

TIGAR™ REPORT REFERENCE LIST:

1. Pearson TA, et al. Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice: A Statement for Healthcare Professionals From the Centers for Disease Control and Prevention and the *American Heart Association*. *Circulation* 2003; 107: 499-511.
2. Ridker PM, Pradhan, A, MacFadyen JG, Libby, P, Glynn RJ. Cardiovascular Benefits and Diabetes Risks of Statin Therapy in Primary Prevention. *Lancet* 2012 August 11; 380(9841): 565-571.
3. Tschritter O, Fritsche A, Thamer C, et al. Plasma Adiponectin Concentrations Predict Insulin Sensitivity of Both Glucose and Lipid Metabolism. *Diabetes* February 2003; vol. 52 no. 2: 239-243.
4. Lindberg S, Jensen JS, Pedersen SH, Galatius S, Frystyk J, Flyvbjerg A, Bjerre M, & Mogelvang R. Low Adiponectin Levels and Increased Risk of T2DM in Patients with Myocardial Infarction. *Diabetes Care*; July 30, 2014; doi: 10.2337/dc14-0932.
5. Mather KJ, Goldberg RB. Clinical use of adiponectin as a marker of metabolic dysregulation. *Clin Endocrin & Metabol* Vol. 28, Issue 1, PP. 107-117, Jan 2014
6. Perreault L, Pan Q, Mather KJ, Watson KE, Hamman RF, Kahn SE. Regression From Prediabetes to Normal Glucose Regulation is Associated with Long-term Reduction in Diabetes Risk: Results from the Diabetes Prevention Program Outcomes Study. *Lancet* 2012 June 16: 379(9833): 2243-2251.
7. Pfützner A, Hanefeld M, Dekordi L, Müller J, Kleine I, Fuchs W, and Forst T. Effect of Pioglitazone and Ramipril on Biomarkers of Low-Grade Inflammation and Vascular Function in Nondiabetic Patients with Increased Cardiovascular Risk and an Activated Inflammation: Results from the PIOace Study. *J of Diab. Sci and Tech*; Vol. 5, Issue 4, July 2011.
8. Forst T, Wilhelm B, Pfützner A, Weber M. et al. Investigation of the vascular and pleiotropic effects of atorvastatin and pioglitazone in a population at high cardiovascular risk. *Diabetes and Vasc Dis Res* 2008 5:298.
9. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DCW, le Roux CW, Ortiz RV, Jensen CB and Wilding JPH. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management, *NEJM* 2015; 373-:11-22 Jul 2, 2015.
10. Pfützner A, Marx N, Lübben G, Langenfeld M, Walcher D, Konrad T, & Forst T. Improvement of Cardiovascular Risk Markers by Pioglitazone is Independent from Glycemic Control: Results from the Pioneer Study. *J Am Coll of Cardiol*. 2005; Vol 45 (12): 1925-31.
11. U. S. Patent 8,329,647, pgs. 4-11.
12. European Patent 2321647 B1, pgs. 2-6.
13. Yale J-f. Oral Antihyperglycemic Agents and Renal Disease: New Agents, New Concepts. *J Am Soc Nephrol* 16: S7-S10, 2005.

14. Glucagon-like peptide-1 (GLP-1) AGONIST – Incretin Mimetics. <http://www.globalrph.com/incretin-mimetics.htm>. Accessed 12/27/2013.
15. DPP-4 INHIBITORS – Dipeptidyl peptidase-4 inhibitor – Gliptins. <http://www.globalrph.com/DPP-4-inhibitors.htm>. Accessed 12/27/2013.
16. Forst, T, Standl E, Höhberg C, Konrad T, Schulze J, Strotmann HJ, Lübben G, Pahler S, Bachinger A, Langenfeld M, & Pfützner A. IRIS II Study: the IRIS-II score—assessment of a new clinical algorithm for the classification of insulin resistance in patients with type 2 diabetes. *Diabet Med* 2004; 21:1149-1153.
17. Pfützner A & Forst T: High-Sensitivity C-reactive protein as Cardiovascular Risk Marker in Patients with Diabetes Mellitus. *Diab. Tech & Ther*; Vol. 8, No. 1 2006 28-36.
18. Pfützner A, Standl E, Hohberg C, Konrad T, Strotmann HJ, Lübben G, Pahler S, Langenfeld MR, Schulze J, & Forst T. IRIS II Study: Intact Proinsulin is confirmed as a Highly Specific Indicator for Insulin Resistance in a Large Cross-Sectional Study Design. *Diabetes Technology & Therapeutics* Vol. 7, No. 3; 2005: 478-486.
19. Hohberg C, Pfützner A, Forst T, Lübben G, Karagiannis E, Borchert M, & Schöndorf. Successful switch from insulin therapy to treatment with pioglitazone in type 2 diabetes patients with residual β -cell function: results from the PioSwitch Study. Selected references *Diabetes, Obesity and Metabolism*, 11, 2009, 464-471.
20. Gupta A, Badyal DK, Khosla PP, Uppal B, Jaison TM, & Chopra S. Effect of atorvastatin on hs-CRP in acute coronary syndrome. *Br J Clin Pharmacol*. 2008 Sep; 66(3): 411-413.
21. AACE /ACE Comprehensive Diabetes Management Algorithm 2015. *Endocrine Practice*. Vol 21 No. 4; April 2015.
22. DeFronzo RA, Goodman AM, & Multicenter Metformin Study Group. Efficacy of Metformin in Patients with Non-Insulin-Dependent Diabetes Mellitus. *N Engl J Med* 1995; 333:541-549 Aug. 31, 1995.
23. UKPDS Group, Diabetes Research Laboratories, Turner R, et. al. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS34). *The Lancet*, Vol 352, Issue 9131; 854-865 12 Sept. 1998.
24. Kapitza C, Forst T, Coester V, Poitiers F, Ruus P, & Hincelin-Méry A. Pharmacodynamic characteristics of lixisenatide once daily versus liraglutide once daily in patients with type 2 diabetes insufficiently controlled on metformin. *Diabet, Obes and Metabol* 15:642-649, 2013
25. Forst T, Weber MM & Pfützner A. Cardiovascular Benefits of GLP-1-Based Therapies in Patients with Diabetes Mellitus Type 2: Effects on Endothelial and Vascular Dysfunction beyond Glycemic Control. *Experimental Diab. Research* 2012; 635472.

26. Forst T, Dworak M, Berndt-Zipfel C, Löffler A, Klamp I, Mitry M, & Pfützner A. Effect of vildagliptin compared to glimepiride on postprandial proinsulin processing in the β cell of patients with type 2 diabetes mellitus. *Diab Obes and Metab*. Feb 6, 2013.
27. Rosenwasser RF, Sultan S, Sutton D, Choksi R & Epstein, BJ. SGLT-2 inhibitors and their potential in the treatment of diabetes. *Diabetes Metab Syndr Obes*. 2013; 6: 453-467.
28. Chao EC. SGLT Inhibitors: A new Mechanism for Glycemic Control. *Clinical Diabetes* 2014; Jan Vol. 32 no. 1 4-11.
29. Galle J, Kleophas W, Dellanna F, HR, Schmid, Forkel C, Dikta G, Krajewski V, Fuchs W, Forst T, & Pfützner A: Comparison of the Effects of Pioglitazone versus Placebo when Given in Addition to Standard Insulin Treatment in Patients with type 2 Diabetes Mellitus Requiring Hemodialysis: Results from the PIOren Study; *Nephron Extra* Vol. 2 No. 1, 2012.
30. Astrup A, Rössner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, Madsen J, Rasmussen MF, and Lean MEJ. Effects of liraglutide in the treatment of obesity: a randomized, double-blind, placebo controlled study. *The Lancet*, Vol. 374, No. 9701, 1606-1616; 7 Nov. 2009
31. Bray GA, Edelstein SL, Crandall JP, Aroda VR, Franks PW, Fujimoto W, Horton E, Jeffries S, Montez M, Mudaliar S, Pi-Sunyer XF, White NH, Knowler WC. Long-Term Safety, Tolerability, and Weight Loss Associated with Metformin in the Diabetes Prevention Program Outcomes Study. *Diabetes Care* 2012 Apr; 35(4): 731-737.
32. Erdmann E, Dormandy J, Wilcox R, Massi-Benedetti M and Charbonnel B. PROactive 07: Pioglitazone in the treatment of type 2 diabetes: Results of the PROactive study. *Vasc Health Risk Manag*. 2007 Aug; 3(4): 355-370. PMID: PMC2291341.
33. Saremi A, Schwenke DC, Buchanan A, Hodis HN, Mack WJ, Banerji A, Bray GA, Clement SC, Henry RR, Kitabchi DT, Mudaliar S, Ratner RE, Stentz FB, Musi N, Tripathy D, Defronzo RA, and Reaven PD. Pioglitazone slows Progression of Atherosclerosis in Prediabetes Independent of Changes in Cardiovascular Risk Factors. *Arterioscler Thromb Vasc Biol*. 2013;33:393-399; Nov. 21, 2012.
34. Defronzo Ra, Tripathy D, Schwenke DC, Banerji MA, Bray GA,, Buchanan Ta, Clement SC, Henry RR, Hodis HN, Kitabchi AE, Mack WJ, Mudaliar S, Ratner RE, Williams K, Stentz Fb, Musi N and Reaven PD. Pioglitazone for Diabetes Prevention in Impaired Glucose Tolerance. *N Engl J Med* 2011; 36:1104-1115 Mar 24, 2011.
35. Dawed AY, Donnelly L, Tavendale R, Carr F, Lesse G, Palmer C, Pearson ER, and Zhou K. CYP2C8 and SLCO1B1 Variants and Therapeutic Response to Thiazolidinediones in Patients with Type 2 Diabetes, *Diabetes Care* 2016 May; dc152464.

36. de Jager J, Kooy A, Lehert P, Wuffele MG, van der Kolk J, Bets D, Verburg J, Donker AJM, and Stehouwer DA. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled study. *BMJ* 2010;340-c2181doi:10.1136.
37. Van Wagner LB and Rinella ME. The role of insulin-sensitizing agents in the treatment of non-alcoholic steatohepatitis. *Therap ADV Gastroenterol.* 2011 Jul; 4(4): 249-263.
38. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC and Inzucchi S. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 diabetes. *NEJM* 2015; 373:2117-2128 November 26, 2015.
39. US FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function {4-8-2016}.
40. Raz I. et al. For the SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 diabetes mellitus. *N Engl J Med* 2013; 369:1317-1326 October 3, 2013.
41. Green JB, and Holman RR et. al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* June 8, 2015/DOI: 10.1056/NEJMoa1501352.
42. Gdovin J, Worley K,, Louder A, Ward M, and Graham J. Retrospective Database Analysis of the Impact of Prior Authorization for Type 2 Diabetes Medications on Health Care Costs in a Medicare Advantage Prescription Drug Plan Population. *JMCP* June 2013; Vol. 19, No. 5: 374-384.
43. Starup-Linde J, Greersen S, Frost M & Vesteraard P. Use of glucose-lowering drugs and risk of fracture in patients with type 2 diabetes. *The Bone J* Feb. 2017; Vol. 95:136-1424.
44. Davignon J. Atherosclerosis: Evolving Vascular Biology and Clinical Implications Beneficial Cardiovascular Pleiotropic Effects of Statins. *Circulation: Journal of American Heart Associations.* 2004; 109: III-39-III-43.
45. Package insert Jardiance™ (Empagliflozin), Boehringer Ingelheim Pharmaceuticals and Eli Lilly & Company web sites new labeling for reduction of risk in cardiovascular disease.
46. Levin D. Pioglitazone, rosiglitazone did not increase bladder cancer risk in patients with type 2 diabetes. *Diabetologia.* 2014; doi:10.1007/s00125-014-3456-9.
47. Levin D, Bell S, Sund R, Hartikainen SA, Tuomilehto J, et.al. on behalf of the Scottish Diabetes Research Network Epidemiology Group. And the Cancer Research Consortium. Pioglitazone and bladder cancer risk: a multi-population pooled, cumulative exposure analysis. *Diabetologia* (2015) 58: 493-504.
48. Hamman RF, Wing RR, Edelstein SL, Lachin JM, Bray GA, Delahanty L, Hoskin M, Kriska AM, Mayer-Davis EJ, Pisunyer X, Regensteiner J, Vendetti B, Wylie-Rosett J, for the Diabetes Prevention Program Research Group. *Diabetes Care.* 2006 Sep; 29(9): 2102-2107. Effect of Weight Loss with Lifestyle Intervention on Risk of Diabetes.

49. Ridker PM. The JUPITER Trial Results, Controversies, and Implications for Prevention. *Circ Cardiovasc Qual Outcomes; AHA J*. DOI: 10.1161/CIRCOUTCOMES.109.868299.
50. Blake GJ, & Ridker PM. Are Statins anti-inflammatory? *Curr Control Trials Cardiovasc Med*. 2000; 1(3): 161-165.
51. Ridker P, Danielson E, Fonseca FAH, Genest J, Gotto Jr. AM, Kastelein JP, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, & Glynn RJ, for the JUPITER Study Group. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-reactive protein. *NEJM*. Nov. 20, 2008; Vol. 359, No. 21. 2195-2207.
52. Albert MA, Danielson E, Rifai N & Ridker P. for the Prince Investigators. The Pravastatin Inflammatory/CRP Evaluation (PRINCE): A Randomized Trial and Cohort Study. *JAMA*, July 4, 2001- Vol 286, No. 1.
53. Rajpathak SN, Kumbhani DJ, Crandall J, Barzilai, Alderman M & Ridker PM. Statin Therapy and Risk of Developing Type 2 Diabetes: A Meta-Analysis *Diabetes Care*. 2009 Oct.; 32(10): 1924-1929.
54. Cederberg H, Stancakova A, Yaluri N, Modi S, Kuusisto J, & Laakso M. Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6 year follow-up study of the METSIM cohort. *Diabetologia* DOI 10.1007/s00125-015-3528-5.
55. Tuccori M, Filion KB, Yin H, Yu OH, Platt RW, & Azoulay I. Pioglitazone use and risk of bladder cancer: population based cohort study. *BMJ* 2016; 352.i1541 / doi: 10.1136/i154.
56. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, Hazlehurst JM, Guo. The LEAN trial team, K, Abouda G, Aldersley MA, Stocken D, Gough SC, Tomlinson JW, Brown RM, Hübscher SG & Newsome PN. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomized, placebo-controlled phase 2 study. *The Lancet* Vol. 387, No. 10019, 679-690 13 Feb. 2016.
57. Portillo-Sanchez P & Cusi K. Treatment of Nonalcoholic Fatty Liver Disease (NAFLD) in patients with type 2 Diabetes Mellitus, a Review Article. *Clinical Diabetes and Endocrinology* DOI: 10.1186/s40842-016-0027-7 12 April 2016.
58. Inzucchi SE, Viscoli CM, Young LH, Furie KL, Gorman M, Lovejoy A, Schwartz GG & Kernan WN. 380-Or / 380 – Diabetes Prevention with Pioglitazone in Insulin Resistant Patients with Cerebrovascular Disease. *American Diabetes Assn. 76th Scientific Session*; June 14, 2014 Session 3-CT-OR14-President's Oral Session.
59. Gerstein AH, Yusuf S, Bosch J, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose or impaired fasting glucose: a randomized controlled trial. *Lancet* 2006; 368:1096-1105.
60. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A & Laakso M. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomized trial. *Lancet* 2002; 359:2072-2077.
61. Rizzo M, Chandalia M, Patti AP, Di Bartolo V, Rizvi AA, Montalto G & Abate N. Liraglutide decreases carotid intima-media thickness in patients with type 2 diabetes: 8-month prospective pilot study. *Cardiovascular Diabetology*; DOI: 10.1186//475-2840-13-49.

62. Gaede P, Oeligaard J, Carstensen BC, Rossing P, Lund-Anderson H, Parving H-H, and Pedersen O. Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial. *Diabetologia* (2016) 59:2298-2307.

63. Pinto SL, Kumar J, Partha G and Bechtol RA. Improving the economic and humanistic outcomes for diabetic patients: making a case for employer-sponsored medication therapy management *ClincoEcon & outcomes Res.* 2013:5153-159.

64. Mikhail Kosiborod, MD, FACC, Presentation at Annual American Association of Cardiology meeting, March 19, 2017, Washington, DC. - See more at: <http://www.acc.org/latest-in-cardiology/articles/2017/03/13/17/58/sun-2pm-cvd-real-study-lower-rates-of-hospitalization-for-hf-in-new-users-of-sgl-2-inhibitors-vs-other-glucose-lowering-drugs-acc-2017#sthash.0yrYMphP.dpuf>.

65. Brunkwall L, Orho-Melander M. The gut microbiome as a target for prevention and treatment of hyperglycaemia in type 2 diabetes: from current human evidence to future possibilities *Diabetologia* (2017) June;60(6):943-951. Doi: 10.1007/s00125-017-4278-3. Epub 2017 Apr 22.

66. Pioglitazone after ischemic stroke or Transient Ischemic attack. Keman WN, Viscol CM, Furie KL, Young LH, Inzuchhi SE, Gorman M, Guarino PD, Lovejoy Am, Peduzzi PN, Conwitt R, Schwartz GG, Adams HP, Berger L, Carolei A, Clark W, Coull B, Ford GA, Kleindorfer D, O'Leary JR, Parsons MW, Ringleb P, Sen S, Spence JD, Tanne D, Wang D & Winder TR. For the IRIS Trial Investigators. *N engl J Med.* 2016 Apr 7; 374(14): 1321-1331.