Supplementary Materials

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| Supplementary Table 1: Rosiglitazone Evidence |
|  |  |  |  |  |  |  |  | **Cardiovascular Thrombotic Events Number** |
| **Manufacturer Study ID** | **Completion****Date** |  |  |  |  |  |  | *Rosiglitazone Arm(s)* | *Control Arm* |
| **Indication** | **ROS Dose** | **Arm** | **Age** | **%Male** | **Duration**  | *Total* | *MI* | *CV Death* | *Total* | *MI* | *CV Death* |
| ***PUBLISHED EVIDENCE*** |
| 49653/011[43](#_ENREF_43) a | 09/97 | T2D | 8mg | ROS | 60.7 | 66.9 | 24wk | 357 | 2 | 1 | 176 | 0 | 0 |
| 4mg | ROS | 59.6 | 64.5 |
|  | PBO | 58.8 | 65.8 |
| 49653/020a | 05/98 | T2D | 8mg | ROS | 60.9 | 57.6 | 52wk | 391 | 2 | 0 | 207 | 1 | 0 |
| 4mg | ROS | 60.4 | 68.2 |
|  | GLY | 60.1 | 70.4 |
| 49653/024 a | 02/98 | T2D | 4mg QD | ROS | 57.5 | 58.6 | 26wk | 774 | 1 | 0 | 185 | 1 | 0 |
| 2mg BID | ROS | 56.8 | 59.1 |
| 8mg QD | ROS | 58.9 | 65.7 |
| 4mgBID | ROS | 56.5 | 59.9 |
|  | PBO | 57.7 | 68.8 |
| 49653/093 a | 04/98 | T2D poorly controlled on MET | 8mg | ROS+MET | 57.8 | 60.0 | 26wk | 213 | 0 | 0 | 109 | 1 | 0 |
| 8mg | ROS | 58.8 | 53.7 |
|  | MET | 59.5 | 67.0 |
| 49653/094 a | 03/98 | T2D poorly controlled on MET | 8mg | ROS+MET | 58.3 | 68.2 | 26wk | 232 | 1 | 1 | 116 | 0 | 0 |
| 4mg | ROS+MET | 57.5 | 62.1 |
|  | MET | 58.8 | 74.3 |
| 49653/284 | 02/03 | T2D | 4/8mg | ROS+MET | 55.5 | 51.1 | 24wk | 382 | 1 | 0 | 384 | 0 | 0 |
|  | MET | 55.6 | 51.0 |
| 49653/015 | 03/98 | T2D | 4mg | ROS+SUL | 60.6 | 53.2 | 24wk | 395 | 2 | 2 | 198 | 1 | 0 |
| 2mg | ROS+SUL | 61.0 | 62.8 |
|  | SUL | 61.9 | 57.3 |
| 49653/080 | 05/00 | T2D | 8mg | ROS | 55.1 | 75.0 | 156wk | 104 | 1 | 0 | 99 | 2 | 0 |
|  | GLY | 56.1 | 70.1 |
| 49653/082 | 08/98 | T2D poorly controlled by insulin | 8mg | ROS+INS | 57.7 | 54.3 | 26wk | 212 | 2 | 1 | 107 | 0 | 0 |
| 4mg | ROS+INS | 57.1 | 56.6 |
|  | INS | 55.6 | 55.8 |
| 49653/125 | 08/00 | T2D | 4mg | ROS+SUL | 54.6 | 45.7 | 26wk | 175 | 0 | 0 | 173 | 1 | 0 |
|  | SUL | 57.3 | 42.4 |
| 49653/145 | 11/00 | T2D | 8mg | ROS+SUL | 61.1 | 57.3 | 26wk | 231 | 1 | 1 | 242 | 0 | 0 |
|  | SUL | 61.9 | 62.7 |
| 49653/147 | 08/00 | Indo-Asian T2D | 8mg | ROS+SUL | 54.3 | 20.2 | 26wk | 89 | 1 | 0 | 88 | 0 | 0 |
|  | SUL | 54.1 | 25.3 |
| 49653/162 | 04/02 | T2D | 8mg | ROS+GLY | 60.0 | 55.1 | 26wk | 168 | 1 | 1 | 172 | 0 | 0 |
|  | GLY | 59.9 | 61.8 |
| 49653/132 | 02/00 | Chinese T2D | 4mg | ROS+SUL | 58.9 | 47.6 | 24wk | 442 | 1 | 1 | 112 | 0 | 0 |
| 8mg | ROS+SUL | 59.0 | 41.4 |
|  | SUL | 58.8 | 45.7 |
| DREAM | 08/03 | Poor glucose tolerance | 4/8mg | ROS | 54.6 | 41.7 | 156wk | 2635 | 15 | 12 | 2634 | 9 | 10 |
|  | PBO | 54.8 | 39.9 |
| ADOPT | 06/02 | New T2D | 4mg | ROS | 56.3 | 55.7 | 208wk | 1465 | 27 | 2 | 2895 | 41 | 5 |
|  | MET | 57.9 | 59.4 |
|  | GLY | 56.4 | 58.0 |
| ***UNPUBLISHED EVIDENCE*** |
| 100684 | 07/05 | Korean T2D | 4/8mg | ROS+GLY | 55.2 | 53.5 | 52wk | 43 | 0 | 0 | 47 | 1 | 0 |
|  | GLY | 54.5 | 45.6 |
| 49653/143 | 01/03 | T2D poorly controlled on GLY | 8mg | ROS+GLY | 52 | 45.3 | 24wk | 121 | 1 | 0 | 124 | 0 | 0 |
|  | GLY | 53 | 48.3 |
| 49653/211 | 11/03 | T2D w/CHF | 4mg | ROS+UC | 64.3 | 84.3 | 52wk | 110 | 5 | 3 | 114 | 2 | 2 |
|  | UC | 63.9 | 79.0 |
| 712753/008 | 12/05 | T2D poorly controlled on MET | 8mg | ROS+MET | 54.6 | 63.2 | 48wk | 284 | 1 | 0 | 135 | 0 | 0 |
| 4mg | ROS+MET | 56.0 | 65.2 |
|  | MET | 56.9 | 53.4 |
| aIncluded in original approval package , T2D=Type 2 diabetes, ROS=rosiglitazone, MET=Metformin, GLY=glyburide, SUL=sulfonylureas, CHF=chronic heart failure, wk=week, MI=myocardial infarction, CV=cardiovascular, INS=insulin, PBO=placebo, UC=usual care, QD=once daily, BID=twice daily, mg=milligrams |

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| Supplementary Table 1 Cont.: Rosiglitazone Evidence[44](#_ENREF_44) |
|  |  |  |  |  |  |  |  | **Cardiovascular Thrombotic Events Number** |
| **Manufacturer Study ID** | **Completion****Date** |  |  |  |  |  |  | *Rosiglitazone Arm(s)* | *Control Arm* |
| **Indication** | **ROS Dose** | **Intervention** | **Age1** | **%Male1** | **Duration**  | *Total* | *MI* | *CV Death* | *Total* | *MI* | *CV Death* |
| ***UNPUBLISHED EVIDENCE*** |
| 49653/079 | 03/98 | T2D poorly controlled on GLY | 4mg | ROS | 59.1 | 63.6 | 26wk | 203 | 1 | 1 | 106 | 1 | 1 |
| 4mg | ROS+GLY | 57.7 | 69.4 |
|  | GLY | 58.5 | 66.7 |
| 49653/085 | 06/01 | T2D | 4/8mg | ROS+INS | 61.3 | 54.0 | 26wk | 138 | 3 | 1 | 139 | 1 | 0 |
|  | INS | 61.5 | 46.8 |
| 49653/095 | 12/98 | T2D poorly controlled on insulin | 8mg | ROS+INS | 57.4 | 58.9 | 26wk | 196 | 0 | 1 | 96 | 0 | 0 |
| 4mg | ROS+INS | 57.8 | 63.9 |
|  | INS | 58.9 | 45.3 |
| 49653/097 | 01/01 | T2D | 8mg | ROS | 55.8 | 72.1 | 156wk | 122 | 0 | 0 | 120 | 1 | 0 |
|  | GLY | 56.0 | 70.8 |
| 49653/127 | 12/99 | T2D poorly controlled on GLY | 8mg | ROS+GLY | 60.0 | 51.0 | 26wk | 56 | 1 | 0 | 58 | 0 | 0 |
|  | GLY | 59.4 | 66.0 |
| 49653/128 | 06/00 | T2D on concurrent SU | 4mg | ROS | 58.3 | 51.3 | 28wk | 39 | 1 | 0 | 38 | 0 | 0 |
|  | PBO | 57.7 | 42.1 |
| 49653/134 | 08/00 | T2D on GLY and MET | 8mg | ROS+GLY+MET | 55.5 | 62.0 | 28wk | 561 | 0 | 1 | 276 | 2 | 0 |
| 4mg | ROS+GLY+MET | 55.6 | 58.0 |
|  | GLY+MET | 55.8 | 61.0 |
| 49653/135 | 10/02 | Elderly T2D | 4/8mg | ROS+GLP | 68.7 | 74.1 | 104wk | 116 | 2 | 2 | 111 | 3 | 1 |
|  | GLP | 68.2 | 71.2 |
| 49653/136 | 11/00 | T2D with CRF on SU or INS | 4/8mg | ROS+SU+INS | 61.1 | 57.3 | 26wk | 148 | 1 | 2 | 143 | 0 | 0 |
|  | SU+INS | 61.9 | 62.7 |
| 49653/234 | 02/02 | T2D | 8mg | ROS+GLM | 62.9 | 44.0 | 26wk | 116 | 0 | 0 | 61 | 0 | 0 |
| 4mg | ROS+GLM | 60.5 | 57.0 |
|  | GLM | 65.0 | 60.0 |
| 49653/330 | 10/04 | Chronic Psoriasis | 8mg | ROS | 44.3 | 65.0 | 52wk | 1172 | 1 | 1 | 377 | 0 | 0 |
| 4mg | ROS | 44.8 | 66.0 |
| 2mg | ROS | 45.0 | 63.0 |
|  | PBO | 44.5 | 63.0 |
| 49653/331 | 10/04 | Chronic Psoriasis | 4mg | ROS | 44.9 | 64.1 | 52wk | 706 | 0 | 1 | 325 | 0 | 0 |
| 2mg | ROS | 45.2 | 62.0 |
|  | PBO | 46.4 | 58.3 |
| 49653/137 | 03/04 | T2D | >2mg | ROS+MET | 60.0 | 63.4 | 32wk | 204 | 1 | 0 | 185 | 2 | 1 |
|  | GLY+MET | 58.8 | 68.9 |
| SB-712753/002 | 06/04 | T2D poorly controlled | 4/8mg | ROS+MET | 58.1 | 58.3 | 24wk | 288 | 1 | 1 | 280 | 0 | 0 |
|  | MET | 57.6 | 56.8 |
| SB-712753/003 | 12/04 | Mild T2D | 4/8mg | ROS+MET | 58.9 | 54.7 | 32wk | 254 | 1 | 0 | 272 | 0 | 0 |
|  | MET | 59.0 | 55.5 |
| SB-712753/007 | 12/04 | T2D previously treated | 2/8mg | ROS+MET | 50.1 | 57.4 | 32wk | 314 | 1 | 0 | 154 | 0 | 0 |
| 4/8mg | ROS | 51.5 | 56.5 |
|  | MET | 50.6 | 58.5 |
| SB-712753/009 | 11/04 | T2D on insulin | 8mg | ROS,MET+INS | 57.2 | 51.8 | 24wk | 162 | 0 | 0 | 160 | 0 | 0 |
|  | INS | 56.9 | 53.1 |
| AVA100193 | 05/05 | Mild to Moderate Alzheimer’s Disease | 2mg | ROS | 71.0 | 44.1 | 24wk | 394 | 1 | 1 | 124 | 0 | 0 |
| 4mg | ROS | 70.0 | 43.8 |
| 8mg | ROS | 71.0 | 34.1 |
|  | PBO | 72.0 | 36.9 |
| AVM100264 | 01/06 | T2D with high BMI poorly controlled on MET | 4/8mg | ROS+MET | 58.5 | 52.7 | 52wk | 294 | 0 | 2 | 302 | 1 | 1 |
|  | MET+SUL | 59.3 | 52.5 |
| BRL49653C/185 | 05/02 | T2D | 4mg | ROS+MET | 58.0 | 65.2 | 32wk | 563 | 2 | 0 | 142 | 0 | 0 |
| 4mg | ROS | 59.0 | 60.2 |
|  | MET | 60.0 | 56.4 |
|  | UC | 57.0 | 60.9 |
| BRL49653/334 | 11/04 | T2D | 4/8mg | ROS | 67.7 | 44.8 | 52wk | 278 | 2 | 0 | 279 | 1 | 1 |
|  | PBO | 67.3 | 47.7 |
| BRL49653/347 | 04/04 | T2D poorly controlled on INS | 4mg | ROS+INS | 52.6 | 48.1 | 24wk | 418 | 2 | 0 | 212 | 0 | 0 |
| 2/4mg | ROS+INS | 52.7 | 60.0 |
|  | INS | 53.8 | 46.2 |
| aIncluded in original approval package , T2D=Type 2 diabetes, ROS=rosiglitazone, MET=Metformin, GLY=glyburide, SUL=sulfonylureas, CHF=chronic heart failure, wk=week, MI=myocardial infarction, CV=cardiovascular, INS=insulin, PBO=placebo, UC=usual care, QD=once daily, BID=twice daily, mg=milligrams |

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| Supplementary Table 2: Meta-Analysis Results Rosiglitazone (Odds Ratio, 95%CI) |
|  | **Published Trials** | **Unpublished Trials** | **All Trials** |  |
| **Person Year Denominator**  | 1.40 (0.95; 2.05) | 1.49 (0.80; 2.76) | 1.42 (1.03; 1.97) |  |
| **Population Denominator** | 1.40 (0.95; 2.05) | 1.49 (0.80; 2.76) | 1.42 (1.03; 1.97) |  |

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| Supplementary Table 3: Rosiglitazone Cumulative Meta-Analyses |
| **Odds Ratio of Myocardial Infarction** |
| **Date** | ***Published Only*** | ***Harbord*** | ***Peter*** | ***Meta-Trim (Fixed)*** | ***Meta-Trim (Random)*** | ***All Evidence*** |
| 9/1/1997 | 4.46 (0.23; 85.24) |  |  |  |  | 4.46 (0.23; 85.24) |
| 2/1/1998 | 1.06 (0.11; 10.18) |  |  | 0.24 (0.02; 2.45) | 0.24 (0.02; 2.45) | 1.06 (0.11; 10.18) |
| 3/1/1998 | 1.48 (0.20; 10.75) |  |  | 0.24 (0.02; 2.45) | 0.24 (0.02; 2.45) | 1.48 (0.20; 10.75) |
| 3/1/1998 | 1.26 (0.27; 5.83) | 1.06 (0.00; 217,643,726.12) |  | 0.51 (0.10; 2.52) | 0.51 (0.10; 2.52) | 1.26 (0.27; 5.83) |
| 3/1/1998 | 1.26 (0.27; 5.83) | 1.06 (0.00; 217,643,726.12) |  | 0.51 (0.10; 2.52) | 0.51 (0.10; 2.52) | 1.03 (0.27; 4.01) |
| 4/1/1998 | 0.86 (0.21; 3.62) | 9.89 (0.00; 3,370,629.23) |  | 0.51 (0.10; 2.52) | 0.51 (0.10; 2.52) | 0.77 (0.21; 2.81) |
| 5/1/1998 | 0.91 (0.27; 3.11) | 6.23 (0.00; 16,902.60) | 0.02 (0.00; 0.32) | 0.66 (0.18; 2.39) | 0.66 (0.18; 2.39) | 0.83 (0.27; 2.58) |
| 8/1/1998 | 1.16 (0.37; 3.59) | 7.86 (0.01; 11,110.73) | 0.02 (0.00; 0.32) | 0.66 (0.18; 2.39) | 0.66 (0.18; 2.39) | 1.03 (0.36; 2.98) |
| 12/1/1998 | 1.16 (0.37; 3.59) | 7.86 (0.01; 11,110.73) | 0.02 (0.00; 0.32) | 0.66 (0.18; 2.39) | 0.66 (0.18; 2.39) | 1.03 (0.36; 2.98) |
| 12/1/1999 | 1.16 (0.37; 3.59) | 7.86 (0.01; 11,110.73) | 0.02 (0.00; 0.32) | 0.66 (0.18; 2.39) | 0.66 (0.18; 2.39) | 1.19 (0.43; 3.29) |
| 2/1/2000 | 1.22 (0.41; 3.69) | 2.57 (0.01; 734.90) | 0.02 (0.00; 0.32) | 0.66 (0.18; 2.39) | 0.66 (0.18; 2.39) | 1.24 (0.46; 3.37) |
| 5/1/2000 | 1.03 (0.38; 2.77) | 1.03 (0.01; 106.45) | 0.75 (0.03; 18.94) | 0.61 (0.20; 1.83) | 0.61 (0.20; 1.83) | 1.07 (0.43; 2.66) |
| 6/1/2000 | 1.03 (0.38; 2.77) | 1.03 (0.01; 106.45) | 0.75 (0.03; 18.94) | 0.61 (0.20; 1.83) | 0.61 (0.20; 1.83) | 1.18 (0.48; 2.87) |
| 8/1/2000 | 0.91 (0.35; 2.37) | 1.70 (0.02; 132.59) | 0.75 (0.03; 18.94) | 0.61 (0.20; 1.83) | 0.61 (0.20; 1.83) | 1.06 (0.44; 2.52) |
| 8/1/2000 | 1.02 (0.40; 2.60) | 1.04 (0.02; 71.23) | 0.75 (0.03; 18.94) | 0.61 (0.20; 1.83) | 0.61 (0.20; 1.83) | 1.16 (0.50; 2.70) |
| 8/1/2000 | 1.02 (0.40; 2.60) | 1.04 (0.02; 71.23) | 0.75 (0.03; 18.94) | 0.61 (0.20; 1.83) | 0.61 (0.20; 1.83) | 0.91 (0.40; 2.05) |
| 11/1/2000 | 1.14 (0.46; 2.83) | 0.72 (0.01; 41.78) | 0.75 (0.03; 18.94) | 0.61 (0.20; 1.83) | 0.61 (0.20; 1.83) | 0.99 (0.45; 2.20) |
| 11/1/2000 | 1.14 (0.46; 2.83) | 0.72 (0.01; 41.78) | 0.75 (0.03; 18.94) | 0.61 (0.20; 1.83) | 0.61 (0.20; 1.83) | 1.07 (0.49; 2.35) |
| 1/1/2001 | 1.14 (0.46; 2.83) | 0.72 (0.01; 41.78) | 0.75 (0.03; 18.94) | 0.61 (0.20; 1.83) | 0.61 (0.20; 1.83) | 0.99 (0.46; 2.13) |
| 6/1/2001 | 1.14 (0.46; 2.83) | 0.72 (0.01; 41.78) | 0.75 (0.03; 18.94) | 0.61 (0.20; 1.83) | 0.61 (0.20; 1.83) | 1.13 (0.56; 2.32) |
| 2/1/2002 | 1.14 (0.46; 2.83) | 0.72 (0.01; 41.78) | 0.75 (0.03; 18.94) | 0.61 (0.20; 1.83) | 0.61 (0.20; 1.83) | 1.13 (0.56; 2.32) |
| 4/1/2002 | 1.25 (0.52; 3.04) | 0.53 (0.01; 26.48) | 0.75 (0.03; 18.94) | 0.61 (0.20; 1.83) | 0.61 (0.20; 1.83) | 1.21 (0.60; 2.43) |
| 5/1/2002 | 1.25 (0.52; 3.04) | 0.53 (0.01; 26.48) | 0.75 (0.03; 18.94) | 0.61 (0.20; 1.83) | 0.61 (0.20; 1.83) | 1.26 (0.63; 2.50) |
| 6/1/2002 | 1.30 (0.84; 2.03) | 1.29 (0.69; 2.41) | 1.34 (0.80; 2.23) | 0.93 (0.45; 1.94) | 0.93 (0.45; 1.94) | 1.30 (0.86; 1.95) |
| 10/1/2002 | 1.30 (0.84; 2.03) | 1.29 (0.69; 2.41) | 1.34 (0.80; 2.23) | 0.93 (0.45; 1.94) | 0.93 (0.45; 1.94) | 1.25 (0.84; 1.86) |
| 1/1/2003 | 1.30 (0.84; 2.03) | 1.29 (0.69; 2.41) | 1.34 (0.80; 2.23) | 0.93 (0.45; 1.94) | 0.93 (0.45; 1.94) | 1.28 (0.86; 1.89) |
| 2/1/2003 | 1.33 (0.86; 2.06) | 1.25 (0.68; 2.32) | 1.34 (0.80; 2.23) | 0.93 (0.45; 1.94) | 0.93 (0.45; 1.94) | 1.30 (0.88; 1.93) |
| 8/1/2003 | 1.40 (0.95; 2.06) | 1.34 (0.79; 2.29) | 1.44 (0.99; 2.10) | 1.08 (0.57; 2.03) | 1.08 (0.57; 2.03) | 1.36 (0.96; 1.94) |
| 11/1/2003 | 1.40 (0.95; 2.06) | 1.34 (0.79; 2.29) | 1.44 (0.99; 2.10) | 1.08 (0.57; 2.03) | 1.08 (0.57; 2.03) | 1.40 (1.00; 1.98) |
| 3/1/2004 | 1.40 (0.95; 2.06) | 1.34 (0.79; 2.29) | 1.44 (0.99; 2.10) | 1.08 (0.57; 2.03) | 1.08 (0.57; 2.03) | 1.37 (0.98; 1.93) |
| 4/1/2004 | 1.40 (0.95; 2.06) | 1.34 (0.79; 2.29) | 1.44 (0.99; 2.10) | 1.08 (0.57; 2.03) | 1.08 (0.57; 2.03) | 1.39 (0.99; 1.95) |
| 6/1/2004 | 1.40 (0.95; 2.06) | 1.34 (0.79; 2.29) | 1.44 (0.99; 2.10) | 1.08 (0.57; 2.03) | 1.08 (0.57; 2.03) | 1.41 (1.01; 1.97) |
| 10/1/2004 | 1.40 (0.95; 2.06) | 1.34 (0.79; 2.29) | 1.44 (0.99; 2.10) | 1.08 (0.57; 2.03) | 1.08 (0.57; 2.03) | 1.42 (1.01; 1.98) |
| 10/1/2004 | 1.40 (0.95; 2.06) | 1.34 (0.79; 2.29) | 1.44 (0.99; 2.10) | 1.08 (0.57; 2.03) | 1.08 (0.57; 2.03) | 1.42 (1.01; 1.98) |
| 11/1/2004 | 1.40 (0.95; 2.06) | 1.34 (0.79; 2.29) | 1.44 (0.99; 2.10) | 1.08 (0.57; 2.03) | 1.08 (0.57; 2.03) | 1.42 (1.01; 1.98) |
| 11/1/2004 | 1.40 (0.95; 2.06) | 1.34 (0.79; 2.29) | 1.44 (0.99; 2.10) | 1.08 (0.57; 2.03) | 1.08 (0.57; 2.03) | 1.43 (1.02; 1.99) |
| 12/1/2004 | 1.40 (0.95; 2.06) | 1.34 (0.79; 2.29) | 1.44 (0.99; 2.10) | 1.08 (0.57; 2.03) | 1.08 (0.57; 2.03) | 1.44 (1.04; 2.01) |
| 12/1/2004 | 1.40 (0.95; 2.06) | 1.34 (0.79; 2.29) | 1.44 (0.99; 2.10) | 1.08 (0.57; 2.03) | 1.08 (0.57; 2.03) | 1.45 (1.05; 2.02) |
| 5/1/2005 | 1.40 (0.95; 2.06) | 1.34 (0.79; 2.29) | 1.44 (0.99; 2.10) | 1.08 (0.57; 2.03) | 1.08 (0.57; 2.03) | 1.46 (1.05; 2.03) |
| 7/1/2005 | 1.40 (0.95; 2.06) | 1.34 (0.79; 2.29) | 1.44 (0.99; 2.10) | 1.08 (0.57; 2.03) | 1.08 (0.57; 2.03) | 1.44 (1.04; 2.00) |
| 12/1/2005 | 1.40 (0.95; 2.06) | 1.34 (0.79; 2.29) | 1.44 (0.99; 2.10) | 1.08 (0.57; 2.03) | 1.08 (0.57; 2.03) | 1.45 (1.04; 2.01) |
| 1/1/2006 | 1.40 (0.95; 2.06) | 1.34 (0.79; 2.29) | 1.44 (0.99; 2.10) | 1.08 (0.57; 2.03) | 1.08 (0.57; 2.03) | 1.42 (1.03; 1.97) |
| **Date Significant** |  |  |  |  |  | 6/1/2004 |

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| Supplementary Figure 1: Contour-Enhanced Funnel Plots |
|  | ***All*** | ***Published*** |
| Person-Year |  |  |
| Population |  |  |

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| Supplementary Table 4: Meta-Analysis Results Rosiglitazone (Odds Ratio, 95%CI) |
|  | **Published Trials** | **Unpublished Trials** | **All Trials** |  |
| ***Myocardial Infarction*** |
| **Person Year Denominator Adjusted** |  |  |  |  |
| *Fixed Effect1* | 1.36 (0.94; 1.99)  | 1.38 (0.75; 2.55) | 1.37 (0.99; 1.89) |  |
| *Random Effect2* | 1.32 (0.89; 1.95) | 1.41 (0.66; 2.99) | 1.34 (0.95; 1.89) |  |
| *Peto Method* | 1.37 (0.94; 2.01) | 1.37 (0.75; 2.50) | 1.37 (0.99; 1.89) |  |
| *I2 Statistic3* | 0.0%, NS | 0.0%, NS | 0.0%, NS |  |
| **Person Year Denominator Unadjusted** |  |  |  |  |
| *Fixed Effect1* | 1.31 (0.91; 1.88) | 1.21 (0.71; 2.05) | 1.27 (0.94; 1.72) |  |
| *Random Effect2* | 1.30 (0.90; 1.88) | 1.23 (0.69; 2.21) | 1.28 (0.94; 1.75) |  |
| *Peto Method* | 1.40 (0.95; 2.05) | 1.49 (0.80; 2.76) | 1.42 (1.03; 1.97) |  |
| *I2 Statistic3* | 0.0%, NS | 0.0%, NS | 0.0%, NS |  |
| **Population Denominator Adjusted** |  |  |  |  |
| *Fixed Effect1* | 1.37 (0.94; 2.00) | 1.38 (0.75; 2.55)  | 1.37 (0.99; 1.89) |  |
| *Random Effect2* | 1.32 (0.89; 1.96) | 1.41 (0.66; 2.99) | 1.34 (0.95; 1.90) |  |
| *Peto Method* | 1.37 (0.94; 2.01) | 1.37 (0.75; 2.50) | 1.37 (1.00; 1.90) |  |
| *I2 Statistic3* | 0.0%, NS | 0.0%, NS | 0.0%, NS |  |
| **Population Denominator Unadjusted** |  |  |  |  |
| *Fixed Effect1* | 1.31 (0.91; 1.88) | 1.20 (0.71; 2.05) | 1.27 (0.94; 1.72) |  |
| *Random Effect2* | 1.30 (0.90; 1.89) | 1.23 (0.69; 2.21) | 1.28 (0.94; 1.75) |  |
| *Peto Method* | 1.40 (0.95; 2.05) | 1.49 (0.80; 2.76) | 1.42 (1.03; 1.97) |  |
| *I2 Statistic3* | 0.0%, NS | 0.0%, NS | 0.0%, NS |  |
| ***Cardiovascular Death*** |
| **Person Year Denominator Adjusted** |  |  |  |  |
| *Fixed Effect1* | 1.39 (0.72; 2.70) | 1.63 (0.72; 3.67) | 1.49 (0.89; 2.48) |  |
| *Random Effect2* | 1.24 (0.62; 2.49) | 1.50 (0.60; 3.78) | 1.33 (0.76; 2.32) |  |
| *Peto Method* | 1.37 (0.72; 2.61) | 1.60 (0.74; 3.45) | 1.46 (0.89; 2.39) |  |
| *I2 Statistic3* | 0.0%, NS | 0.0%, NS | 0.0%, NS |  |
| **Person Year Denominator Unadjusted** |  |  |  |  |
| *Fixed Effect1* | 1.29 (0.70; 2.41) | 1.39 (0.68; 2.83) | 1.33 (0.83; 2.13) |  |
| *Random Effect2* | 1.27 (0.67; 2.39) | 1.37 (0.64; 2.91) | 1.31 (0.81; 2.13) |  |
| *Peto Method* | 1.49 (0.77; 2.89) | 1.89 (0.83; 4.30) | 1.64 (0.98; 2.74) |  |
| *I2 Statistic3* | 0.0%, NS | 0.0%, NS | 0.0%, NS |  |
| **Population Denominator Adjusted** |  |  |  |  |
| *Fixed Effect1* | 1.39 (0.72; 2.70) | 1.63 (0.72; 3.67) | 1.49 (0.89; 2.48) |  |
| *Random Effect2* | 1.24 (0.62; 2.50) | 1.50 (0.60; 3.78) | 1.33 (0.76; 2.32) |  |
| *Peto Method* | 1.38 (0.72; 2.62) | 1.60 (0.74; 3.45) | 1.46 (0.89; 2.40) |  |
| *I2 Statistic3* | 0.0%, NS | 0.0%, NS | 0.0%, NS |  |
| **Population Denominator Unadjusted** |  |  |  |  |
| *Fixed Effect1* | 1.29 (0.69; 2.41) | 1.38 (0.68; 2.82) | 1.33 (0.83; 2.13) |  |
| *Random Effect2* | 1.27 (0.67; 2.39) | 1.37 (0.64; 2.90) | 1.31 (0.80; 2.13) |  |
| *Peto Method* | 1.49 (0.77; 2.89) | 1.89 (0.83; 4.30) | 1.64 (0.98; 2.74) |  |
| *I2 Statistic3* | 0.0%, NS | 0.0%, NS | 0.0%, NS |  |
| 1Fixed effect meta-analysis performed via Mantel-Hanszel model, 2Random effect meta-analysis performed via DerSimonian and Laird model, *3 I2 is reported for* Mantel-Hanszel model |

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| Supplementary Table 5: Rosiglitazone Cumulative Meta-Analysis |
|  | **Zero Unadjusted** | **Zero Adjusted** |
|  | ***All*** | ***Published*** | ***Difference*** | ***All*** | ***Published*** | ***Difference*** |
| ***Myocardial Infarction*** |
| **Person-Year Denominator** |  |  |  |  |  |  |
| Fixed Effect | 06/14/2007 | 06/14/2007 | 0 months | 06/14/2007 | 06/14/2007 | 0 months |
| Random Effect | 06/14/2007 | 06/14/2007 | 0 months | 06/14/2007 | 06/14/2007 | 0 months |
| Peto | 06/01/2004 | 06/14/2007 | 36 months | 12/01/2004 | 06/14/2007 | 30 months |
| **Population Denominator** |  |  |  |  |  |  |
| Fixed Effect | 06/14/2007 | 06/14/2007 | 0 months | 06/14/2007 | 06/14/2007 | 0 months |
| Random Effect | 06/14/2007 | 06/14/2007 | 0 months | 06/14/2007 | 06/14/2007 | 0 months |
| Peto | 06/01/2004 | 06/14/2007 | 36 months | 12/01/2004 | 06/14/2007 | 30 months |
| ***Cardiovascular Death*** |
| **Person-Year Denominator** |  |  |  |  |  |  |
| Fixed Effect | NS | NS | 0 months | NS | NS | 0 months |
| Random Effect | NS | NS | 0 months | NS | NS | 0 months |
| Peto | NS | NS | 0 months | NS | NS | 0 months |
| **Population Denominator** |  |  |  |  |  |  |
| Fixed Effect | NS | NS | 0 months | NS | NS | 0 months |
| Random Effect | NS | NS | 0 months | NS | NS | 0 months |
| Peto | NS | NS | 0 months | NS | NS | 0 months |

**TECHNICAL APPENDIX**:

The central method was cumulative meta-analysis (CMA). CMA is a version of meta-analysis that performs serial pooling of the evidence through time to evaluate how a pooled estimate for treatment effect evolves over time.[23](#_ENREF_23) In practice this can identify the time at which the body of evidence reached a certain level of clinical relevance and statistical significance. For example, when does the confidence interval for the risk of a drug’s serious adverse event exclude the null.

While CMA can provide a visual representation of how the evidence accumulates in both published-only and comprehensive data sets, the question remains whether available methods for statistical adjustment can be used to predict the comprehensive set of studies from the published set using available methods for adjustment. The most commonly used method for adjustment for publication bias, the trim and fill, uses the funnel plot to identify the asymmetric studies around the presumed mean from larger studies and then reflect these studies on the opposite side of the plot to create a symmetrical appearance.[24](#_ENREF_24) Additionally numerous regression based methods are available that incorporate known characteristics of the studies that are available to impute the likely missing studies. Examples of weighted regression techniques for adjusting for publication bias include Harbord,[25](#_ENREF_25) Peters,[26](#_ENREF_26) and Conditional Harbord.[27](#_ENREF_27)

There are a number of regression models that test for the presence of publication bias by measuring the association between study effects size ($T\_{i}$) and some measure of its precision. When such an association is present it is suggestive that there may be a pattern of publication bias. This regression line is then evaluated for the scenario where within-study standard error is zero thereby predicting the result of a study with infinite sample size and thereby presumably estimating the underlying true global effect size ($θ$).[41](#_ENREF_41) One of the most commonly used methods for doing this is the Egger regression. The Egger method was developed to better understand the discordance between meta-analyses and later published large trials that contradicted the results of the meta-analysis.[45](#_ENREF_45) The plot of study level $z\_{i}$ against $prec\_{i}$ that this regression corresponds to the Galbraith radial plot.[46](#_ENREF_46) In the absence of any publication bias this method would predict the linear regression would travel through the origin on the radial plot ($β\_{0}=0$). The slope of this regression indicates the direction and size of the global treatment effect ($θ$). This test has shown erratic performance and a high false positive rate with binary event data,[47-49](#_ENREF_47) and so we have chosen not to use this method in our analysis. Instead the only regression-based methods we have utilized are the Harbord and Peter’s regression.

The Harbord regression was developed to evaluate small study effects which is a broader term for the phenomenon of larger effect sizes in smaller trials that encompasses publication bias as well as other issues around trial quality and sample selection. The model is based on the component scores of the score test, the $Z\_{i}$ or efficient score and the score variance $V\_{i}$. In practice, the Harbord regression is a test of non-zero slope in a linear regression of ($Z\_{i}/V\_{i}$) against $1/\sqrt{V\_{i}}$ with weights of $V\_{i}$.[25](#_ENREF_25) The regression form of this model is expressed as ($Z\_{i}/V\_{i}=β\_{0}+^{β\_{1}}/\_{\sqrt{V\_{i}}}+ω\_{i}$) where $ω\_{i}∼N(0,^{σ^{2}}/\_{V\_{i}} ×ϕ)$ .[41](#_ENREF_41) The validation of this test suggests that it significantly reduces the number of false positive results generated by Egger Test methods. The intercept for the Harbord test provides the estimate of effect size adjusted for publication bias and small study effects.

The Peters regression uses an ordinary least squares regression that does not require structural dependence between effect size and variance. For a binary outcome, this takes the functional form:

$E\left[\hat{θ}\_{i}\right]=α+\frac{β}{a\_{i}+b\_{i}+c\_{i}+d\_{i}}+ε\_{i}$ weighted by $\left(\frac{1}{a\_{i}+b\_{i}}+\frac{1}{c\_{i}+d\_{i}}\right)^{-1}$ where $ε\_{i}∼N(0,se\_{i}^{2} ×ϕ)$

with $a\_{i}$and $b\_{i}$ representing those with the outcome of interest in the treatment and control groups respectively and $c\_{i}$and $d\_{i}$ representing those without the outcome of interest in the treatment and control groups of the $i^{th}$study.[41](#_ENREF_41) Similar to Harbord above, this method reduces type 1 error and has the added advantage of breaking the structural dependence of effect size and variance in the regression form.[26](#_ENREF_26)

Finally, we utilized the non-parametric Trim and Fill method to assess its performance in our cases. The ‘Trim and Fill’ method quantifies the asymmetry present in this plot in order to estimate how the overall effect size would change if studies were added to improve symmetry. The main intent of this procedure in practice is a sensitivity analysis of how responsive the results of a meta-analysis are to unpublished information. The main assumption of this method is that those studies with the most extreme lower-left effect sizes go unpublished. For the set of studies under consideration we first define ($n$) as the number of observed studies around the same clinical question. For this set of studies, there is an assumed global effect size ($θ$) that each study attempts to measure. Each study ($i$) produces an effect size ($T\_{i}$) that approximates ($θ$) with a study-level variance of ($v\_{i}$). As well as the ($n$) studies that were observed, the method assumes there were ($k\_{0}$) unreported studies such that the true number of completed studies is defined as ($N=n+k\_{0}$). There are three proposed estimators for ($k\_{0}$) (equations 1a-c):

1a)$ L\_{0}=\frac{4S\_{rank}-n(n+1)}{2n-1}$ , where $S\_{rank}$ is the Wilcoxon statistic

1b)$ R\_{0}=γ-1$ , where $γ$ is the length of the rightmost run of ranks ≥1 for ($T\_{i}-θ$)

1c)$ Q\_{0}=n-(^{1}/\_{2})-\sqrt{2n^{2}-4S\_{rank}+^{1}/\_{4}}$

The method works by in the following discrete and iterative steps:

1. The global effect size ($\hat{θ}\_{n}$) is calculated using either a fixed or random effect model
2. This estimate ($\hat{θ}\_{1}$) is used to calculate ($S\_{rank}$) and thereby ($k\_{0}$)
3. ($k\_{0}$) number of studies are ‘trimmed’ from the right-hand side of the plot
4. A new adjusted global effect size ($\hat{θ}\_{n+1}$) is calculated using either a fixed or random effect model. Usually the value of ($\hat{θ}\_{n+1}$) will be to the left of ($\hat{θ}\_{n}$) on the funnel plot
5. Steps b-d are repeated until the estimate for ($\hat{θ}$) stabilizes, this usually happens in 2-3 iterations
6. All trimmed studies are then reflected around this final ($\hat{θ}$) with the distance from this adjusted mean determined by their original ($T\_{i}$)
7. Finally the ($\hat{θ}\_{adjusted}$) is recalculated including the reflected ($k\_{0}$) studies on both sides of the final ($\hat{θ}$) calculated in step f

In practice, various combinations of fixed and random effects models can be used for the trim and filling (steps a-f) and the final ($\hat{θ}$) estimation (step g). Combined with the different potential estimators for $k\_{0}$ ($L\_{0},R\_{0}, Q\_{0}$) this means that there are 12 potential ways to adjust via trim and fill methods. The relative performance of these three different methods is the subject of some debate among methodologists. For our purposes we chose the native adjustment methods within our Stata software package ($L\_{0}$) to conduct only two analyses with either a fixed or random effect estimator for both trimming and filling.

Refernce

Rottingen JA, Regmi S, Eide M, *et al* (2013) Mapping of available health research and development data: What’s there, what’s missing, and what role is there for a global observatory? *Lancet* 382, 1286–1307.