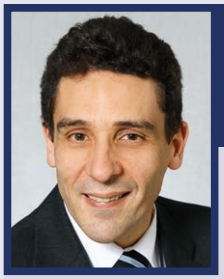

CANVAS trial – cardiovascular benefits, amputations and fractures

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The CANVAS (Canagliflozin Cardiovascular Assessment Study) outcome trial has been eagerly anticipated since the publication of the EMPA-REG OUTCOME trial (Zinman et al, 2015), which demonstrated dramatic reductions in all-cause and cardiovascular (CV) mortality in empagliflozin-treated patients with type 2 diabetes and high CV risk.

The data were merged from two outcome trials, CANVAS and CANVAS-R (CANVAS-Renal). Although both had similar inclusion criteria, patient populations and interventions, the trial durations were different and there were differences in the significance level of some findings in the different arms.

The pooled data (summarised alongside) showed that the risk of the primary outcome of three-point major adverse cardiovascular events (MACE) – CV death, non-fatal myocardial infarction and non-fatal stroke – was 14% lower in canagliflozin recipients compared with placebo among people with type 2 diabetes who were known to have or who were at high risk of cardiovascular disease (CVD). However, despite a trend towards reduction in all-cause death, CV death, myocardial infarction and stroke, none of these showed statistical significance as individual outcomes. The canagliflozin-treated patients also had a 33% reduction in heart failure admissions and a 27% reduction in progression of albuminuria.

During the average follow-up of 296 weeks in CANVAS and 108 weeks in CANVAS-R, the rate of the primary MACE outcome per 1000 person-years was 26.9 in the canagliflozin group versus 31.5 with placebo.

However, the CANVAS trial also raised significant safety concerns, with a 97% increase in lower-limb amputations and a 26% increase in fracture rates in the canagliflozin group. For every 1000 person-years, those treated with canagliflozin had an increased risk of amputation of the toes, feet or legs, with a rate of 6.3 versus 3.4 in the placebo group. In the pooled data, those treated with canagliflozin had more fractures, with respective rates in the canagliflozin and placebo groups of 15.4 versus 11.9 per 1000 person-years. Interestingly, this increase was statistically significant in the longer CANVAS trial, but not in CANVAS-R.

Since the EMPA-REG study, there has been interest in seeing if the substantial CV benefits would be replicated with other agents in the sodium–glucose cotransporter 2 (SGLT2) inhibitor class. The CANVAS study, along with the recently presented retrospective database analysis, CVD-REAL (also summarised alongside), would suggest that the reductions in heart failure admissions and CV and renal benefits probably are a class effect, extending to canagliflozin and dapagliflozin.

The CANVAS results also expand the group of patients who are likely to benefit from treatment with this class, as the participants in this study included those at high risk of CV events and not just those with established CVD. This would suggest that, as a class, SGLT2 inhibitors do provide cardiorenal protection, at least for high-risk patients.

What are the implications for clinical practice?

I believe we now have enough data from EMPA-REG, CANVAS and, to a lesser extent, CVD-REAL, to have to consider SGLT2 inhibitors as a class with additional benefits beyond glucose-lowering for people with type 2 diabetes and high CV risk. However, the increased risk of amputations and fractures seen in CANVAS certainly impacts the benefit-to-risk calculation for canagliflozin.

For every 1000 person-years of exposure, treatment with canagliflozin prevented 4.6 MACE events at a cost of 2.9 amputations and 3.5 fractures. A history of amputation or peripheral artery disease at baseline did not help to identify those at higher risk of subsequent amputation, making it difficult to recommend specific higher-risk groups who should avoid canagliflozin.

Given that these problems have not been identified with empagliflozin (Kohler et al, 2017), I find it hard to imagine a situation where an informed patient would choose canagliflozin as their preferred SGLT2 inhibitor. Indeed, until we see the CV safety results for dapagliflozin in the DECLARE-TIMI 58 trial (estimated completion in 2019), empagliflozin would perhaps seem to be the safest option for providing this CV benefit to high-risk patients. ■

Kohler S, Zeller C, Iliev H et al (2017) Safety and tolerability of empagliflozin in patients with type 2 diabetes: pooled analysis of phase I–III clinical trials. *Adv Ther* **34**: 1707–26

Zinman B, Wanner C, Lachin JM et al (2015) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* **373**: 2117–28

ADA 77th Scientific Sessions

N Engl J Med

CANVAS trial: CV outcomes of canagliflozin

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! Factor	✓✓✓✓

1 Results of CANVAS, the compulsory cardiovascular (CV) safety study of the sodium–glucose cotransporter 2 inhibitor canagliflozin, were published simultaneously at ADA and in the *New England Journal of Medicine*. Data were pooled from two trials, CANVAS and CANVAS-Renal, from 667 centres in 30 countries.

2 A total of 10 142 people with type 2 diabetes, either ≥30 years of age with a history of symptomatic CV disease or ≥50 years of age with two or more CV risk factors, were randomised to canagliflozin or placebo, in conjunction with clinician-led treatment.

3 After a median follow-up of 126 weeks, the primary outcome (a composite of CV death, non-fatal myocardial infarction [MI] or non-fatal stroke) was significantly less likely in the canagliflozin groups (hazard ratio [HR], 0.86).

4 The risks of heart failure (HR, 0.67) and all-cause hospitalisation (HR, 0.94) were also reduced. However, while the individual outcomes of all-cause death, CV death, MI and stroke were all less common in canagliflozin recipients, the differences between groups were not significant.

5 Canagliflozin was superior in terms of albuminuria progression (HR, 0.73) and the composite renal outcome (sustained 40% reduction in estimated glomerular filtration rate, need for dialysis or renal death; HR, 0.60).

6 However, these benefits were offset by a higher risk of lower-limb amputation (HR, 1.97) and fractures (HR, 1.26).

Neal B, Perkovic V, Mahaffey KW et al (2017) Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 12 Jun [Epub ahead of print]

Circulation

SGLT2 inhibitors and CV outcomes: The CVD-REAL study

Readability	✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! Factor	✓✓✓✓

1 The CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes) study compared the risk of hospitalisation for heart failure (HHF), death, and the combined endpoint of HHF or death in adults with T2D who were new users of sodium–glucose cotransporter 2 (SGLT2) inhibitors with those who were new to other glucose-lowering drugs (oGLDs).

2 Real-world data were collected in six countries – the US, Norway, Denmark, Sweden, Germany and the UK.

3 After propensity score matching, 309 056 people (154 528 in each treatment group) were identified. Canagliflozin, dapagliflozin and empagliflozin accounted for 53%, 42% and 5% of total exposure time in the SGLT2 inhibitor group.

4 During a follow-up of 190 164 person-years, there were 961 HHF events (incidence rate [IR], 0.51/100 person-years). Excluding Germany (no data collected), death occurred in 1334 (IR, 0.87/100 person-years), and HHF or death in 1983 (IR, 1.38/100 person-years).

5 Compared with oGLDs, new use of SGLT2 inhibitors showed lower rates of HHF (hazard ratio [HR], 0.61), death (HR, 0.49), and HHF or death (HR, 0.54; all $P<0.001$). There was no heterogeneity by country.

6 The results suggest that the benefits seen previously with empagliflozin may be a class effect that extends in real-world practice to individuals with T2D at lower risk of heart failure.

Kosiborod M et al; the CVD-REAL Investigators and Study Group (2017) Lower risk of heart failure and death in patients initiated on SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL Study. *Circulation* 18 May [Epub ahead of print]

ADA 2017

Increased risk of T2D eliminated in men who lose excess weight in their teens

1 In this Danish registry-based study, the authors evaluated the effects of weight loss in young adulthood among men who were overweight or obese in childhood.

2 A total of 62 565 men who had their weight measured at age 7 years and again at 17–26 years were evaluated. Overall, 5.4% and 8.2% were overweight in childhood and young adulthood, respectively.

3 Excess weight in childhood (hazard ratio [HR], 1.53 [95% confidence interval (CI), 1.40–1.68]) and in young adulthood (HR, 2.96 [95% CI, 2.78–3.15]) were both associated with increased risk of developing T2D at age ≥30 years.

4 Overall, 60% of boys who were overweight in childhood lost their excess weight in adolescence. These men had a similar risk of T2D as those who were never overweight (HR, 1.01 [95% CI, 0.87–1.16]).

5 Men who were persistently overweight (HR, 2.88 [95% CI, 2.40–3.44]) or became overweight in young adulthood (HR, 2.95 [95% CI, 2.53–3.45]) had a threefold increased risk of T2D compared with those who lost weight in adolescence.

6 These results offer hope that the adverse metabolic consequences of being overweight in childhood are reversible, and they emphasise the need to normalise weight in overweight children as soon as possible.

Bjerregaard LG, Jensen BW, Ängquist L et al (2017) Are adverse effects of child overweight on risk of type 2 diabetes reversible by remission to normal weight in young adulthood? *ADA 77th Scientific Sessions*: abstract 11-OR

> ***"These results offer hope that the adverse metabolic consequences of being overweight in childhood may be reversible, and emphasise the need to normalise weight in overweight children as soon as possible."***

ADA 77th Scientific Sessions

"Full or partial remission of major depression was 12.4 times more likely with cognitive behavioural therapy and 5.8 times more likely with exercise."

N Engl J Med

DEVOTE trial: Insulin degludec vs glargine CV outcomes

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! Factor	✓✓

1 The results of DEVOTE, the cardiovascular (CV) safety trial of the ultralong-acting basal insulin degludec, were presented at ADA and simultaneously published in the *New Englad Journal of Medicine*.

2 A total of 7637 people with T2D and high CV risk (aged ≥50 years with established CV or renal disease [85% of participants], or aged ≥60 years with one or more CV risk factor [15% of participants]) were randomised 1:1 to insulin degludec or insulin glargine 100 units/mL.

3 After a median follow-up of 2 years, the primary outcome (CV death, non-fatal myocardial infarction or non-fatal stroke) occurred at similar rates in the degludec and glargine groups (8.5% vs 9.3%; hazard ratio, 0.91 [95% confidence interval (CI), 0.78–1.06]; *P*<0.001 for noninferiority).

4 In addition to the confirmed CV non-inferiority, rates of severe hypoglycaemia, a prespecified secondary outcome, were significantly lower in the degludec group (4.9% vs 6.6%; odds ratio, 0.73 [95% CI, 0.60–0.89]).

5 Adverse event rates were similar between the groups, and HbA_{1c} levels were identical, at 58 mmol/mol (7.5%). The study had a treat-to-target design.

6 The number needed to treat with degludec versus glargine to avoid one severe hypoglycaemic event was 40 over the study period.

7 The overall hypoglycaemia rate was approximatley 8% per year.

Marso SP, McGuire DK, Zinman B et al (2017) Efficacy and safety of degludec versus glargine in type 2 diabetes. *N Engl J Med* 12 Jun [Epub ahead of print]

ADA 2017

Exercise and CBT to treat major depression in T2D

1 ACTIVE II was a 2×2-factorial randomised controlled trial to compare the effectiveness of cognitive behavioural therapy (CBT) and exercise on depression and glycaemic control in adults with major depressive disorder and T2D.

2 In total, 140 adults were randomised to usual care, CBT (10 individual sessions), exercise (12 weeks of a community-based programme plus six classes led by personal trainers) or CBT plus exercise.

3 Post-intervention, compared with usual care, participants in the intervention groups were around five times more likely to have full remission from depression (odds ratio, 5.0, 6.8 and 5.9 in the CBT, exercise and CBT+exercise groups, respectively; *P*<0.02 for all comparisons).

4 The combined endpoint of full or partial remission was 12.4 times more likely with CBT and 5.8 times more likely with exercise. Interestingly, CBT+exercise was not significantly more effective than usual care.

5 Improvements in depressive symptoms, diabetes-related distress and quality of life scores were also observed in the intervention arms.

6 In people with a baseline HbA_{1c} ≥53 mmol/mol (7.0%), exercise resulted in a clinically meaningful improvement in HbA_{1c} of 8 mmol/mol (0.7%; *P*=0.04) compared to those receiving CBT or usual care.

7 The study is ongoing, and follow-up at 6 and 12 months is planned.

de Groot M, Hornsby G, Saha C et al (2017) Program ACTIVE II: a comparative effectiveness trial to treat major depression in T2DM. *ADA 77th Scientific Sessions*: abstract 376-OR

ADA 2017

Semaglutide's retinopathy risk explained by rapid increase in glycaemic control

1 Results of SUSTAIN-6, the cardiovascular safety trial of the once-weekly glucagon-like peptide-1 analogue semaglutide, were published in 2016. The agent demonstrated a significant 26% reduction in the risk of major adverse cardiac events.

2 However, semaglutide was also associated with an increased risk of diabetic retinopathy (DR) complications. The composite outcome of vitreous haemorrhage, diabetes-related blindness and need for photocoagulation or intravitreal agents occurred in 3.0% of semaglutide recipients versus 1.8% of placebo recipients (hazard ratio, 1.76).

3 Further analysis of the SUSTAIN-6 data to determine the reasons behind this were presented at ADA 2017.

4 People who developed DR complications were characterised by known DR at baseline, longer diabetes duration and poor baseline glycaemic control.

5 The increased risk of DR with semaglutide was only observed in people with pre-existing DR; the risk was comparable between semaglutide and placebo in people without DR at baseline.

6 DR complications occurred in people who had rapid reductions in HbA_{1c}, regardless of treatment arm.

7 These findings suggest that the increased risk of DR with semaglutide was a result of rapidly improving glycaemic control, as has also been observed in people with poor control who initiate insulin.

Vilsbøll T (2017) Cardiovascular outcomes with semaglutide in subjects with type 2 diabetes mellitus (SUSTAIN 6). *ADA 77th Scientific Sessions*: session 1-AC-SY09

ADA 77th Scientific Sessions

JAMA Intern Med

Home SMBG not useful in most people with T2D not on insulin

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓

1 MONITOR was a pragmatic, open-label randomised controlled trial of home self-monitoring of blood glucose (SMBG) in people with T2D not treated with insulin.

2 A total of 450 people were randomised to no SMBG, once-daily SMBG or once-daily SMBG supplemented with automated messaging (designed to educate and motivate participants).

3 After 1 year, mean HbA_{1c} and quality-of-life scores were unchanged in all groups. The authors conclude that routine SMBG is not beneficial in this group of patients.

Young LA, Buse JB, Weaver MA et al (2017) Glucose self-monitoring in non-insulin-treated patients with type 2 diabetes in primary care settings: a randomized trial. *JAMA Intern Med* **177**: 920–9

ADA 2017

BCG vaccine reverses T1D autoimmunity

1 Repeated BCG vaccination was shown to increase regulatory T cell (T_{reg}) numbers and alter the expression of genes that control T_{reg} potency in three people with T1D.

2 This may help to prevent the immune system attack that characterises T1D. Studies are ongoing to determine the clinical effects of BCG vaccination in T1D.

Kuhtreiber W, Plager S, Kim T et al (2017) Permanent epigenetic changes in T_{reg} signature genes of type 1 diabetic subjects after *in vivo* BCG vaccinations. *ADA 77th Scientific Sessions*: abstract 1816-P

ADA 2017

Metformin to prevent T2D most effective in women with prior gestational diabetes

1 In the US DPP (Diabetes Prevention Program), metformin was found to reduce the 3-year risk of developing T2D by 31% compared with placebo.

2 Subgroup analysis showed that participants aged <60 years at baseline, those with a BMI ≥35 kg/m^2 and women with a prior history of gestational diabetes (GDM) had the greatest responses to metformin, with 44%, 53%, and 51% reductions in T2D risk, respectively.

3 In the DPP Outcomes follow-up study, placebo was stopped and metformin was prescribed open-label to all participants. The 15-year outcomes of this intervention were presented at ADA.

4 In the overall study cohort, the 31% risk reduction with metformin decreased to 18% by 10 years and has remained stable since then.

5 Metformin's benefits continued in younger age groups (risk reduction, 18–27% compared with no significant reduction in those aged ≥60 years) and in those with BMI ≥35 kg/m^2 (22% risk reduction).

6 In addition, metformin decreased the risk of T2D in women with a prior history of GDM (n=233) by 40.6% (95% confidence interval, 16–58), compared with 9.7% (–6 to 23) in parous women with no history of GDM (n=1223).

7 These findings suggest that women with a history of GDM will gain particular benefit from metformin therapy.

Nathan DM, Crandall JP, Dabelea D et al (2017) Effect of metformin on diabetes prevention at 15 years: identification of subgroups most likely to benefit, Diabetes Prevention Program (DPP) Research Group. *ADA 77th Scientific Sessions*: abstract 169-OR

ADA 2017

PCSK9 inhibition for cholesterol reduction in people with T2D

1 The efficacy and safety of alirocumab, a proprotein convertase subtilisin kexin 9 (PCSK9) inhibitor approved in the US as second-line treatment for high cholesterol, was investigated in two cohorts of people with diabetes.

2 In ODYSSEY DM-Insulin, 441 people with insulin-treated T2D, high cardiovascular (CV) risk and LDL-cholesterol levels ≥1.8 mmol/L were randomized 2:1 to 24 weeks of subcutaneous alirocumab every 2 weeks or placebo, both in conjunction with usual care.

3 At 24 weeks, alirocumab recipients had a reduction in LDL levels of 48.2%, compared with a 0.8% increase in the placebo group (P<0.0001 for comparison).

4 In ODYSSEY DM-Dyslipidemia, 413 people with T2D, high CV risk and mixed dyslipidaemia despite maximally tolerated statin treatment were randomised.

5 At 24 weeks, non-HDL was significantly lowered in the alirocumab arm (37.3% vs 4.7% reductions; P<0.0001).

6 Treatment-emergent adverse event rates were similar between the active drug and placebo, no new safety signals were identified and glycaemic control was unaffected.

7 Further data on CV outcomes will be required; however, these results support alirocumab as a treatment option in people with T2D.

Leiter LA (2017) Alirocumab and insulin-treated diabetes – insights from the ODYSSEY DM-Insulin study. *ADA 77th Scientific Sessions*: session 1-AC-SY12

Henry RR (2017) Alirocumab vs. usual care in diabetes with mixed dyslipidemia – ODYSSEY DM-Dyslipidemia study. *ADA 77th Scientific Sessions*: session 1-AC-SY12

"These findings suggest that women with a history of gestational diabetes will gain particular benefit from metformin therapy."