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Best Achievements in Clinical Medicine in Diabetes and Dyslipidemia in 2020

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Over the last two decades, our understanding of diabetes and treatment strategies have evolved tremendously, from scientific, mechanistic, and human perspectives. The categories of anti-diabetic medications expanded from a few to numerous, enabling clinicians to personalize diabetes care and treatment. Thanks to rapid growth in the field of science and medical engineering, newer treatment options are coming to the market with various advantages and disadvantages to be aware of. Therefore, clinicians should rapidly adopt new trends based on guidelines and data from many clinical trials in the field of diabetes. In the treatment of dyslipidemia, trends and guidelines are changing every year, and novel therapies are being developed. In this review, we would like to summarize the major achievements in clinical medicine in 2020 in the field of diabetes mellitus and dyslipidemia.

Keywords: Diabetes mellitus; Dyslipidemias; Incretins; Sodium-glucose transporter 2 inhibitors; Glucagon-like peptide-1 receptor; Insulin infusion systems; Pancreas, artificial; Blood glucose self-monitoring; Eicosapentaenoic acid

ACHIEVEMENTS IN CLINICAL MEDICINE IN DIABETES MELLITUS IN 2020

According to the Ninth Diabetes Atlas, one in 11 adults (463 million) have diabetes worldwide, although one in two people with diabetes are not aware that they have diabetes [1]. The increasing incidence of diabetes is especially prominent in the Asia-Pacific area and the increased prevalence of young-onset diabetes is a serious problem in this region, since younger patients with diabetes have a lifelong risk for cardiovascular (CV) complications, mortality, and microvascular complications that would lead to a deterioration of quality of life [2,3].

Over the last two decades, tremendous advances in diabetes treatment modalities have been achieved thanks to rapid growth in the fields of science and medical engineering. Most of all, the discovery of incretin therapy and recently developed sodium-glucose cotransporter 2 (SGLT2) inhibitors have been the most successful treatment modalities in diabetes treatment. Recent guidelines have actively adopted the results of outcome trials of cardiovascular disease (CVD) and recommended glucagon-like peptide-1 receptor agonists (GLP-1RA) and SGLT2 inhibitors as the second-line therapy after metformin in patients with indi-

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cators of high-risk or established atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), or chronic kidney disease (CKD) [4,5]. In addition, recent developments in the field of biomedical engineering have brought the use of continuous glucose monitoring (CGM) systems and artificial pancreas devices—referred to as a closed-loop system (CLS)—closer to the everyday life of patients with diabetes.

In this section, we would like to briefly review the major achievements in clinical medicine in the field of diabetes mellitus in 2020.

CGM and time in range

The use of CGM systems has grown rapidly during recent years, and their beneficial effects on various glycemic indices have been reported in patients with both type 1 and type 2 diabetes mellitus (T1DM and T2DM, respectively). Time in range (TIR), which is accurately measured by CGM, is an intuitive metric that refers to the time that a patient spends within a desired glycemic range [6]. As TIR can detect valuable information that is not captured by hemoglobin A1c (HbA1c), it has been suggested as a key metric and a crucial measure in diabetes management.

Lu et al. [7] analyzed the association between TIR and mortality in patients with T2DM. In a total of 6,225 Chinese patients with T2DM, TIR was measured with CGM at baseline, the participants were stratified into four groups according to TIR, and mortality risk was followed up for 6.9 years. The results showed a significant inverse association of TIR with the risk of all-cause and CVD mortality, with a high mortality risk in those with lower TIR, supporting the validity of TIR as a surrogate marker of long-term adverse clinical outcomes in patients with T2DM.

Another meta-analysis analyzing randomized controlled trials (RCTs) of CGM systems was published [8]. This study selected 15 RCTs that assessed changes in HbA1c and TIR in both T1DM and T2DM and lasted 12 to 36 weeks, involving 2,461 patients. Compared with usual care, CGM use was associated with a moderate reduction in HbA1c (weighted mean difference [WMD], –0.17%; 95% confidence interval [CI], –0.29 to –0.06) and an increase in TIR (WMD, 70.7 minutes; 95% CI, 46.7 to 94.8). TIR improvement was independent of the type of diabetes, method of insulin delivery, and reason for CGM use. In subgroup analysis, real-time CGM was associated with better control of HbA1c, TIR, and a lower rate of hypoglycemia and hyperglycemia, whereas intermittently scanned CGM and the use of a sensor-augmented pump were associated with a greater decline in time with hypoglycemia. This study result suggests that CGM improves glycemic control by expanding TIR and decreasing hypoglycemia and hyperglycemia in both T1DM and T2DM.

Closed-loop control in children with T1DM

Today, we are in the midst of dramatic progress in development in diabetes technologies. Closed-loop insulin delivery systems (also known as artificial pancreas systems) take the technology to the next level by integrating CGM with an insulin pump and an algorithm that automates insulin delivery, resembling a real pancreas [9]. This system is used in patients with T1DM and has the potential to improve glycemic outcomes and quality of life, including reductions in hypoglycemic episodes in these patients.

Currently, various commercial CLSs are available on the market. The Medtronics 670G system (Minimed Medtronics, Northridge, CA, USA) and Tandem Control- IQ system (Tandem Inc., San Diego, CA, USA) are two widely used CLSs globally. Medtronic has launched the Minimed 780G and the main difference between the 780G and 670G appears to be that there is more flexibility in setting a personal target [10]. With the 670G, the blood glucose target was automatically set at 6.7 mmol/L (120 mg/dL) and could not be adjusted. However, with the 780G, the user can select one of three targets. The new system has been shown to be better than 670G at preventing highs and lows, and has been reported to be easier to use.

The T:slim X2 insulin pump with the Control-IQ system was recently approved by the Food and Drug Administration (FDA) for clinical use in the treatment of T1DM patients 14 years of age or older based on the results of a previous 6-month RCT [11]. In 2020, a multicenter RCT involving children with T1DM who were 6 to 13 years of age to assess the efficacy and safety of this CLS was released [12]. In this 16-week, multicenter, randomized, open-label, parallel-group trial, a total of 101 children underwent randomization into two groups (78 to the closed-loop group and 23 to the control group, with only a CGM system and insulin pump) and followed up for 16 weeks. The mean percentage of time that glucose levels were in the target range increased from 53%±17% to 67%±10% in the closed-loop group and from 51%±16% to 55±13% in the control group. In both groups, the median percentage of time with hypoglycemia was low. The results of this study show that this CLS increased the time that glucose levels were in the target range compared with the use of a simple sensor-augmented insulin pump.

Hypoglycemia is one of the most dangerous and frightening adverse events during glucose control in patients with diabetes. Recent studies have developed dual-hormone (DH) systems that

automatically deliver glucagon in addition to insulin to further reduce hypoglycemia. In a study published by Wilson et al. [13], the researchers compared DH-CLS with insulin and glucagon with an insulin-only CLS. In their study, 23 patients with T1DM used three modes of the Oregon artificial pancreas system: (1) DH-CLS; (2) insulin-only single-hormone (SH) CLS; and (3) a predictive low-glucose suspend system, and compared the percentage of time in hypoglycemia from the start of aerobic exercise to 4 hours after. DH-CLS reduced hypoglycemia compared with SH during and after exercise, and DH resulted in some increase in hyperglycemia compared with SH-CLS. The authors concluded that this study demonstrated the feasibility of glucagon in a CLS and that DH-CLS reduced hypoglycemia during and after exercise, despite some increase in hyperglycemia.

VERTIS CV trial

SGLT2 inhibitors have recently been highlighted in many guidelines regarding their effects on CV and the renal protective effects observed in large clinical trials such as the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG OUTCOMES) and Dapagliflozin Effect on CardiovascuLAR Events (DECLARE) studies [3,4,14,15]. Based on the results of those trials, recent guidelines strongly suggest prescribing SGLT2 inhibitors along with metformin in patients with T2DM with indicators of high-risk or established ASCVD, CKD, or HF.

Ertugliflozin is an oral selective SGLT2 inhibitor that was approved by the FDA that is third in class for use in patients with T2DM. In 2020, the results of the Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV) study, which evaluated the long-term effects of ertugliflozin on CV and renal outcomes in patients with T2DM, were published [16]. In this trial, 8,246 patients with T2DM and ASCVD were randomly assigned to receive 5 or 15 mg of ertugliflozin or placebo once-daily and followed for a mean of 3.5 years. A major adverse CV event occurred in 11.9% of patients in the ertugliflozin group and in 11.9% of patients in the placebo group, with a hazard ratio (HR) of 0.97 (95.6% CI, 0.85 to 1.11; $P<0.001$ for noninferiority). CV death or hospitalization for heart failure (HHF) occurred in 8.1% of patients in the ertugliflozin group and 9.1% in the placebo group, with an HR of 0.88 (95.8% CI, 0.75 to 1.03; $P=0.11$ for superiority). When the events were analyzed individually, the HR for CV death was 0.92 (95.8% CI, 0.77 to 1.11) and the HR for HHF was 0.70 (95.8% CI, 0.54 to 0.90). In conclusion, ertugliflozin was noninferior to placebo with respect to major adverse CV events, but failed to show superiority.

Effects of SGLT2 inhibitors on HF in patients with and without diabetes

The effect of another SGLT2 inhibitor, dapagliflozin, on HF has previously been described [17]. The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) study examined the HF effects of dapagliflozin in 4,744 patients with and without T2DM who had HF with a reduced ejection fraction, and dapagliflozin reduced the composite of worsening HF or CV death by 26%. This study showed that the effects in patients with diabetes were similar to those in patients without diabetes.

In 2020, the results of the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) were published, and showed the effects of empagliflozin (another SGLT2 inhibitor) in patients with HF with and without diabetes [18]. In this trial, 3,730 patients with class II, III, or IV HF and an ejection fraction of 40% or less were assigned to receive empagliflozin (10 mg) once-daily or placebo, in addition to recommended therapy, during a median of 16 months of follow-up. The empagliflozin group showed a 25% risk reduction in the composite of CV death or hospitalization for worsening HF (HR, 0.75; 95% CI, 0.65 to 0.86; $P<0.001$), and the effect was consistent regardless of the presence or absence of diabetes. Empagliflozin treatment reduced the risk for HHF by 30% (HR, 0.70; 95% CI, 0.58 to 0.85) and slowed the annual rate of decline in the estimated glomerular filtration rate (eGFR) than placebo (–0.55 mL/min/1.73 m^2 vs. –2.28 mL/min/1.73 m^2 per year, $P<0.001$).

The results of a meta-analysis for the effects of SGLT2 inhibitors on HF that analyzed DAPA-HF and EMPEROR-Reduced were released [19]. Among 8,474 patients combined from both trials, the estimated treatment effect was a 13% reduction in all-cause death and a 14% reduction in CV death. SGLT2 inhibitor treatment was accompanied by a 26% relative reduction in the combined risk of CV death or first HHF. Similar results were observed in patients with and without diabetes, suggesting the possibility of SGLT2 inhibitors as a treatment option for HF.

Diabetes prevention by dapagliflozin treatment

At the 80th annual meeting of the American Diabetes Association (ADA), which was held virtually, an interesting pre-specified exploratory analysis from DAPA-HF was presented [20]. The investigators of DAPA-HF assessed whether dapagliflozin reduced the incidence of T2DM in the 2,605 trial participants (55%) who did not have diabetes at baseline. New-onset diabe-

tes was defined as HbA1c ≥6.5% measured at two consecutive study visits post-randomization or investigator-reported new T2DM (with the initiation of a glucose-lowering agent). During the 18-month study period, 157 patients developed diabetes, 150 (95.5%) of whom had prediabetes at baseline. Those with incident diabetes had a higher mean baseline HbA1c, greater body mass index, and lower eGFR than those who remained non-diabetic. Dapagliflozin treatment reduced new-onset diabetes by 32% (placebo: 93/1,307 [7.1%] vs. dapagliflozin: 64/1,298 [4.9%]; HR, 0.68; 95% CI, 0.50 to 0.94; P=0.019). These results are promising regarding the possibility that diabetes prevention could be another benefit of SGLT2 inhibitors. We could expect the full paper to be published within this year.

Effects of dual SGLT1/2 inhibitors in T2DM patients with HF and CKD

As discussed above, SGLT2 inhibitors represent the most advanced therapeutic developments among anti-diabetic medications regarding their consistent effects on prevention of HF, CKD, and major CV events. Sotagliflozin is an SGLT2 inhibitor that also has some inhibitory effects on SGLT1 in the gastrointestinal tract [21]. SGLT2 inhibition increases glucose excretion in urine, whereas SGLT1 inhibition reduces postprandial glucose levels by inhibiting intestinal glucose absorption.

The Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial was designed to observe whether sotagliflozin would reduce the risks of CV death, HHF, and urgent visits for HF in patients with T2DM and recent worsening of HF with either reduced or preserved ejection fraction when administered soon after an episode of decompensated HF [22]. A total of 1,222 patients were randomized to the sotagliflozin group or placebo administered before or right after discharge, and followed for a median of 9.0 months, at which point the trial was ended early because of loss of funding from the sponsor. The proportions of CV deaths, HHF, and urgent visits for HF were lower in the sotagliflozin group than in the placebo group (HR, 0.67; 95% CI, 0.52 to 0.85). Diarrhea was more common in the sotagliflozin group than in the placebo group, as was severe hypoglycemia. The results of this study support the effect of sotagliflozin on the composite of CV death and HHF in diabetes patients with worsening HF.

The Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial was published back to back with the above mentioned SOLOIST-WHF trial [23]. The SCORED trial was designed to see whether sotagliflozin would reduce the total number of CV deaths, HHF, and urgent visits for HF in patients with diabetes and CKD. In total, 10,584 subjects were randomized to sotagliflozin or placebo and followed up for a median of 16 months. The median eGFR of the subjects was 44.4 mL/min/1.73 m^2. Although the trial ended early owing to loss of funding, sotagliflozin treatment resulted in a 26% reduction in the composite of CV death, HHF, and urgent visits for HF (HR, 0.74; 95% CI, 0.63 to 0.88). For the coprimary endpoint of the first occurrence of CV death, nonfatal myocardial infarction (MI), or nonfatal stroke, the HR was 0.84 (95% CI, 0.72 to 0.99). The incidence of diarrhea, genital mycotic infections, and diabetic ketoacidosis was more common with sotagliflozin than with placebo. Together with the result of SOLOIST-WHF, the results of the SCORED study support the effects of sotagliflozin, a dual SGLT1/2 inhibitor, on the reduction of composite of CV death and HHF in patients with T2DM with worsening HF.

Teplizumab, an anti-CD3 antibody for delaying T1DM

T1DM is caused by the autoimmune destruction of insulin-producing beta cells in the pancreas, which leads to insulin deficiency and T1DM. Despite the development of novel therapeutics and insulin treatment, the desired glycemic targets are difficult to achieve and patients must be treated with multiple daily injections of insulin or an insulin pump. Furthermore, once it is diagnosed, T1DM is incurable and causes various diabetic complications at early ages.

In 2019, the results of a trial addressing the effect of teplizumab, an anti-CD3 antibody, on progression to T1DM in relatives at high-risk for development of T1DM, was released [24]. In total, 76 participants of the TrialNet Natural History Study, who were relatives of patients with T1DM and had high-risk for T1DM, were randomized to the teplizumab group (44 patients) and the placebo group (32 patients) for a 14-day course of treatment and followed for progression to T1DM. They found out that the median time to the diagnosis of T1DM was nearly twice as long in the teplizumab group (48.4 months) than in the placebo group (24.4 months).

Last year, at the 80th ADA annual virtual meeting, the secondary outcomes of the previous study on teplizumab were presented [25]. Teplizumab treatment was associated with a greater on-study C-peptide area under the curve (AUC) than placebo (1.94 nmol/L vs. 1.73 nmol/L, P=0.009). In the teplizumab-treated group, C-peptide AUC mean slopes over the study period significantly increased compared to the study entry. Insulin

secretion during the first hour of the oral glucose tolerance test (OGTT) also increased in those treated with teplizumab at 6 months, while this declined in placebo group. The authors concluded that declines in the C-peptide response to OGTT in high-risk individuals prior to study treatment improved in the 6-month period after teplizumab treatment. These results suggest the potential of teplizumab as the first disease-modifying drug with data showing a long-term delay to insulin dependence in high-risk patients for T1DM. Teplizumab is expected for an FDA decision as soon as the middle of this year.

Once-weekly insulin for T2DM without previous insulin treatment

Early insulinization is a very important strategy to reduce clinical inertia in the management of T2DM to shorten the delays that have been reported for insulin initiation. Decreasing the number of injections could also help improve adherence to insulin treatment among patients with T2DM, potentially improving glycemic control [26]. In this regard, long-acting insulin (e.g., once-weekly) formulations are in development.

Insulin icodec is a basal insulin analogue administered once-weekly with a time to maximum concentration of 16 hours and a half-life of approximately 1 week, with a profile suitable for once-weekly injection [27]. The findings of a phase 2 clinical trial designed to investigate the efficacy and safety of once-weekly insulin icodec as compared with once-daily insulin glargine U100 in T2DM patients without a previous history of insulin injection in whom T2DM was inadequately controlled with metformin with or without a dipeptidyl peptidase-4 inhibitor. A total of 247 patients with T2DM were randomly assigned to insulin icodec once-weekly or insulin glargine once-daily for 26 weeks and changes in HbA1c and safety endpoints were compared. The estimated mean change from baseline in HbA1c was –1.33% in the icodec group and –1.15% in the glargine group with between-group difference of –0.18% (95% CI, –0.38% to 0.02%; $P=0.08$). The observed rates of hypoglycemia were low in both groups and there were no significant between-group differences in key insulin-related adverse events. The results of this study suggest that once-weekly insulin icodec has a similar glucose-lowering efficacy and safety profile compared to once-daily insulin glargine in patients with T2DM.

Efficacy, safety, and CV outcomes of once-daily oral semaglutide: The PIONEER program

Until recently, all available GLP-1RAs were given subcutaneously. Semaglutide, a GLP-1RA with once-weekly injection that was approved in patients with T2DM, showed a consistently significant reduction in HbA1c in the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) clinical trials [28]. Oral semaglutide, a co-formulation with the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate, is the first oral GLP-1RA that has been approved for clinical use for improving glycemic control in patients with T2DM in the United States [29].

As phase 3 studies, the Peptide InnOvatioN for Early DiabEtes Treatment (PIONEER) program was designed to test oral semaglutide across the spectrum of disease and background therapies, from patients with early T2DM to those requiring daily insulin and in patients with comorbidities such as CVD and CKD [30]. PIONEER 1 was conducted in T2DM patients treated with only diet and exercise, and it was a monotherapy trial. PIONEER 2, 3, 4, and 7 were conducted in T2DM patients who took oral hypoglycemic agents (OHAs), such as metformin, sulfonylurea, SGLT2 inhibitors, and their combinations. PIONEER 5, 6, and 8 were conducted in patients on insulin plus OHAs and with comorbidities such as CKD or CVD. PIONEER 9 and 10 were conducted in Japanese patients with OHAs and were compared with other GLP-1RA injections. The summary of PIONEER results was published in 2020 [30].

In general, oral semaglutide was effective in reducing HbA1c across the continuum of T2DM. Over periods of up to 78 weeks, oral semaglutide (7 and 14 mg once-daily) reduced HbA1c by 0.9% to 2.0% and body weight by 0.8 to 1.5 kg depending on the trial design and patient group, and improved other diabetes-related endpoints. Oral semaglutide provided better efficacy than placebo and commonly used OHAs from the dipeptidyl peptidase-4 and SGLT2 inhibitor classes, as well as the GLP-1RA injections liraglutide and dulaglutide. Oral semaglutide was well-tolerated with transient gastrointestinal events, similar to other GLP-1RAs. For CV safety, oral semaglutide was non-inferior to placebo for the incidence of first major adverse CV events, with an HR of 0.79 (95% CI, 0.57 to 1.11; $P<0.001$ for noninferiority), and significantly lower rates of CV death and all-cause death compared to placebo were observed [31]. The results of the PIONEER program suggest that oral semaglutide is efficacious and well-tolerated for glycemic control in patients with T2DM.

ACHIEVEMENTS IN CLINICAL MEDICINE IN DYSLIPIDEMIA IN 2020

CVD remains the leading cause of mortality and morbidity

worldwide, with a high medical and socioeconomic burden. In subjects aged 40 to 75 years, elevated low-density lipoprotein cholesterol (LDL-C) constitutes a main treatment target for prevention of ASCVD in all international guidelines [32]. Societal CVD prevention guidelines do not offer specific treatment recommendations for people in the remaining age groups (20 to 39 years or ≥75 years). Despite the effects of statins on reducing CVD and slowing the progression of atherosclerosis, significant CV risk remains. In such patients, elevated triglyceride (TG) levels serve as an independent marker for an increased risk of CVD. Icosapent ethyl (IPE) added to a statin was shown to reduce CVD events, although its mechanisms have not yet been fully explained. Studies that could answer these important questions were conducted in 2020.

LDL-C in younger people aged 20 to 40 years or in older people aged 70 to 100 years

Most CVD prevention guidelines do not offer specific treatment recommendations for persons younger than 40 years in the absence of severely elevated LDL-C (≥190 mg/dL) [32]. Park et al. [33] investigated the risk of MI and stroke associated with abnormalities in lipid profiles in individuals 20 to 39 years of age from the Korean National Health Insurance Service. Park et al. [33] reported that in young patients aged 20 to 39 years, the baseline levels of total cholesterol, LDL-C, and TG were closely associated with MI, with significant differences emerging at mildly elevated levels (total cholesterol ≥223.4 mg/dL, LDL-C ≥139.5 mg/dL). The overall incidence rate in this sample was low (0.18 to 0.35 events per 1,000 person-years), reflecting the fact that MI is a rare event in individuals younger than 40 years, although lifetime risk is substantial, with 7.7% to 43.6% of individuals experiencing a first CVD event over 30 years in another study [34]. Young adults experiencing prolonged exposure to higher total cholesterol levels had a substantially increased lifetime risk of coronary heart disease, supporting the important role of cholesterol screening in the younger population [35].

Meanwhile, there is increasing interest in investigating the importance of lipid abnormalities in older people aged 70 to 100 years. In 2003 to 2015, 91,131 individuals were enrolled in the Copenhagen General Population Study, including 13,779 individuals aged 70 to 100 years and 77,352 aged 20 to 69 years [36]. At baseline, all individuals had neither ASCVD nor DM and were not using statins. During a mean 7.7 years of follow-up, 1,515 individuals had a first MI and 3,389 developed ASCVD. MI and ASCVD events rates increased with both higher LDL-C levels and older age. In individuals with LDL-C levels of 5.0 mmol/L or higher (≥193 mg/dL), the MI event rate was nearly four times higher in people aged 80-100 years than in those aged 20 to 69 years (adjusted HR, 3.7; 95% CI, 1.6 to 8.8) [5]. The number of MI events per 1,000 person-years for every 1.0 mmol/L (38.7 mg/dL) increase in LDL-C was 2.5 for individuals aged 80 to 100 years, 1.3 for those aged 70 to 79 years, 0.7 for those aged 60 to 69 years, 0.5 for those aged 50 to 59 years, and 0.6 for those aged 20 to 49 years [36]. Therefore, individuals aged 70 to 100 years had the lowest estimated number needed to treat in 5 years to prevent one event [36]. Indeed, guidelines in many countries primarily advise cholesterol lowering with statins in those aged 40 to 75 years [32]. Most previous studies have suggested that the association of elevated LDL-C with an increased risk of MI and ASCVD decreases substantially with increasing age. However, most previous studies investigating the association of elevated cholesterol with risk of ischemic heart disease were based on cohorts that enrolled patients decades ago (i.e., enrolling participants in 1970 to 1980). Life expectancy is now more than 80 years in most high-income countries, and many people who reach age 80 years will also survive until an age of 90 years. High LDL-C in apparently healthy people older than 70 years is not a benign finding because it is associated with a substantially higher risk of developing MI and ASCVD [36]. This study suggested that statin therapy in people aged 70 to 100 years with elevated LDL-C will help many older people live additional years free of MI and ASCVD before the end of life [36].

A comparison of two LDL-C targets after ischemic stroke

The current guidelines of the American Heart Association and the American Stroke Association recommend intense statin therapy after an ischemic stroke of atherosclerotic origin but do not stipulate a target level of LDL-C because there are limited data on outcomes with different targets for LDL-C [37]. The Treat Stroke to Target trial was performed to answer this very important question. Patients with ischemic stroke in the previous 3 months or a transient ischemic attack (TIA) within the previous 15 days were enrolled [38]. Eligible patients were randomly assigned at a 1:1 ratio to a target LDL-C level of less than 70 mg/dL (lower-target group) or a target range of 90 to 110 mg/dL (higher-target group). A total of 2,860 patients were enrolled and followed for a median of 3.5 years. The mean achieved LDL-C level was 65 mg/dL in the lower-target group and 96 mg/dL in the higher-target group. The composite primary endpoint occurred in 121 patients (8.5%) in the lower-target group and in 156 (10.9%) in the higher-target group (adjusted

HR, 0.78; 95% CI, 0.61 to 0.98; P=0.04) [38]. According to data in TIAregistry.org, after atherothrombotic ischemic stroke or TIA, the mean LDL-C level was 94 mg/dL. What we have learned is that a target LDL-C level of less than 70 mg/dL could provide a further risk reduction in patients with ischemic stroke or TIA, such as in patients with coronary artery disease [38]. Whether reducing the LDL-C level to a target below 50 mg/dL is beneficial is unknown and could be tested in other studies.

Effect of IPE on progression of coronary atherosclerosis in patients with elevated TG on statin therapy

IPE is a highly purified and stable eicosapentaenoic acid ethyl ester that has been shown to reduce TG levels and is used as an adjunct to diet in adult patients who have TG levels of at least 500 mg/dL [39]. IPE may have anti-inflammatory, antioxidative, plaque-stabilizing, and membrane-stabilizing properties. The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) examined the effects of IPE on the risk of CV events [39]. Patients were enrolled if they were 45 years of age or older and had established CVD or were 50 years of age or older and had DM and at least one additional risk factor. Eligible patients had a fasting TG level of 150 to 499 mg/dL and an LDL-C level of 41 to 100 mg/dL and had been receiving a stable dose of a statin for at least 4 weeks. The primary endpoint was a composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina. The patients were randomly assigned to receive 2 g of IPE twice daily (total daily dose, 4 g) or placebo. A primary endpoint event occurred in 17.2% of the patients in the IPE group, as compared with 22.0% of the patients in the placebo group (HR, 0.75; 95% CI, 0.68 to 0.83; P<0.001) [39]. The observed CV benefits were similar across baseline levels of TG. Moreover, the significantly lower risk of major adverse CV events with IPE occurred irrespective of the TG level attained at 1 year, which suggests that the CV risk reduction was not associated with attainment of a more normal TG level [39]. The true mechanism of the benefits has not been fully characterized. We highlight, below, a study published by Budoff et al. [40]. The Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy (EVAPORATE) study evaluated the effects of 4 g of IPE per day as an adjunct to statin therapy in patients with elevated fasting TG levels on coronary computed tomographic (CT) angiography plaque volumes over 18 months [40]. Patients with known coronary atherosclerosis (narrowing of ≥20% in one coronary artery by coronary CT angiography), elevated fasting TG levels (135 to 499 mg/dL), LDL-C levels of 40 to 115 mg/dL, and on stable statin therapy were enrolled. Participants underwent a multidetector computed tomography (MDCT) scan at baseline and a final MDCT scan at 18 months. The primary endpoint was change in low-attenuation plaque (LAP) volume at 18 months between the IPE and placebo groups. There was a significant reduction in the primary endpoint, as IPE reduced LAP plaque volume by 17%, while in the placebo group LAP plaque volume more than doubled (109%) [40]. Since LAP is associated with vulnerability and future MI, reducing this necrotic core with IPE is highly supportive of the clinical findings from REDUCE-IT [40]. The IPE-driven robust reduction in plaque regression without any significant difference in LDL-C or TG compared with placebo is consistent with pleiotropic, non-lipid effects.

CONCLUSIONS

In this review, we summarized the major achievements of clinical medicine in the field of diabetes and dyslipidemia in 2020 (Table 1). Although we could not address all achievements that have been published in the literature in this review due to space and time constraints, we have tried our best to cover the main findings from large clinical trials and important therapeutic modalities in these fields.

The developments in biomedical engineering were breathtaking. The progress of the technical development of CGM systems and artificial pancreas systems was so fast that the published papers could not cover the actual mechanical development of the machines, although an appropriate number of clinical trials in patients must be performed for those machines to enter the market and be applied to our patients. The developments in CLS may shed light on ways to achieve easier glycemic control in patients with T1DM, and we hope to see more studies in patients with T2DM receiving multiple daily injections.

The development of oral GLP-1RA would help broaden treatment choices and facilitate the adoption of earlier GLP-1RA treatment in the paradigm of T2DM management. We would be more than happy to see SGLT2 inhibitors indicated for patients with prediabetes. Furthermore, it was amazing to confirm our expectations regarding their positive effects for the prognosis of worsening HF in patients with and without diabetes. It was encouraging to see the protective effect of ertugliflozin on HF in the VERTIS CV trial, although the secondary preventive effects for other CVD were not as strong as we had hoped. The development of weekly-based insulin and anti-CD3 antibody could

Table 1. Summary of the Best Achievements in Clinical Medicine in Diabetes and Dyslipidemia in 2020

Study	Title	Findings
Lu et al. [7]	Time in range in relation to all-cause and cardiovascular mortality in patients with type 2 diabetes: a prospective cohort study	There was a significant inverse association of TIR with the risk of all-cause and CVD mortality, supporting the validity of TIR as a surrogate marker of long-term adverse clinical outcomes in patients with T2DM.
Cannon et al. [16]	Cardiovascular outcomes with ertugliflozin in type 2 diabetes	Among patients with T2DM and atherosclerotic CVD, ertugliflozin was non-inferior to placebo with respect to major adverse CV events, but failed to show superiority.
Packer et al. [18]	Cardiovascular and renal outcomes with empagliflozin in heart failure	The empagliflozin group showed a 25% risk reduction in the composite of CV death or hospitalization for worsening HF, and the effect was consistent in patients regardless of the presence or absence of diabetes.
Rosenstock et al. [27]	Once-weekly insulin for type 2 diabetes without previous insulin treatment	Once-weekly treatment with insulin icodec had glucose-lowering efficacy and a safety profile similar to those of once-daily insulin glargine U100 in patients with type 2 diabetes.
Thethi et al. [30]	Efficacy, safety and cardiovascular outcomes of once-daily oral semaglutide in patients with type 2 diabetes: The PIONEER programme	Oral semaglutide is efficacious and well-tolerated for glycemic control of T2DM.
Park et al. [33]	Mildly abnormal lipid levels, but not high lipid variability, are associated with increased risk of myocardial infarction and stroke in "statin-naive" young population	Modestly abnormal lipid levels (total cholesterol >223 mg/dL) were associated with a higher risk for MI in the young population.
Mortensen et al. [36]	Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70–100 years: a contemporary primary prevention cohort	People aged 70–100 years with elevated LDL-C had the highest absolute risk of MI and atherosclerotic CVD compared with people aged 20–69 years.
Amarenco et al. [38]	Treat stroke to target investigators. A comparison of two LDL cholesterol targets after ischemic stroke	After ischemic stroke, patients who had a target LDL-C <70 mg/dL had a lower risk of subsequent CVD.
Budoff et al. [40]	Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial	Icosapent ethyl led to a significant regression of low-attenuation plaque volume on MDCT.

TIR, time in range; CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus; CV, cardiovascular; HF, heart failure; MI, myocardial infarction; LDL-C, low-density lipoprotein cholesterol; MDCT, multidetector computed tomography.

also be of great help for the treatment of T1DM patients.

Research into LDL-C in younger people aged 20 to 30 years is essential to establish the potential benefits of lipid-lowering treatment earlier in life. Furthermore, research on LDL-C in older people aged 70 to 100 years is also essential to determine primary prevention strategies and guidelines aimed at managing and reducing ASCVD in the growing older population. Therefore, additional studies to address the insufficient evidence in guidelines for dyslipidemia treatment were actively conducted, helping to make the guidelines more robust.

In conclusion, the best achievements in clinical medicine in the field of diabetes in 2020 were in diabetes technology and anti-diabetic agents. Furthermore, the best achievements in clinical medicine in the field of dyslipidemia in 2020 related to the effects of IPE and lipid abnormalities in young adults or the elderly. We expect further developments and progress next year, which will lead to benefits for our patients. We are always headed towards a better future for our patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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