Is it time to REWIND the cardiorenal clock in diabetes?

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See Articles pages 121 and 131

Following the regulatory requirements of 2008, randomised trials of glucose-lowering therapies have demonstrated safety, and in some cases superiority, with respect to cardiorenal outcomes. Sodium-glucose co-transporter-2 (SGLT2) inhibitors have been shown to reduce cardiorenal outcomes across a broad spectrum of type 2 diabetes in the presence or absence of established vascular disease, and across a broad range of kidney function.[1] These benefits appear independent of glycaemic control and are mediated through a range of mechanisms including effects on systemic and renal haemodynamics.[2] The greatest cardiovascular benefit is seen for heart failure, with a relative risk reduction of more than 30% observed across the trials.[1,2] These therapies have also shown kidney protection, decreasing the risks of kidney failure and reduction in kidney function by a third on top of standard of care.[1,3,4]

The dipeptidyl peptidase-4 inhibitors have shown, in patients with established atherosclerotic vascular disease or multiple risk factors, neutrality for major adverse cardiovascular events and composite renal outcomes.[5] Heterogeneity in cardiovascular outcomes has been noted with the glucagon-like peptide-1 (GLP-1) receptor agonists, with some showing superiority for major adverse cardiovascular events, and others neutrality.[6] From a renal perspective, GLP-1 receptor agonists reduced albuminuria but did not prevent a decline in estimated glomerular filtration rate (eGFR) or end-stage kidney disease.[6,7] Incretin-based therapies have not consistently affected rates of hospital admission for heart failure, and in some instances, might have worsened this outcome.

In *The Lancet*, Hertzel Gerstein and colleagues[8,9] report cardiovascular and renal outcomes from the REWIND trial. 9901 individuals (46% women, mean age 66 years) with type 2 diabetes, inadequate glycaemic control, and an eGFR of at least 15 mL/min per 1·73 m^2 were randomly assigned to the GLP-1 receptor agonist dulaglutide (1·5 mg once weekly) or placebo, in addition to baseline medical therapies. More than two-thirds of the participants were considered to be in the primary cardiovascular prevention with risk factors category; the secondary prevention cohort included patients with atherosclerotic vascular disease with or without history of a cardiovascular event (myocardial infarction or ischaemic stroke). The primary outcome (the first occurrence of the composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes or unknown causes) occurred in 594 (12·0%) of 4949 participants in the dulaglutide group and in 663 (13·4%) of 4952 participants in the placebo group (hazard ratio [HR] 0·88, 95% CI 0·79–0·99, p=0·026), with consistent benefits observed in the primary and secondary prevention cohorts.[8] The renal composite outcome, which was studied in an exploratory analysis, occurred in 848 (17·1%) participants in the dulaglutide group and in 970 (19·6%) participants in the placebo group (HR 0·85, 95% CI 0·77–0·93, p=0·0004).[9] Dulaglutide was associated with a modest reduction in glycated haemoglobin A_{1c} (HbA_{1c}), bodyweight, and blood pressure, and a small increase in heart rate. There was no imbalance in serious adverse events between groups.

Several features of the REWIND trial deserve mention. Compared with previous studies of GLP-1 receptor agonists, individuals included in the REWIND trial were at a lower risk of cardiovascular events, with an average incidence of major adverse cardiovascular events in the placebo group of 2·7%. The study enrolled the largest primary prevention cohort as far as we are aware thus far, and showed no heterogeneity in efficacy relative to those with established atherosclerotic vascular disease. As has been reported in previous GLP-1 receptor agonist trials,[10,11] the absolute risk reduction was higher in patients with atherosclerotic vascular disease compared with those without the condition (number needed to treat for dulaglutide to prevent one cardiovascular event over 5·4 years was 18 in patients with a previous cardiovascular event and 60 in those with type 2 diabetes and additional cardiovascular risk factors). The REWIND trial, to our knowledge, had the longest follow-up (5·4 years), highest proportion of women (46%), and lowest baseline median HbA_{1c} (7·2%), as well as showing efficacy over and above excellent background therapy, which, similar to other GLP-1 receptor agonist studies, was independent of baseline glycaemia, duration of

diabetes, and weight.[12] The magnitude of benefit on the composite cardiovascular outcome (12%) was modest, and numerically lower than that seen in the positive GLP-1 receptor agonist studies—namely, LEADER, SUSTAIN-6, and Harmony Outcomes—but consistent with the overall effect size from a meta-analysis of all previous GLP-1 receptor agonist trials.[6] The primary outcome seemed to be driven largely by a reduction in stroke; a trend that was also observed with semaglutide in SUSTAIN-6.[13] No difference was seen between groups in hospital admission for heart failure.

From a renal perspective, the composite outcome of the first occurrence of new macroalbuminuria, a sustained decline in eGFR of 30% or more from baseline, or chronic renal replacement therapy was reported on the basis of an exploratory analysis. The renal benefits are noteworthy, particularly the observation that dulaglutide reduced the risk of eGFR decline when assessed by either a 30%, 40%, or 50% decline in eGFR, with an intriguing suggestion of clearer benefits for the latter two outcomes alone or in combination with end-stage kidney disease. The magnitude of eGFR preservation (between-group difference of 0·42 mL/min per 1·73 m^2) was observed as a result of most patients being on an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, and in the context of a baseline median eGFR of 75 mL/min per 1·73 m^2, although it appears to be of smaller magnitude than that seen with the SGLT2 inhibitors.[1,4] Although mechanisms of action were not studied, the vascular and renal benefits of GLP-1 receptor agonists, mediated independently of HbA_{1c}, blood pressure, and weight changes, are well described.[3,14,15] REWIND also adds to the emerging thesis that human GLP-1 receptor agonists show superiority (versus exendin-4 based agents) in terms of major adverse cardiovascular events. Limitations of the REWIND trial include that about a quarter of the patients were not on study drug at the completion of the study (similar to other studies of GLP-1 receptor agonists in which duration of follow-up was shorter), and the renal outcomes were exploratory and should be studied in further trials.

How do we integrate this growing body of evidence into a treatment approach? Although SGLT2 inhibitors and GLP-1 receptor agonists are recommended in patients with established atherosclerotic vascular disease, we now have evidence from the DECLARE-TIMI 58[6] and REWIND trials that SGLT2 inhibitors and GLP-1 receptor agonists afford cardiovascular superiority even in primary prevention; with SGLT2 inhibitors preventing heart failure and GLP-1 receptor agonists preventing atherosclerotic events, and both potentially affording renal protection. If we are to reduce the burgeoning pump, pipes, and filter complications of diabetes,[16] we will need to overcome clinical inertia, and embrace these disease-modifying therapies early, and preferably in combination. The REWIND trial makes a strong case in this regard.

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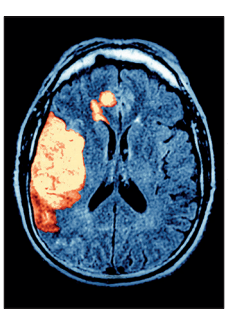
Late thrombolysis for stroke works, but how do we do it?

Thrombolysis for ischaemic stroke is recommended up to 4·5 h from stroke onset.[1] Beyond 4·5 h, endovascular clot retrieval[2] is the standard of care in selected patients up to 24 h after the time they were last known to be well.[3] However, immediate endovascular clot retrieval will not be available for all patients. In *The Lancet,* Bruce Campbell and colleagues[4] report the findings of their meta-analysis of individual patient data from three intravenous thrombolysis trials (EXTEND,[5] ECASS4-EXTEND,[6] and EPITHET[7]) of late window (4·5–9 h) or wake-up stroke. All three trials included either CT perfusion or diffusion–perfusion MRI in their imaging protocol. Among the 410 patients included in the intention-to-treat analysis set in the three trials, the primary outcome—excellent functional outcome (modified Rankin Scale score 0–1) at 3 months, adjusted for baseline age and clinical severity—was achieved in 76 (36%) of 211 patients in the alteplase group and 58 (29%) of 199 patients in the placebo group (adjusted odds ratio [OR] 1·86, 95% CI 1·15–2·99, p=0·011). These results show that patients treated with intravenous alteplase for thrombolysis in a 4·5–9 h window or with wake-up stroke had a reduction in disability compared with individuals given placebo. As expected, symptomatic intracranial haemorrhage was more common in the alteplase group than in the placebo group (ten [5%] of 213 patients *vs* one [<1%] of 201 patients; adjusted OR 9·7, 1·23–76·55, p=0·031). A major limitation of these results is the small sample size despite pooling of data from three trials.

All patients included in the trials had perfusion imaging; however, whether mismatch on perfusion imaging was used as an inclusion criterion for trial enrolment differed between the three trials. In a prespecified subgroup analysis using automated perfusion software designed to identify a mismatch between infarct core and tissue at risk, the authors suggest that most of the benefit in terms of the primary outcome was in patients with prespecified mismatch; however, a statistical test of interaction did not reach significance. Patients with mismatch did not have a lower rate of symptomatic intracranial haemorrhage than those without mismatch. Moreover, significant differences were identified in the baseline characteristics of patients without mismatch; patients in the alteplase group had worse baseline prognosis than those in the control group, including more severe stroke (median National Institutes of Health Stroke Scale score 10 [IQR 7–17; n=46] *vs* 6·5 [IQR 5–15; n=55]), more evidence of large vessel occlusion, and a larger ischaemic core at baseline. Despite these baseline differences in prognosis, the adjusted point estimate of effect for benefit with alteplase in patients without mismatch was higher than 1. Moreover, the small number of patients without mismatch (n=98 [45 patients in the placebo group and 53 patients in the alteplase group]) limits the validity of any



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See **Articles** page 139