Cardiovascular disease in type 1 diabetes: the elephant in the clinic
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Twenty years ago, diabetes conferences and journals made little mention of cardiovascular disease. For a young researcher at that time with an interest in hypertension, this seemed counter-intuitive given that most people with type 2 diabetes also had high blood pressure and that heart attacks, strokes and peripheral vascular disease were the most frequent causes of premature morbidity and mortality. Fortunately, that situation has transformed in the last 10 years: the diabetes community is now accustomed to the regular publication of well-powered randomized cardiovascular outcome trials [1]. These studies have nicely delineated the long-term effects of members of the newer classes of glucose lowering agents at least on rates of myocardial infarction, stroke and heart failure. They have made great strides towards an evidence base that forms the basis for much more robust clinical guidelines, and each has involved many thousands of people with diabetes.

So far, so good – but there remains a striking imbalance in the field. With the notable exception of the Diabetes Control and Complications Trial and its postrandomization long-term epidemiological follow-up (DCCT-EDIC) [2], almost all cardiovascular research in diabetes to date has focused on type 2 diabetes. The number of clinical trials in type 1 diabetes that have randomized more than 200 individuals and followed them up for more than 6 months for any cardiovascular outcome can be counted on the fingers of one hand.

As demonstrated by the articles in this Special Issue, this has not been because type 1 diabetes is associated with a lower risk of cardiovascular disease than type 2 diabetes. In fact, it has become increasingly clear that the onset of cardiovascular complications is at a much younger age and the reduction in life expectancy is higher. Type 1 diabetes clinical guidelines are able to state with confidence that achieving long-term target glycaemia is an effective strategy for preventing cardiovascular (and other) complications [3]. However, when discussing clinical decisions related to cardiovascular prevention with my patients in the clinic (Table 1), the best underpinning evidence available is often based on extrapolation from type 2 diabetes. This makes little sense as the underlying metabolic and inflammatory milieu in which blood vessels find themselves are completely different in types 1 and 2 diabetes (besides sharing the hallmark of hyperglycaemia).

Twenty years ago, few could have imagined the massive investment in diabetes research that followed changes in regulatory advice by the US Food and Drugs Administration in 2008 [4]. Once it was made clear to pharmaceutical companies that their share of the burgeoning type 2 diabetes market was dependent on demonstrating long-term cardiovascular safety and efficacy, they rose to the challenge. In sharp contradistinction, the marketplace has offered no such drivers in relation to investment in type 1 diabetes research. Ten times fewer people are affected, their numbers are relatively stable, and regulation is still ‘glucocentric.’ Public sector agencies have made some impact in funding trials assessing the impact of structured education and applying technological interventions in type 1 diabetes (e.g. insulin pumps, closed loop systems), but there remains a reluctance to invest monies raised for ‘diabetes research’ in the charitable sector in areas beyond glucose control.

A recent theme that may have started to break the mould is investment by the pharmaceutical industry in sodium-glucose cotransporter-2 (SGLT2) inhibitors as adjunct therapy in type 1 diabetes. One of more of these compounds (dapagliflozin, sitagliptin, empagliflozin) looks set to gain an indication in type 1 diabetes on the basis of phase 3 trials involving hundreds of people with diabetes [5]. However, as with the pre-2008 trials in type 2 diabetes, the underpinning studies had follow-up periods of only 6 months (with extensions in some cases to 12 months) and were not powered for cardiovascular outcomes.

An important lesson from the recent REMOVAL trial of metformin over 3 years in type 1 diabetes was that reductions

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<thead>
<tr>
<th>Table 1</th>
<th>Difficult cardiovascular questions in the type 1 diabetes clinic</th>
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<td>When should I start a statin?</td>
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<td>How low should my blood pressure be?</td>
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<td>Do my blood glucose spikes put me at increased risk?</td>
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<td>How can I stop smoking?</td>
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<td>Will taking metformin/an SGLT2 inhibitor protect me from heart disease?</td>
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<td>Should I have a scan to see if I have heart disease?</td>
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SGLT, sodium–glucose cotransporter.
in glycated haemoglobin over the first 6 months of follow-up with an adjunct therapy may not be sustained [6]: this is probably because over time people with type 1 diabetes tend to down-titrate their insulin doses to achieve a habitual ‘comfort zone’ for risk of hypoglycaemia. Once SGLT2 inhibitors are fully launched with an indication in type 1 diabetes, some clinicians (and people with diabetes) may assume by extrapolation that this will not apply to these agents, that longer term use in type 1 diabetes will result in similar cardiovascular benefits as in type 2 diabetes, and that these benefits will outweigh the much greater risk of ketoacidosis they confer in type 1. However, that assumption is really just a hypothesis that currently looks set to go untested. It can be speculated that trials in type 1 diabetes with SGLT2 inhibitors may have been conducted more with the aim of generally enhancing their profile in the diabetes marketplace rather than genuinely attempting to tackle the specific complications of the condition.

My vision is that by 2040, the number of dollars spent worldwide on types 1 and 2 diabetes research will be similar on a per capita basis by means of a ramping up of investment in type 1 diabetes research (i.e. this is not a zero sum game). Strategies for achieving that aim may involve advocating for changes in regulation, and pressure by people with diabetes on public sector funding agencies. At the very least, investigators going forward need to be clear whether ‘insulin-requiring’ individuals they recruit into trials actually have types 1 or 2 diabetes. Perhaps we will look back on this Special Issue of Cardiovascular Endocrinology and Metabolism as playing a small role in the beginning of a big transformation.

Acknowledgements

Conflicts of interest

J.R.P. has served on an Advisory Board for AstraZeneca and Endpoint Committees for Boehringer Ingelheim related to SGLT2 inhibitor trials. He was Chief Investigator of the JDRF-funded REMOVAL trial.

References