Commentary S C Bain

The controversy as to whether glucose-lowering medications reduce the elevated cardiovascular (CV) risk seen in people with type 2 diabetes appeared to have been settled by the landmark United Kingdom Prospective Diabetes Study (UKPDS) published in 1998. This trial showed that tight glycaemic control from diagnosis significantly reduced the risk of diabetes-specific, microvascular complications but had a lesser impact on large vessel disease, such as myocardial infarction and stroke.

Then, in 2007, a meta-analysis suggested that a thiazoladinedione glucose-lowering therapy actually increased CV risk. This led the FDA to mandate that novel anti-diabetes drugs demonstrate CV safety and heralded an era of diabetes CV outcomes trials (CVOTs). Cue the EMPA-REG OUTCOME trial in 2015, which to general surprise showed CV superiority for a sodium-glucose transporter 2 inhibitor over placebo; this was followed by positive CVOTs for three glucagon-like peptide receptor agonists (GLP-1RAs). The presumption was that the CV benefit from these medicines was due to pleiotropic effects on pathologies such as heart failure and atherosclerosis.

The publication by Fralick et al. in this journal brings us full circle (REF). The authors meta-regression analysis suggests that, for newer classes of glucose-lowering drugs at least, reduction in CV events is partly explained by reduction in HbA1c. Furthermore, this effect was most pronounced for the GLP-1RAs, which have generally had the largest reductions in HbA1c versus placebo in CVOTs. The relationship between glucose-lowering and CV events has yet to be fully expalined; expect more twists and turns….