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REVIEW

Management of hyperglycemia in diabetics with cardiovascular disease

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Abstract

Diabetes mellitus is a syndrome characterized by hyperglycemia and dyslipidemia; and is associated with various systemic complications including acute metabolic emergencies and chronic complications, which includes microvascular and macrovascular manifestations. Coronary artery diseases are the major causes of morbidity and mortality. Various studies have convincingly demonstrated that managing hyperglycemia adequately is important for controlling diabetic complications, but macrovascular complications have not shown as significant reduction as have microvascular diseases. The cardiac safety of various anti-diabetic agents available to us also vary, which suggests that both euglycemia per se, as well the agent used to achieve it, are important considerations for cardiovascular safety. The Food and Drugs Administration of the United States of America has now stipulated that all anti-diabetic medications must undergo cardio-vascular outcome trials to prove cardiac safety before they are approved for use. Most currently available anti-diabetics are neutral on the heart, and may be continued safely in patients with chronic stable coronary artery disease (CAD). However, recent data from cardio-vascular outcome trials involving SGLT2-inhibitors and GLP1R-analogs demonstrate impressive cardiac safety data. Insulin still remains the agent of choice during recent acute coronary events and critical-care management.

Keywords: diabetes mellitus; hyperglycemia; macrovascular complication; coronary artery diseases; cardio-vascular outcome trials

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Introduction

Unlike the diabetic 'triopathy' comprising of microvascular changes in the eyes, kidneys and peripheral nerves in type-1 diabetics, cardiovascular diseases are the primary cause of morbidity and mortality in type-2 diabetes. Various studies have convincingly demonstrated that managing hyperglycemia adequately is important for controlling diabetic complications, but macrovascular complications have not shown as significant reduction as microvascular diseases with strict euglycemia [1, 2].

The United Kingdom Prospective Diabetes Study (UKPDS) [1] has shown that a reduction of glycated

hemoglobin (HbA1c), a marker of average glycemic control over the previous three months, by 1% reduces microvascular complications significantly (37%, p<0.0001). Conversely, myocardial infarction in the same study was reduced to a much lesser extent (14%) with the same kind of glycemic control.

The subjects in the UKPDS were young, having been inducted into the study at diagnosis of diabetes. Further, the target HbA1c in the intensive treatment group was 7%, much higher that the 'non-diabetic' range. It was subsequently thought that studying older patients with more diseased hearts, and targeting near-normal blood glucose levels (HbA1c of 6.5% or even 6%) would probably provide better cardio-protection. However, this was not to be. Three studies (ACCORD, ADVANCE and VADT) [3-5] not only failed to produce better cardio-protection, but ACCORD actually reported significantly higher mortality in the intensive-treatment arm. Among the three studies, only ADVANCE showed a significant improvement in nephropathy in the intensive treatment group; all other complications were no different among groups.

Glycemic control and cardiovascular risk management

In order to understand better the interplay between cardiovascular risk management and anti-diabetic drug therapy in diabetes, we need to discuss the following aspects of glycemic control: (i) Prevention of heart diseases in diabetics, (ii) Management of hyperglycemia in chronic stable heart disease, (iii) Hospital management of blood glucose in acute setting in the presence of an acute coronary event.

Prevention of heart diseases in diabetics

In 2011, the Food and Drugs Administration (FDA) of the United States of America stipulated that all anti-diabetic medications must prove cardiac safety before they would be approved for use. The FDA stipulates that all such drugs should have a relative risk (RR) of 1.3 or lower as compared to placebo to pass the test. Agents with a RR of 1.3 to 1.8 would get a provisional clearance, but would require dedicated cardiovascular disease (CVD) outcome post-marketing trials to prove cardiac safety. Those scoring above 1.8 RR would not be cleared for use [6].

The FDA has further laid down that that the CVD safety data must be event-related: for clearing the cut-off of 1.8 RR, each arm of these trials must have at least 100 to 140 CVD events which must be independently adjudicated. To achieve an RR of 1.3, there must be 600 to 700 events in each arm.

Are existing anti-diabetics different in terms of cardiac safety? Certain agents certainly seem to be worse-off. Rosiglitazone (now withdrawn from the Indian market), in a meta-analysis of 42 randomized clinical trials [7], showed an Odds-Ratio of 1.43 for myocardial infarction and 1.64 for CVD death, both values were statistically significant.On the other hand, metformin not only appears to be safe, but in addition exerts beneficial effects on blood pressure and lipid levels. Not surprisingly, the metformin monotherapy group in UKPDS had protective effects on the heart, which persisted ten years after study completion, in spite of comparable glycemic control between the groups after the completion of the study: the 'good glycemic memory' or the 'legacy effect' [8].

Sulfonylureas (SU), the oldest group of oral anti-diabetics in our repertoire, have had a particularly bad press when it comes to cardiac safety. It is true that older sulfonylureas like tolbutamide(not available any more) resulted in excessive CVD deaths in the infamous UGDP study, but subsequent 'newer' SU-s have not shown any demonstrable CVD adverse outcome. Glibenclamide (gliburide), the SU used in the UKPDS study, did not show any CVD issues when compared to other anti-diabetics, suggesting that it is the glycemic control that is more important, and not the agent used.

Among the other 'older' anti-diabetics, acarbose is the only alpha-glucosidase inhibitor (AGI) that has beneficial CVD data in the STOP-NIDDM trial [9]. Other AGI-s (miglitol, voglibose) and glinides (repaglinide, nateglinide) currently do not have dedicated randomized clinical trials looking at CVD safety.

The incretin pathway-related agents have emerged as safe and effective anti-diabetics. In addition to their stimulating insulin secretion in a glucose-dependent manner (thus with very little hypoglycemia potential), they also lower glucagon levels, which reduces hepatic gluconeogenesis.

Glucagon-like Peptide-1 receptor agonists (GLP1-Ra) exenatide and liraglutidehave been shown to have cardiovascular benefits including enhanced cardiac myocyte viability after ischemic injury, increased systolic function in preclinical models and humans, coronary arterial vasodilatation, improved endothelial function, increased sodium excretion, and protection of neural cells against hyperglycemic injury. Both agents exert these effects [10].

Dipeptyl peptidase-4 inhibitors (DPP4i) are oral agents which initially demonstrated good CVD risk profiles. Of these, large randomized clinical trials looking at cardiovascular non-inferiority have been recently published [saxagliptin (SAVOR-TIMI), alogliptin (EXAMINE) and sitagliptin (TECOS)], which have demonstrated favorable CVD profile (see below).

The only prospective randomized clinical trial (RCT) looking at CVD safety of insulin (ORIGIN trial) involving the basal insulin analog glargine, also demonstrated non-inferiority in terms of CVD risk. In this study, insulin glargine showed a Hazards Ratio (HR) of 1.02 (95%CI 0.94-1.11), which means that basal insulin was neither protective nor harmful to the heart [11].

Management of hyperglycemia in chronic stable heart disease

Most anti-diabetics are considered to be safe for patients with existing cardiac co-morbidity. The possible exceptions are:

'Older' SU-s like glibenclamide (gliburide) are better avoided in established ischemic heart disease, since they act on potassium channels on the cardiac myocytes. Newer agents like glimepiride do not, and are probably safer. However, there are no head-to-head data assessing the different SU-s. The relative safety of SU-s as a group has been questioned by retrospective studies, which have found metformin monotherapy to be statistically superior to SU-s [12], but prospective RCT-s supporting this are lacking. Used with caution, SU-s can be safe and effective in patients with established CVD, as shown by the ADVANCE study [4], which used gliclazide.

Pioglitazone (the only available thiazolididione in most countries, including India) does not share the CVD concern of rosiglitazone. The PROactive study [13] has shown that it is relatively safe on the heart (time to primary endpoint HR 0.904; 95% CI 0.802-1.018, p=0.0951). It, however, causes water-retention and increases the chances of de-novo congestive heart failure (CHF – HR 1.41; 95% CI 1.10-1.80, p=0.007 in the PROactive study), and thus should be used cautiously.

Metformin should be used with caution in patients having severe left-ventricular dysfunction, as this may enhance the risk for lactic acidosis. For patients being advised coronary angiography using radiographic contrast dye, metformin should be discontinued 2-3 days prior to the procedure.

On the other hand, the incretin-based anti-diabetics are not only safe, but also have beneficial effects on the cardiovascular system. The major incretins in the body are glucagon-like petide-1 (GLP-1), and glucose-dependent insulinotropic peptide (GIP). The incretin-based agents available for treating diabetes include GLP1 receptor analogs, and DPP4i-s.

DPP4-I are, as a class, safe on the heart, as has been proven by large RCT-s involving high-risk patients [14-16].Alogliptin [14] is not available in India. Saxagliptin [15] has proven cardiac safety (HR for primary end-points 1.0; 95%CI 0.89-1.12). There was a significantly increase in the number of admissions with CHF in the saxagliptin group, however, this did not seem to affect outcome. Also, repeat CHF events were not more common after the initial six months of the study. Sitagliptindid not report an increase in CHF cases in the recently published TECOS study [16], while proving to be non-inferior to placebo in terms of cardiac safety (HR for primary end-points 0.98; 95%CI 0.88-1.09). All three drugs thus achieved non-inferiority for the primary end-points as compared to placebo, thus proving cardiac safety.

Hospital management of blood glucose in acute setting in the presence of an acute coronary event

Most admitted patients, especially the critically ill, are managed on insulin. Earlier studies claiming better clinical outcome with aggressive insulin therapy in surgical critical care wards [17] were not duplicated in medical CCU patients in the NICE-SUGAR study [18], and current targets in critical-care patients remain at 140-180 mg/dl. Oral anti-diabetics are generally omitted during such admissions.

In patients diagnosed with recent acute coronary event, insulin is recommended during the critical-care management, and also on subsequent follow-up, as shown in the DIGAMI study [19]. However, subsequent studies including DIGAMI-2 [20] were not able to duplicate the DIGAMI results. This was due in parts to improved standard of care for all CVD patients, especially the use of statins and angiotensin-converting enzyme inhibitors/ angiotensin-receptor blockersin all subjects. The DIGAMI-2 study actually failed to show any difference between outcomes in insulin-users versus non-insulin-users. Nevertheless, insulin use (preferably intravenous infusion) is recommended in critical cardiac care, and, with the exception of the incretin-based agents, other anti-diabetic agents are not recommended.

Schwartz and DeFronzo, enumerating the various studies that have assessedincretin-based agents in critical care [21], argue that the time has come for GLP-1Ra-s. The authors recommend that critically ill patients receive GLP-1Ra therapy (liraglutide, 0.6–1.2 mg/day s.c. or exenatide, 5–10 mg bid s.c.) to achieve blood glucose levels in the 90–130 mg/dL range, while avoiding hypoglycemia.

Saraiva and Sposito [22] reviewed the cardiovascular effects of GLP-1Ra, both in animal studies and in humans. They quoted studies that showed that GLP-1Ratherapy in human subjects improves left-ventricular ejection fraction (LVEF), myocardial ventilation oxygen consumption, 6-min walk distance, and quality of life In both diabetic andnon-diabetic patients presenting with class II/IV heart failure [23]; achieves better glycemic control and comparablehemodynamic recovery without the requirements for high-doseinsulin or inotropes when infused peri-operatively in patients with CAD and preserves LV function in subjects scheduled toundergo coronary artery bypass grafting [24]; and elicits a significant improvement in LVEF in patients with acute MI and LVEF <40% aftersuccessful primary angioplasty when compared withcontrol [25]. There were alsomore frequent arrhythmias requiring anti-arrhythmic agents in the control group [24]. The authors of the review [22] concluded that the potential cardiovascular benefits expected fromthis new therapeutic approach (viz., GLP-1Ra) to obtain glycemic control in type-2 diabetes raises a possibility of changing the excessivecardiovascular burden related to this disease in both developedand developing countries worldwide.

Exenatide has been shown to be beneficial as an adjunct to primary percutaneous coronaryintervention in patients with ST-segment–elevation myocardial infarction (STEMI) [26]. In this study, intravenous exenatide or placebo continuous infusion was commenced 15 minutes before intervention and maintained for 6 hours after the procedure. Exenatide treatment was associated with a 30% decrease in final infarct size inpatients with short system delay (time of ambulance call or first medical contact and time of first balloon), whereas no cardio-protective effect in patients with long system delay was seen.

DPP4i are considered neutral in terms of CVD safety; however, there is limited data regarding this group in the immediate post-ACS period. The EXAMINE study [14], using alogliptin, recruited patients who had had an acute coronary event 15-90 days prior to randomization, and reported no adverse cardiac outcome.TheAcuteCoronarySyndromeIsraeliSurvey [27] categorized patients into 3 groups according to glucose lowering medications at time of admission for ACS: 1) DPP 4 inhibitors (as monotherapy or in combination; DPP4i), 2) metformin (monotherapy or in combination, excluding DPP4i) and 3) other oral hypoglycemics.Patients in the DPP4i group displayed a significantly lower in-hospital complication rate (post MI angina,re-infarction, pulmonary edema, infections, acute renal failure and better KILLIP class) (9.7%), lower rates of 30-dayMACE (12.9%) and a shorter hospital stay (5.4 ± 3.8 days) as compared with patients treated with metformin(24.4%, 31.6% and 5.6 ± 5.0 days respectively) or other oral hypoglycemic drugs (45.5%, 48.5% and 7.5 ± 6.5 daysrespectively). The authors concluded that chronic treatment with DPP4i may have cardio-protective effects in diabetespatients presenting with acute coronary syndrome. A small pilot study [28] found that a single dose of the DPP4i sitagliptin (100 mg) improves the myocardial response to dobutamine stress and mitigatesstunning in patients with coronary artery disease.

Cardio-protective antidiabetics

Recent cardiovascular outcome trials with newer molecules like empaglifozin (a sodium glucose transporter-2 [SGLT-2]-inhibitor) and liraglutide (a GLP-1 receptor-agonist, see above) have shown that there indeed can be anti-diabetic medicines which can be superior (and not just non-inferior)

to placebo at cardio-protection. Empagliflozin has shown remarkable results [in the EMPA REG OUTCOME study]: 14% reduction in primary end-points; 38% reduction in CV-deaths; and 35% reduction in hospitalization for heart failure. Although it also showed a non-significant increase in ischemic strokes, the EMPA REG RENAL data showed that empagliflozin also was significantly nephro-protective. Liraglutide [in the LEADER trial] has also demonstrated significant cardio-protection as compared to placebo. Recently, another once-a-week GLP1Ra, semaglutide, has also shown cardio-protection [the SUSTAIN-6 trial]. The last molecule is currently not available in India.

Conclusion

Most current anti-diabetics are neutral on the heart, and may be continued safely in patients with chronic stable CAD (see above for exceptions). However, recent data from cardio-vascular outcome trials involving SGLT2-inhibitors and GLP1R-analogs demonstrate impressive cardiac safety data, especially in patients at high risk for CVD. Given the obvious safety data for these newer agents, authorities are re-looking at the hierarchy of usage of these molecules in our daily practice. In the settings of severe, symptomatic hyperglycemia, and following an acute coronary event, however, insulin therapy still remains the mainstay during hospitalization.

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Conflicts of interest

The author declare no conflicts of interest.

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