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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.

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