

Diabetes drug development: time for a shift in paradigm



Gregory C Jones speaks to Daphne Boulicault, Commissioning Editor: Gregory C Jones, MbChB, FRCPG, is a Consultant Physician in general (internal) medicine, diabetes and endocrinology at Western Infirmary and Gartnavel General Hospital, Glasgow, UK appointed in 2001. He is Honorary Associate Clinical Professor at the University of Glasgow. He graduated in medicine from the University of Dundee in 1991, and undertook general medical training in Coventry, England and specialist training in Edinburgh, Scotland. He was a Wellcome Clinical Research Fellow at Edinburgh University. His principal research interests are

pharmacotherapy in Type 2 diabetes, service delivery and in-patient diabetes care. He has written several papers in this field. He has a wide experience as a leader in medical education. He was previously the Training Program Director for Diabetes and Endocrinology and is currently Associate Director of Medical Education, Academic Foundation Programme Director and Chair of Academic Foundation Medicine for Scotland. He was previously Clinical Director of Emergency Care and Specialist Services for West Glasgow (2009–2013). He has been a contributor to Scottish Inter-collegiate Group Guidelines and Scottish Government Working Groups on Diabetes and acts as a specialist advisor to the Scottish Medicines Consortium. He is an approved assessor for the DVLA. He has a wide national experience of delivering diabetes teaching to healthcare professionals.

Q How did you come to work in the field of diabetes?

In fact, it was partly by chance; by the time I had left medical school I knew I wanted to work in a chronic disease setting as I enjoyed getting involved in a patients' journey rather than just sorting out a single issue. I also wanted to work in Scotland, where I grew up. When a post opened in Edinburgh within the field diabetes I jumped at the opportunity and I have never looked back!

Q What are your current priorities both in terms of research & in the clinic?

My priorities, both clinically and in research, are to improve outcomes for my patients. Specifically, I am interested in how we can apply scientific research to enhancing patient experience and how we can use data in to guide and monitor the healthcare system in the UK (and beyond).

Q The link between hypoglycemia & cardiovascular morbidity has been fairly hypothetical in the past, have there been any recent advances in this area? What are the priorities moving forward?

We now have data on many levels linking hypoglycemia to cardiovascular harm. We have seen the link between hypoglycemia and mortality in numerous data sets in a



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variety of settings. Additionally, it has now been observed that there are ‘high-risk’ changes on ECG monitoring during hypoglycemia. There is little doubt, therefore, that there is an association between cardiovascular outcome and hypoglycemia.

What we need to know is: How big is the risk? At what level of hypoglycemia and in what patient groups is it important? How should we quantify this risk when modeling outcomes from new therapies compared with older therapies? What are the best approaches to avoiding this risk?

Q There is some suggestion that the recently changed lipid guidelines will need to be changed again, what impact do you think this will have on the management of cardiovascular disease in diabetic patients? We are starting to see data for that suggest nonstatin cholesterol-lowering treatments might be impactful on hard outcomes. The 18,000-patient IMPROVE-IT trial was the first to demonstrate a reduction in cardiovascular events following the administration of a nonstatin drug.

We now need to figure out, if the number of patients needed to treat (NNT) is enough to warrant additional therapy to statins and in which patient groups. The trial revealed that you need to treat 50 patients for 7 years to prevent one event. We also need to think, if this impact is also there in nonstatin-treated patients.

Q In recent times, there has been increasing attention on the value of real-world data in drug development. What are the effects of the current reliance on clinical trial data? Trials answer the questions they ask. The trouble is that they often ask narrow questions in narrow groups of patients. Some groups are massively under represented (e.g., elderly populations and Asian populations). We practice medicine in a real, murky, imperfect world. If we always wait for perfect data, we will seldom treat anyone.

The challenge is to apply data from clinical trials into the real world. One way we can do this is to look at real-world prescribing data and try and see if studies’ effects are replicated in groups that differ from trial populations. However, real-world data are fraught with biases and recording issues. The key is to learn what you can from it but not to overstretch.

Q What work is currently being undertaken to overcome this bias? What challenges are associated with this change in thinking? We are lucky in Scotland that we have a unified universal coverage health system. We also have excellent joined up databases. We are, therefore, in a unique position to get broad and deep data on the impacts of treatments. The challenges in doing this are overcoming the protectionism of data which, understandably, is there to protect public confidence but can also stifle research.

We also need to prioritize data linkage and system ‘searchability.’ For instance, we have been able to look at real-world data in Scotland since the launch of the SGLT2 class of drugs. The first drug dapagliflozin has, rightly or wrongly, been used in a different set of patients to study protocols since its launch. We are now able to look at efficacy and treatment withdrawals in these patients. It has been striking so far that the efficacy seems very similar to that seen in the controlled environment of clinical studies.

Q The lack of real-world data are clearly a barrier to truly personalized diabetes care, what other barriers have we yet to overcome? We still treat Type 2 diabetes as one disease, when it is really the glucose manifestation of a complex set of genetic and environmental risks and we are still very glucocentric. Hopefully, we can start to be more granular and complex in our understanding and then our treatment of this disease. We should also be better weighing other outcomes like weight, blood pressure and low glucose when choosing treatments.

Q Are there any drugs in the pipelines that have you excited? The last 10 years have seen Type 2 diabetes treatment choices vastly improving. GLPs, DPP4 inhibitors and SGLT2s have finally given us an armamentarium that might allow safe, tight control for a large group of patients without adverse weight and hypoglycemia profiles. The next wave of treatments will revolve around combinations of therapies such as DPP4s and SGLT2s, rather than GLP and insulin combinations, which could well improve patient acceptability of treatments and encourage early use of combinations.

Q How do you see your field progressing in the next 5–10 years? There are so many exciting new drug treatments in development. The FGF21 analogues

for instance help fat cells take up glucose and are an example of how we are moving away from diabetes as an insulin action–inaction disease toward a more complex whole system metabolism model.

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