06 | (10.25) | 58.58 | (9.98) |
| Gender | | | | | | |
| Male | 118,637 | (55.66) | 159 | (69.43) | 954 | (69.43) |
| Female | 94,506 | (44.34) | 70 | (30.57) | 420 | (30.57) |
| Mean length of follow up yrs (SD) | 0.36 | (0.44) | .70 | (0.48) | 0.46 | (0.49) |
| Concomitant diseases | | | | | | |
| Hyperlipidemia | 58,424 | (27.41) | 72 | (31.44) | 456 | (33.19) |
| Hypertension | 80,438 | (37.74) | 112 | (48.91) | 608 | (44.25) |
| Concomitant medication use | | | | | | |
| Diuretics | 43,308 | (20.32) | 83 | (36.24) | 343 | (24.96) |
| B blockers | 30,606 | (14.36) | 142 | (62.01) | 245 | (17.83) |
| ACE inhibitors | 76,732 | (36.00) | 137 | (59.83) | 561 | (40.83) |
| Lipid_lowering drugs | 72,982 | (34.24) | 150 | (65.50) | 565 | (41.12) |
| Nitrate use | 2,067 | (0.97) | 85 | (37.12) | 17 | (1.24) |

## Results

The overall incidence rate of MI in the diabetic cohort was 2.94 per thousand person-years (95% CI = 2.58 - 3.35 per thousand person-years).

Two hundred and twenty nine incident cases of MI hospitalizations were matched to 1,374 controls.

Compared to insulin monotherapy, TZD use was associated with 49% reduction in the risk of MI (95% CI = 0.27-0.95). Among specific TZDs, the adjusted odds ratio for rosiglitazone on MI risk was 0.43 (95% CI = 0.19-0.97) and that for pioglitazone was 0.61 (95% CI = 0.27-1.39).

**Table 2: Risk of MI by current use (within past 3 months) of specific antidiabetic therapy* regimens among diabetic patients in the IHCIS database, 1997-2002:**

| | Reference group= no therapy | | |
|---|---|---|---|
| | Controls n=1374 | Cases n=229 | Adjusted OR** |
| **Oral Monotherapy** | | | |
| SU | 324 (23.58) | 48 (20.96) | 0.55 (0.36-0.84) |
| Metformin | 157 (11.43) | 20 (8.73) | 0.54 (0.31-0.95) |
| **Oral Dual Bicombinations** | | | |
| Metformin with SU | 221 (16.08) | 27 (11.79) | 0.50 (0.30-0.82) |
| **Thiazolidinediones** | | | 0.45 (0.25-0.83) |
| Rosiglitazone | 83 (6.04) | 9 (3.93) | 0.39 (0.18-0.85) |
| Pioglitazone | 62 (4.51) | 8 (3.49) | 0.55(0.24-1.23) |

*Categories of antidiabetic exposure are mutually exclusive.
** Adjusted for age, gender, index-year, ACE inhibitor use, Beta-blocker use, diuretic use, nitrate use, drugs to treat hyperlipidemia, hyperlipidemia diagnosis, hypertension diagnosis.

**Table 3: Risk of MI by current use (within past 3 months) of specific antidiabetic therapy* regimens among diabetic patients in the IHCIS database, 1997-2002**

| | Reference group=Insulin monotherapy | | |
|---|---|---|---|
| | Controls n=1374 | Cases n=229 | Adjusted OR** (95% CI) |
| **Oral Monotherapy** | | | |
| SU | 324 (23.58) | 48 (20.96) | 0.62 (0.39-0.98) |
| Metformin | 157 (11.43) | 20 (8.73) | 0.61 (0.34-1.09) |
| **Oral Dual Combinations** | | | |
| Metformin with SU | 221(16.08) | 27 (11.79) | 0.56 (0.33-0.95) |
| **Thiazolidinediones** | | | 0.51 (0.27-0.95) |
| Rosiglitazone | 83( 6.04) | 9 (3.93) | 0.43 (0.19-0.97) |
| Pioglitazone | 62 (4.51) | 8 (3.49) | 0.61(0.27-1.39) |

*Categories of antidiabetic exposure are mutually exclusive.
** Adjusted for age, gender, index-year, ACE inhibitor use, Beta-blocker use, diuretic use, nitrate use, drugs to treat hyperlipidemia, hyperlipidemia diagnosis, hypertension diagnosis.

## Conclusions

TZD use is associated with a with a significant decrease in the likelihood of MI in type 2 diabetic patients compared those taking insulin and to those not taking medication.

This potentially translates into economic benefit.

Numerous outcomes studies are in progress to prospectively confirm these findings.

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