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CARDIOVASCULAR OUTCOME TRIALS IN TYPE 2 DIABETES: RELIABLE OR BIASED!

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Several recent multinational clinical trials have suggested improvement in cardiovascular outcomes with antihyperglycemic agents in subjects with type 2 diabetes.[1-4] First and foremost, the designs implemented in these trials appear to lack uniformity of methods due to variable management strategies permitted at the discretion of individual investigators in different countries in different parts of the world.[1-8] Moreover, the different ethnic backgrounds, differences in body mass indices or degree of obesity may yield different results since the pathophysiology is apparently dissimilar as well.[9-21] Rise in insulin resistance is a major abnormality in obese subjects with PreDiabetes and diabetes in USA and other western countries in contrast to the decline in insulin secretion as a prime defect in non obese subjects in USA as well as the rest of the world, especially countries in south east Asia documented in several studies.[9-21]

In fact, in recent multinational clinical trials, one using SGLT 2 inhibitor Empagliflozin and the other with Liraglutide showed no improvement in cardiovascular outcomes in subjects with type 2 diabetes in USA in contrast to populations in other countries.[1,4-8] Similar findings are also reported in several multinational studies in subjects manifesting acute heart failure sponsored and funded by drug manufacturers.[22-24] Therefore, the reliability, the validity and the unbiased nature of studies sponsored and funded by the manufacturers of the drugs used in these trials must be questioned as suggested in recently published editorials.[25,26] This concern regarding studies sponsored by drug manufacturers is apparently emboldened by recent publication of a post hoc analysis of SCALE clinical trials conducted by independent investigators showing no improvement in cardiovascular outcomes following therapy with Liraglutide in obese subjects without diabetes in stark contrast to a multinational clinical trial (LEADER) conducted by the manufacturer of Liraglutide documenting improvement in cardiovascular outcomes in subjects with type 2 diabetes.[3-6,27] Therefore, it is distinctly crucial that the reliability and the validity of the conclusions in trials sponsored and funded by manufacturers of the drugs needs be proven and affirmed by evaluation of the data by auditors independent of both the manufacturers as well as participating investigators. Alternatively, these trials must be sponsored by organizations and conducted by investigators independent of drug manufacturers similar to Diabetes Control Complications Trial (DCCT) in subjects with type 1 diabetes as well UKPDS, GRADE, ADVANCE, VADT and ACCORD studies in subjects with type 2 diabetes.[28-43] Unfortunately, FDA approved indication for both Empagliflozin and Liraglutide regarding cardiovascular outcomes despite lack of such an evidence in US population as well as the biased nature of the data.[7]

Finally, the improvement in cardiovascular outcomes in subjects with type 2 diabetes in these clinical trials[1-4] match the data in UKPDS showing lowering of these events including deaths by 14-20% with a decline of 1% in HbA1c.[32-34] Moreover, the failure of Liraglutide to provide cardiovascular benefits in obese subjects without diabetes in contrast to its efficacy in inducing the decline in cardiovascular events in subjects with type 2 diabetes affirms the role of improvement in glycemic control in 'Leader' trial.[2,27] Alternatively, the data in these trials[1-4] appear to be similar to the 'Metabolic memory effect' in DCCT and 'Legacy effect' described in UKPDS, the largest and the longest trials ever conducted in subjects with type 1 and type 2 Diabetes respectively.[30,31,35] Therefore, cardiovascular benefits in these trials if confirmed in independent studies may still be attributed to improvements in glycemic control and are unlikely to be inherent direct influence of the drugs.

REFERENCES

1. Zinman, B., Wanner, C., Lachin, J.M. et al, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England Journal of Medicine, 2015; 373; 2117-2128.
2. Marso SP, Daniels GH, Brown-Frandsen K, et al, Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes.N Engl J Med, 2016; 375(4): 311-22. doi: 10.1056/NEJMoa1603827. Epub 2016 Jun 13.

3. Bruce Neal, M.B, ChB, PhD. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med, 2017; 377(7): 644-657.
4. Schnell O, Rydén L, Standl E, et al, Updates on cardiovascular outcome trials in diabetes. Cardiovasc Diabetol, 2017; 16(1): 128. doi: 10.1186/s12933-017-0610-y.
5. Kabadi UM, Improved All Cause and Cardiovascular Mortality and Morbidity by Empagliflozin: Too Good to Be True! Journal of Diabetes Mellitus, 2016; 6: 132-135. Published Online May 2016 in SciRes. http://www.scirp.org/journal/jdm http://dx.doi.org/10.4236/jdm.2016.62013.
6. Naci, H., Basu, S. and Yudkin, J.S. Preventing Cardiovascular Events with Empagliflozin: At What Cost? The Lancet Diabetes & Endocrinology, 2015; 3: 931. http://dx.doi.org/10.1016/S2213-8587(15)00439-8.
7. Rutten GE, Tack CJ, Pieber TR, et al, cardiovascular risk profiles of US and European participants in the LEADER diabetes trial differ. Diabetol Metab Syndr, 2016; 8: 37. doi 10.1186s13098-016-0153-5.eCollection 2016.
8. Tanaka A, Node K.Increased amputation risk with canagliflozin treatment: behind the large cardiovascular benefit? Cardiovasc Diabetol, 2017; 16(1): 129. doi: 10.1186/s12933-017-0611-x.
9. Berntorp K, Eriksson KF, Lindgärde F. The importance of diabetes heredity in lean subjects on insulin secretion, blood lipids and oxygen uptake in the pathogenesis of glucose intolerance. Diabetes Res, 1986; 3(5): 231-6.
10. Kelley DE, Mokan M, Mandarino LJ. Metabolic pathways of glucose in skeletal muscle of lean NIDDM patients. Diabetes Care, 1993; 16(8): 1158-66.
11. Pigon J, Giacca A, Ostenson CG. et al. Normal hepatic insulin sensitivity in lean, mild noninsulin-dependent diabetic patients. J Clin Endocrinol Metab, 1996; 81(10): 3702-8.
12. Kim J, Choi S, Kong B, Oh Y. et al. Insulin secretion and sensitivity during oral glucose tolerance test in Korean lean elderly women. J Korean Med Sci, 2001; 16(5): 592-7.
13. Amoah AG, Owusu SK, Schuster DP. et al. Pathogenic mechanism of type 2 diabetes in Ghanaians, the importance of beta cell secretion, insulin sensitivity and glucose effectiveness. S Afr Med J, 2002; 92(5): 377-84.
14. Gastaldelli A, Ferrannini E, Miyazaki Y. et al. San Antonio metabolism study. Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study. Diabetologia, 2004; 47(1): 31-9.
15. Alvarsson M, Wajngot A, Cerasi E. et al. K-value and low insulin secretion in a non-obese white population: predicted glucose tolerance after 25 years. Diabetologia, 2005; 48(11): 2262-8.
16. Elder DA, Prigeon RL, Wadwa RP. et al. Beta-cell function, insulin sensitivity, and glucose tolerance in obese diabetic and nondiabetic adolescents and young adults. J Clin Endocrinol Metab, 2006; 91(1): 185-91.
17. Tura A, Mari A, Winzer C. et al. Impaired beta-cell function in lean normotolerant former gestational diabetic women. Eur J Clin Invest, 2006; 36(1): 22-8.
18. P B. The lean patient with type 2 diabetes: characteristics and therapy challenge. Int J Clin Pract Suppl, 2007; (153): 3-9.
19. Suraamornkul S, Kwancharoen R, Ovartlarnporn M. et al. Insulin clamp-derived measurements of insulin sensitivity and insulin secretion in lean and obese asian type 2 diabetic patients. Metab Syndr Relat Disord, 2010; 8(2): 113-8.
20. Morimoto A, Tatsumi Y, Deura K. et al. Impact of impaired insulin secretion and insulin resistance on the incidence of type 2 diabetes mellitus in a Japanese population: the Saku study. Diabetologia, 2013; 56(8): 1671-9.
21. Kabadi UM, Major Pathophysiology in Prediabetes and Type 2 Diabetes: Decreased Insulin in Lean and Insulin Resistance in Obese J. Endocr. Soc, 2017; 1(6): 742-750. DOI: https://doi.org/10.1210/js.2016-1116.
22. Pollesello P1, Papp Z, Nieminen MS.Lessons from Lisbon on AHF drug treatment: is it really true that all-old-failed-all-new-will-succeed? Int J Cardiol, 2013 Oct 12; 168(5): 4798-9. doi: 10.1016/j.ijcard.2013.07.042. Epub 2013 Jul 23.
23. McCullough PA. How Trialists and Pharmaceutical Sponsors Have Failed Us by Thinking That Acute Heart Failure Is a 48-Hour Illness.Am J Cardiol, 2017; 120(3): 505-508. doi: 10.1016/j.amjcard.2017.04.056. Epub 2017 May 11.
24. Cotter G. RELAX-AHF, BLAST-AHF, TRUE-AHF, and other important truths in acute heart failure research. Eur J Heart Fail, 2017. doi: 10.1002/ejhf.934. [Epub ahead of print].
25. Holleman, F., Uijldert, M., Donswijk, L.F. and Gale, E.A. Productivity of Authors in the Field of Diabetes: Bibliographic Analysis of Trial Publications. BMJ, 2015; 351: h2638. http://dx.doi.org/10.1136/bmj.h2638.
26. Wager, E. Are Prolific Authors Too Much of a Good Thing? BMJ, 2015; 351: h2782. http://dx.doi.org/10.1136/bmj.h2782.
27. Davies MJ, Aronne LJ, Caterson ID, et al, Satiety and Clinical Adiposity - Liraglutide Evidence in individuals with and without diabetes (SCALE) study groups. Liraglutide and cardiovascular outcomes in adults with overweight or obesity: A post hoc analysis from SCALE randomized controlled trials. Diabetes Obes Metab, 2017. doi: 10.1111/dom.13125. [Epub ahead of print].
28. DCCT Research Group: Intensive diabetes treatment and complications in IDDM. N Engl J of Med, 1993; 329(14): 977-986.

29. Kabadi UM: DCCT. Medical and Economical Message. Exp. Clin Endo Diabetes, 1999; 10(Suppl 2): S24-S29.
30. Nathan DM, Cleary PA, Backlund JY, et al, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Groupw. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med, 2005; 353(25): 2643-53.
31. Nathan DM; DCCT/EDIC Research Group. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. Diabetes Care, 2014; 37(1): 9-16. doi: 10.2337/dc13-2112.
32. UK Prospective Diabetes Study (UKPDS) Group* Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33), The Lancet, 1998; 353: 9131, 837–853.
33. UK Prospective Diabetes Study (UKPDS) Group*Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34), The Lancet, 1998; 352: 9131, 854–865.
34. Kabadi, U.M. United Kingdom Prospective Diabetes Study: A Different Perspective. Endocrine Practice, 2002; 8, 61-64. http://dx.doi.org/10.4158/EP.8.1.61.
35. Holman RR, Paul SK, Bethel MA, et al, 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med, 2008; 359(15): 1577-89. doi: 10.1056/NEJMoa0806470. Epub 2008 Sep 10.
36. Nathan, D.M., Buse, J.B., Kahn, S.E., et al, Rationale and Design of the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE). Diabetes Care, 2013; 36: 2254-2261. http://dx.doi.org/10.2337/dc13-0356.
37. Gerstein HC, Miller ME, Byington RP, et al, Action to Control Cardiovascular Risk in Diabetes Study Group, Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med, 2008; 358(24): 2545-59.
38. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, et al, Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med, 2008; 358(24): 2560-72. doi: 10.1056/NEJMoa0802987. Epub 2008 Jun 6.
39. Zoungas S, de Galan BE, Ninomiya T, et al, Combined effects of routine blood pressure lowering and intensive glucose control on macrovascular and microvascular outcomes in patients with type 2 diabetes: New results from the ADVANCE trial. Diabetes Care, 2009; 32(11): 2068-74. doi: 10.2337/dc09-0959. Epub 2009 Aug 3.
40. Wong MG, Perkovic V, Chalmers J, et al, .Long-term Benefits of Intensive Glucose Control for Preventing End-Stage Kidney Disease: ADVANCE-ON.Diabetes Care, 2016 May; 39(5): 694-700. doi: 10.2337/dc15-2322. Epub 2016 Mar 2.
41. Duckworth W1, Abraira C, Moritz T, et al, Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med, 2009; 360(2): 129-39. doi: 10.1056/NEJMoa0808431. Epub 2008 Dec 17.
42. Hayward RA, Reaven PD, Wiitala WL, et al, Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. N Engl J Med, 2015; 372(23): 2197-206. doi: 10.1056/NEJMoa1414266.
43. Saremi A, Schwenke DC, Bahn G, et al, The effect of intensive glucose lowering therapy among major racial/ethnic groups in the Veterans Affairs Diabetes Trial. Metabolism, 2015; 64(2): 218-25. doi: 10.1016/j.metabol.2014.10.010. Epub 2014 Oct 17.