COMMENTARY

Report from the 4th Cardiovascular Outcome Trial (CVOT) Summit of the Diabetes & Cardiovascular Disease (D&CVD) EASD Study Group

Oliver Schnell1*, Eberhard Standl1, Doina Catrinoiu2, Baruch Itzhak3, Nebojsa Lalic4, Dario Rahelic5, Jan Skrha6, Paul Valensi7 and Antonio Ceriello8,9

Abstract
The 4th Cardiovascular Outcome Trial (CVOT) Summit of the Diabetes & Cardiovascular Disease (D&CVD) EASD Study Group was held in Munich on 25–26 October 2018. As in previous years, this summit served as a reference meeting for in-depth discussions on the topic of recently completed and presented CVOTs. This year, focus was placed on the CVOTs CARMELINA, DECLARE-TIMI 58 and Harmony Outcomes. Trial implications for diabetes management and the impact of the new ADA/EASD consensus statement treatment algorithm were highlighted for diabetologists, cardiologists, endocrinologists, nephrologists and general practitioners. Discussions evolved from CVOTs to additional therapy options for heart failure (ARNI), knowledge gained for adjunct therapy of type 1 diabetes and, on the occasion of the 10 year anniversary of the FDA’s “Guidance for Industry: "should CVOTs be continued and/or modified?" The 5th Cardiovascular Outcome Trial Summit will be held in Munich on 24–25 October 2019 (http://www.cvot.org).

Keywords: Cardiovascular risk, Diabetes, CVOT, CARMELINA, DECLARE-TIMI 58, Harmony Outcomes, ODYSSEY OUTCOMES

Background
Coronary heart disease, cerebrovascular disease and peripheral arterial disease of atherosclerotic origin, collectively termed atherosclerotic cardiovascular disease (ASCVD), are the major cause of mortality in patients with diabetes mellitus [1, 2]. Diabetes patients experience an up to 50% increased risk of cardiovascular (CV)-related death [3]. A variety of studies has shown that an improvement in glycemic control can positively impact long-term CV disease (CVD) risk in patients with type 2 diabetes mellitus (T2DM) [4, 5]. However, other trials like the UGDP [6] and ACCORD trial [7], as well as studies on muraglitazar [8] and rosiglitazone [9], raised concerns for elevated CV risk [10]. This prompted the Food and Drug Administration (FDA) to release a “Guidance for Industry” in 2008, for the evaluation of CV safety of new antidiabetic therapies in T2DM in order to prevent an unacceptable increase of CV risk [11]. In consequence, CV outcome trials (CVOTs) for glucose lowering therapies were introduced. In CVOTs, combined CV endpoints are evaluated as primary outcome, usually including CV mortality, non-fatal myocardial infarction (MI) and non-fatal stroke (3-point major adverse CV event, 3P-MACE). Secondary outcomes often include hospitalisation for heart failure (HF), death from CV causes, all-cause mortality and renal outcomes. Since 2008, every newly approved glucose lowering drug has undergone a CVOT to evaluate its CV safety (hazard ratio (HR) < 1.8) [12]. So far, this has encompassed four main classes of substances: (1) dipeptidyl-peptidase-4 inhibitors (DPP-4i) (SAVOR-TIMI
53—saxagliptin; EXAMINE—alogliptin; TECOS—sitagliptin); (2) glucagon-like peptide-1 receptor agonists (GLP-1 RA) (ELIXA—lixisenatide; LEADER—liraglutide; SUSTAIN-6—semaglutide; EXSCEL—exenatide); and (3) sodium/glucose co-transporter-2 inhibitors (SGLT-2i) (EMPA-REG OUTCOME—empagliflozin; CANVAS—canagliflozin) as well as two insulins (ORIGIN—insulin glargine; DEVOTE—insulin degludec) [13–23], previously summarised by Schnell et al. [24, 25].

In 2018, the list of published CVOTs was further increased with CARMELINA (linagliptin, DPP-4i) [26], Harmony Outcomes (albiglutide, GLP-1 RA) [27] and DECLARE-TIMI 58 (dapagliflozin, SGLT-2i) [28]. In addition, a CV safety study for alirocumab (ODYSSEY OUTCOMES), a proprotein convertase subtilisin/kexin type-9 inhibitor (PCSK-9i), was published [29]. As in previous years [30–32], we present and summarise the key aspects discussed at the 4th CVOT Summit in October 2018.

**Updates on CVOTs**

A summary of characteristics and results of CVOTs published in 2018 is listed in Tables 1 and 2.

| Study name       | Study status | Drug          | Drug class          | Intervention                           | Primary outcome                                                                 | n     | Follow up [years] | Start and end date | Clinicaltrials.gov ID |
|------------------|--------------|---------------|---------------------|----------------------------------------|---------------------------------------------------------------------------------|-------|-------------------|---------------------|----------------------|
| CARMELINA        | Completed    | Linagliptin   | DPP-4 inhibitor     | Linagliptin 5 mg daily vs. placebo     | CV death, non-fatal MI, non-fatal stroke                                        | 6,980 | 4.5               | 07.2013–01.2018     | NCT01897532          |
| Harmony Outcomes | Completed    | Albiglutide   | GLP-1 receptor agonist | Albiglutide 30 mg to 50 mg weekly vs. placebo | CV death, non-fatal MI, non-fatal stroke                                        | 9,574 | ≥ 1.5             | 07.2015–02.2018     | NCT02465515          |
| DECLARE-TIMI 58  | Completed    | Dapagliflozin | SGLT-2 inhibitor    | Dapagliflozin 10 mg daily vs. placebo   | CV death, MI, ischemic stroke, hospitalisation due to heart failure            | 17,276| 6                 | 04.2013–07.2018     | NCT01730534          |
| ODYSSEY OUTCOMES | Completed    | Alirocumab    | PCSK9 inhibitor     | Alirocumab 75 mg or 150 mg two-weekly vs. placebo | CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalisation | 18,924| 2.8               | 10.2012–01.2018     | NCT01663402          |

DPP-4 inhibitors

The CARMELINA trial [26] investigated the effect of once-daily linagliptin on CV and kidney outcomes in patients with T2DM at high risk of CV and kidney events. With respect to kidney outcomes, CARMELINA was the first DPP-4i CVOT to investigate a composite kidney outcome in a statistically adequately powered manner [26]. Inclusion criteria for the 6979 patients comprised high risk of vascular events (e.g. history of MI, stroke or coronary artery disease) or impaired renal function with or without CV comorbidities [33]. In the primary endpoint (3P-MACE: CV mortality, non-fatal MI and non-fatal stroke), linagliptin showed CV safety (HR 1.02 (95% CI 0.89–1.17), p<0.001 for non-inferiority) compared to placebo but did not demonstrate a CV benefit. No significant benefit was observed in the secondary kidney composite outcome (HR 1.04 (95% CI 0.89–1.22), p=0.62) compared to placebo. Exploratory kidney and microvascular outcomes showed a significant reduction of albuminuria progression (HR 0.86 (95% CI 0.78–0.95), p=0.003) and a significant reduction in the composite microvascular endpoint (HR 0.86 (0.78–0.95), p=0.003) in the linagliptin group compared to placebo [26].
GLP-1 receptor agonists

In the Harmony Outcomes CVOT, CV effects of once-weekly albiglutide in patients with T2DM were evaluated [27]. A total of 6493 participants with approximately 100% prior CVD was followed for a median of 1.6 years and assessed for 3P-MACE. With respect to the primary outcome (3P-MACE: CV mortality, non-fatal MI and non-fatal stroke), albiglutide showed superiority compared to placebo (HR 0.78 (95% CI 0.68–0.90), p = 0.0006; p < 0.0001 for non-inferiority). Statistically significant secondary outcomes included a reduced expanded composite outcome (death from CVD, non-fatal MI, non-fatal stroke or urgent revascularisation for unstable angina; HR 0.78 (95% CI 0.69–0.90), p = 0.0005) and a reduction of fatal or non-fatal MI (HR 0.75 (95% CI 0.61–0.90), p = 0.003). Incidences of acute pancreatitis, pancreatic cancer and medullary thyroid carcinoma did not differ between the albiglutide and placebo group [27].
SGLT-2 inhibitors
CV safety of dapagliflozin was investigated in the DECLARE-TIMI 58 trial [28]. The trial encompassed 17,160 patients who were followed during a median of 4.2 years. A hitherto unique aspect of the DECLARE-TIMI 58 trial was its high proportion of patients in primary prevention, as 59.4% of the enrolled patients had no prior ASCVD. Dapagliflozin showed non-inferiority to placebo with respect to 3P-MACE (p < 0.0001 for non-inferiority), yet not superiority (p = 0.17 for superiority). As pre-defined co-primary superiority endpoint, a significant reduction of CVD death or hospitalisation for HF (HR 0.83 (95% CI 0.73–0.95), p = 0.005) was demonstrated. In addition, reduction of the renal composite endpoint (≥ 40% decrease in estimated glomerular filtration rate (eGFR) to < 60 mL/min/1.73 m², new end-stage renal disease or death from renal or cardiovascular causes; HR 0.76 (95% CI 0.67–0.87)) and reduction of death from any cause (HR 0.93 (95% CI 0.82–1.04)) were observed. Adverse events included a significant increase of diabetic ketoacidosis (0.3% vs. 0.1%, p = 0.02), a significant increase in the rate of genital infections (0.9% vs. 0.1%, p < 0.001) but no increase in the risk of amputation with dapagliflozin compared to placebo [28].

PCSK-9 inhibition
The ODYSSEY OUTCOMES study was designed to assess CV outcomes of alirocumab in 18,924 patients with prior acute coronary syndrome and low-density lipoprotein (LDL) cholesterol levels of at least 70 mg/dL, non-high-density lipoprotein (HDL) cholesterol levels of at least 100 mg/dL or an apolipoprotein B level of at least 80 mg/dL, and who were receiving statin therapy at high or maximum tolerated dose [29]. 28.5% of the alirocumab study population had diabetes mellitus. Alirocumab significantly decreased CV outcomes (composite of death from coronary heart disease, non-fatal MI, fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalisation; HR 0.85 (95% CI 0.78–0.93), p < 0.001) compared to placebo. Secondary endpoints included a significant reduction of any coronary heart disease event (death from coronary heart disease, non-fatal MI, unstable angiotensin-receptor–neprilysin-inhibition (ARNI) therapy, was discussed.

In the PARADIGM-HF trial, ARNI (valsartan/sacubitril) was compared to enalapril. A significant reduction in the primary composite endpoint (death from CV causes or first hospitalisation for worsening HF; death from CV causes, hospitalisation for HF and death from any cause) was observed [36]. A post hoc analysis of the PARADIGM-HF trial revealed that valsartan/sacubitril compared to enalapril, also has a significantly greater effect on the reduction of brain natriuretic peptide (NT-proBNP) among patients with HF with reduced ejection fraction, who were hospitalised for acute decompensated HF [38]. Also, no differences in the rates of worsening renal function, symptomatic hypotension, and hyperkalemia were observed [38]. Thus, it can be concluded that ARNI might present a valuable therapy option for patients with diabetes and HF.

ADA/EASD consensus statement 2018: new treatment algorithms for T2DM
On 4 October 2018, new treatment algorithms for T2DM were published based on knowledge gained from CVOTs [39]. In contrast to previous suggestions, the new treatment algorithm recommends a highly patient centred, individualised approach of treatment instead of pushing towards standardised treatment goals. As before, guidelines recommend metformin and lifestyle changes as primary treatment option. Major changes were introduced for second- and third-line therapy: before choosing a second-line therapy, practitioners are encouraged to differentiate between present comorbidities and escalate the therapy accordingly and individually. In case of
established CVD, if ASCVD predominates, GLP-1 RA with proven CV benefit or SGLT-2i with proven CV benefit (if eGFR adequate) are recommended. If HF or chronic kidney disease (CKD) predominate, SGLT-2i with evidence of reducing HF and/or CKD progression in CVOTs (if eGFR is adequate) are recommended [39]. In cases without ASCVD, HF or CKD, various choices are offered, depending on the individual patient or setting: if there is a compelling need to minimise hypoglycaemia, if weight gain needs minimising or if costs are a major issue. For injectable therapies, step-wise therapy escalation is recommended, again considering GLP-1 RA options before insulin [39].

Key topics discussed during the 4th CVOT Summit
For the treatment of diabetes, CVOTs only evaluate effects of selected glucose lowering agents for T2DM, yet not combinatorial approaches. Hence, the question of efficacy of these agents (i.e. SGLT-2 inhibitors) in adjunct therapy of T1DM was addressed. Last but not least, parallel to this year’s CVOT Summit, a FDA advisory board re-evaluated the benefit and perpetuation of CVOTs. Likewise, this was debated at the 4th CVOT Summit.

Adjunct therapy in T1DM
As in T2DM, T1DM is associated with a considerably increased risk of CV events which were shown to occur at a younger age than in non-diabetic individuals [40]. Variations in glucose level and hyperglycaemia in children with T1DM have been associated with persistent cognitive dysfunction [41, 42] and both, hyper- and hypoglycaemia were linked to various adverse CV events [43, 44], although the relationship of severe hypoglycaemia in T2DM seems to be bi-directional [45]. However, as patients with T1DM are mainly treated with insulin, CV safety of new glucose lowering agents was only investigated in the context of T2DM. As of now, a variety of studies has started to investigate the use of glucose lowering medication typically used in T2DM, like metformin, pramlintide, GLP-1 RA, SGLT-2i and dual SGLT-1 and -2i as adjunctive therapy for T1DM, particularly in patients who have inadequate insulin control and/or are overweight [46].

When looking at GLP-1 RA (liiraglutide and exenatide) as adjunct therapy in T1DM, one is confronted with significant inter-study variability regarding reduction of HbA1c, postprandial plasma glucose and insulin doses (summarised in [46]). In the ADJUNCT ONE trial [47], evaluating the use of liiraglutide as adjunctive therapy in T1DM, inconsistent results regarding HbA1c reduction and reduction of daily insulin dose were obtained across three liiraglutide doses compared to placebo. Adverse events included increased rates of symptomatic hypoglycaemia and an increase in hyperglycaemia with ketosis [47].

Various studies investigated the efficacy of SGLT-2i (empagliflozin [48, 49], dapagliflozin [50, 51], canagliflozin [52] and the dual SGLT-1 and -2i sotagliflozin [53, 54]) in the treatment of T1DM. All studies reported a significant decrease in HbA1c [48–54] and some also reductions in body weight [49, 51–53] and daily insulin dose [49]. Adverse events included an increase in genital infections [51, 52] and diabetic ketoacidosis (DKA) [52]. Strategies for the prevention of DKA need to be further established and defined. The strong educational need of health care professionals and diabetes teams was highlighted.

It can be summarised that, although no direct comparison of T1DM and T2DM can be made, agents demonstrating CV safety in CVOTs may also exert beneficial effects when provided as adjunct therapy in T1DM. However, more and larger studies are needed to evaluate if CV safety or benefit demonstrated for those agents in T2DM, next to reductions in HbA1c, bodyweight and insulin dose, also hold true in T1DM.

Diabetes comorbidities: “Is the future of the treatment of diabetes with CVD in the hands of general practitioners, diabetologists, cardiologists, nephrologists?” During the 4th CVOT Summit, the question of whose responsibility the treatment of diabetes with CVD should be in future arose—general practitioners (GPs), diabetologists, cardiologists or nephrologists. All disciplines are tightly interwoven in the field of diabetes, also reflected in the spectrum of available treatment options. Looking at patient numbers only, GPs and diabetologists might treat the majority of diabetes patients. However, CVOTs have provided further knowledge on CV and renal comorbidities, making integration of cardiologists and nephrologists in treatment of diabetes indispensable and/or promote further training of diabetologists in cardiovascular medicine and of cardiologists in diabetes. Thus, CVOTs promoted the exchange of knowledge and tightened the close network between disciplines, also reflected in the new ADA/EASD consensus statement and future guidelines.

CVOTs in diabetes: how should we continue? On the 10 year anniversary of the FDA “Guidance for Industry” [11] in 2018, a FDA advisory board re-evaluated the benefit and perpetuation of CVOTs, parallel to the 4th CVOT Summit in October 2018. Among the issues addressed by the FDA advisory board were: (1) the impact of the recommendations in the 2008 “Guidance
for Industry” on the assessment of CV risk for drugs indicated to improve glycaemic control in patients with T2DM; (2) the transferability of CV safety findings from members of a drug class to the entire class of drugs, and (3) whether an unacceptable increase in CV risk needs to be excluded for all new drugs to improve glycaemic control in patients with T2DM, regardless of the presence or absence of a signal for CV risk in the development program [10]. The FDA panel voted for continuation, yet improvement of CVOTs [55].

Questions of similar manner were discussed at the 4th CVOT Summit. On the one hand, positive aspects of CVOTs were reflected by, for example, the detection of unexpected benefits as observed in EMPA-REG OUTCOME [20], CANVAS [21], DECLARE-TIMI 58 [28], LEADER [17], SUSTAIN-6 [18] and Harmony Outcomes [27]. These benefits often are not restricted to CV endpoints; e.g. the CANVAS trial revealed a positive effect of canagliflozin on renal outcomes [21]. These safety and benefit analyses led to the refinement of treatment algorithms as stated in the 2018 ADA/EASD Consensus Statement [39] and the integration of new drugs as “preferred” or “safe” second- or third-line therapy into new guidelines [39, 56]. On the other hand, limitations of current CVOTs, such as the lack of generalisability (i.e. participants often are at high risk for a CV event or death, thus not representative for a larger population), relatively short time-lines for assessing potential harms or benefits and the placebo-controlled design of CVOTs [12] were addressed. Room for improvement of cost-effectiveness and cost-sharing options as well as modification of end points and analyses were also discussed [12]. In summary, concomitant with the FDA panel vote, it was concluded that continuation but modification of CVOTs is highly beneficial as they provide safety aspects relevant to all T2DM patients and create a broad body of evidence to base new guidelines and therapies on.

Conclusion
The 4th CVOT Summit of the D&CVD EASD Study Group discussed key results of recently completed and published CVOTs in T2DM (CARMELINA, Harmony Outcomes, and DECLARE-TIMI 58) and CV safety studies of PCSK-9 inhibition (ODYSSEY OUTCOMES) in an interactive, multi-disciplinary format. The summit considered both potentials and limitations of current CVOT designs as well as the implementation of CVOTs in the newly published guidelines by the ADA/EASD consensus statement. Learnings for adjunct therapy of T1DM and continuation and modification of CVOT trials were discussed. The D&CVD EASD Study Group will continue its activity. In-depth discussions and presentations of upcoming CVOTs like REWIND, PIONEER-6, VERTIS CV Study or CREDESC, will be resumed at the 5th CVOT Summit, which will be held from 24–25 October 2019 in Munich (http://www.cvot.org).

Abbreviations
3P-MACE: 3-point major adverse cardiovascular event; 4P-MACE: 4-point MACE; ADA: American Diabetes Association; ACCORD: Action to Control Cardiovascular Risk in Diabetes; ARNI: angiotensin-receptor–neprilysin-inhibitors; ASCVD: atherosclerotic cardiovascular disease; CANVAS: Canagliflozin Cardiovascular Assessment Study; CARMELINA: Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus; CI: confidence interval; CKD: chronic kidney disease; CV: cardiovascular; CV: cardiovascular disease; CVOT: cardiovascular outcome trial; DECLARE: Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes; DEPICT-1: efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes; DEVOTE: Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events; DPP-4i: dipeptidyl-peptidase-4 inhibitors; eGFR: estimated glomerular filtration rate; ELIXA: Evaluation of Lixisenatide in Acute Coronary Syndrome; EASD: European Association for the Study of Diabetes; EMA: European Medicines Agency; EXAMINE: Examination of Cardiovascular Outcomes with Allopurinol versus Standard of Care; EXSCEL: Exenatide Study of Cardiovascular Event Lowering; FDA: Food and Drug Administration; GLP-1 RA: glucagon like peptide-1 receptor agonist; Harmony Outcomes: albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease; Hba1c: glycated haemoglobin A1c; HDL: high-density lipoprotein; HF: heart failure; HR: hazard ratio; LEADER: Liaglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; LDL: low-density lipoprotein; MI: myocardial infarction; NT-proBNP: brain natriuretic peptide; ORIGIN: Outcome Reduction With Initial Glargine Intervention, PARADIGM-HF: Prospective Comparison of ARNI (Angiotensin Receptor–Neprilysin Inhibitor) with ACEI (Angiotensin-Converting-Enzyme Inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial; PCSK-9i: proprotein convertase subtilisin/kexin type-9 inhibitor; REMOVAL: Cardiovascular and biochemical effects of metformin in patients with type 1 diabetes; SAVOR: Saxagliptin Assessment of Vascular Outcomes Recorded in Subjects with Diabetes Mellitus; SGLT-2i: sodium/glucose co-transporter-2 inhibitors; SUSTAIN-6: Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; TECOS: Trial Evaluating Cardiovascular and Other Long-term Outcomes with Semaglutide in Patients with Type 2 Diabetes; TECOS: Trial Evaluating Cardiovascular and Other Long-term Outcomes with Semaglutide in Patients with Type 2 Diabetes; TECOS: Trial Evaluating Cardiovascular and Other Long-term Outcomes with Semaglutide in Patients with Type 2 Diabetes; TIDM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; TECOS: Trial Evaluating Cardiovascular and Other Long-term Outcomes with Semaglutide in Patients with Type 2 Diabetes; TECOS: Trial Evaluating Cardiovascular and Other Long-term Outcomes with Semaglutide in Patients with Type 2 Diabetes; TECOS: Trial Evaluating Cardiovascular and Other Long-term Outcomes with Semaglutide in Patients with Type 2 Diabetes; TECOS: Trial Evaluating Cardiovascular and Other Long-term Outcomes with Semaglutide in Patients with Type 2 Diabetes; TECOS: Trial Evaluating Cardiovascular and Other Long-term Outcomes with Semaglutide in Patients with Type 2 Diabetes; TECOS: Trial Evaluating Cardiovascular and Other Long-term Outcomes with Semaglutide in Patients with Type 2 Diabetes; TECOS: Trial Evaluating Cardiovascular and Other Long-term Outcomes with Semaglutide in Patients with Type 2 Diabetes; TECOS: Trial Evaluating Cardiovascular and Other Long-term Outcomes with Semaglutide in Patients with Type 2 Diabetes; TECOS: Trial Evaluating Cardiovascular and Other Long-term Outcomes with Semaglutide in Patients with Type 2 Diabetes.

Authors’ contributions
OS, ES, DC, BI, NL, DR, JS, PV and AC contributed to the discussion and content of the report. All authors read and approved the final manuscript.

Author details
1 Forschunggruppe Diabetes e.V., Ingolstaedter Landstrasse 1, Neuherberg, 85764 Munich, Germany. 2 Internal Medicine Department, Clinical County Emergency Hospital Constanta, Tomis Blvd. No. 145, 900591 Constanta, Romania. 3 Clalit Health Services and Technion Faculty of Medicine, 3 Zivoni Street, Haifa, Israel. 4 Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Dr Subotica 13, Belgrade 11000, Serbia. 5 Diabetes and Metabolic Disorders, Dubrava University Hospital, Avenija Gojka Suška 6, 10000 Zagreb, Croatia. 6 3rd Department of Internal Medicine, 1st Faculty of Medicine, Charles University, U Nemocnice 1, 128 08 Prague 2, Czech Republic. 7 Department of Endocrinology Diabetology Nutrition, CINFO, CRNH-IIdF, Jean VERDIER Hospital, Paris 13 University, Avenue du 14 Juillet, 93140 Bondy, France. 8 Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) and Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Barcelona, Spain. 9 Department of Cardiovascular and Metabolic Diseases, IRCCS Multimedica, Via Milanese 300, 20099 Sesto San Giovanni, MI, Italy.
Acknowledgements
We would like to thank all speakers and participants of the 4th CVOT Summit for their active involvement in the scientific discussions leading to the present report. Moreover, we want to acknowledge the industry for their support of the meeting.

Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
Data sharing not applicable to this article as no datasets were generated during the current study.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Not applicable.

Funding
No funding supported the generation of this manuscript.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 30 January 2019   Accepted: 4 February 2019

Published online: 11 March 2019

References
1. ADA. 9. Cardiovascular disease and risk management: standards of medical care in diabetes—2018. Diabetes Care. 2018;41(1):S86–104.
2. Sharma A, et al. Causes of death in a contemporary cohort of patients with type 2 diabetes and atherosclerotic cardiovascular disease: insights from the TECOS trial. Diabetes Care. 2017;40(12):1763–70.
3. Barnett KN, et al. A 12-year follow-up study of all-cause and cardiovascular mortality among 10,532 people newly diagnosed with type 2 diabetes in Tayside, Scotland. Diabet Med. 2010;27(10):1124–9.
4. Bergenstal RM. Glycemic variability and diabetes complications: does it matter? Simply put, there are better glycemic markers! Diabetes Care. 2015;38(8):1615–21.
5. Turnbull FM, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia. 2009;52(11):2288–98.
6. Meintz CL, et al. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. Diabetes. 1970;19:789–830.
7. Gerstein HC, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545–59.
8. Nissen SE, Wolski K, Topol EJ. Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. JAMA. 2005;294(20):2581–6.
9. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007;356(24):2457–71.
10. FDA Background Document: Endocrinologic and metabolic drugs advisory committee meeting. 24/25 October 2018. https://www.fda.gov/downloads/AdvisoryCommittees/ CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugAdvisoryCommittee/UCM639131.pdf. Accessed 16 Jan 2019.
11. Guidance for industry diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes, FDA, Editor. 2008.
12. Cefalu WT, et al. Cardiovascular outcomes trials in type 2 diabetes: where do we go from here? Reflections from a diabetes care editor’s expert forum. Diabetes Care. 2018;41(1):14–31.
13. Scirica BM, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369(14):1317–26.
14. Zannad F, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. Lancet. 2015;386(9982):2067–76.
15. Green JB, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015;373(3):232–43.
16. Pfeffer MA, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med. 2015;373(23):2247–57.
17. Marso SP, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375(4):311–22.
18. Marso SP, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1894–44.
19. Holman RR, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017;377(13):1228–39.
20. Zinman B, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117–28.
21. Neal B, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644–57.
22. Marso SP, et al. Efficacy and safety of degludec versus glargine in type 2 diabetes. N Engl J Med. 2017;377(8):723–32.
23. Gerstein HC, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med. 2012;367(4):319–28.
24. Schnell O, et al. Current perspectives on cardiovascular outcome trials in diabetes. Cardiovasc Diabetol. 2016;15(1):139.
25. Schnell O, et al. Updates on cardiovascular outcome trials in diabetes. Cardiovasc Diabetol. 2017;16(1):128.
26. Rosenstock J, et al. Effect of linaclotide vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CAMELLIA randomized clinical trial. JAMA. 2018. [Epub ahead of print]
27. Hernandez AF, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet. 2018;392(10157):1519–29.
28. Wiviott SD, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):347–57.
29. Schwartz GG, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med. 2018;379(22):2097–107.
30. Schnell O, et al. Report from the 3rd Cardiovascular Outcome Trial (CVOT) Summit of the Diabetes & Cardiovascular Disease (D&CVD) EASD Study Group. Cardiovasc Diabetol. 2018;17(1):30.
31. Schnell O, et al. Report from the 2nd Cardiovascular Outcome Trial (CVOT) Summit of the Diabetes and Cardiovascular Disease (D&CVD) EASD Study Group. Cardiovasc Diabetol. 2016;15:33.
32. Schnell O, et al. Report from the 1st Cardiovascular Outcome Trial (CVOT) Summit of the Diabetes & Cardiovascular Disease (D&CVD) EASD Study Group. Cardiovasc Diabetol. 2016;15:33.
33. Rosenstock J, et al. Rationale, design, and baseline characteristics of the CARDiAvascular safety and Renal Microvascular outcome Study with LINAglitin (CARMELINA): a randomized, double-blind, placebo-controlled clinical trial in patients with type 2 diabetes and high cardio-renal risk. Cardiovasc Diabetol. 2018;17:39.
34. Sabatine MS, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017;367(18):1713–22.
35. Shah AD, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 19 million people. Lancet Diabetes Endocrinol. 2015;3(2):105–13.
36. McMurray JJV, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993–1004.
37. Seferovic JP, et al. Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: a post hoc analysis from the PARADIGM-HF trial. Lancet Diabetes Endocrinol. 2017;5(5):333–40.
38. Velazquez EJ, et al. Angiotsin–neprilysin inhibition in acute decompenated heart failure. N Engl J Med. 2018;380(6):539–48.
39. 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):2669–701.
40. de Ferranti SD, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Diabetes Care. 2014;37(10):2843–63.
41. Fox LA, et al. Persistence of abnormalities in white matter in children with type 1 diabetes. Diabetologia. 2018;61(7):1538–47.
42. Musen G, et al. Cognitive function deficits associated with long-duration type 1 diabetes and vascular complications. Diabetes Care. 2018;41(8):1749–56.
43. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353(25):2643–53.
44. Hanefeld M, Frier BM, Pistrosch F. Hypoglycemia and cardiovascular risk: is there a major link? Diabetes Care. 2016;39(Supplement 2):S205–9.
45. Standl E, et al. Increased risk of severe hypoglycemic events before and after cardiovascular outcomes in TECOS suggests an at-risk type 2 diabetes frail patient phenotype. Diabetes Care. 2018;41(3):596–603.
46. Warnes H, et al. Metabolic control in type 1 diabetes: is adjunctive therapy the way forward? Diabetes Ther. 2018;9(5):1831–51.
47. Mathieu C, et al. Efficacy and safety of iraglutide added to insulin treatment in type 1 diabetes: the ADJUNCT ONE treat-to-target randomized trial. Diabetes Care. 2016;39(10):1702–10.
48. Pieber TR, et al. Empagliflozin as adjunct to insulin in patients with type 1 diabetes: a 4-week, randomized, placebo-controlled trial (EASE-1). Diabetes Obes Metab. 2015;17(10):928–35.
49. Perkins BA, et al. Sodium–glucose cotransporter 2 inhibition and glycemic control in type 1 diabetes: results of an 8-week open-label proof-of-concept trial. Diabetes Care. 2014;37(5):1480–3.
50. Tamez HE, et al. Dapagliflozin as an adjunct therapy to insulin in the treatment of patients with type 1 diabetes mellitus. J Diabetes Metab Disord. 2015;14:78.
51. Dandona P, et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes: the DEPICT-1 52-week study. Diabetes Care. 2018;41(12):2352–9.
52. Henry RR, et al. Efficacy and safety of canagliflozin, a sodium–glucose cotransporter 2 inhibitor, as add-on to insulin in patients with type 1 diabetes. Diabetes Care. 2015;38(12):2258–65.
53. Sands AT, et al. Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct therapy to insulin in type 1 diabetes. Diabetes Care. 2015;38(7):1181–8.
54. Garg SK, et al. Effects of sotagliflozin added to insulin in patients with type 1 diabetes. N Engl J Med. 2017;377(24):2337–48.
55. Phend C. FDA advisors: tweak, don’t dump CV outcomes trials. 2018. https://www.medpagetoday.com/cardiology/prevention/75938. Accessed 06 Dec 2018.
56. Standl E, et al. Integration of recent evidence into management of patients with atherosclerotic cardiovascular disease and type 2 diabetes. Lancet Diabetes Endocrinol. 2017;5(5):391–402.