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Risk factor control and medical therapy of coronary artery disease in Taiwan – Review and Recommendations – Part III: Blood sugar management for patients with coronary artery disease

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Abstract: Cardiovascular disease (CVD) is the leading cause of death in the world and the second important cause of death in Taiwan. Atherosclerosis CVD (ASCVD) especially coronary artery disease (CAD) is the major cause of CVD [1]. Clinically, the presentation of CAD can be divided into acute unstable disease, so-called acute coronary syndrome (ACS) and chronic stable disease. Up to now, the main risk factors for CAD are known as hyperlipidemia, hypertension, hyperglycemia, smoking and family history. The control of the above risk factors and lifestyle modifications can improve the prognosis of CAD patients [1,2]. Here, we described the blood lipid control, blood pressure control, blood glucose control, and lifestyle modifications for CAD in Taiwan. The followings are the part III for blood glucose control. Type 2 Diabetes mellitus (T2DM) has been suggested a CAD equivalent. The risk of CAD may be correlated with the baseline HbA1c. Numerous studies have demonstrated the benefits of controlling modifiable CV risk factors in people with diabetes. Therefore, in patients with documented CAD, DM control is recommended.Because the benefits of intensive glucose control emerge slowly, while the harms can be immediate, people with longer life expectancy have more to gain from intensive glucose control. The 4 randomized clinical trials (RCTs), including UKPDS, ACCORD, ADVANCE, VADT trials, or large meta-analyses, testing intensive glucose control vs. conventional glucose control did not show positive results in reducing major adverse cardiovascular events (MACE) in individual trials. There are also lack of HbA1c target CV outcome trials in patients with CAD. The impact of glucose control on macrovascular complications is less certain. In the consensus, glycemic treatment targets should be individualized based on patient characteristic, including frailty and comorbid conditions, and risk of adverse effects of therapy (e.g., hypoglycemia and weight gain), to balance the benefit and risks of glycemic control, rather than the strengthen the HbA1c target in patients with documented CAD.

1. Optimal HbA1c level for CAD patients

The risk of CV and total mortality has a linear relationship with the level of HbA1c. The risk of MI starts to increase from a level of HbA1c of 6% or above. For every 1% increase in HbA1c, the risk of fatal and non-fatal MI increased by 14%. However, the 4 randomized clinical trials (RCTs), including UKPDS, ACCORD, ADVANCE and VADT trials, testing intensive glucose control vs. conventional glucose control did not show positive results in reducing MACE in individual trial. Intensively treated patients have significantly higher major hypoglycemic event.

According to the "*Executive summary of the DAROC clinical practice guidelines for diabetes care-2018*", HbA1c is recommend less than 7%, range of fasting glucose level is 80-130 mg/dL, and 2 hours postprandial glucose level is less than 160mg/dL [1]. The balance the benefit and risks of glycemic control is very important, especially the hypoglycemic risk in patients with sulfonylureas (SU), glinides and insulin. Given that most of the new anti-diabetic agents have a low risk of hypoglycemia, the consensus recommended HbA1c less than 7.0% as the treatment target for the diabetic patients with CAD. In fragile patients, including heart failure subjects, less intensive glycemic target (HbA1c <8%) could be suggested. On the other hand, an HbA1c less than 6.5% may be considered in selected patients who are younger, highly educated and highly motivated, and have a low hypoglycemic risk, fewer co-morbidities, and short diabetes duration.

2. Choice of drugs

Efficacy in reducing hyperglycemia, along with tolerability and safety are primary factors in glucose-lowering medication selection, using single anti-glycemic agent or combination therapy.

Although lack of large RCTs testing the efficacy of anti-diabetic agent in T2DM patients with CAD, most of the recent CV outcome trials enrolled patients with a history of cardiovascular disease, including a large proportion of patients with CAD. Moreover, fatal and non-fatal MI is generally a major component of the 3-point MACE, providing important information for this consensus. Because of the new evidence for the benefit of specific medications to reduce mortality, heart failure (HF), and progression of renal disease in the setting of established CAD, their use is considered compelling in this patient group.

The majority of achieved HbA1c was around 7-8% in these new anti-diabetic agents' trials, and most did not increase the CV risks. The major change from prior consensus reports is based on new evidence that specific sodium–glucose cotransporter 2 (SGLT2) inhibitors or glucagon-like peptide 1 (GLP-1) receptor agonists improve cardiovascular outcomes, as well as secondary outcomes such as HF and progression of renal disease, in patients with established CVD or CKD [1–3].

The consensus group recommended metformin as the first line therapy for patients with diabetes and CAD, and SGLT2 inhibitors or GLP-1 receptor agonists with proven cardiovascular benefit are recommended as part of glycemic management.

The consensus group gave a high priority to SGLT-2 inhibitors in patients with diabetes and a history of CAD based on positive CV protection results, especially in hospitalization heart failure, from EMPA-REG OUTCOME (76% CAD), CANVAS (56.4% CAD), DECLARE (33% CAD) trials [4].

Based on LEADER and SUSTAIN-6 trial, GLP1-RAs significantly reduced 3-P MACE in T2DM patients with CAD. The available evidence for cardiovascular event reduction in T2DM patients with CAD is derived from trials in which the participants were not meeting glycemic targets (HbA1c <7% at baseline). Thus, we recommend that patients with clinical CVD not meeting individualized glycemic targets while treated with metformin (or in whom metformin is contraindicated or not tolerated) should have a SGLT2 inhibitor or a GLP-1 receptor agonist with proven benefit for cardiovascular risk reduction added to their treatment program. The use of SGLT2i should be based on eGFR. The CV outcomes of DPP4i inhibitors (SAVOR, TECOS, EXAMINE and CARMELINA) were neutral. In the PROactive trial, only the main secondary endpoint (all-cause mortality, non-fatal MI, and stroke) did show a positive effect in pioglitazone group, comparing the placebo group (HR 0.84, 0.72-0.98, p =

0.027) [5]. SU had diverse controversial results, probably due to higher hypoglycemic risk. Therefore, it is reasonable to recommend that DPP4i (if no GLP1-RA), basal insulin, TZD may be considered if HbA1c above the goal after second line therapy. The consensus group gave sulfonylureas a low priority in the treatment of diabetic patients with CAD. Given the heterogeneity of these RCTs, the universal HbA1c target is not recommended in patients with CAD [6].

3. Recommendations

1. In patients with type 2 diabetes mellitus and coronary artery disease, the target HbA1c is <7.0%. In patents with frailty or limited life expectancy, the target HbA1c could be < 8% (**Class I, LOE: C**).
2. First line monotherapy may be metformin, SGLT2 inhibitors and GLP-1 receptor agonists are recommended as part of glycemic management in type 2 diabetes mellitus patients with CAD (**Class I, LOE: C**).

Conflicts of Interest:
The authors declare no conflict of interest.

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