Reflections on the 50th annual meeting of the EASD

Dr Mike Gwilt reports from the conference of the European Association for the Study of Diabetes in Vienna, Austria, 13-19 September, 2014

Introduction

As the dust settles on the recent EASD congress,[1] the world's largest diabetes meeting with over 18,000 delegates, we can reflect on where pharmacotherapy for type 2 diabetes stands today. Here is a personal selection of interesting items from the meeting, with abstract numbers so that interested readers can see the presentations or posters for themselves on the EASD website.[1]

Metformin – 57 years of therapeutic use and still going strong

It is remarkable that a drug first used clinically in 1957[2] can still have two sessions all to itself in a major congress. The annual Michael Berger Debate saw Professors Harold E Lebovitz and Rury R Holman debate whether the evidence for metformin is "overwhelming" or "unclear". The debate was nuanced (unsurprisingly as RRH was lead investigator of the trial that first demonstrated cardiovascular protection with metformin[3]). Prof. Lebovitz cited the two randomised trials demonstrating improved cardiovascular outcomes with metformin,[3,4] while Prof. Holman looked forward to the "GLINT" study[5] as the final arbiter, taking the opportunity to nail some recurring myths about the UKPDS (the metformin arm was not a sub-study, and was conducted in 732 patients including controls).

It is a testament to the maintained therapeutic status of metformin that GLINT will be conducted in non-diabetic individuals, as it is problematic to withhold metformin from control patients. Elsewhere, we saw further evidence of the low risk of lactic acidosis with metformin (#220), and potentiation of circulating GLP-1 levels as one of metformin's numerous mechanisms of action (#217).

Newer therapies: much promise, but lingering safety concerns

GLP-1 agonists

Multiple presentations concerned FDCs of GLP-1 agonists with basal insulin: IDegLira is liraglutide-degludec (#78, #243, #835, #836) and LixiLan is lixisenatide-glargine (#241). These combinations appear to provide additional efficacy versus either agent alone, while limiting each agent's side-effects. Effects are durable, so far (up to one year).

Lixisenatide, the newest available GLP-1 agonist, featured strongly (#75, #241, #829, #841, #843, #846, #926). For other agents, we now have data from type 2 diabetes patients treated for 6 years with once-weekly exenatide (#77), 3 years with albiglutide (#41, #830, #831, #837, #838), and 18 months with dulaglutide (#38; both also once-weekly injections). For an even longer dosing interval, see ITCA650 – an implantable exenatide mini-pump that only needs changing every 3 or 6 months (#242).

Your reporter saw no new data on the continuing concerns over GLP-1 agonists and pancreatic safety, but the EASD/ADA incretin symposium provided some reassurance.[1] We must wait for more of the ongoing cardiovascular safety/outcomes trials with these agents to support an authoritative meta-analysis.

DPP-4 inhibitors

The main clinical trials for these agents are behind us now, and most presentations concerned mechanistic aspects or data cuts in special populations. An increased incidence of CHF in the active treatment group of the SAVOR-TIMI53 trial (post-hoc, and only hypothesis generating) continues to focus attention on safety (#186, #885, #888, #890). This issue needs resolution, especially as a once-weekly DPP-4 inhibitor is in development (#115). Dr Hertzel C Gerstein (Canada) appealed for CHF events to be collected prospectively in large trials as pre-specified endpoints, rather than as adverse events (as is usually the case), so that we can define their true incidence.

SGLT-2 inhibitors

FDCs of SGLT-2 inhibitors and DPP-4 inhibitors may be coming to your practice soon (#1, #4, #851). How these agents will be used seems an open question: first-line use will require one or both classes to displace metformin from the top of the algorithm, while second-line use will require a leap from monotherapy to triple therapy.

In other reports, exposures to dapagliflozin of up to 4 years (#807, #848), and of other agents up to 2 years (#2, #5) were reported. Benefits of these agents (use irrespective of diabetes duration or other treatments [subject to renal function status], modest BP lowering, modest weight reduction) are balanced against their side-effects (urinary/genital infections, adverse events related to volume-depletion). Interestingly, patients taking these agents respond to the loss of energy via increased glycosuria by eating more (#3, #820), thus limiting the weight loss achieved.

Abbreviations and acronyms

ADA	American Diabetes Association
BP	blood pressure
CHF	congestive heart failure
DCCT	Diabetes Control and Complications Trial
DPP-4	dipeptidyl peptidase-4
EASD	European Association for the Study of Diabetes
EDIC	Epidemiology of Diabetes Interventions and Complications trial
FDC	fixed-dose combination(s)
GLINT (study)	Glucose Lowering In Non-diabetic hyperglycaemia Trial
GLP-1	glucagon-like peptide 1
SAVOR-TIMI53	Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction Study Group 53
SGLT-2	sodium-glucose cotransporter-2
UKPDS	United Kingdom Prospective Diabetes Study

No "legacy effect" for intensive glycaemic management in ADVANCEd type 2 diabetes?

Reports of post-trial follow-up from the ADVANCE study (ADVANCE-ON) were the nearest we came to disclosure of new data

on the effects of antidiabetic pharmacotherapy on clinical outcomes. Mean HbA_{1c} rapidly became similar, after the end of randomised treatment, for patients previously randomised to a more versus less intensive intervention. This was reminiscent of the post-randomisation follow-up from the UKPDS (in patients with newly diagnosed type 2 diabetes) and from the DCCT (a post-trial follow-up termed EDIC, in which people with type 1 diabetes received more versus less intensive management with insulin).[6,7] Intensive management of glycaemia in both the UKPDS and the DCCT led to a long-term reduction in the risk of adverse cardiovascular events (the so-called "legacy effect"), despite no long-term glucose lowering effect following the end of the formal trial and even though such benefits had not been clearly apparent during randomised treatment.[6,7] By contrast, in ADVANCE-ON, the overall incidence of macrovascular and microvascular events remained the same for patients previously in either randomised treatment group, i.e. there was no legacy benefit from intensive glycaemic management. The protection of the kidney seen with intensive glycaemic management in the main phase of the trial continued throughout the post-trial period, however.

Intensive BP control in ADVANCE had reduced the risk of adverse cardiovascular outcomes in the main trial and this benefit persisted during ADVANCE-ON (reduced risk of myocardial infarction, stroke or death). Intriguingly, intensive BP control had not provided a legacy benefit in the UKPDS post-trial follow-up, despite markedly improving outcomes during the main trial phase.[8]

Why was there enduring benefit for intensive control of BP but not blood glucose in ADVANCE-ON? Certainly, the patients in ADVANCE were older and further down the road of diabetes and its complications than the newly-diagnosed populations in the UKPDS and relatively young population of the DCCT. Intervening early, intensively (but above all, safely) to control glycaemia and other cardiovascular risk factors remains the main lesson from outcomes trials evaluating the potential benefits of intensive diabetes management.

Reflections

Overall, we saw some interesting new facets of available therapies, without major breaking news, e.g. the results of a new outcomes trial. The world of antidiabetic pharmacotherapy may be in a phase of consolidation, following the sudden, recent expansion of available therapies. We now look forward to the conclusion of outcomes trials with the incretin agents, which will hopefully reassure us of their safety and, who knows, may even show the way to improving cardiovascular outcomes in type 2 diabetes.

References

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