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No reduction in the incidence of diabetic peripheral neuropathy between 4 glucose-lowering medications when added on to metformin

Aims: To compare the effectiveness of 4 commonly used glucose-lowering medications in achieving and maintaining a HbA1C <7% and the impact on microvascular and cardiovascular disease outcomes.
Methods: The trial conducted in 36 centres was a parallel group comparative effectiveness clinical trial where glucose-lowering medications (U-100/glargine, glimepiride, liraglutide and sitagliptin) were randomly assigned and administered in accordance with their labelling, in combination with metformin. The prespecified secondary outcomes with respect to microvascular and cardiovascular disease included hypertension and dyslipidaemia, confirmed moderately or severely increased albuminuria or an eGFR<60 ml/min/1.73m^2, diabetic peripheral neuropathy (DPN) based on the Michigan Neuropathy Screening Instrument (questionnaire score ≥7 and/or examination score ≥2.5), major adverse cardiovascular events (MACE), hospitalization for heart failure, or an aggregate outcome of any cardiovascular event, and death.
Results: 5074 people with type 2 diabetes (age 57.2 years, duration 4.2 years) were followed for 5 years. There were no differences in development of hypertension and dyslipidaemia, and in microvascular outcomes, with the exception of any cardiovascular disease with hazard ratios of 1.1 in both the glargine and glimepiride group, 0.7 in the liraglutide group, and 1.2 in the sitagliptin group. Regarding DPN, there were no major differences in the incidence of DPN. The overall linearized hazard rate was 16.7 events per 100 participant years, with DPN developing in approximately 20% of the participants over the first year and reaching approximately 70% by the end of the trial.
Conclusion: The incidences of microvascular complications and death were not different among the four treatment groups. The possible differences among the groups in the incidence of any cardiovascular disease need to be evaluated further.

Comments. The addition of the second agent after metformin is often a difficult decision for clinicians. We know the benefits of individual agents with regards to cardiovascular and renal outcomes, but few have studied the head-to-head impact on microvascular complications, in particular DPN, which is the focus of this commentary. The overall trial showed differences among the four agents in their ability to reach and maintain HbA1C <7% with glargine and liraglutide being more effective than glimepiride and sitagliptin. Liraglutide may have had a relative benefit on blood pressure, while the glargine group may have had more incident hypertension.
The analysis of secondary outcomes reports no difference in relation to microvascular complications, including DPN, despite differences between the groups with respect to glycaemia and hypertension, which are risk factors for microvascular complications in type 2 diabetes. It was interesting to note that by 5 years approximately 70% of the participants free of DPN at baseline developed DPN. This highlights magnitude of the problem with regards to prevention of DPN. The development of DPN is multifactorial beyond the highlighted risk factors and still goes on to develop in those with a target HbA1C of 7%. The absence of the expected effect of lower glycemia on microvascular complications has been previously ascribed to limitations which include inadequate separation of glycaemic levels over time, insufficient trial duration, threshold effects or inadequate power all of which may be relevant in this trial. We know the DPN impact on mortality and quality of life and the current treatment paradigms as highlighted by the current study are not sufficient to reduce this. The clinical end point of MNSI may have even underestimated the prevalence of neuropathy in this cohort.
There was a potential signal for difference amongst the groups in cardiovascular outcomes favouring liraglutide and as this commentary is focussed on neuropathy it is important to note this, yet not discussed further here.
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Reference. GRADE Study Research Group. Nathan DM, Lachin JM, Bebu I, Burch HB, Buse JB, Cherrington AL, Fortmann SP, Green JB, Kahn SE, Kirkman MS, Krause-Steinrauf H, Larkin ME, Phillips LS, Pop-Busui R, Steffes M, Tiktin M, Tripputi M, Wexler DJ, Younes N. Glycemia reduction in type 2 diabetes—microvascular and cardiovascular outcomes. New England Journal of Medicine. 2022 Sep 22;387(12):1075-88. doi: 10.1056/NEJMoa2200436. PMID: 36129997.
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