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RESEARCH ARTICLE

CARDIOVASCULAR RISK PROFILE OF ORAL ANTI DIABETIC DRUGS

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ABSTRACT

Oral anti diabetic drugs currently approved for treatment of type 2 diabetes mellitus(DM) consist of five main groups; biguanides, sulfonylureas, meglitinides, glitazones, alpha glucosidase inhibitors. Newer compounds like incretinmimetic drugs - glucagon like peptide 1 (GLP 1) analogues, dipeptidyl peptidase 4 inhibitors, dual peroxisome proliferator activated receptor (PPAR) agonists (glitazars), amylin mimetic analogues and Sodium glucose transporter 2 inhibitors are also being used nowadays as anti diabetic drugs.

We have attempted to consider the cardiovascular effects of commonly used oral anti diabetic drugs. Though tight glycemic control is known to decrease cardiovascular morbidity and mortality, the review of literature states the increased cardiovascular risks mainly with sulfonylureas, biguanides and glitazones either alone or in combination. Sulfonylureas exert their action by closing ATP dependent K^+ channels on pancreatic beta cells, which are also known to affect cardiac ATP dependent K^+ channels and thus prevent the protective hyperpolarization of the myocardial cells during myocardial ischemia.

Biguanides like metformin hamper gastrointestinal absorption of vitamin B group and folic acid and increase blood homocysteine levels which accelerate atherosclerosis. Hence it is not surprising that long term use of sulfonylurea and metformin combination may prove detrimental. Effects of meglitinides are similar to sulfonylureas. Glitazones due to their action of sodium and water retention and weight gain are unsafe in NYHA class III and IV. Long term adverse effects of alpha glucosidase inhibitors on morbidity and mortality are not unequivocally recorded.

The newer class of drugs need to have close follow up for early detection of their adverse effects on cardiovascular system. SGLT 2 inhibitors are likely to produce hypotension or postural hypotension in diabetics with autonomic involvement or with concurrent use of diuretics. To summarize, the first four groups of anti diabetic drugs though are very potent, indispensable and effective they still warrant a word of caution regarding their use, due to their possible cardiac adverse effects.

INTRODUCTION

Diabetes mellitus (DM) has become a global health threat. 90% of these patients belong to type 2 diabetes mellitus. DM is a major cause for coronary artery disease and contributes about 90% for its etiology, leading to cardiac morbidity and mortality. Incidence of DM is increasing at an alarming rate bestowing the title of 'Diabetic capital of the world' to India.[1] While initiating treatment for DM oral anti diabetic drugs are preferred. But this might eventually lead to failure of these oral drug therapies after their long term use. This calls for introduction of insulin therapy which is not very safe due its parenteral mode of administration and adverse reactions like weight gain, lipid disorders and hypoglycemic potential. [2]

Available literature suggests that long term use of drugs like sulfonylureas[3,4], metformin[5-7], glitazones[8] invite their own cardiac adverse effects. Meglitinides are also being insulin secretogogues like sulfonylureas can have cardiac adverse effects. When monotherapy does not achieve the targeted goal of tight glucose control then usually combination therapy is implemented. Sulfonylureas with metformin are usually preferred. However, long term safety of such combination is questionable. Whether ongoing cardiac complications in a diabetic patient can be attributed solely to the disease process

or to adverse effects of oral anti diabetic drugs needs to be scrutinized.

The five types of anti diabetic drugs commonly used for treatment of type 2 DM are biguanides, sulfonylureas, meglitinides, glitazones and alpha glucosidase inhibitors. The newer anti diabetic drugs are incretin mimetic drugs, dipeptidyl peptidase-4 inhibitors, dual peroxisome proliferator activated receptor (PPAR) agonists- glitazars, amylin mimetic drugs and sodium glucose transporters- 2 inhibitors. [3]

We will briefly consider the cardiovascular effects of the most commonly used anti diabetics which will improve awareness regarding adverse cardiac effects of these drugs, so that their earliest detection and if needed discontinuation or change of drugs may prove beneficial.

Biguanides

The biguanides are the most commonly used first line oral anti diabetics. They are preferred in overweight diabetics. They do not induce hypoglycemia like insulin or Insulin secretogogues. Biguanides by activation of AMP dependent protein kinase(AMPK) play a crucial role in controlling hyperglycemia.[9] These suppress hepatic neoglucogenesis and hence reduce glucose output from liver. They also stimulate peripheral glucose uptake and its disposal in skeletal muscles and fat .Reduction in absorption of glucose from GI tract and suppression of appetite and weight loss contributes in the controlling of diabetic status. Though the presence of insulin is needed for their action, biguanides do not stimulate pancreatic beta cells and hence they lack hypoglycemic potential.[9] Weight reduction and favourable modification of lipid profile are the advantages of this class of drugs which might contribute to reduction of cardiac complications. The United Kingdom prospective diabetic study (UKPDS) showed that metformin therapy was associated with risk reduction of 32% for any diabetes related micro and macro vascular endpoints as compared to insulin or sulfonylureas like glibenclimide. It also showed 42% reduction in diabetes related death and 36% in all cause mortality. Hence metformin is recommended as first line oral antidiabetic drug.[10,11]

Meta-analysis done by Lammana C *et al* 2011 showed prolonged use of metformin reduced CV events as compared to placebo.[12]

Similarly metformin treatment given for 3-4 years reduced macrovascular complications as compared to placebo. [13] Metformin is known to decrease plasma triglyceride levels by reducing lipoprotein secretion form liver. [14] Animal studies have shown that administration of metformin can limit the size of myocardial infarction and also reduce cardiac remodeling. The possible mechanism attributed for this beneficial effect are either through the inhibition of the opening of mitochondrial permeability transition pores or by reducing oxidative stress on myocytes.[15] Calvert J W [2008] correlated this cardioprotection by metformin against myocardial infarction through endothelial nitric oxide synthase[eNOS] mediated signaling.[16]

Even though metformin is considered as a safe and preferred drug in diabetics it has its own adverse effects. GI disturbances like epigastric distress, pain, nausea, vomiting and diarrhoea are the common adverse effects. Probably more serious is the decreased GI absorption of Vit. B12 and folic acid.[17] Deficiency of these vitamins leads to increased plasma homocysteine levels. Homocysteine is known to accelerate progression of vascular diseases due to its adverse effects on platelets, clotting factors and endothelium. Increase in homocysteine levels enhances the chances of coronary artery disease.[18] The other biguanide, phenformin was discontinued long back due to its risk of lactic acidosis. But metformin can also produce lactic acidosis due to underlying predisposing complications like cardiac failure, recent myocardial infarction and renal or hepatic failure. Metformin is excreted through the kidney and is known to have drug interactions with the cardiovascular drugs. For example nifedipine, furosemide are known to increase plasma levels of metformin. Digoxin, quinidine and triamterine may modify metformin excretion by competing with it at proximal renal tubular transport systems.[19] Increased mortality due to coronary artery disease was observed in patients taking metformin for more than 5 years. But this study was non randomized and provided inadequate information about severity of illness and dose of metformin. It was noted that there was lesser morbidity in patients with heart failure and more favourable cardiac outcomes in patients taking metformin as compared to sulfonylureas. Studies have even reported lesser duration of hospitalization and decrease in the incidence of mortality due to cardiac complications. [20]

Sulfonylureas

It is equally important class of oral anti diabetic drug either used as a single agent or in combination with non insulin secretagogues like metformin. They release insulin from beta cells of pancreas by binding to ATP dependent potassium channels K^+-ATP channel complex (the sulfonylurea receptor 1- SUR 1) and by closing them. Thus sulfonylureas are insulin secretagogues. It is necessary to know that cardiac and coronary vascular sulfonylurea receptor K^+-ATP channel complex bear different structure from that of pancreatic beta cells.[21] They are SUR 2 A/B type receptors. Drug like glibenclamide and glimeperide nonspecifically affect SUR 1 and 2 receptors and are more prone to induce cardiac adverse effects.SUR l/SUR2 selectivity of glibenclamide is about 6.4 and that of glimeperide is 1.35. In this contrast gliclazide bind to SUR 1 receptor more selectively and reversibly as compared to their cardiac counterpart.SUR 1/SUR2A selectivity of gliclazide is about 16000. [22,23] Hence it is safer in terms of cardiac adverse effects. Sulfonylureas have been reported to decrease blood flow of the resting myocardium and they also have pro arrhythmic effect.[24] Sulfonylureas impair recovery of cardiac contractility after experimental ischemic conditions and are known to increase the ultimate infarct size.[25,26] They also abolish ischemic preconditioning in animal models possibly by interacting with adenosine A1 receptors.[26,27] They are found to increase early mortality in patients after the angioplasty done for acute MI due to DM. Clinical trials have inferred deterrent effect of glibenclamide on myocardial pre conditioning.[28] Sulfonylureas hinder the phenomenon of ischemic preconditioning. During the phase of myocardial ischemia this prevents the opening of ATP dependant K^+ channels and also the necessary hyperpolarization which protects the myocytes by blocking Ca^{++} influx from injury. [27]

Like insulin, sulfonylureas also have potential to induce hypoglycemia. Direct correlation between the episodes of hypoglycemia and cardiovascular mortality was observed by meta-analysis.[29] Hypoglycemia may increase the cardiac mortality by triggering compensatory sympathetic over

activity, prolonging QT interval and precipitating cardiac arrhythmias. Inflammation and rupture of plaque adds to the complications.[30] This negates the benefits arising out of tight glucose control. Hence it is suggested by many authors that maximum cardiovascular benefits may be obtained by those anti diabetics like metformin, alpha glucosidase inhibitors and pioglitazone which do not cause hypoglycemia, rather than insulin and insulin secretogogues like sulfonylureas and meglitinides.[30]

Meglitinides

Meglitinides are also insulin secretogogues like sulfonylureas and release insulin by closing ATP dependent K+ channels. They do not bind to single binding site, since possibly 3 different meglitinide receptor binding sites have been found on beta cells.[31] Nateglinide and repaglinide have dissimilar responsiveness to hyperglycemia. Nateglinide has lesser tendency for hypoglycemia induction than repaglinide as it exerts more physiological effect on insulin secretion and the response is dependent more on blood glucose levels.[32]

The cardiovascular safety of nateglinide and repaglinide is still not very certain. In one study when the repaglinide and glibenclamide were given for one year, the increased incidence of CAD was observed. But when adjustments were made, the relative risk declined.[33] Nateglinide has less affinity for K^+-ATP channels than repaglinide and it also inhibits GLP-1 degradation. Definite statement cannot be made about the cardiovascular adverse effects of meglitinides. They being insulin sectretogogues like sulphonylureas which have confirmed adverse effects, can possibly have similar adverse effects. Hence caution needs to be exercised while prescribing meglitinides for long term, specifically when combined with metformin.[34]

Glitazones

Glitazones are thiazolidinediones and include drugs like troglitazone, pioglitazone and rosiglitazone. Troglitazone was the first to get introduced in the market among this group but was later on withdrawn due to severe hepatotoxicity.[35] These drugs are insulin sensitizers and bind to PPARγ receptors which enhance glucose transporters expression and also enhance sensitivity of insulin especially for adipocytes, skeletal muscle and liver. In addition they inhibit hepatic gluconeogenesis without modifying insulin secretion.[36] PPAR are the transcriptional factors belonging to nuclear receptors which have 3 isoforms α, β/δ, γ. They are responsible for glucose homeostasis, lipid metabolism, local inflammation and immune response, tumor development and thrombosis. They also express anti atherogenic effects. These drugs also modify lipid levels. Rosiglitazone modifies it in adverse way leading to increased risk of ischemic heart diseases and cardiac mortality. Despite this, the drug continues to be available in the market.[37] Glitazones are known to induce weight gain as a result of lowering of leptin levels. Pioglitazone does modify lipid profile favourably, but is known to induce edema in about 5% of patients like rosiglitazone and hence glitazones are contraindicated in NYHA class III and IV. [38] Rosiglitazone when was combined with metformin or sulfonylureas for the duration of 12 months, ambulatory BP was reduced significantly as compared to combination of metformin and sulfonylureas only. [39]

It seems that differential effects of pioglitazone and rosiglitazone on metabolism may be responsible for apparent disparity of their action. [40]

Alpha glucosidase inhibitors

Alpha glucosidase inhibitors like acarbose, voglibose, miglitol inhibit the alpha glucosidase, a membrane bound enzyme in the brush border of the small intestine and inhibit the hydrolysis of oligosaccharides and disaccharides to monosaccharides like glucose. Hence they delay the generation of glucose required for the absorption. They do not have hypoglycemic potential like sulfonylureas. The frequent adverse effects of these drugs are flatulence, diarrhoea and abdominal pain due to non digested carbohydrates.[41] The STOP NIDDM trial is the largest randomized trial where treatment with acarbose resulted in to reduced incidence of hypertension and cardiovascular disease. It was also observed that there was about 25% reduction in the risk of development of type 2 DM and 34% reduction of risk of development of hypertension. Cardiovascular event was observed to be reduced by 49%.[42] Voglibose along with inhibiting the enzyme alpha glucosidase also stimulates GLP 1 secretion and decreases plasma DPP4 which offers an additional cardiovascular protection.[43,44]

Though this review is concerned with the cardiovascular effects of oral antidiabetic drugs, it becomes imperative to discuss incretins as DPP4 inhibitors increase the incretin levels as part of their mechanism of action.

Incretins

Native GLP 1 exerts action via GLP 1 receptors but they also have GLP1 receptor independent effects. GLP 1 receptors are not only expressed on pancreatic cells but they are proved to be present in the lungs, kidneys, intestine and peripheral and central nervous systems.[45]

They are also expressed in human cardiovascular system. They have been demonstrated to be present in human heart and coronary artery endothelial cells.[46] Data collected by animal studies and pilot clinical studies points towards the cardiac protective effects of GLP1 under ischemic conditions and following ischemic injury.[47] GLP-1 has also been found to improve endothelial functions in type 2 diabetes mellitus. Sjoholm after preclinical studies supported the hypothesis in favour of GLP 1 receptor independent pathway involved in cardioprotective effects of GLP 1. GLP1 analogues by reducing body weight and by modifying unfavourable dyslipidemia to favourable one, offer cardiovascular benefits, as these two risk factors are known to enhance CV mortality. [48] The clinically available GLP-1 receptor agonist reduce systolic blood pressure [SBP]. Reduction in SBP was also observed before major weight loss suggesting that weight reduction is not the sole reason to reduce the SBP. [49]

Along with weight loss, natriuresis and vasodialation are the likely contributing factors for lowering of SBP by GLP-1 receptors agonists. This was attributed to cAMP/Epac 2 dependent atrial natriuretic peptide release. GLP-1 receptor dependent nitric oxide release and endothelium independent vasodilator effect of GLP-1 have been identified in animal studies.[50]

Effects of GLP1 analogues showed marginal rise in heart rate. The mechanism behind this though not very clear, may be

attributable to a compensatory phenomenon in response to decrease in systolic BP. [51-54]

Regarding the effect of GLP-1 analogues on QT interval, it was found to be prolonged in one study. But other studies observed no change in QT interval. [55,56]

Considering the studies available in animal models cardioprotective effect of native GLP-1 under ischemic conditions were favourable in terms of limiting infarct size following ischemic reperfusion injury. [57,58]

Cardioprotective effects of GLP-1 were reported in patients with acute myocardial infarction showing significant improvement in left ventricular systolic functions.[59]

Mechanism of GLP1 dependent cardio protection during ischemia though has been extensively studied the relevant underlying mechanisms are still not fully understood. On cellular basis GLP-1 was found to reduce cardiomyocytic apoptosis arising as a result of ischemic reperfusion injury.[60] This can be attributed to GLP 1 dependent activation of PI3K, AKT and ERK1/2 which together are known as RISK pathway. An additional anti apoptotic action of GLP1 is attributable to inhibition of GSK3 β as another downstream target of RISK pathway.[61]

Finally GLP-1 was found to increase the expression of redox sensitive transcription factors namely nuclear erythroid derived factor 2 (Nrf 2) and peroxisome proliferation activated receptor (PPAR) delta.[61]

GLP1 has vasoprotective effects. GLP1 dependent improvement of vascular function was reported in healthy subjects as well as in patients with type 2 diabetes mellitus with coronary artery disease.[62,63] In various experiment models, GLP1 increased vasorelaxation in coronary or pulmonary arteries which was mediated by cyclic AMP and eNOS.[64,65] This vasorelaxitive effect of GLP1 might explain the antihypertensive effect observed in long term clinical studies using exenatide, liraglutide or DPP-4 inhibitors, though most of this fall in BP may be as a result of weight loss. [66-68] Studies reported decreased vascular inflammation due to GLP1 which was attributed to variety of immune and vascular cell responses. GLP1 was found to[69-74]

1. Reduce liposaccharide dependent cytokine release from macrophages
2. Inhibit migration of T cells
3. Decrease endothelial cell adhesion molecule expression
4. Impair vascular smooth muscle cell proliferation.

In macrophages, anti inflammatory effect of GLP1 have been attributed to inhibition of Nf-kB in a cAMP and protein kinase a (pka) dependent manner.[69] Anti-inflammatory effects of GLP1 may modulate coagulation system favourably with a decreased expression of plasminogen activator inhibitor in endothelial cells in response to liraglutide.[72] GLP1 down regulate receptors for advanced glycation end products (RAGE) in endothelial cells, which are responsible for vascular inflammation in diabetics as a result of hyperglycemia.[71,75] Generation of reactive oxidant species arising as a response to advanced glycation end products were reduced by treatment with GLP1 agonist.

Dipeptidyl peptidase 4 inhibitors

Dipeptidyl peptidase 4 (DPP-4) is a complex molecule which exists as a membrane spanning cell anchored protein, expressed in many cell types and also as soluble form in circulation. Both these forms possess proteolytic activity. Both GLP1 and GIP are substrates of DPP-4. Orally administered DPP4 inhibitors like sitagliptin and vildagliptin improve the glycemic control by inhibiting degradation of incretin hormones resulting in to postprandial rise in levels of biologically active intact GLP1 and GIP.[76]

DPP4 inhibitors inhibit the degradation of GLP 1 and potentiate the secretion of insulin and suppress the release of glucagon from the pancreas in response to meal related hyperglycemia. They are less likely to induce hypoglycemia as potential release of insulin by them declines after the blood sugar normalizes. Their beneficial effects are increase in circulating levels of GLP 1 in animals and humans, increase in genesis, proliferation and differentiation of beta cells of pancreas and inhibition of their apoptosis. They enhance insulin secretion, reduce fasting and post prandial glucose and also reduce the HbA1c levels. It should be noted that incretin mimetics are pharmacologically more specific than DPP 4 inhibitors except for their disadvantage of parenteral therapy.[77]

Available studies regarding cardiovascular effects of DPP 4 inhibitors suggests cardio protective effect of these molecules. In the study on mice, treatment with sitagliptin showed reduction in size of infarct and this protective effect was attributed to protein kinase A. [78]

In diabetics with coronary heart disease, therapy with sitagliptin improved the cardiac function and coronary artery perfusion as demonstrated by echo dobutamine test.[78]

Retrospective study published by Fedrich *et al* regarding effect of saxaglitpin therapy on cardiovascular morbidity and mortality did not substantiate the increased cardiovascular risk. On the contrary they observed minimal, non significant advantage.[79] DPP4 inhibitors have also been shown to reduce systolic BP by 2-3 mm of Hg and 1.6 – 1.8 mm of Hg of diastolic BP, observed by 24 hours ambulatory BP measurements. Mistry *et al* observed that DPP4 inhibitors also have favourable effects on lipid profile.[80] Matikaine *et al* showed that vildagliptin therapy improved plasma triglycerides and apolipoprotein B levels.[81]

Boschmann *et al* suggested that DPP4 inhibitors increase PP lipid mobilization and oxidation by activating sympathetic system rather than a direct metabolic effect.[82] Hsieh *et al* found that DPP4 inhibition reduces intestinal secretion of triglycerol, cholesterol and apo lipoprotein B 48.[83]

Results of meta-analysis done by Karagionnias T *et al* conclude that DPP4 inhibitors do not seem to have any cardiac adverse outcome and risk of heart failure except saxagliptine which was associated with increased risk of heart failure and hospitalization. This was observed more in patients with chronic kidney disease, preexisting heart failure.[84]

These and other ongoing studies at present can give hope for the clinicians that the DPP4 inhibitors as a group of drugs will have beneficial effects not only on blood glucose levels but also on heart and coronary artery functions.

Dual PPAR agonists

There are 3 PPARs agonists subtypes like PPAR – α, PPAR-γ AND PPAR-β/δ. PPAR-ά activation enhances synthesis of HDL cholesterol, stimulates reverse cholesterol transport and reduces triglycerides.[85] PPAR-γ stimulation results in insulin sensitization and anti diabetic action whereas, PPAR– δ may prevent development of overweight.[86] Compounds which have dual PPAR- α and PPAR- γ activity with optimized balance of their agonistic activity might prove beneficial in patients of DM type 2. Several potent and newer dual PPAR α/γ agonists which are commonly designated as glitazars are developed for clinical use. These agents have prominent effects on peripheral and hepatic insulin sensitivity. On the basis of their mechanism of action it is expected that these agents may modify cardiovascular risk by improving endothelial activity, reducing BP and improving lipid profile. But due to detection of their various toxic effects in clinical trials the development of these drugs could not progress beyond phase 2 trial e.g tesaglitazar caused severe renal impairment, muraglitazor was linked with cardiovascular adverse effects. Ragaglitazar and farglitazar had severe liver toxicity and development of tumors in rodents. But in the recent synchrony study, the newer compound aleglitazar was tried .In dose of 600mcg it produced hemodilution, edema and weight gain. However in doses less than 300 mcg no patient had congestive heart failure. Frequency of onset of edema was less than pioglitazone and also was the weight gain.[87,88]

Newer dual PPAR agoinst seroglitazar has become available in the Indian market for patients with diabetes and hyperlipidemia whose safety need to be confirmed by more and more authentic long term clinical trials.

Sodium glucose co-transporters 2 [SGLT 2] inhibitors

This is new class of drugs for the treatment of type 2 diabetes mellitus. They reduce plasma glucose levels by decreasing glucose reabsorption from proximal renal tubules resulting in to its enhanced excretion. Presently two SGLT 2 inhibitors are approved, they are dafagliflozine and canagliflozine. Canagliflozine may increase plasma concentration of digoxin which warrants therapeutic drug monitoring when co-administered with this SGLT 2 inhibitor. They induce osmotic diuresis as a result of glycosuria. Hence they are preferred in diabetics with hypertension and in patients with compromised cardiac function. But this osmotic diuresis might lead to depletion of intravascular volume which may progress to small but consistent drop in blood pressure and may lead to increased incidence of postural hypotension. Pharmacological drug interactions may occur with thiazides and loop diuretics leading to excessive diuresis, dehydration and electrolyte imbalance. Renal tubular handling of K+ by SGLT 2 inhibitors might lead to hyperkalemia and should be warned against combining these drugs with ACE inhibitors or potassium sparing diuretics and in patients with renal function impairment. Drug interactions between digoxin, diuretics ACE inhibitors deserve special mention as these are important drugs to treat compromised cardiac function which may arise as result of diabetes mellitus itself. [89,90]

The EMPA-RAG OUTCOME study demonstrate the CV risk reduction (38%) in T 2 DM patients by addition of empagliflozine. Studies suggest that this beneficial effect of empagliflozin to lower CV mortality is mostly due to its hemodynamic rather than metabolic effect which is as a result of decrease in blood pressure, diuretic effect resulting into decrease in extra cellular fluid volume, reduction in arterial stiffness and decrease in sympathetic tone. [91]

CONCLUSION

Oral anti diabetic drugs currently approved for treatment of type 2 diabetes mellitus (DM) consist of five main groups; biguanides, sulfonylureas, metglitinides, glitazonesand alpha glucosidase inhibitors. Newer compounds like incretin mimetic drugs- GLP 1 (glucagon like peptide 1) analogues, dipeptidyl peptidase 4 inhibitors, dual peroxisome proliferator activated receptor (PPAR) agonists (Glitazars), amylinmimetic analogues and Sodium glucose transporter 2 inhibitors are also being used nowadays as anti diabetic drugs. Though tight glycemic control might decrease cardiovascular morbidity and mortality, the review of literature states the increased cardiovascular risks mainly with sulfonylureas, biguanides and glitazones either alone or in combination. Biguanides like metformin act by hampering gastrointestinal absorption of vitamin B group and folic acid and by increasing blood homocysteine levels can accelerate atherosclerosis. Hence it is not surprising that long term use of sulfonylurea and metformin combination may prove detrimental. Effects of meglitinides are similar to sulfonylureas. Glitazones due to their action of sodium and water retention and weight gain are unsafe in NYHA class III and IV. Long term adverse effects of alpha glucosidase inhibitors on morbidity and mortality are not unequivocally recorded.

The newer class of drugs need to have close follow up to point out their adverse effects on cardiovascular system. SGLT 2 inhibitors are likely to produce hypotension or postural hypotension in diabetics with autonomic involvement or with concurrent use of diuretics. To summarize, the first four groups of anti diabetic drugs though are very potent, indispensable and effective still warrant a word of caution regarding their possible cardiac adverse effects. Anti diabetic drug with less potential to induce hypoglycemia should be preferred over the drug which has strong hypoglycemic effect.

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