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Commentary

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Improvement in cardiovascular and renal outcomes in type 2 diabetes: effect of glycemic control, not drugs

Keywords: type 2 diabetes, hemoglobin, cardiovascular, glycemic control, UKPDS

Abbreviations: HbA1c, hemoglobin; CV, cardiovascular; UKPDS, United Kingdom diabetes study; SGLT2, sodium-glucose cotransporter-2

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Authors of a recent Systematic Review and Network Meta-analysis made it clear that the comparisons for glycemic efficacy, safety and other outcomes are best demonstrated on administration in drug naive subjects with type 2 diabetes.[1] The objective of this perspective is to examine the design, the results and conclusion of these studies specifically because of them sponsored and funded by pharmaceutical manufacturers. I believe that comparisons can be deemed valid only if glycemic efficacy is assessed as percent fall from the baseline glycated hemoglobin (HbA1c) in subjects administered the equivalent or maximum daily doses of drugs as approved by regulatory as demonstrated previously.[2] A fall of HbA1c points may be acceptable only if the HbA1c levels prior to administration of individual agents are not significantly different and the daily dose of agents are equivalent e.g. Maximum recommended daily dose. Finally, therapeutic interventions of other accompanying disorders must be identical to establish the validity of these studies. Unfortunately, most of the comparative trials especially between newer agents and the old established drugs e.g. Metformin and Sulfonylureas have been conducted with the maximum recommended daily dose of the newer drugs with minimal to about half the maximum daily dose of the older drug e.g. Linagliptin 5 mg vs Glimepiride 1-4 mg.[3,4] These trials therefore are less than valid and are not reliable. Finally, this proposed design is appropriate for assessments of all endpoints, e.g. glycemic efficacy, hypoglycemia, body weights, side effects, costs as well as other long term outcomes including cardiovascular (CV) events.

In documented clinical of trials, the benefits in cardiovascular and renal outcomes may be attributed to improvement in glycemic control as was well documented in United Kingdom Diabetes Study (UKPDS).[5–7] Percentage improvement in CV and renal outcomes for the fall in HbA1c in these trials matched almost identically to that observed in UKPDS. e.g. 20 % decline in overall mortality and 14-16 % lowering in myocardial infarctions and decline of almost 40% in renal complications for each 1 point drop in HbA1c.[5–7] Investigators of LEADER Trial using Liraglutide conceded recently that lowering of HbA1c was the major contributor to improvement in CV outcomes.[8] Similarly, investigators of CANVAS program and CREDENCE TRIAL recently reported lack of reduction in events of myocardial infarction.[9] Thus, the finding of lowering of CV events with lowering of HbA1c is consistent with several studies showing increased adverse CV out comes with rising HbA1c in a population irrespective of the presence of diabetes.[10–15] In fact, recent reports documented 18-23 % increased occurrence of myocardial infarction for each point HbA1c rise over 6.5-7 %, an almost identical finding in UKPDS.[10–15] Moreover, none of these trials have been examined for 'Legacy effect' documented in UKPDS.[16,17] Finally, it is apparent that some of these trials may have exaggerated the benefits.[18,19] Furthermore, many of the trials with newer agents touting cardiovascular and renal benefits are ill designed with several limitations as noted in recent reports.[18,19] Interpretations of results of Multinational trials are especially worrisome because of different pathophysiologic mechanisms among individual nations due diverse ethnicities, body weights, life styles, dietary patterns etc. Moreover, lack of uniformity in therapeutic guidelines in management of associated chronic disorders among individual nations allowed in multinational trials is further likely to influence the results as well. Finally, the validity and reliability of the conclusions derived from these trials may be biased since they are sponsored and funded by pharmaceutical manufacturers interested in promoting their drugs. Therefore, regulatory government agencies should mandate that the results from pharmaceutical company sponsored and funded trials be duplicated and confirmed by independent entities,[5–7,20–23] before awarding a tacit approval for prescribing by practicing providers. Improvement in congestive heart failure following administration of Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors may be attributed to osmotic diuresis induced by glycosuria.[1] The role of glycosuria in inducing remission of congestive heart failure was evident in another study which documented the same outcome with lapse of glycemic control with resultant glycosuria.[24] However, serious consequences of glycosuria including sepsis due to urinary tract bacterial infections, genitourinary mycotic infections, Fourniet's gangrene, as well as several other adverse effects along with prohibitive costs render SGLT2 inhibitors distinctly less favorable and acceptable when compared with older more effective and less expensive agents e.g. Furosemide, bumetinide, thiazides and other diuretics with proven long term record over several years.[23–25]

In conclusion, comparative clinical trials between newer and older drugs in assessing safety and efficacy in management of hyperglycemia are less than valid because of lack of administration of equivalent daily doses in drug naive subjects. Moreover, the data regarding impact of new drugs on cardiovascular and renal outcomes is overstated as these trials demonstrate no additional improvement beyond that achieved by improvement in glycemic control. Finally

the results and conclusions based on clinical trials sponsored by manufacturers of the drugs require confirmation by studies conducted by independent entities such as UKPDS.

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Conflicts of interest

The author declares that there is no conflict of interest.

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