Conference Highlights

The 80th Annual (Virtual) Conference of the American Diabetes Association: June 12–16, 2020

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Abstract

A large number of presentations on clinical, basic science, and genetics were discussed at the first virtual American Diabetes Association conference held in June 2020. Studies of relevance to practicing clinicians included the results of the VERTIS-CV study that confirmed the SGLT2 inhibitor ertugliflozin was similar to other drugs in the group in terms of cardiovascular safety, heart failure, and renal benefits. A symposium on heart failure also highlighted the benefits of this group of drugs for treating heart failure both in patients with and without diabetes. The new Food and Drug Administration guidance for new diabetes drugs was presented and created a lively discussion about the pros and cons of these new rules. Another lively debate on whether there is a place for sulfonylureas in the era of the modern diabetes medications reached the conclusion that there is probably still a place for these old and established drugs. On the lipid front, the safety of statins was emphasized in face of negative publicity in the social media, while the recently published REDUCE-IT study showed that tackling low-density lipoprotein cholesterol only may not be enough in the battle against increased cardiovascular risk in diabetes. Looking to the future, a weekly basal insulin may be in sight in a few years' time.

Keywords: American Diabetes Association, annual conference, virtual

INTRODUCTION

The annual conference of the American Diabetes Association (ADA) is the main event in the diabetes calendar each year, with new research findings being launched at it annually. The 80th annual ADA conference was planned to be held in Chicago, USA, but due to the COVID-19 pandemic, it turned out to be the first ADA conference to be held virtually because of the lockdown. The online virtual arrangements worked very well. Sessions were recorded a few days before the meeting and were released online at the allocated times during the conference. There was a chance to send feedback and questions during and after the sessions with responses from the speakers. The ADA will keep the recordings available online for

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those registered for the conference up to September 2020.

The online interaction, overall, appeared to have worked well, but whether it will compensate for the personal interaction and networking usually held in these conferences is open to debate. The ADA was a massive conference with large numbers of presentations on clinical, basic science, and genetic studies presented. In this summary, we highlight the sections that we felt are most relevant to practicing clinicians.

COVID-19 AND DIABETES

In a Chinese study, 1099 patients with COVID-19 were assessed, the primary endpoint of ICU admission, the need for ventilation or death occurred in 6%.[1] Patients with diabetes and COVID were more likely to have a worse outcome as they represented 7% of the whole population but 27% of those with the primary endpoint. A similar outcome was seen in an American study that assessed 1122 patients.[2] Mortality from COVID-19 was seen in 6% of those without diabetes and 29% of those with diabetes or uncontrolled hyperglycemia. The authors felt that the higher vulnerability to COVID-19 in patients with diabetes was not only from diabetes but possibly also from lack or delayed access to health care due to the lockdown. The take-home message from these studies is that diabetes is a risk factor for poor outcomes in COVID-19 patients, and extra care is needed to reduce this risk.

DEBATE ON THE NEW FOOD AND DRUG ADMINISTRATION GUIDANCE ON CARDIOVASCULAR OUTCOME TRIALS

The 2008 guidance from the Food and Drug Administration (FDA) on cardiovascular outcome trials (CVOTs) for modern diabetes drugs (DPP-4 inhibitors, glucagon-like peptide-1 receptor agonists [GLP-1 RAs], and SGLT2is) lead to a proliferation of CVOTs that have been reported over the last decade. So far, 26 trials have been performed (19 completed and 7 still ongoing), a total of 197,000 patients took part. CVOTs held since 2008 showed that none of the drugs caused excess CV risk. Reductions in cardiovascular risk or mortality were shown for some drugs, while

new benefits were suggested, such as reduced hospitalization for heart failure (HHF) and reduced progression of chronic kidney disease (CKD). There were also some unexpected safety signals with some such as excess HHF with saxagliptin. However, a question has been raised on whether we should move on from the FDA guidance that has mandated these trials for good reasons in 2008. The arguments for the need to move on from the 2008 guidance are that the trials are expensive, and none has shown increased atherosclerotic cardiovascular disease (ASCVD) risk. The FDA has responded to this and issued new guidance in March 2020 for the pharmaceutical industry about investigations of new diabetes drugs. These new recommendations for trials with new diabetes drugs include the following requirements: ≥4000 patient-years of exposure in phase 3 trials, ≥1500 patients exposed for 1 year, and ≥500 patients exposed for 2 years. Besides, the trials should include at least 500 patients with stage 3–4 CKD, 600 patients with established CVD, and 600 patients >65 years old. There is no longer a need for premarketing and postmarketing CV risk margins. During the discussion, concerns were raised by Steve Nissen (who suggested the original guidance to the FDA in 2008) that the new guidance is unwise as he feels it would allow manufactures to get away with licensing new drugs without proper scrutiny for CV effects; he feels the numbers proposed in the new guidance will not be enough to provide reassurance on CV safety. He voiced his fears that we will be returning to a glucocentric approach where drugs just shown to reduce A1c will be marketed without proper scrutiny of their CV safety. The reply to these concerns came from the FDA team that the FDA tries to strike a balance between allowing the pharmaceutical industry to innovate and test new diabetes drugs while retaining robust CV safety measures. They argued that the A1c is still essential as it is strongly associated with microvascular complications. They also defended the new guidance as not being glucocentric and will not mean a return to the situation before 2008 as flexibility is retained, and the FDA still has the authority to ask for CVOTs from the manufacturers where necessary.

VERTIS CV Study

The results of this large CVOT to test the SGLT2 inhibitor ertugliflozin's cardiovascular safety were presented at the conference. The study ran from December 2013 to December 2019 and 8246 patients were randomized 1:1:1 to placebo (2747), ertugliflozin 5 mg (2752), and ertugliflozin 15 mg (2747). The mean age was 64 years, 70% were male, and 88% were Caucasian. The mean follow-up period was 3.5 years. The mean duration of diabetes was 13 years, and baseline A1c was 8.2%, body mass index was 32, estimated glomerular filtration rate (eGFR) was 75, and 22% of patients had an eGFR <60. The history of ASCVD was present in 100% of cases.

The main results revealed that the A1c decreased by 0.5% (at 18 weeks), weight by 2.6 kg, and systolic blood pressure (BP) by 3 mmHg. The hazard ratio (HR) for the primary outcome of 3-point MACE was 0.97, with a $P < 0.001$ for noninferiority but no superiority for ertugliflozin against placebo. The secondary outcomes of CV death had a HR of 0.92, nonfatal myocardial infarction (MI):HR 1.0, and nonfatal stroke: HR 1.0. CV death or heart failure had an HR of 0.88, $P = 0.11$. HHF had an HR of 0.70, $P = 0.006$, but for the composite renal outcome, the HR was 0.81 with a $P = 0.08$. Adverse effects were similar to other SGLT2i, with no excess amputations, and no new risks were identified. There was no difference between the 2 doses of ertugliflozin (5 and 15 mg daily) in efficacy or side effects. The take-home message from this study is that ertugliflozin is noninferior to placebo, and the HHF benefit is confirmed but no CVD or CKD benefit.

Following the VERTIS-CV study, the authors updated the meta-analysis of all four SGLT2 inhibitors with adding of VERTIS-CV results. The pooled estimate for MACE for all four SGLT2 inhibitors was 0.90 compared with 0.89 before VERTIS-CV, i.e., it remained unchanged. In conclusion, the updated meta-analysis supports the current guidelines on the use of SGLT2 inhibitors. The independent commentator also concluded that the study is not dissimilar to other SGLT2i CVOTs and confirms they are all from the same class.

Do Sulfonylureas Still have a Place in Type 2 Diabetes Treatment?

A debate was held on this critical issue with the widespread use of modern diabetes drugs, DPP4 inhibitors, the GLP-1 RAs, and the SGLT2 inhibitors.

The arguments against retaining sulfonylureas (SUs) for type 2 diabetes treatment included that the ADOPT study showed their effect not to be durable when compared against metformin or rosiglitazone.[3] They cause excess hypoglycemia and modern drugs such as the GLP-1 RAs and the SGLT2 inhibitors have shown CV benefit, whereas there is still a question mark about the CV risk of SUs as shown by a recent large Danish retrospective study that showed excess CV risk and mortality for SUs when compared with other second-line drugs for type 2 diabetes.[4]

Arguments for continued use of SUs included the long experience (60 years) of these drugs, their proven efficacy in reducing microvascular complications, not only from the UKPDS[5] but also from the ADVANCE study,[6] their low cost, and easy accessibility all over the world. Some studies have also shown that the real-world incidence of hypoglycemia with SUs is very low.[7] Regarding the excess CV risk, this should no longer be considered an issue after the recent results of the CAROLINA study.[8] It was also argued that with the wide diversity of type 2 diabetes, there is a need for more and not fewer options of treatment. Finally, it should be remembered that they are the drugs of choice for some types of monogenic diabetes such as MODY and neonatal diabetes.

Adjunctive Therapies in T1D

All speakers in this session concurred on the need for adjunctive therapies for patients with type 1 diabetes to mitigate some of the undesirable effects of insulin. Potential for a few agents was discussed:

Metformin

The REMOVAL trial studied 428 patients with T1D randomized to metformin 1 g bd or placebo.[9] The mean age was 55 years, the mean diabetes duration was 33 years, and baseline A1c was 8%. The

results showed no change in the primary outcome of improvement of atherosclerosis as assessed by carotid intima-media thickness. There were minor benefits for metformin in reducing A1c by only 0.13% and weight by 1.1 kg, but no change was seen in total insulin dose or hypoglycemia. Therefore, the results of the REMOVAL study do not support the use of metformin in type 1 diabetes.

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

The drugs studied in this group included liraglutide (in the ADJUNCT trials),[10,11] albiglutide, and exenatide. The conclusion from these studies is that there were minor benefits in weight loss and reduced insulin dose but at the expense of excess hypoglycemia.[12] The take-home message was that GLP-1 RAs are of no use in type 1 diabetes, and manufacturers have stopped the programs of further studies.

SGLT2 INHIBITORS

This is the most promising group for adjunctive therapy and the most widely investigated. A total of >6000 patients were studied (canagliflozin, empagliflozin, dapagliflozin, and sotagliflozin). Studies have shown benefits on weight, reduced glycemic variability, and systolic BP. However, DKA is a real risk; it occurred in 4% of patients in randomized studies despite mitigation measures employed, so in real life, the risk is expected to be higher.[13] Sotagliflozin has been licensed for type 1 diabetes in Europe but not in the USA. The take-home message is that SGLT2i may be considered in very selected cases and with extreme caution.

BENEFITS VERSUS RISKS OF STATINS

There is much misinformation on the Internet/social media that leads to patients declining or discontinuing statins, which has resulted in an increased risk of ASCVD. To put benefits/risks of statins in perspective, the following model that has been extracted from several studies and meta-analyses was presented[14] [Box 1]. The take-home message was that statins' benefits far outweigh any risks, and clinicians should make more efforts to dispel myths about statin risks spread by social media.

Box 1: Benefits and risks of statin therapy*	
Benefits	
Major vascular events prevented (secondary prevention)	1000
Major vascular events prevented (primary prevention)	500
Risks	
Newly diagnosed diabetes cases	100
Muscle symptoms (CK not increased)	<100
Myopathy	5
Rhabdomyolysis	1
Severe liver disease	<1

*The outcomes are expected in 10,000 patients treated with a statin for 5 years resulting in an LDL-C reduction of 2 mmol/L. LDL-C: Low density lipoprotein-cholestrol

REDUCE-IT STUDY

There is wide use of fish oil products (20% in the US). Meta-analyses have confirmed that combined omega-3 supplements (Eicosapentaenoic Acid (EPA) combined with Docosahexaenoic Acid (DHA)) are of no benefit in reducing CV risk.[15] The REDUCE-IT study tested the effect of EPA on CV risk.[16] 8179 patients were randomized 1:1 to icosapent ethyl (EPA) 2 g bd (4089) or placebo (4090). The baseline triglyceride level was 150–500 mg/dl, low-density lipoprotein: 41–100 mg/dl. 100% of patients were on statins, 70% had previous CVD, and 30% had diabetes + ≥ 1 CV risk factor. The mean follow-up duration was 4.9 years. The primary outcome of 5-point MACE occurred at a HR of 0.75, $P < 0.001$; the number needed to treat to prevent a CVD event was 28. Safety was similar to placebo, with only a minor increase in the risk of nonserious bleeding and a slightly increased risk of atrial fibrillation. Consequently, the use of EPA has been endorsed by the FDA, ADA, AHA, AACE, NLA, and ESC. The cost-effectiveness issue is crucial as it is a relatively expensive drug, but one study showed that it is cost-effective for use in the US health system. One of the points that came up in the discussion is what to do with the current widespread prescription by clinicians (sometimes by demand from patients) of omega 3 while there is no good evidence for benefit in reducing CV risk, and it has been recommended by speakers that clinicians should actively start to de-prescribe omega-3 products.

FUTURE DEVELOPMENTS: WEEKLY BASAL INSULIN DEVELOPMENT

There is an unmet need for even longer-acting basal

insulins. It could be a popular choice in type 2 diabetes patients reluctant to start insulin, especially those who are already on a weekly GLP-1 RA. Challenges to weekly basal insulin include dose titration and adjustment for intercurrent illness. Several weekly insulin preparations have been tested in preclinical, phase 1, and phase 2 studies (Icodec from Novo, BIF from Lilly, and others from AstraZeneca and Sanofi). All companies have stopped further work on weekly insulin except Novo, who is still working on insulin Icodec. This weekly basal insulin has been tested in several phase 1 and phase 2 studies involving over 1000 patients, compared against insulin glargine and insulin degludec. Early results indicate comparable efficacy against daily basal insulins, no excess hypos, and no new risks. The take-home message is that it is promising, but still, a long way to go before it becomes available.

Diabetes Prevention Program Observational Study, 20-Year Results

The DPP randomized 3234 patients to placebo, intensive lifestyle (ILS), or metformin.[17] After a 20-year follow-up, it was shown that there was no difference between the three groups in nephropathy or retinopathy. However, patients who did not progress from prediabetes to diabetes had small reductions in risk of retinopathy. Regarding major adverse cardiovascular events (MACE), there was no difference between the placebo and the metformin or the ILS groups. However, those who did not progress to diabetes had a 39% lower risk of MACE. Regarding cancer, metformin resulted in a 12% risk reduction and ILS in a 4% risk reduction (both not significant). There was also no difference in cognitive function between the groups.

Diabetes and Heart Failure

Heart failure is one of the most prevalent cardiovascular complications of diabetes but has remained largely under-recognized. There has been a renewed interest in the issue of heart failure in patients with diabetes after several CVOTs using SGLT2 inhibitors demonstrated that these drugs are beneficial in preventing HHF in patients with diabetes. Moreover, the recently published DAPA-HF study confirmed that the use of the SGLT2 inhibitor dapagliflozin, in patients with heart failure with reduced ejection fraction, resulted in a 25% reduction of the composite endpoint of CV death and urgent heart failure visits.[18] This outcome was observed in both patients with and without diabetes. This finding highlights the role of this class of drugs in broader populations beyond those with diabetes. Speakers in the session underscored the role of the diabetologist in the early identification of patients with heart failure, especially those presenting with nonclassical symptoms such as fatigue and reduced exercise tolerance. More use should be made of NT-pro BNP testing in at-risk patients to identify those who need more assessment by echocardiography and referral to cardiologists. The choice of drugs for treating glycemia in patients with type 2 diabetes and heart failure has also been recognized in the recent guidelines by recommending SGLT2 inhibitors and avoiding drugs with adverse effects on heart failure such as pioglitazone and saxagliptin.[19]

Conclusions

The first virtual ADA conference has proven to be a great success similar to its physical predecessors. It witnessed a large number of essential diabetes studies and developments presented, which can have an impact on clinical practice.

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Conflicts of interest
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Compliance with ethical principles
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References

1. Guan W, Ni Z, Hu Y, Liang WH, Ou CQ, He JX, *et al*. Clinical characteristics of coronavirus 19 in China. N Engl J Med 2020;382:1708-20.
2. Bode B, Garrett V, Messler J, McFarland R, Crowe J, Booth R, *et al*. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. J Diabetes Sci Technol 2020;14:813-21.
3. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, *et al*. Glycemic durability of rosiglitazone, metformin or glyburide monotherapy. N Engl J Med 2006;355:2427-43.
4. Jensen MH, Kjolby M, Hejlesen O, Jakobsen PE, Vestergaard P. Risk

of major adverse cardiovascular events, severe hypoglycemia, and all-cause mortality for widely used antihyperglycemic dual and triple therapies for type 2 diabetes management: A cohort study of all Danish users. Diabetes Care 2020;43:1209-18.

5. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:837-53.

6. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, *et al.* Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560-72.

7. Edridge CL, Dunkley AJ, Bodicoat DH, Rose TC, Gray LJ, Davies MJ, *et al*. Prevalence and incidence of hypoglycemia in 532,542 people with type 2 diabetes on oral therapies and insulin: A systematic review and meta-analysis of population-based studies. PLOS One 2015;10:e0126427.

8. Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, *et al*. CAROLINA Investigators. Effect of linagliptin vs. glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: The CAROLINA randomized clinical trial. JAMA 2019;321:69-79.

9. Petrie JR, Chaturvedi N, Ford I, Brouwers MCGJ, Greenlaw N, Tillin T, *et al*. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): A double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 2017;5:597-609.

10. Mathieu C, Zinman B, Hemmingson J, Woo V, Colman P, Christiansen E, *et al*. Efficacy and safety of liraglutide added to insulin treatment in type 1 diabetes: The ADJUNCT ONE treat to target randomized trial. Diabetes Care 2016;39:1702-10.

11. Ahern B, Hirsch I, Pieber T, Mathieu C, Gómez-Peralta F, Hansen TK, *et al*. efficacy and safety of liraglutide added to capped insulin treatment in subjects with type 1 diabetes: The ADJUNCT TWO randomized trial. Diabetes Care 2016;39:693-701.

12. Dejgaard F, Frandsen C. Holst J, Madsbad S. Liraglutide for treating type 1 diabetes. Expert Opin Biol Ther 2016;16:579-90.

13. Muso G, Gambino R, Cassader M, Paschetta E. Efficacy and safety of dual SGLT1/2 inhibitor sotagliflozin in type 1 diabetes: Meta-analysis of randomised controlled trials. BMJ 2019;365:I1328.

14. Newman C, Preiss D, Tobert JA, Jacobson TA, Page RL 2nd, Goldstein LB, *et al*. Statin safety and associated adverse events. A scientific statement from the American Heart Association. Arterioscler Thromb Vasc Biol 2018;38:e00.

15. Aung T, Halsey J, Kromhout D, Gerstein HC, Marchioli R, Tavazzi L, *et al*. Association of omega-3 fatty acid supplemental use with cardiovascular risks. Meta-analyses of 10 trials involving 77,917 individuals. JAMA Cardiol 2018;3:225-34.

16. Bhatt D, Steg P, Miller M, Brinton EA, Jacobson TA, Ketchum SB, *et al*. Cardiovascular risk reduction with icosapentethyl for hypertriglyceridemia (REDUCE-IT). N Engl J Med 2019;380:11-22.

17. Knowler W, Barrett-Connor E, Fowler S, Hamman RF, Lachin JM, Walker EA, *et al*. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.

18. McMurray JJV, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, *et al*. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). Eur J Heart Fail 2019;21:665-75.

19. Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, *et al*. 2019 update to: 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 2020;43:487-93.

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