

Recent advances in management of diabetes

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Diabetes is one of the largest global non-communicable epidemic of the 21st century. In 2017, the International Diabetes Federation (IDF) reported a prevalence of 415 million adults aged 20-79 years and estimated that it could affect almost 700 million people by 2045. Moreover, over 350 million adults are currently at high risk of developing type 2 diabetes.

In Pakistan, a recent National Diabetes Survey 2016-2017, showed that more than 26% population of Pakistan is suffering from type 2 diabetes, which means that around 35 to 38 million Pakistanis above the age of 20 years have diabetes, while 14.47% of people have pre-diabetes.²

Management of diabetes is constantly evolving. Intensification of diabetes control has proven benefits in the reduction of microvascular complications, while reduction in macrovascular complications, like Cardiovascular diseases, remains controversial. However, in recent years, several important clinical trials have changed the way, diabetes was treated. After the results of ACCORD and ADVANCE trials, a tight control of diabetes can result in harm rather than the benefit. Secondly, cardiovascular safety of anti-diabetic drugs, have also become a major concern. US FDA has made a mandatory requirement for all new drugs to have a proven cardiovascular safety before their approval.

The American Diabetes Association's (ADA) annual guidelines for 2018 include new recommendations for use of glucose-lowering drugs with proven cardiovascular benefit, optimization of care in elderly patients and glucose screening of high-risk adolescents. Based upon the results of multiple cardiovascular outcome trials (CVOT), new treatment recommendations suggest a pathway for people with heart disease that, after lifestyle management and metformin, should include a medication validated to improve heart

health. ADA also recommends that most adults with diabetes and hypertension should have a target blood pressure of <140/90 mmHg and that risk-based individualization to lower targets, such as 130/80 mmHg, may be appropriate for some patients.

Metformin is always being a first line treatment in the type 2 diabetes. Its use in the patients with renal insufficiency has recently been highlighted by FDA and concluded that the contraindication for use of metformin in chronic kidney disease, is no longer necessary for certain patients with reduced kidney function. The FDA states that all patients taking metformin should now have their eGFR checked at least annually. The elderly and others at increased risk for renal impairment should be tested more frequently.

Also see pages 4, 8 and 180

The use of Metformin in obese type 1 diabetes, is also recommended by the ADA and other bodies, in order to improve HbA1c and reduce insulin requirements. However, its use in other clinical parameters, is recently been studied in REMOVAL trial. The findings of this trial originally cast doubts but did show some effects on body weight, LDL cholesterol, and on atherosclerosis progression by a tertiary endpoint.⁹ The trial shows that metformin actually reduces the attenuation of estimated eGFR that is normally seen in type 1 diabetes, with an effect size of about 1 mL/min/year of eGFR measured by cystatin C, not just by creatinine. There was also a strong trend in the reduction of microalbuminuria as a categorical variable.

Another impactful new recommendation from the ADA calls for use of a glucose-lowering agents with proven cardiovascular benefits in terms of mortality reduction - such as the glucagon-like peptide 1 (GLP-

1) agonist liraglutide (Victoza, Novo Nordisk) and sodium glucose cotransporter-2 (SGLT2) inhibitor empagliflozin (Jardiance, Boehringer Ingelheim/Lilly)⁶ in type 2 diabetes patients with established atherosclerotic cardiovascular disease (ASCVD) who don't meet glycemic targets with lifestyle modification and metformin. Liraglutide was associated with a 13% reduction in risk for cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke compared with those who received placebo. The EMPA-REG OUTCOME trial, based on SGLT-2 inhibitor empagliflozin, showed that it was associated with a 38% relative risk reduction in cardiovascular death and a 32% risk reduction in all-cause mortality compared with placebo.

Women with a history of gestational diabetes are at greater risk for cardiovascular events - especially myocardial infarction. This is indicated in a new analysis from the prospective Nurses' Health Study. A new finding is "a borderline 30% higher relative risk for CVD events in women with a history of gestational diabetes who did not subsequently develop type 2 diabetes". However, this finding was reduced to a 20% increased relative risk (after adjustment for relevant risk factors), so women who maintain a healthy lifestyle through their middle years may reduce their CVD risk despite having a history of gestational diabetes.

Another important finding shared in International Diabetes Congress 2017 was that patients with type 2 diabetes can reverse their diabetes if they stick to a very low-calorie liquid diet of around 850 kcal per day for 3 to 5 months, and then gradually reintroduce food, with ongoing support for maintenance of weight loss. This is the message from the 1-year results of the primary-care led weight management for remission of type 2 diabetes (Diabetes Remission Clinical Trial [DiRECT]) open-label randomized trial.

Monitoring of serum/blood glucose is always a key in the management of diabetes. Beside traditional glucometers, the evolution of Continuous Glucose Monitoring Sensors (CGMS) have changed the way

glucose is being monitored. A recent new intermittent ("flash") glucose monitoring device, the FreeStyle Libre (Abbott), has been recently approved in the US for adult use. It is currently freely available in Europe. However, FDA is requiring a 12-hour warm-up period, which means that for the first 12 hours after the device is put on the arm, it cannot be used for blood glucose readings. According to the manufacturer recommendations, this CGM lasts for about 14 days but FDA has approved it for 10 days only.

In summary, the management of diabetes is in constant evolution and cardiovascular safety of available and forth-coming drugs remained the focus of all clinical trials. Moreover, with the technological advancements, new monitoring devices are being made, which have revolutionized the treatment of diabetes.

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