Viswanathan opines that increased cardiovascular risk with sulfonylurea (SU) therapy may be due to their mechanism of action: a direct increase in myocardial infarction and stroke risk. However, other studies suggest that SU therapy may improve cardiovascular outcomes through improved glycemic control, highlighting the potential for both benefit and harm. Therefore, it is crucial to consider the individual risk profile of each patient when prescribing SUs, considering alternative therapies when appropriate.
only hypothesis that can be generated is that SUs are cardiovascu-larly unsafe? This hypothesis can only be tested by a dedicated prospective RCT, but there is no prospect of such a trial ever taking place. The closest we will get is the CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes) study (commenced in 2010 and due to end in 2018), a double blind RCT comparing the dipeptidyl peptidase-4 inhibitor [DPP4i] linagliptin with the SU glimepiride in patients with type 2 diabetes at high cardiovascular risk. The results will be very interesting.

If these studies suggest that SUs may be less safe than metformin and may incur increased cardiovascular morbidity, perhaps metformin is cardiovascu-larly protective while the SUs are neutral? A small subgroup of 342 obese patients in the UKPDS did indeed demonstrate a 39% reduced risk of MI, but few would accept that such a small study is truly informative. No other study has convincingly showed cardiovascular benefits from metformin use, although several have failed to do so. These include two meta-analyses by Hemmingsen and colleagues and Boussageon and colleagues. Prescribers of alternative, newer drugs will be heartened by a study recently published by Morgan and colleagues. Using the UK’s Clinical Practice Research Database, 34,000 patients taking metformin–DPP4i (gliptin) dual therapy were compared with 8000 patients taking metformin–DPP4i dual therapy. Conscious that this was yet another observational study, participants were matched by age, sex, diabetes duration, BMI, renal status, and Hba1c. In the directly matched group, there was an astonishing 85% increase in mortality in the SU group. Surely we need to be more cautious about prescribing SUs? NICE should endorse newer guidance, such as the 2012 American Diabetes Association/European Association for the Study of Diabetes position statement. SUs will continue to have small but specific indications, such as in certain monogenic forms of diabetes and in newly-diagnosed hyperglycaemic patients. GPs should now question the demands of commissioners seeking to compel them to use SUs in preference to newer and better drugs in the majority of their patients.

The nation’s 600,000 users of SUs will be bewildered that so many decades have passed without an appropriate clinical trial to demonstrate SU safety and will wonder if regulators have adequately sought an answer to such an important question. They will be astonished that in today’s safety-obsessed health environment, so much uncertainty has been tolerated for so long.

If the UK’s SU users were all to change to a DPP4i, the cost to the NHS would be around £200 million per annum. Let us hope this appalling vista does not discourage further examination of the issue.

References