Drug Corner

Cardiovascular Outcome Trials in Indian Perspective : A Call to Indian Drug Regulators

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India's gradual approach in being the Diabetes Capital of the World, has vulnerably exposed its diabetic population to multiple anti-diabetic drugs. At this very outset, it is important to adjudge the cardiovascular safety of these anti-diabetic medications, evidenced by good quality RCTs.Though US FDA has recommended to evaluate cardiovascular safety of anti-diabetes agents during their development process, there are still a few such drugs which is present in Indian pharmaceutical market without any cardiovascular outcome data. Thus, any antidiabetic drug being permitted for marketing in India should undergo cardiovascular outcome trial (CVOT) and Indian drug regulators should be much vigilant in this regard. The present review tried outlining some basics of CVOTs, with special reference to its conduct in Indian population.

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Statistics suggest that 2 out of 3 deaths in diabetes are due to cardiovascular (CV) disease. Management of diabetes should be a holistic approach, which should not only focus on HbA1c lowering but also take CV risk into its account. To monitor cardiovascular outcomes while prescribing antidiabetic drug is of utmost importance. After the 'rosiglitazone saga' in 2007 where FDA revealed its own meta-analysis of CV events with rosiglitazone which showed a statistically significant increase in risk (RR = 1.4). In October 2007, FDA had issued a 'black box warning' of ischaemic events for rosiglitazone and finally on December 2008 drug manufacturers were directed for the requirement of CV outcomes trials (CVOTs) for anti diabetes medications. The year 2008 acts as a watershed line prior which prime focus of diabetes management was targeting glycaemia, post 2008 diabetes management also emphasizedextra-glycemic targets like CV protection and CV safety concerns.

FDA's guidance on CVOT :

As per 2008 FDA guidance, adequate evaluation of CV safety is warranted in development of type 2 diabetes drug developments. It is required that the phase 2 and 3 trials of this kind should include patients with high risk of CV events(CV mortality, MI, stroke,hospitalization for ACS, urgent revascularization procedures, HF hospitalization), with trials having adequate sample size and considerable duration to detect CV events thus allowing a meaningful evaluation of CV risk. Independent adjudication of CV events followed by meta-analysis of the phase 2 and 3 trials to be conducted at the end of the research program. Substantial premarketing data analysis comparing the CV events due to candidate drug vis-à-vis control group is mandated. An upper limit of a two-sided 95% CI of the estimated risk ratio is less than1.8 should be accomplished in a separate, large CV safety trial, if the same cannot be done through meta-analysis. For agents whose upper limit of 95% CI falls between 1.3 and 1.8 in premarketing analysis, completion of a post-

Editor's Comment :

- Diabetes patients have higher risk to develop cardiovascular diseases
- US FDA recommended to evaluate cardiovascular safety of anti-diabetes agents during their development process
- Indian population are more vulnerable to cardiovascular diseases compared to western population
- There are a few anti diabetes drugs which is present in Indian pharmaceutical market without any cardiovascular outcome data
- Indian drug regulators need to be more vigilant regarding such dugs
- Considering the cost of CVOTs industry may consider different adaptive design to reduce time and expenditure.

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marketing trial or continuation of a premarketing trial after approval may be needed. Insulin was specifically excluded from its CV safety evaluation in the FDA's guidance.

Why India is so important in this regard ?

In India, more than 10.5 million deaths occur annually, and it was reported that CVD led to 20.3% of these deaths in men and 16.9% of all deaths in women. Prevalence data of cardiovascular diseases in South Asian population is suggestive of a dreadful condition. Studies conducted on South Asians in western countries have revealed earlier onset, higher incidence, and higher standardized mortality rates from ASCVD in South Asians compared with others. The major biological mechanisms contributing to this excess risk are their alteredmetabolic profile including elevated plasma insulin levels, altered plasma lipid profile, and higher truncal skin-fold thickness. South Asians exhibit at least two times increased T2DM prevalence, a higher incidence of new-onset diabetes mellitus, and a higher prevalence of impaired glucose tolerance. Studies comparing South Asian individuals residing in India with those residing in the United States reveals that South Asians in the United States have higher plasma levels of triglycerides, total cholesterol, and LDL-C and lower levels of HDL-C, which can be probably attributed to higher prevalence of insulin resistance in this populationand abnormalities in CETP. The MASALA study and others have demonstrated that South Asians and Asian Indians have a high prevalence of CAD despite a lower prevalence of some traditional risk factors for CAD. Moreover, Asian, Americans are also shown to be at a higher risk for renal disease and renal failure compared with NHWs, and diabetes mellitus and high blood pressure appear to be contributing factors, among others. Amongst various nonbiological mechanisms, lower physical activity rate, use of tobacco products adds to increased risk of ASCVD in south Asians. Moreover, diets here are rich in carbohydrate, saturated fats and low fruits and vegetables.

Median scores for South Asians was higher in QRISK2 algorithm which has been derived and validated to accurately estimate CVD risk and detect subclinical CVD in different ethnic groups in England and Wales and takes into account South Asian ethnicity as an additional risk factor.

CT has been able to demonstrate the following :

South Asians display more severe CAD on CT as determined by both increased mean percent stenosis and a higher number of patients with multiple diseased vessel segments. 47 Asian Indian race is a significant independent predictor of CAC severity, even when controlling for traditional risk factors for CHD. The prevalence of high CAC burden (scores >100) among Asian Indians is greater than in all other ethnic groups (NHWs, Asians, Hispanics, and blacks among those >60 years of age). A longer duration of residence in the United States has been associated with higher levels of CAC in South Asians in the MASALA study.

Antidiabetic Drugs in India and CVOT :

With India's gradual approach in being the Diabetes Capital of the World and Indians being more vulnerable to develop cardiovascular diseases, we are vulnerably exposed to multiple anti-diabetes drugs. Antidiabetic drugs thus being permitted for marketing in India also should undergo CVOT and Indian drug regulators need to be more vigilant on this regard. It is extremely important to prescribe anti diabetes drugs with proven CV safety profile. Though full result of CAROLINA is still awaited, of available new anti-diabetic drugs in India,sitagliptin and linagliptin are cardio safe. Empagliflogin, canagliflogin, dapagliflogin show benefits in CVOTs. Liraglutide and dulaglutide also show benefits in their respective CVOTs. Lixisenatide is CV safe as per their CVOT.

Teneligliptin, evogliptin and remogliflozin are marketed in India without any cardiovascular outcome

Class	Trial	Intervention	Primary Outcome	Secondary Outcome	CV Death
DPP-4 inhibitors	SAVOR-TIMI EXAMINE TECOS	Saxagliptin Alogliptin Sitagliptin	3-point MACE1.00 (0.89–1.12) 3-point MACE0.96 (95% UL≤1.16) 4-point MACE0.98 (0.89–1.08)	Expanded MACE 1.02 (0.94-1.11) 4-point MACE0.95 (95% UL ≤1.14) 3-point MACE0.99 (0.89–1.10)	1.03 (0.87–1.22) 0.85 (0.66–1.10) 1.03 (0.89–1.19)
SGLT2 inhibitors	EMPA-REG CANVAS	Empagliflozin Canagliflozin	3-point MACE0.86 (0.74–0.99) 3-point MACE0.86 (0.75–0.97)	4-point MACE0.89 (0.78–1.01)	0.62 (0.49–0.77) 0.96 (0.77–1.18
GLP-1 receptor agonists	ELIXA LEADER SUSTAIN-6 EXSCEL	Lixisenatide Liraglutide Semaglutide Exenatide	4-point MACE1.02 (0.89–1.17) 3-point MACE0.87 (0.78–0.97) 3-point MACE0.74 (0.58–0.95) 3-point MACE0.91 (0.83–1.00	Expanded MACE 1.00 (0.90–1.11) Expanded MACE 0.88 (0.81–0.96) Expanded MACE 0.74 (0.62–0.89)	0.98 (0.78–1.22) 0.78 (0.66–0.93) 0.98 (0.65–1.48) 0.88 (0.76–1.02)

trials. It signifies the inappropriateness of using these drugs in diabetics associated with cardiovascular diseases. Though opposed school of thought impresses upon the huge cost of therapy due to these CVOTs, designs like factorial design and adaptive design may reduce the time and expenditure for doing CVOTs. CVOTs can be performed along with phase 2 and 3 trials and data may be obtained suggesting the safety of the candidate drug.

Appeal to Regulators :

Each diabetic patient possesses the right to access a cardio safe antidiabetic medication, evidenced by good quality RCTs. It thus remains a responsibility of Indian regulators to respect such rights and be much more vigilant in allowance of these drugs in Indian market only with robust CV safety data.

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