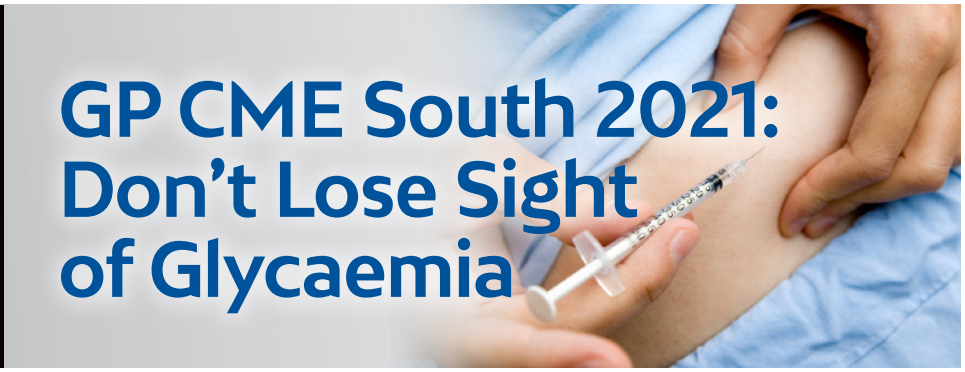
A RESEARCH REVIEW™
SPEAKER SERIES

GP CME South 2021: Don't Lose Sight of Glycaemia



Making Education Easy 2021

About the speaker

Russell Scott
BMedSc MB ChB (Otago)
PhD (Monash) FRACP

Russell is a Clinical Professor of Medicine, Christchurch School of Medicine and Health Sciences, University of Otago, New Zealand. He is also the Director, Lipid and Diabetes Research Group and Physician, Internal Medicine, Canterbury District Health Board and Physician: Diabetes, Lipids and metabolic disorders at the Don Beaven Medical Research Centre. He has been a principal investigator in approximately 250 clinical trials and has a special interest in CVD end point trials using lipid and glucose modifying treatments. He has 240 publications and 12 book chapters in the endocrinology literature.

Abbreviations used in this review
DPP4 = dipeptidyl peptidase-4
GAD = glutamic acid decarboxylase
GLP1 = glucagon-like peptide-1
IA2 = islet cell
ICA = islet cell antibodies
RRR = relative risk reduction
SGLT2 = sodium glucose co-transporter 2

The annual GP CME South conference took place virtually from 27-29 August, 2021. Professor Russell Scott provided an overview of the pivotal clinical trials that have guided the management of type 1 and type 2 diabetes from the 1980s to present. He also included a case study and covered key messages for the management of type 2 diabetes. This review is a synopsis of Professor Scott's presentation that was supported by unconditional funding from Sanofi.

A historical snapshot

During the 1960s and 1970s the association between diabetes complications (particularly microvascular complications) and hyperglycaemia had not been strenuously established with data. The link was considered plausible and likely, but importantly it was not known what level of glycaemia was "too high" and when treatment could be relaxed. The microvascular complications of diabetes were thought to be interlinked via the environment, genetics, obesity, hypertension, and glycaemia, however, perceptions changed in 1993.

By 2009, heart and vascular disease associated with Type 2 diabetes (T2D) were considered *not* to be reversible by improved glucose control. Furthermore, caution was recommended in lowering HbA1c levels too far in patients with longstanding T2D and established cardiovascular disease (CVD).

Two trials launched in the 1980's set the scene for a paradigm shift in the perception of hyperglycaemia and its role in causing multi-organ damage.[1,2]

The Diabetes Control and Complications (DCCT) Trial

The DCCT trial investigated the effects of tight glycaemic control on the microvascular complications of diabetes.[1] The trial compared usual care versus intensive care in 1,441 patients with T1D over 9.5 years.[1] Usual care comprised 1-2 insulin injections per day, with a review every 6 months.[1] Intensive care involved basal bolus insulin or pump therapy, with frequent reviews of all aspects of care.[1] Usual care achieved a mean HbA1c of 75 mmol/mol over the course of the study, whereas intensive care achieved a sustained mean HbA1c of 53 mmol/mol.[1]

There was a 76% relative risk reduction (RRR) for the development of retinopathy and a 34% RRR for the development of microalbuminuria in intensively treated patients without retinopathy at baseline, compared to usual care ($p<0.001$ and $p<0.04$ respectively).[1] In patients with retinopathy at baseline, there was a 54% RRR for the progression of retinopathy and a 43% RRR for the development of microalbuminuria, compared to usual care ($p<0.001$ and $p=0.001$ respectively).[1] The prevalence of neuropathy in patients receiving usual care was approximately twice that of the intensively treated patients over the course of the study.[1]

The DCCT trial provided irrefutable data, for the first time, that tighter glucose control limited the progression of retinopathy, albuminuria, and neuropathy. There was, however, no benefit for CVD, although this was not an end point of the study. The DCCT trial resulted in haemoglobin A1c (HbA1c) levels becoming the standard measurement for evaluating quality of diabetes care.

Microvascular glycaemic legacy

Several months after the DCCT study finished, HbA1c levels reverted to pre-study levels in the patients receiving intensive diabetes care, demonstrating that tight glycaemic control required a support network.

The Epidemiology of Diabetes Interventions and Complications (EDIC) trial was a follow-up of patients from the DCCT trial for an additional 30 years.[3] This study showed that the cumulative incidence of retinopathy was lower in patients who had previously been exposed to intensive glycaemic control, compared to patients receiving usual care (**Figure 1**).[3] This effect became known as glycaemic legacy, i.e. the microvascular benefits of tight glycaemic control persist for two decades after the cessation of tight control, even if lower HbA1c levels are not sustained.

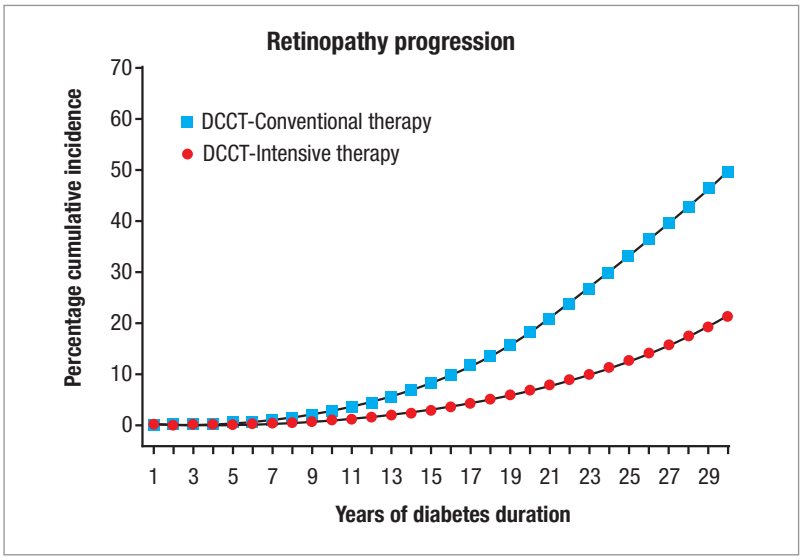


Figure 1: Progression of retinopathy during post DCCT follow up (EDIC)[3], adapted from Scott (2021)

The United Kingdom Prospective Diabetes Study (UKPDS)

The UKPDS involved 5,100 patients newly diagnosed with T2D who were studied for 5 years with a 10-year follow up.[2] Patients were randomised to usual care (primarily diet and lifestyle) or intensive treatment, including early initiation of metformin and other glucose-lowering medicines. UKPDS replicated the glycaemic legacy effect for microvascular complications in patients with T2D (**Figure 2**).[2] However, there were no significant CV benefits associated with intensive glycaemic control in the UKPDS study, compared to usual care. This led to the role of glucose intensification in CV outcomes to continue to be questioned.

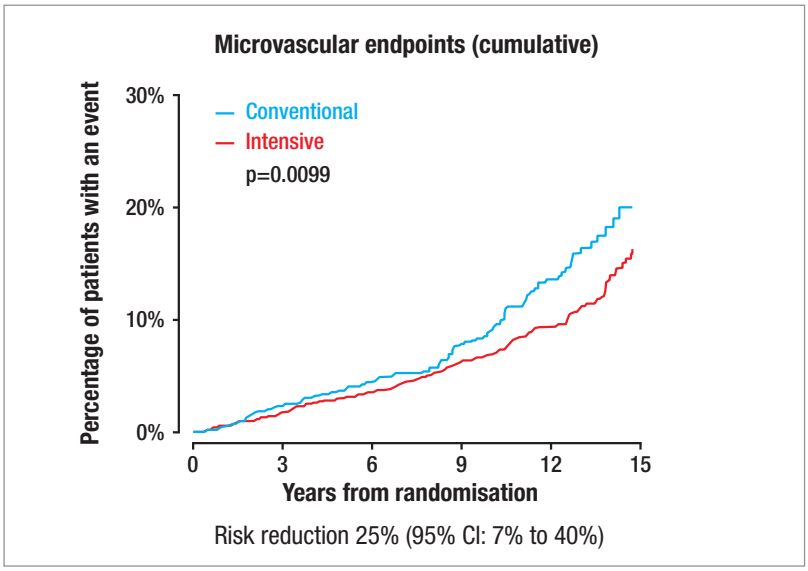


Figure 2: Cumulative incidence of microvascular endpoints (renal failure or death, vitreous haemorrhage or photocoagulation) in patients receiving usual or intensive care in the UKPDS study,[2] adapted from Scott (2021).

ACCORD, ADVANCE and VADT

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was an aggressive, "treat-to-target" study published in 2008.[4] ACCORD was designed to determine if cardiovascular (CV) events could be reduced by intensively lowering HbA1c levels to 42 mmol/mol (n=5,119), compared to a less aggressive target of 53-63 mmol/mol (n=5,109).[4] The study had a mean duration of follow-up of 3.5 years.[4] Compared with standard therapy, intensive therapy to target low HbA1c levels did not significantly reduce major CV events, but did significantly increase mortality.[4] The higher mortality rate in the intensive-therapy group resulted in the early discontinuation of this arm of the study.

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial was similar to ACCORD, but aimed for a less aggressive HbA1c target of 48 mmol/mol in the intensive arm.[5] The ADVANCE trial found that compared with standard therapy, an intensive HbA1c target of 48 mmol/mol for 5 years did not significantly reduce major CV events, but did significantly increase hospitalisation rates and hypoglycaemia.[5]

The Veterans Affairs Diabetes Trial (VADT) included a large number of patients with co-morbidities and targeted an HbA1c of 48 mmol/mol in the intensive arm for up to 7.5 years.[6] The study found that intensive therapy did not significantly reduce major CV events, compared with standard therapy.[6]

Was this the end of the CVD glucose story?

All four studies to this point investigating the effect of intensive glucose control on CV outcomes in patients with T2D had failed to demonstrate a benefit. Intensive glucose control was therefore regarded by many as a trade-off between eye, kidney and neurological benefits, against a lack of CV gain and even harm and mortality.

A multifactorial approach to improving CV risk

The Steno-2 trial investigated a multi risk factor intervention embodying the idea that the best way to improve CV risk in patients with diabetes was to do "a little bit of everything well", e.g. blood pressure, lipids, antiplatelet, weight loss, diet, without aggressively targeting any one risk factor.[7]

Following the ACCORD, ADVANCE and VADT trials, glucose control (target 53 mmol/mol) was viewed as being important, but aggressive control in those with existing CVD was widely discouraged with a target of 65 mmol/mol preferred.

The Steno-2 trial demonstrated that intensive multifactorial control of CV risk factors reduces CV events in patients with T2D and microalbuminuria (**Figure 3**).[7]

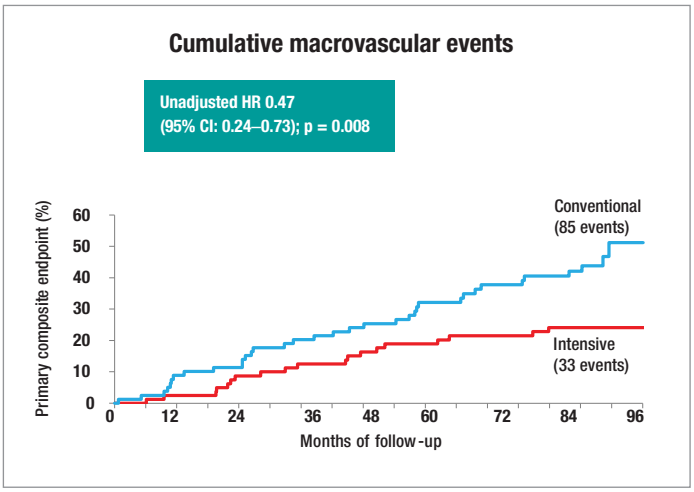


Figure 3: Cumulative rates of macrovascular events (CV death, non-fatal MI, non-fatal stroke, revascularisation, and amputation) in patients with T2D and microalbuminuria receiving intensive multifactorial control of CV risk factors, compared to usual care,[7] adapted from Scott (2021).

The macrovascular legacy of glycaemic control

The concept of legacy with respect to the vascular system also began to take hold around the time that the results of Steno-2 were published.

Legacy means that the unfavourable effects of hyperglycaemia persist for a decade or more, even after corrected, and the benefits of improved glycaemia take a decade or more to emerge.

The legacy concept contrasted with statin treatment and CV risk where a benefit was observed in 3 or 4 years.

Macrovascular legacy confirmed:

A 20-year follow-up of UKPDS confirmed the legacy effect of intensive glucose control for CV risk in patients with T2D. After 20 years, intensive glucose control was associated with a 15% RRR in MI (p=0.014) and a 13% RRR in all-cause mortality (p=0.007), compared to usual care.[8]

The DCCT/EDIC trial in patients with T1D also began to show a RRR in MI, stroke or CV death associated with intensive glucose control after 8 to 9 years, with a 57% reduction in the risk of non-fatal MI, stroke or death from CVD after 17 years of follow-up (p=0.02).[9] A subsequent study showed a reduction in all-cause mortality in these patients over an average of 27 years after entering the trial (p=0.045).[10]

The Steno-2 trial also reported a legacy effect in the reduction of CV events in patients who had previously received intensive glucose control after approximately 14 years of follow-up.[11]

Glycaemic legacy summary:

- The beneficial effect of glycaemic control on macrovascular risk takes well over a decade to emerge. Poor glucose control after diagnosis impacts CV outcomes adversely for many years.
- Intensive glucose control takes over a decade to reduce CVD risk .
- The beneficial effects of LDL-cholesterol lowering,[12] antihypertensive[13] and antiplatelet therapy[14] on CV risk are well established so a multifactorial approach is recommended to control CV and microvascular risk.[12,15]

New T2D Guidelines

The recently released New Zealand Society for the Study of Diabetes (NZSSD) guidelines have now been harmonised with those published by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).[16,17]

The 2021 New Zealand guidelines recommend:[17]

- Starting T2D treatment with lifestyle and metformin, if tolerated
- The target HbA1c for most patients is < 53 mmol/mol
- Start insulin immediately if HbA1c > 90 mmol/mol or if insulin deprivation is suspected
- Assess CV and renal status at diagnosis as this determines the choice of next level agent

Start insulin when lifestyle and oral agents are not achieving targets:

- Treat to a target glucose of 5-7 mmol/L in the morning – glargine or NPH is preferred
  - Usually given in the evening
- If post-prandial blood glucose elevations occur, start mealtime insulin, i.e. Apidra® (glulisine), Novorapid® (aspart), or Humalog® (lispro)
  - Apidra® and Novorapid® have disposable pens which in Professor Scott's experience patients like
- Dose adjustments require glucose data
  - Standard self-monitoring blood glucose (SMBG) is needed
  - "Smart" glucose monitoring or continuous glucose monitoring system (CGMS) is essential for some

Technology is an essential part of diabetes management when using insulin:

- Most practices should be equipped with some diabetes technology
- Downloading of glucose meters is a must so that the patient's data can be analysed
- The LibreView® software interfaces with FreeStyle® Libre® devices and allows for seamless transmission to the practice
- CGMS is becoming more widely used, although it is expensive for many patients
- HbA1c is a useful target, but it is an average:
  - Glucose levels are instructive and indicate what happens after meals and can guide treatment change
  - The most appropriate measure of control is 'time in range'; patients who are 70-75% in range are doing very well[18]

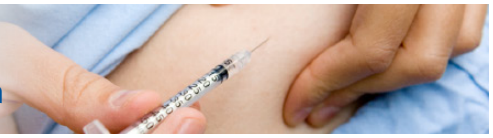
Type 1 versus Type 2 diabetes

It is important to try and identify adult-onset patients who have Type 1 diabetes (T1D) but have been initially classified as T2D. This is not a small group of patients. Patients with T1D may be any age at diagnosis, but T1D is more common in those diagnosed at younger age rather than older age, or in those with a family history of autoimmune diseases.

Rapid glycaemic deterioration within 4-5 years of diagnosis is a sign of insulin deprivation. Glutamic acid decarboxylase (GAD), islet cell (IA2) and islet cell antibodies (ICA) tests are helpful in detecting patients with T1D. Insulin C-peptide levels can be requested by clinicians with a special interest in diabetes, although these results can be difficult to interpret.

Insulin is the primary treatment for T1D and should be started immediately, once a diagnosis has been made.

GP CME South 2021: Don't Lose Sight of Glycaemia



Case Study

Professor Scott presented a 50-year-old male with diabetes for 10 years. The patient is intolerant to metformin and is focused on lifestyle management and currently weighs 76 kg (a loss of 8 kg). The patient has been treated with vildagliptin, plus gliclazide, plus empaglifozin (in the last 6 months); several other medicines, e.g. pioglitazone, have been trialled and withdrawn. The patient's HbA1c was 66-70 mmol/mol over the past 6 months. The patient does not have any significant co-morbidities or complications, e.g. BP is satisfactory with no evidence of neuropathy.

Due to the patient's poor glycaemic control over a sustained period, insulin should be initiated. Glargine insulin, once daily, is Professor Scott's recommended initial option for this patient. For a typical bodyweight the starting dose is 20-24* units of insulin taken in the evening, with adjustments of 4 units every 4-5 days, if required. The treatment target is a waking glucose of 6-8 mmol/L. Nocturnal hypoglycaemia is the potential adverse effect of major concern.

Additional treatments are not recommended for the patient at this stage. Professor Scott recommends stopping the DPP4 inhibitor (vildagliptin) and the sulfonylurea; these medicines do not usually add benefit when given in combination and insulin initiation is the appropriate treatment when oral agents are not realising target glycaemia. The goal is to improve glycaemic control for a substantial period to produce a legacy benefit and improve long-term outcomes.

**The Lantus datasheet recommends a starting dose of 10 IU*

Diabetes from the 1980's to 2021

- Controversy often
- Confusion at times
- Epic studies from 1980 to 2020 changed the landscape
- We know what we know through these clinical trials, some lasting 20 years
- Guidelines are strong and functional for 2021 for what we must use, do and achieve

KEY MESSAGES FOR DIABETES TREATMENT IN 2021

1. **Start tight glucose control as soon as possible after diabetes is detected – for all types of diabetes**
2. **Do glucose control well from the start; it is easier early on and becomes more difficult with time**
3. **Embrace the concept of long-term legacy of glucose control**
4. **Treat all CV risk factors at the same time; do not focus on one at the expense of others**

REFERENCES:

1. Diabetes Control and Complications Trial Research Group, et al DM. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-986.
2. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes. Lancet. 1998;352(9131):854-865.
3. EDIC Research Group. Epidemiology of Diabetes Interventions and Complications (EDIC). Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. Diabetes Care. 1999;22(1):99-111.
4. Action to Control Cardiovascular Risk in Diabetes Study Group, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545-2559.
5. ADVANCE Collaborative Group, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358(24):2560-2572.
6. Duckworth W, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360(2):129-139.
7. Gaede P, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med. 2003;348(5):383-393.
8. Holman RR, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577-1589.
9. Nathan DM, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353(25):2643-2653.
10. Writing Group for the DCCT/EDIC Research Group, et al. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. JAMA. 2015;313(1):45-53.
11. Gaede P, et al. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358(6):580-591.
12. Cholesterol Treatment Trialists' (CTT) Collaborators, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380(9841):581-590.
13. Emdin CA, et al. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA. 2015;313(6):603-615.
14. American Diabetes Association. Standards of Medical Care in Diabetes - 2015. Diabetes Care. 2015;38(Suppl. 1):S1-S94.
15. Authors/Task Force Members, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J. 2013;34(39):3035-3087.
16. Davies MJ, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018;41(12):2669-2701.
17. New Zealand Society for the Study of Diabetes. Management Algorithm for Type 2 Diabetes. Published online 2021. https://t2dm.nzssd.org.nz/Management-Algorithm.html
18. American Diabetes Association, 6. Glycemic Targets: Standards of Medical Care in Diabetes - 2021. Diabetes Care. 2021;44(Suppl 1):S73-S84.