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Diabetes management gains: teaching old dogs new tricks

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In the world of diabetes management there is a lot be thankful for. Over the past three decades, excess mortality rates in people with diabetes relative to the general population have declined substantially in high-income countries such that those with diabetes are living longer than ever. That said, the gap in life expectancy remains at an average of ~ 6 years in those diagnosed with diabetes in middle age, with considerably more life years lost when diabetes presents much earlier in life [1]. This is an issue because the numbers presenting earlier are rising, leading to greater challenges in care. Part of this mortality benefit must arise from a

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narrowing of the gap between the true onset of diabetes and actual clinical diagnosis, verified in part by lower retinopathy rates at diagnosis. However, the more recent (post 2000) benefits in mortality rates cannot have come from treatment of glucose alone; rather, substantial contributions from guidelines recommended targeting of blood cholesterol and blood pressure levels have been critical. In our meta-analysis of intensive glucose-lowering trials conducted in 2009 [2], the trial data suggested that more cardiovascular events were being prevented by lipid and blood pressure management. By contrast, these same intensive glucose-lowering trials did not lower overall mortality and, in some cases, there were signals for harm [3]. Whilst glucose control remained 'king' in diabetes care, and in many places still does, these results led to much consternation among the diabetes community. Regulators reacted by demanding that all novel diabetes agents undergo cardiovascular outcome trials.

If we wind the clock forwards 10 years to the present day, it is remarkable how much the diabetes landscape has changed. As elegantly reviewed by Bain and expert diabetes colleagues from around England, Wales and North Ireland, multiple positive trials demonstrating the superiority of novel classes of diabetes agents for either cardiovascular or renal outcomes have emerged [4]. In some cases, total mortality was also reduced and extremely positive signals for the prevention of heart failure were noted [5]. All positive trials come either from the sodium–glucose cotransporter 2 (SGLT2) inhibitor class or the glucagon like peptide-1 receptor agonist (GLP-1RA) class of drugs [6]. These therapies are not without some side effects but overwhelmingly, if used with some degree of care and common clinical sense, their outcome benefits substantially outweigh potential harms. Consequently, as Bain and colleagues argue, given the benefits of these novel agents on hard outcomes (an absolute 'must' in the care of people with diabetes), many guidelines around the world upgraded the use of such drugs in their diabetes algorithms, with several directly

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naming the initial successful drugs in each class (Empagliflozin and Liraglutide), although other drugs have since been added to this list. Most guidelines prioritized the use of such agents in people with existing cardiovascular disease, the group in which the majority of trials were conducted. That said, further results from newer trials in people with diabetes who are at elevated risk of cardiovascular disease have begun to emerge and more are imminent so that guidance can be further extended or nuanced as required. Notably, however, the prevention of heart failure or cardiovascular death, or prevention of meaningful renal outcomes seems to occur to broadly similar extents in people with existing cardiovascular disease or in those with multiple risk factors in the trials of SGLT2 inhibitors [6,7].

On the basis of these data, as well as positive results from cost-effectiveness analyses, Bain and colleagues suggest that even if some countries have not yet updated their diabetes guidelines, it is important for doctors to consider an individual's cardiovascular risk when selecting their diabetes therapy. Many agree, as do I. In some respects, these authors are expressing a minor degree of frustration that their national guidelines seem to be lagging behind others, although it appears that this deficit will soon be rectified.

Of course, newer drugs cost more money and doctors must be careful not to 'break the bank'; some sensible 'rationing' of newer therapies must be in place. Nevertheless, if we return to the cost-effectiveness argument, Bain and colleagues correctly point out that current cost-effective analyses of SGLT-2is and GLP-1RAs were based on reducing hyperglycaemia *per se* and did not consider their wider benefits on cardiovascular outcomes. Nor did the analyses consider the use of other healthcare resources, so we may be underestimating benefits. It would further be helpful if such analyses could better consider outcomes reported by the

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person with diabetes, because although reducing the risk of hard outcomes is a must, more research is needed to determine how different drugs influence a person's quality of life and capacity to work. In this respect, it can only be a plus that newer agents help lower weight – in some cases quite considerably – and do not increase hypoglycaemia risk *per se*.

So, how are doctors reacting to this new evidence? It appears rather slowly for now [8]. The major issue is that diabetes is diagnosed on the basis of hyperglycaemia and so its treatment has fixated on such targets. Yet, these new trials have taught us several important points, including that some drugs developed to lower glucose have outcome benefits via mechanisms largely independent of glucose lowering *per se*. How do we know this? In several of the trials, the outcome benefits were evident regardless of any glucose lowering. Furthermore, we have learned that pathogenic pathways leading to common outcomes in diabetes go well beyond measurable hyperglycaemia, or other targeted risk factors; for example, we appear to have underestimated the importance of 'hidden' factors such haemodynamic perturbances, potentially critical to renal and heart failure outcomes [9]. Finally, it must now be obvious all to that one cannot predict the outcome benefits of new diabetes drugs on the basis of their effects on glucose or known cardiovascular risk factors, and only trials will lead us to the eventual truth. Trials can also uncover hidden risks or alleviate concerns on postulated risks.

Where do we go from here? The landscape has changed so dramatically that many of us are failing to keep apace, and this is why we need guidelines. Even so, all doctors should be grateful to have in their toolbox diabetes agents that meaningfully lessen mortality and/or cardiovascular or cardiorenal risks. In short, the healthcare community needs to understand that the focus in care on reducing glucose alone is no longer appropriate; it is time for 'old

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dogs to learn new tricks'. Yes, glycaemia levels matter, but so does the choice of drug dependent on an individual's risk characteristics, irrespective of any effects on glucose levels *per se*. This subtle shift in emphasis is not easy task and 'education, education, education' must be the mantra so that as many suitable people with diabetes as possible benefit. Hopefully, the forthcoming updated National Institute of Health and Care Excellence guidelines point the way.

Finally, we must not forget that newer diabetes drugs are not the only game in town. Recent studies have reminded us that there are potential outcome benefits in diabetes prevention [10] and also merit in diabetes remission for some, perhaps many, early after their diagnosis [11]. Both interventions are cost-effective and it is surely better to prevent disease than treating it when advanced. Still, evidence-based benefits at both ends of the diabetes spectrum are welcome and add much more to our toolbox than ever before to help improve the lives of those with diabetes.

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