INTRODUCTION

The EMPA REG and LEADER trials recently reported impressive improvements in long-term vascular outcomes in high-risk patients with type 2 diabetes mellitus (T2DM) who were treated with empagliflozin and liraglutide, respectively.[1,2] These trials have been discussed as landmarks in diabetology, with the potential to revolutionize the way we approach and manage diabetes. The comprehensive 360° improvement in all outcomes, including all-cause mortality, cardiovascular mortality and microvascular outcomes, with liraglutide therapy, has been appreciated.[2,3] Debate has also been published on the relative strengths and weaknesses of LEADER and EMPA-REG OUTCOME, as well as liraglutide and empagliflozin.[4] Such analysis provides insight into the pathophysiology and natural history of diabetes while allowing us to craft ever-better means of preventing and managing diabetes.

In recent decades, academic diabetology has moved from a pure glucocentric axis to a more comprehensive outcome-centered analysis. While earlier studies such as the United Kingdom Prospective Diabetes Study (UKPDS) reported improvement as a factor of HbA1c reduction,[5] modern studies (like LEADER and EMPA-REG) tend to highlight absolute outcomes improvements, including HbA1c reduction as one of many verticals. This is expected, and appropriate too, as advances in clinical
trial design, coupled with regulatory requirements, have changed the way primary and secondary outcomes are decided.

Somewhere along the way, however, we seem to have lost sight of the comprehensive nature of diabetes management. Unwarranted focus on glucose lowering, using purely glucose-lowering drugs, has given way to equally narrow focus on outcome lowering, using glucose-lowering drugs. The INTERHEART (Effect of Potentially Modifiable Risk Factor associated with Myocardial Infarction in 52 Countries) study showed that hypertension and diabetes account for approximately 17.9% and 9.9% of the population-attributable risk of a myocardial infarction.[8] The INTERSTROKE study revealed that with respect to stroke, hypertension and diabetes contributed to 51.8% and 5.0% of the population attributable risk.[7] Thus, blood pressure control becomes a relatively more important strategy of diabetes care, in our aim to reach the elusive goal of “good outcomes.” Keeping this in mind, we take a vasculocentric or blood pressure-centered approach to the results of EMPA REG and LEADER, comparing them with earlier landmark outcome trials, conducted using antihypertensive drugs.

We discuss the MICROHOPE trial, which evaluated ramipril in persons with diabetes, as part of the larger HOPE trial,[9] and ADVANCE, which assessed the role of a perindopril + indapamide fixed dose combination in diabetes, along with an intensive glucose-lowering strategy.[9] We highlight uncanny similarities with regards to the degree of blood lowering, time taken to achieve benefits, differences in cardiovascular and cerebrovascular results, and discrepancy in macro- and micro-vascular risk reduction, between some of these trials. This makes the few dissimilarities stand out starkly and suggests ideas for further research.

**Older Studies: HOPE and ADVANCE**

The MICRO Heart Outcomes Prevention Evaluation (HOPE) study evaluated 3577 people with T2DM and at least one high-risk factor, comparing the effect of ramipril with placebo.[9] Ramipril was able to significantly reduce the risk of combined primary outcome (myocardial infarction, stroke, or cardiovascular death) by 25%, myocardial infarction by 22%, and stroke by 33%, and cardiovascular death by 37% and total mortality by 24%. A significant reduction was also noted in the occurrence of overt nephropathy (24%).

The blood pressure lowering noted with ramipril (2.4/1.0 mm Hg) could not explain the benefits completely. Risk reduction with ramipril was evident within a year of the study and was sustained throughout the trial. The authors suggest the could be due to blood-pressure-independent effects of ACE inhibition, including those mediated by ACE on the tissue, and those due to increased bradykinin availability.

The ADVANCE trial randomized 11,140 persons, aged ≥55 years, with established T2DM and an additional risk factor for a vascular event, in a factorial design. ADVANCE assessed whether intensive glucose lowering (using gliclazide magnetic resonance based regime) and blood pressure lowering (using perindopril + indapamide) could modify outcomes. The active blood pressure lowering strategy led to a significant fall in major cardiovascular events (9%), cardiovascular mortality (18%), and all-cause mortality (14%). Significant reduction occurred in occurrence of all renal events (21%), new or worsening of nephropathy (18%), new onset microalbuminuria (20%), and new onset macroalbuminuria (31%)

Even though the difference in blood pressure levels between the active and control group had disappeared, 6 years of completing the trial, participants randomized to the intensive blood pressure lowering arm continued to enjoy significantly lowered risk of all-cause mortality (hazard ratio [HR] 0.91) and cardiovascular mortality (HR 0.88).[10] Thus, a vascular-based mechanism of metabolic memory has been proposed.[11,12] We suggest that vascular legacy, or vascular memory, rather than metabolic memory, may be at play with interventions such as ramipril or perindopril + indapamide.

**Blood Pressure Lowering**

LEADER and EMPA-REG were studies of glucose-lowering drugs.[1,2] Yet, they demonstrated significant pleiotropic benefits, including a reduction in blood pressure. Systolic blood pressure fell by 1.2 mmHg, and diastolic pressure rose by 0.6 mm Hg, in the liraglutide-treated group of LEADER. Small blood pressure falls were noted with empagliflozin in EMPA-REG OUTCOME.

The MICRO-HOPE substudy, which was stopped 6 months early, because of a consistent benefit of ramipril compared with placebo, began with a baseline of 141.7/80 mm Hg in the ramipril arm. Blood pressure fell by 1.92/3.30 mm Hg in the ramipril arm, as compared to a change of +0.55/−2.30 mm Hg in the placebo cohort. In ADVANCE, the mean reduction in blood pressure was 5.6/2.2 mm Hg with perindopril + indapamide, as compared to placebo, achieved over an entry level of 145/81 mm Hg. Thus, an
ACEi + diuretic combination seemed to achieve better results than ACEi monotherapy (as prescribed in MICRO-HOPE).

**Cardio-cerebral Discordance**

EMPA-REG results are marked by a clear cardio-cerebral dissociation of outcomes. While there was an excellent reduction in the primary outcomes (composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke), it was driven only by a reduction in death with empagliflozin. There was no improvement in stroke: In fact, there was a numerically higher risk of nonfatal stroke in participants exposed to empagliflozin.

In LEADER, no such increase was reported with liraglutide use. However, the highly significant benefits noted in the reduction of cardiovascular mortality and all-cause mortality did not extend to nonfatal stroke. It must be noted though that a trend toward benefit was noted with liraglutide use for all individual macrovascular outcomes.

The MICRO-HOPE results did not show such cardio-cerebral dissociation. The improvements in all cardiovascular outcomes, including stroke and myocardial infarction, were statistically significant. In ADVANCE, however, statistical significance was achieved for reduction in cardiovascular death (relative risk [RR]: 0.82; \(P = 0.027\)), total coronary events (RR: 0.86; \(P = 0.20\)), and not for total cerebrovascular events (RR 0.94; \(P = 0.42\)).

**Reno-retinal Discordance**

The reno-retinal dissociation in therapeutic outcomes noted in LEADER and EMPA-REG is evident in HOPE and ADVANCE as well. In both these studies, renal outcomes improved markedly, while retinal outcomes showed no improvement with empagliflozin or liraglutide.

In MICRO-HOPE, the reduction in composite microvascular endpoints (overt nephropathy, laser therapy, or dialysis) with ramipril was significant (RR 0.84; \(P = 0.036\)). This was driven entirely by renal health: Overt nephropathy was reduced by 24% (\(P = 0.027\)). There was no change in need for laser therapy between the groups (RR 1.22; \(P = 0.24\) for the ramipril group).

In ADVANCE, active treatment led to a 21% reduction in all renal events with a borderline significant reduction in new or worsening nephropathy (RR 0.82, \(O < 0.055\)) and a significant reduction in the development of microalbuminuria (RR 0.81, \(P < 0.0001\)). However, the rate of new or worsening retinopathy (RR 1.01, \(P = 0.94\)) need for retinal photocoagulation (RR 1.14, \(P = 0.23\)) and other secondary outcomes of visual deterioration (RR 0.95; \(P = 0.10\)) did not improve with perindopril + indapamide therapy.

Thus, reno-retinal dissociation seems to mark all interventions in diabetes. It is possible that ACE inhibition, GLP1 receptor agonism, and SGLT2 inhibition exert local effects at the nephron, which lead to beneficial renal outcomes that are independent of their glucose-lowering or macro-vasculoprotective effect. One exception to this rule is fenofibrate, which has demonstrated significant benefits on retinal protection in the FIELD study.[13]

**Time Taken to Achieve Vascular Benefit**

Another similarity between HOPE, ADVANCE, and LEADER is the time frame in which cardiovascular benefits begin to emerge. It took 12–18 months for survival curves to diverge in all studies, as opposed to the rapid onset benefit noted (within 4–6 weeks) with empagliflozin in EMPA-REG. This suggests that ACE inhibitors and liraglutide may have similar atherosclerosis modifying mechanism of action.

**Miles to Go Before We Rest**

Recently conducted outcome studies provide encouraging results for modern glucose-lowering drugs, which are proving to be cardiovascular-safe, as well as beneficial. These data add to the hopes and advances achieved with (relatively) older blood pressure lowering drugs. However, much more remains to be done.

The cardiovascular benefits achieved in these trials do not seem to be associated with the degree of blood pressure lowering. Benefits are not consistent across all vascular beds. These are subtle cardio-cerebral dissociation of benefits, and easily visible reno-retinal discordance, in most trials. Even where the benefit is achieved, at best, the advantage is accrued by one-third of people with diabetes. This implies that even if current glucose-lowering and blood pressure lowering therapies are used, a significant residual risk of cardiovascular morbidity will remain.

ADVANCE-ON, the posttrial follow-up of the ADVANCE trial, reported a significant and positive legacy effect of blood pressure control. No such legacy was noted for members of the intensive glucose lowering cohort.[14] However, follow-up of the UKPDS reported an antipodal scenario: Long-term outcomes were improved with intensive glucose lowering, but not with intensive blood pressure control.
Thoughts for Research

This should spark curiosity about the long-term benefits of empagliflozin and liraglutide, which can be answered only by similar follow-up studies. It would also be interesting to pair evidence-based cardiovascular beneficial drugs, based on “good clinical sense”\[15\] and assess their effectiveness. Ideal combinations, based upon the four trials we have discussed, would be empagliflozin + ramipril, and liraglutide + perindopril + indapamide. Whether such trials will ever be conducted is a matter of conjecture.

Summary

Evidence suggests the cardiovascular benefits can be achieved in people with diabetes using glucose-lowering drugs such as empagliflozin and liraglutide, and blood pressure lowering drugs like ramipril or perindopril + indapamide. The drugs exhibit similarities and few differences in degree of blood pressure lowering, relative benefits on coronary and cerebral vascular beds, relative benefits on macro- and micro-vasculature, and time taken to achieve such benefits. In spite of commendable advances in drug design, there is still an unacceptably high burden of cardiovascular risk in people with diabetes. Further research should focus on how best to use existing drugs, in various combinations, to achieve maximal cardiovascular benefit.

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Conflicts of interest
There are no conflicts of interest.

References

1. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.
2. Marso SP, Daniels GH, Brown-Andersen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311-22.
3. Kalra S. Lessons from leader: All-round leadership. Eur Endocrinol 2016;12:76-8.
4. Kalra S. One small step for empagliflozin, one giant leap for diabetology. Diabetes Ther 2015;6:405-9.
5. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:837-53.
6. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. Lancet 2004;364:937-52.
7. O’Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): A case-control study. Lancet 2010;376:112-23.
8. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet 2000;355:253-9.
9. Patel A; ADVANCE Collaborative Group, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): A randomised controlled trial. Lancet 2007;370:829-40.
10. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577-89.
11. Ceriello A, Ihnat MA, Thorpe JE. Clinical review 2: The “metabolic memory”: Is more than just tight glucose control necessary to prevent diabetic complications? J Clin Endocrinol Metab 2009;94:410-5.
12. Jax TW. Metabolic memory: A vascular perspective. Cardiovasc Diabetol 2010;9:51.
13. Keech AC, Mitchell P, Summanen PA, O’Day J, Davis TM, Moffitt MS, et al. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): A randomised controlled trial. Lancet 2007;370:1687-97.
14. Zoungas S, Chalmers J, Neal B, Billot L, Li Q, Hirakawa Y, et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med 2014;371:1392-406.
15. Kalra S, Gupta Y. Good clinical sense in diabetology. J Pak Med Assoc 2015;65:904-6.