Case Report

Empagliflozin role in the treatment of type 2 diabetes with cardiovascular disease and subclinical cardiovascular disease in outpatient setting: case reports

Abstract

SGLT2 inhibitors based on recent evidence have shown promising Cardio vascular benefits apart from Glycemic Control in T2DM management. ESC-EASD 2019 clearly suggest that All SGLT2i reduces CV risk (3P MACE), HHF, worsening of Nephropathy .Only Empagliflozin has been recommended for reducing the Risk of CV death in T2DM with ASCVD & the CV death remains independent of baseline HbA1c or control of HbA1c. Empagliflozin CV death is very unique because the consistency of Mortality benefit remains very significant in patients of T2DM with various CVD (like Single Vessel disease CAD, Multiple Vessel Disease CAD, Prior CABG, Prior MI, Prior Stroke, Prior HHF, PAD).

Keywords: type 2 diabetes, cardiovascular disease, subclinical cardiovascular disease, coronary artery disease, left ventricular mass index, peripheral arterial disease

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Abbreviations: LVMi, left ventricular mass index; T2DM, type 2 diabetes; CAD, coronary artery disease; SGLT2, sodium-glucose co-transporter-2; ASCVD, atherosclerotic-cardio vascular diseases; PAD, peripheral arterial disease; CV, cardio-vascular; CVD, cardiovascular disease; MACE, major cardiovascular event; PAD, peripheral arterial disease; MI, myocardial infarction

Case presentations

Case I: type 2 diabetes with hypertension with CVD

Clinical case: A 55-year old female patient with T2DM (5 yrs) and hypertension (12 yrs), presented with complaint of recent-onset chest-pain on cycling.

Current medication:

- Tab Metformin 1g BD
- Tab amlodipine 5 mg OD
- Tab Perindopril 4 mg OD
- Tab Rosuvastatin 10 mg OD

Examination Findings: BP: 128 / 84 mmHg HbA1c: 7.5%, FPG: 120 mg/dl; PPG: 192 mg/dl

Urine albumin-creatinine ratio: 200 mg/dL (microalbuminuria)

Serum creatinine: 0.8 mg/dL; eGFR CKD-EPI: 83 mL/min/1.73m^2

Total-cholesterol: 193 mg/dl, LDLc: 110 mg/dl; HDLc: 50 mg/dl; TG: 167 mg/dl

Cardiac MR imaging report indicated ischemic heart disease; left ventricular (LV) mass-index was slightly increased; LV volumes, and ejection fraction were within normal range.

Changes Made to the Medication Regimen: Tab Rosuvastatin 20 mg OD, Empagliflozin 10mg OD was added, Tab Aspirin 75mg OD was added regarding this patient.

Among people with T2DM and CAD, SGLT2 inhibition with empagliflozin was associated with significant reduction in LVMi over 6 months, which may account in part for the beneficial cardiovascular outcomes observed in the EMPA-REG OUTCOME trial.[1] LVMi is strong and independent predictor of CV and all-cause mortality.[2] Based on precise quantative myocardial perfusion, microvascular angina might more correctly be called "no stenosis angina" with 4 physiologically diverse, evidence-based subcategories or "primary" prototypes quantified objectively as follows: subendocardialischemia due to diffuse epicardial atherosclerosis (most common),-overlooked epicardial stenosis, diffuse microvascular dysfunction or microvasculopathies and-nonischemic cardiac pain mechanisms (rare), or a mix of these prototypes, over 95% of which are associated with risk factors, and subclinical or clinically manifest coronary atherosclerosis needing vigorous risk factor treatment.[3]

Case II: Indian patient with T2DM and subclinical CAD

History: 52 yr old male, nonsmoker, K/c/o T2DM (3 yrs); HT (9 yrs)

Moderately active lifestyle

Weight 76 Kg; BMI 26 Kg/m^2

Blood Pressure 130 / 86 mmHg

Present drug-regimen: Metformin 2.0g per day

- Perindopril 8 mg OD
- Amlodipine 5 mg OD

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- Atorvastatin 10 mg OD

Investigation: HbA1c: 7.8%

FPG: 154 mg/dL; PPG: 238 mg/dL

eGFRCKD-EPI: 86 mL/min/1.73m^2

UACR: 60 mg/gCr

Total-cholesterol: 191 mg/dLLDLc: 96 mg/dL; HDLc: 40 mg/dL; TG: 156 mg/dL

Recent Exercise TMT +ve

Coronary CT angiography: 50% stenosis of Left-main coronary artery (s/o CAD)

Change in medication: adding 10 mg Empagliflozin and Statin dose changed to 20 mg Atorvastatin.

In EMPA-REG OUTCOME, >99% Patients had Established CVD Established CVD in EMPA-REG OUTCOME[4]

Coronary artery disease / OR Prior MI / OR Prior Strok

Coronary artery disease (any of)

- Multi-vessel disease or Left main disease (≥50% luminal narrowing), OR

- Single-vessel disease (≥50% luminal narrowing); plus

  ☐ Provocableischaemia, or

  ☐ Unstable angina within 12 months prior

Peripheral arterial disease (any of)

- Presence of ≥50% luminal narrowing on angiography or non-invasive method, OR

- Ankle brachial index<0.9, OR

- Limb angioplasty, stenting, bypass, OR

- Limb or foot amputation due to circulatory insufficiency

Conclusion

Case I: Empagliflozin use first of its kind among SLT2 Inhibitors, for confirmatory evidence of LVMi regression with an SGLT2-I, LVMi regression was observed early, within 6 months of therapy, LVMi regression was greater in patients with higher baseline LVMi. The CV Death benefit is significant irrespective of HbA1c level at baseline means CV death benefit is observed in well controlled T2DM patients means HbA1c<7%, in uncontrolled T2DM patients means HbA1c>7-9%. The CV death benefit of Empagliflozin remains significant regardless of subclinical cardiovascular disease or MI, Stroke, HF, CKD at baseline.

Case II: Subclinical CVD remains a very important aspect in T2DM management. Symptomatic CVD can be easily classified on the basis of patient History but universal Screening for Asymptomatic/ Subclinical CVD is not possible in 100% diabetic patients in country like India due to many reasons. So we can look for various Risk-factors of ASCVD (Asymptomatic Cardio Vascular Diseases) like LDL-cholesterol>100 mg/dl, high blood pressure, smoking, chronic kidney disease, albuminuria, PAD and family history of premature CV death, and once we get the idea of CV risk then we can go for specific diagnostic tests for ruling out the ASCVD**.** Empagliflozin use in subclinical cardiovascular disease also results in significant all cause mortality and CV death reduction in future.

This is a Type 2 DM with subclinical CAD and therefore as per the evidence from EMPA REG trial adding SGLT2 Inhibitor Empagliflozin will reduce CAD in future Figure 1, all-cause mortality, CV death and 3 MACE.[5] Over 2/3rd of Asymptomatic patients of T2DM have CAD.[6] Figure 2 Over Half of which may have Significant Obstruction in South Asia population.[7] Framingham offspring study shows Findings over 2/3rd of patients of DM have Subclinical CVD DM sees the Risk of Subclinical CVD by 4.3-fold.[8]

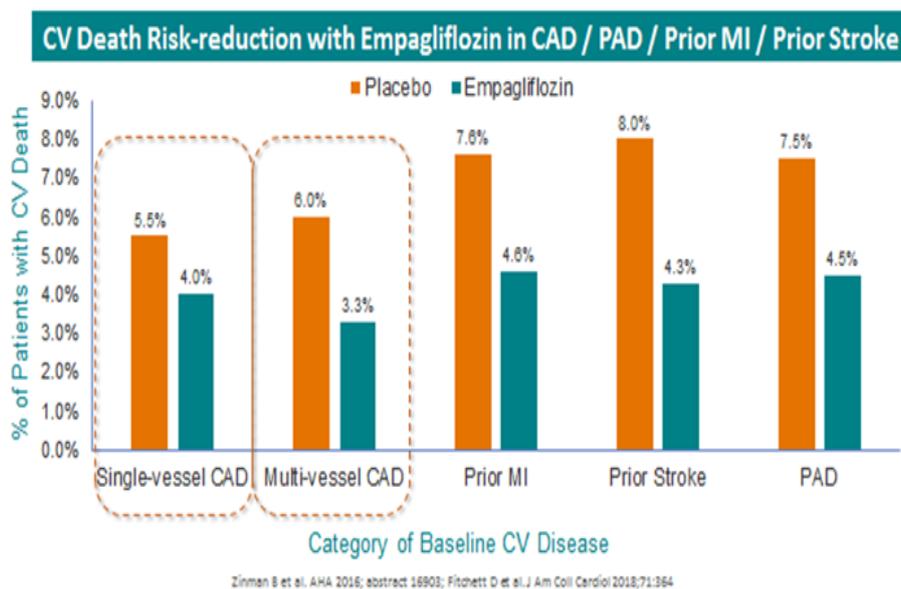Empagliflozin Consistently Reduced CV Death in Patients of T2DM and CVD with / without Prior Event

CV Death Risk-reduction with Empagliflozin in CAD / PAD / Prior MI / Prior Stroke

Zinman B et al. AHA 2016; abstract 16903; Fitchett D et al. J Am Coll Cardiol 2018;71:364

Figure 1 Empagliflozin consistently reduced CV death in patients of T2DM and CVD with/without prior event.

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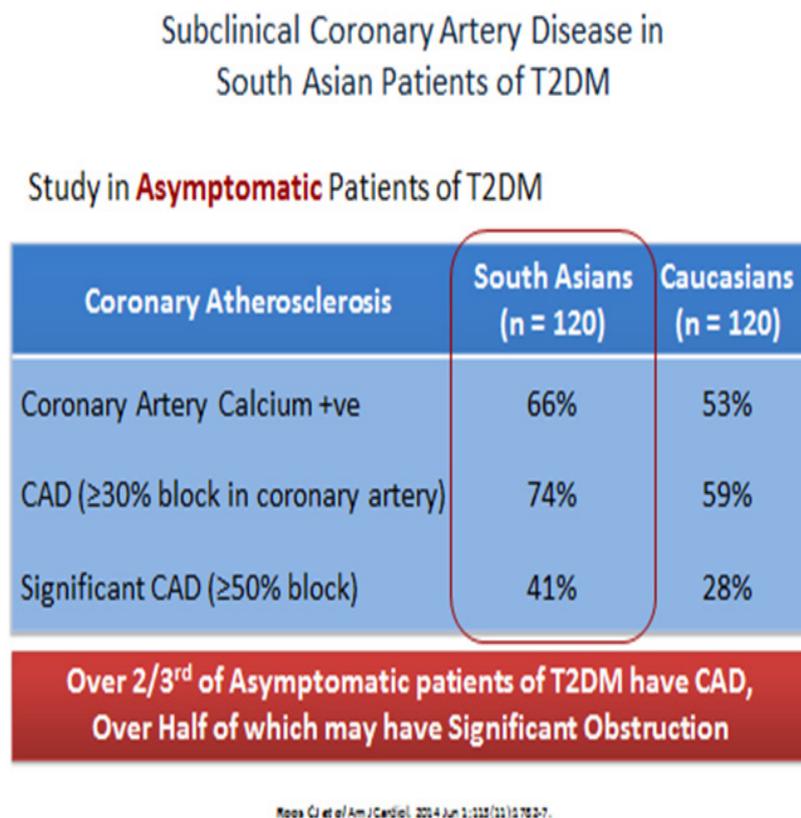**Figure 2** Subclinical coronary disease in South Asian patients of T2DM.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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