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Prescription Pattern of Empagliflozin and Linagliptin Combination among Indian Health Care Practitioners

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Abstract: ***Diabetes mellitus is a growing threat in India. The South Asian phenotype, which predisposes to diabetes and cardiovascular disease, is characteristic of Indians. Prescribing Practice of Empagliflozin and Linagliptin in Indian Cardio-Diabetes Patients (PELICARD) evaluated the prescription of empagliflozin and linagliptin among Indian doctors, and elucidated the patient profile for which these drugs were used. DPP4 inhibitors and SGLT2 inhibitors were the preferred add-on drug class. Empagliflozin, linagliptin and their combination were commonly prescribed after using two other anti-hyperglycemic agents, after diabetes duration of 3-5 years, among patients aged 40-49 years, and at HbA1c 7-8%. Indian doctors perceive that empagliflozin and linagliptin may be better suited in the Indian population.***

Keywords: empagliflozin, linagliptin, cardiovascular disease, renal disease, anti-hyperglycemic agents, diabetes

1.Introduction

Being the second most populous country in the world, India has a large burden of diabetes. In fact, it is thought that a large number of these cases are undetected, and can also have co-morbidities [1]. The India State Level Disease Burden Initiative Diabetes Collaborators reported in 2018 that the estimated burden of diabetes in India was 65 million in 2016, as compared to 26 million in 1990. It is noteworthy that compared to 1990, the difference in prevalence in 2016 was significantly higher for men aged 50-54 years (10.1% vs.13.6%), and for women aged 55-59 years (10.4% vs.13.5%), indicating the incidence of diabetes in Indians is shifting towards a lower age group [2].

An interesting facet of the risk of diabetes is the South Asian phenotype, wherein the prevalence of diabetes and premature atherosclerosis can be possibly explained by metabolic syndrome and abdominal obesity in genetically predisposed individuals. A higher prevalence of diabetes is noted despite a lower body mass index (BMI) of South Asians, and is associated with reduced high-density lipoprotein (HDL) cholesterol and elevated triglyceride levels [3]. This is reflected in the increasing age-standardised prevalence of cardiovascular disease (CVD) in India from 1990 to 2006 (5, 450 per 100, 000 to 5, 681 per 100, 000), and a decrease in the prevalence of CVD in USA over the same period (8, 277 per 100, 000 to 7, 405 per 100, 000) [4]. There is also a higher prevalence of significant coronary artery disease (CAD) in South Asians compared to Caucasians (41% vs.28%) [5].

To lower this excess cardiovascular (CV) risk, optimising blood glucose control is of importance. The choice of anti-hyperglycemic therapy is crucial, and can impact treatment outcomes. The use of anti-hyperglycemic drugs which could reduce hyperglycemia as well as the risk of CVD are key to tackling this dual threat [6]. The sodium-glucose cotransporter 2 (SGLT2) inhibitor, empagliflozin, and the dipeptidyl peptidase 4 (DPP4) inhibitor, linagliptin, have potential pleiotropic effects which are beneficial to type 2 diabetes mellitus (T2DM) patients [7, 8].

Prescribing Practice of Empagliflozin and Linagliptin in Indian Cardio-Diabetes Patients (PELICARD) was a cross-sectional study that aimed to survey the prescribing practice of Indian consulting physicians, endocrinologists and diabetologists for T2DM patients with respect to the newer anti-hyperglycemic drugs, empagliflozin and linagliptin. The study also evaluated the use of these drugs

in patients with CVD risk and renal complications. The study evaluated the factors leading to the prescription of empagliflozin, linagliptin and the combination of empagliflozin plus linagliptin in Indian patients. This analysis aimed to identify the patient profile that doctors consider suitable to be treated with empagliflozin plus linagliptin.

2.Methods

Collection of data:

PELICARD was a cross-sectional study involving consulting physicians, endocrinologists, diabetologists, cardiologists and nephrologists. Doctors with diabetes practice were selected randomly across four zones of the country. A structured questionnaire was provided electronically to 865 doctors in the month of March and April 2021. The questions had multiple-choice answers except for four questions that evaluated the rank of factors considered for selection of anti-hyperglycemic agents. Questions were divided under three heads: "patient characteristics", "prescribing practice for anti-hyperglycemic agents" and "place of empagliflozin and linagliptin in your practice".

The following patient characteristics were collected: age group at diagnosis of diabetes, proportion of patients with HbA1c over 8% at the time of diagnosis; proportion of patients aged less than 50 years; proportion of patients with co-morbid CVD, or renal complications or both; proportion of patients with co-morbid hepatic complications; proportion of patients requiring combination therapy.

In terms of prescribing practice for anti-hyperglycemic agents, data collected included HbA1c at which combination therapy is prescribed, the most common add-on anti-hyperglycemic agents; the most common add-on anti-hyperglycemic agents for diabetic patients at high risk of CVD; factors taken into account when prescribing anti-hyperglycemic agents (to be ranked in order).

Finally, in assessing the place of empagliflozin and linagliptin in clinical practice, the SGLT2 and DPP4 inhibitors of choice were evaluated. Specifically with respect to empagliflozin, the duration of diabetes after which empagliflozin was prescribed, as well as whether it was used as initial treatment, the number of drugs given prior to prescribing empagliflozin, average age group at which empagliflozin is prescribed, HbA1c at which empagliflozin is prescribed and the co-morbidities in patients to whom empagliflozin is prescribed, were assessed. Similar parameters were assessed for patients receiving linagliptin, as well as the combination of empagliflozin plus linagliptin. Finally, with respect to the combination of empagliflozin plus linagliptin, whether it was prescribed sequentially or as a fixed-drug combination was evaluated.

Data analysis:

Data was entered in Microsoft Excel 2010, and then imported into Statistical Package for the Social Sciences (SPSS) version 16 (SPSS Inc., USA) for data analysis. For all parameters, the data was derived as proportions and percentages. Where relevant, comparisons between the responses of doctors of different qualifications, or between the responses obtained for the individual drugs, were carried out to assess statistical significance. To determine statistical significance, Chi-square test was considered.

3.Results

The cohort of 865 doctors surveyed in this perception mapping study included 433 consulting physicians (50.1%), 104 endocrinologists (12%), 290 diabetologists (33.5%), 20 cardiologists (2.3%) and 18 nephrologists (2.1%).

Patient characteristics:

Overall, 58.8% of doctors reported that the age group of 40-49 years at diagnosis was the most common. This was followed by the age group of 30-39 years (22.22%), 50-59 years (17.25%), and lastly 60-69 years that made up only 1.74% of responses. Thus, doctors responded that ~80% of patients were aged under 50 years at diagnosis. Overall, 46.3% of doctors reported that over 40% of their patients presented with HbA1c >8%. Among the endocrinologists, 17.8% reported that over 50% of patients had HbA1c at presentation compared with only 6.9% of consulting physicians. Conversely, 15.5% of endocrinologists reported HbA1c >8% in 30% of patients, while 20.9% of consulting physicians reported 30% of patients had HbA1c >8% at presentation. The *P* value for trend was <0.0001.

Approximately one-third of doctors reported that 21-25% of their patients had CVD, while ~19% reported that 26-30% of their patients had CVD. The cumulative percentage of doctors reporting CVD in 21-30% of patients was 53.66% [Figure 1]. One-third of doctors reported that 21-25% of their patients had renal complications, while ~16% reported that 26-30% of their patients had renal complications. In contrast to CVD, doctors reporting renal complications in >30% of their patients were only 7.41%. More endocrinologists reported >30% of their patients had renal complications compared with consulting physicians (10.2% vs.5.3%, $P = 0.008$) [Figure 2]. The proportion of doctors reporting >40% of patients required combination therapy was ~33%, and an equal proportion reported that 20-29% required combination therapy [Figure 3].

Prescribing practice for anti-hyperglycemic agents:

Over half of doctors (52.66%) initiated combination therapy when HbA1c was over 8%, while a minority (5.09%) initiated combination therapy when HbA1c was over 10% [Figure 4]. The most preferred class of add-on anti-hyperglycemic agents were DPP4 inhibitors (41.78%) followed by SGLT2 inhibitors (37.27%). However, for

patients at risk of CVD, the preferred add-on therapy was with SGLT2 inhibitors (60.65%) followed by DPP4-inhibitors (25.58%) [Figure 5]. Statistical analysis revealed a significant difference in the choice between DPP4 inhibitors ad SGLT2 inhibitors for the comparison of T2DM patients and T2DM patients at risk of CVD (χ^2 = 79.3664, P < 0.00001). A comparison of drug preference among consulting physicians and endocrinologists is presented in Figure 6. The ranking of factors for the selection of anti-hyperglycemic medication showed that age of the patient was the most important factor, followed by the duration of T2DM, family history of CVD, CV safety of the drugs, family history of renal conditions and lastly, the renal safety of the drugs.

Place of empagliflozin and linagliptin in practice:

When analyzing the choice of DPP4 inhibitor and SGLT2 inhibitor, it was noted that there was an overwhelming preference of linagliptin over sitagliptin [Figure 7A], and empagliflozin over dapagliflozin and canagliflozin [Figure 7B]. Furthermore, 60.07% of doctors preferred prescribing the fixed-drug combination (FDC) of empagliflozin plus linagliptin, rather than introducing these agents sequentially. In case of sequential use of empagliflozin and linagliptin, empagliflozin was preferred to be added to therapy first, as compared to linagliptin.

While evaluating the patient characteristics favoring the administration of empagliflozin, a preference to prescribe this agent after using two other anti-hyperglycemic agents, after diabetes duration of 3-5 years, among patients aged 40-49 years, and at HbA1c >7 to 8% were noted [Table 1]. The perceived preferable patient profile for prescribing linagliptin was similar to that of empagliflozin [Table 2], as was that for the FDC of empagliflozin plus linagliptin [Table 3]. Empagliflozin, linagliptin and the combination of empagliflozin plus linagliptin are often prescribed to patients with co-morbidities [Figure 8]. It was noted that the doctors preferred linagliptin in patients with renal disease rather than CVD (n=623 [72.11%] vs. n=463 [53.59%]), while they preferred empagliflozin in patients with CVD rather than renal disease (n=405 [46.88%] vs. n=591 [68.4%]). The comparison was statistically significant (χ^2 = 57.992, P < 0.00001; Figure 9). The combination of the two drugs, however, was preferred in patients with renal disease (71.88%) as well as in patients with CVD (70.49%). Figures 10 and 11 in the Supplementary file describe the prescribing practice for the combination of empagliflozin and linagliptin in all respondents, and in the consulting physicians and endocrinologists.

4.Discussion

The findings of the PELICARD study highlighted the perception of Indian consulting physicians (50.1%), endocrinologists (12%), diabetologists (33.5%), cardiologists (2.3%) and nephrologists (2.1%) with respect to the use of empagliflozin and linagliptin among Indian diabetic patients. The study noted a high usage of empagliflozin and linagliptin as well as the combination of empagliflozin plus linagliptin in patients with a diabetes duration of 3-5 years, having taken two prior anti-hyperglycemic agents, aged 50-59 years and with HbA1c 7 to <8% at the time of initiation of the anti-hyperglycemic agent (s) in question.

Current guidelines for the pharmacological management of T2DM from the American Diabetes Association (2021) indicate that after lifestyle modification and initial metformin therapy, patients with indicators of high-risk or established atherosclerotic cardiovascular disease (ASCVD) or heart failure (HF) should receive SGLT2 inhibitors with proven CV benefit. For patients with high-risk or established chronic kidney disease (CKD), SGLT2 inhibitors with evidence of reducing CKD progression are indicated. Additionally, DPP4 inhibitors are indicated if the HbA1c target is not met [6]. Indian guidelines from the Research Society for the Study of Diabetes in India and Endocrine Society of India (RSSDI-ESI) state that in T2DM patients with renal impairment, gliptins are preferred as the add-on therapy to metformin, and linagliptin does not require dose adjustment in such patients. SGLT2 inhibitors are preferred as add-on drugs in patients with established CVD, and in case of HF with CKD. Linagliptin is preferred over conventional sulfonylureas for patients at increased risk of CVD or with CVD [9].

Despite this, published literature from India has indicated the continued use of metformin and sulfonylureas, with a low uptake of SGLT2 inhibitors and DPP4 inhibitors among the doctors [10-14]. At a tertiary care center, the most common combination therapy among inpatients was metformin plus glimepiride, followed by metformin plus glimepiride plus saxagliptin [10]. A study among patients attending the outpatient department at a tertiary care hospital reported that after metformin, glimepiride was the most commonly used drug. The combination of metformin + vildagliptin accounted for 26% of FDCs, while metformin + glimepiride accounted for 14% [11]. In both studies, empagliflozin and linagliptin were not prescribed [10, 11]. At a rural medical college, DPP4 inhibitors were prescribed to 7.2% of patients, and metformin + glimepiride was the maximally prescribed FDC [12]. More recently, a tertiary care teaching hospital reported that DPP4 inhibitors were prescribed to 29.78% of patients [13]. Interestingly, in Indian patients with CKD, DPP4 inhibitors are used by 9.5% of patients [14].

However, this literature is in stark contrast to the changing trend of prescribing practices for diabetes noted around the world. Engler, *et al.* reported the prescription patterns for over 10, 000 diabetes patients from 2012 to 2018. They noted a significant increase in prescriptions of SGLT inhibitors from 0.06% to 23.4%, as well as for DPP4 inhibitors (23.3% to 34.1%). There was a concomitant decrease in the prescription of sulfonylureas and alpha-glucosidase inhibitors, while that of glitazones remained stable. In terms of combination therapy as well, the most prevalent combination of oral drugs was metformin with DPP4 inhibitors, followed by metformin with SGLT2 inhibitors. Triple therapy with metformin + SGLT2 inhibitors + DPP4 inhibitors was reported in 4.2% of patients [15]. Similarly, Wilkinson, *et al.* reported a 17-

year trend showing a growing preference for DPP4 inhibitors and SGLT2 inhibitors, which accounted for 42% and 22% of drugs used for intensification, respectively [16]. The findings of the current study are in consonance with current global trends, which have defined a shift from the earlier usage of sulfonylureas to the newer oral anti-hyperglycemic agents.

SGLT2 inhibitors have been considered crucial tools in the treatment of diabetes. In addition to glycemic control, empagliflozin leads to reduction in systolic blood pressure (SBP) of up to 3.89 mmHg in 12 weeks [17], weight loss of up to 2 kg in 24 weeks along with reductions in total body fat and visceral adiposity [18]. Benefits of SGLT2 inhibitors culminate in a reduced risk for major adverse CV events, hospitalisation for HF or CV death, as well as kidney outcomes [19]. The EMPA-REG OUTCOME trial reported that empagliflozin reduces the risk of CV death by 38%, and the risk of hospitalisation for HF by 35% [20]. Empagliflozin also reduced the risk of incident or worsening nephropathy by 39% [21]. It has been suggested that the renal effects of SGLT2 inhibitors could contribute to reduction in CV risk, possibly through decrease in inflammation and generation of reactive oxygen species (ROS) [22]. However, a study has reported that only 5% of eligible patients are treated with SGLT2 inhibitors [7].

Linagliptin is known to significantly decrease total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels [23]. The CARMELINA trial demonstrated that linagliptin did not increase the cardiorenal risk in elderly patients with established CVD with albuminuria or CKD [24]. The use of linagliptin in diabetic patients with CKD is shown to significantly reduce the risk of renal progression [25]. It has also been reported that the combination of empagliflozin and linagliptin leads to reduction of body weight by 1.53 kg after 52 weeks of treatment, as well as reduction of SBP by 3.8 mmHg and diastolic blood pressure (DBP) by 1.8 mmHg [26].

5.Conclusion

The benefits of empagliflozin and linagliptin have been demonstrated in clinical trials, and these agents are now recommended by expert organisations as the preferred add-on therapy in T2DM patients with known CV or renal conditions, or at high risk of developing these conditions. The use of such agents can translate into not just improved diabetes outcomes, but also improved CV and renal outcomes. Based on the findings of the PELICARD study, it can be inferred that doctors in India consider empagliflozin and linagliptin as a crucial components in the management of diabetic patients, especially in those with cardiac and renal co-morbidities. These findings are encouraging, as glycemic benefits could lead to subsequent renal and CV benefits. This is of importance in the complex pathology of T2DM, CVD and CKD, and empagliflozin and linagliptin could be the pillars of diabetic care.

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Tables

Table 1: Patient profile for which Indian doctors prescribe empagliflozin

Parameter	Variables	Response, n/N (%)	Parameter	Variables	Response, n/N (%)
Number of prior anti-hyperglycemic drugs	1	160/865 (18.52%)	Age group at initiation of empagliflozin (years)	40-49	416/865 (48.15%)
	2	537/865 (62.15%)		50-59	368/865 (42.59%)
	3	159/865 (18.40%)		60-69	75/865 (8.68%)
	4	8/865 (0.93%)		>70	5/865 (0.58%)
Disease duration (years)	1-2	158/865 (18.29%)	HbA1c at time of initiation of empagliflozin (%)	7	86/865 (9.9%)
	3-5	372/865 (43.06%)		>7 to 8	412/865 (47.6%)
	5-7	228/865 (26.39%)		>8 to 9	307/865 (35.5%)
	7-9	83/865 (9.61%)		>9	60/865 (6.9%)
	9-10	23/865 (2.66%)			

Table 2: Patient profile for which Indian doctors prescribe linagliptin

Parameter	Variables	Response, n/N (%)	Parameter	Variables	Response, n/N (%)
Number of prior anti-hyperglycemic drugs	1	225/865 (26.04%)	Age group at initiation of linagliptin (years)	40-49	400/865 (46.3%)
	2	508/865 (58.80%)		50-59	361/865 (41.78%)
	3	124/865 (14.35%)		60-69	88/865 (10.19%)
	4	7/865 (0.81%)		>70	15/865 (1.74%)
Disease duration (years)	1-2	190/865 (21.99%)	HbA1c at time of initiation of linagliptin (%)	7	98/865 (11.3%)
	3-5	386/865 (44.68%)		>7 to 8	494/865 (57.1%)
	5-7	191/865 (22.11%)		>8 to 9	232/865 (26.8)
	7-9	86/865 (9.95%)		>9	41/865 (4.7%)
	9-10	11/865 (1.27%)			

Table 3: Patient profile for which Indian doctors prescribe empagliflozin + linagliptin

Parameter	Variables	Response, n/N (%)	Parameter	Variables	Response, n/N (%)
Number of prior anti-hyperglycemic drugs	1	210/865 (24.31%)	Age group at initiation of empagliflozin + linagliptin (years)	40-49	362/865 (41.90%)
	2	477/865 (55.21%)		50-59	407/865 (47.11%)
	3	158/865 (18.29%)		60-69	87/865 (10.07%)
	4	19/865 (2.2%)		>70	8/865 (0.93%)
Disease duration (years)	1-2	146/865 (16.9%)	HbA1c at time of initiation of empagliflozin + linagliptin (%)	7	82/865 (9.5%)
	3-5	376/865 (43.52%)		>7 to 8	387/865 (44.7%)
	5-7	241/865 (27.89%)		>8 to 9	307/865 (35.5%)
	7-9	89/865 (10.3%)		>9	89/865 (10.3%
	9-10	12/865 (1.39%)			

Figures:

Figure 1: (A) Responses of doctors regarding proportion of their type 2 diabetes mellitus patients with co-morbid cardiovascular disease (B) Proportion of doctors reporting co-morbid cardiovascular disease in >30% of their patients

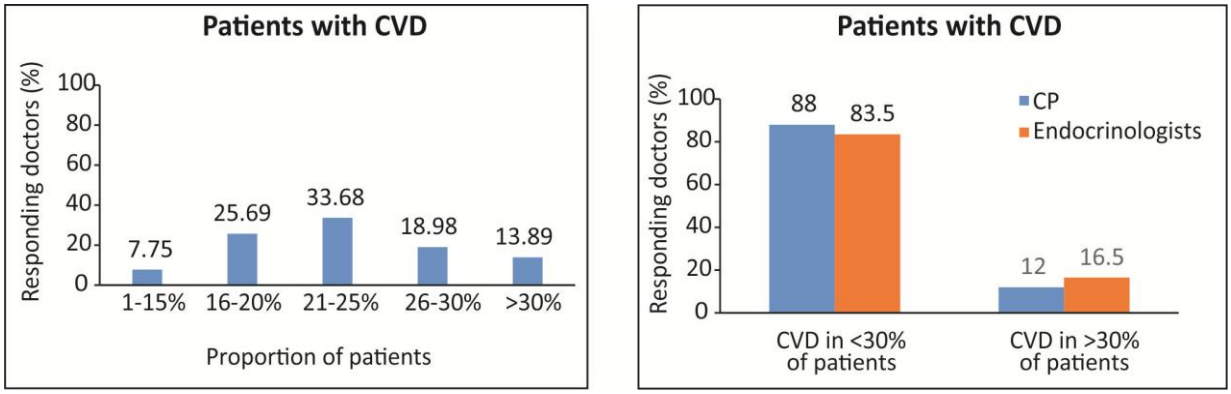


Figure 2: (A) Responses of doctors regarding proportion of their type 2 diabetes mellitus patients with co-morbid renal complications (B) Proportion of doctors reporting co-morbid renal complications in >30% of their patients

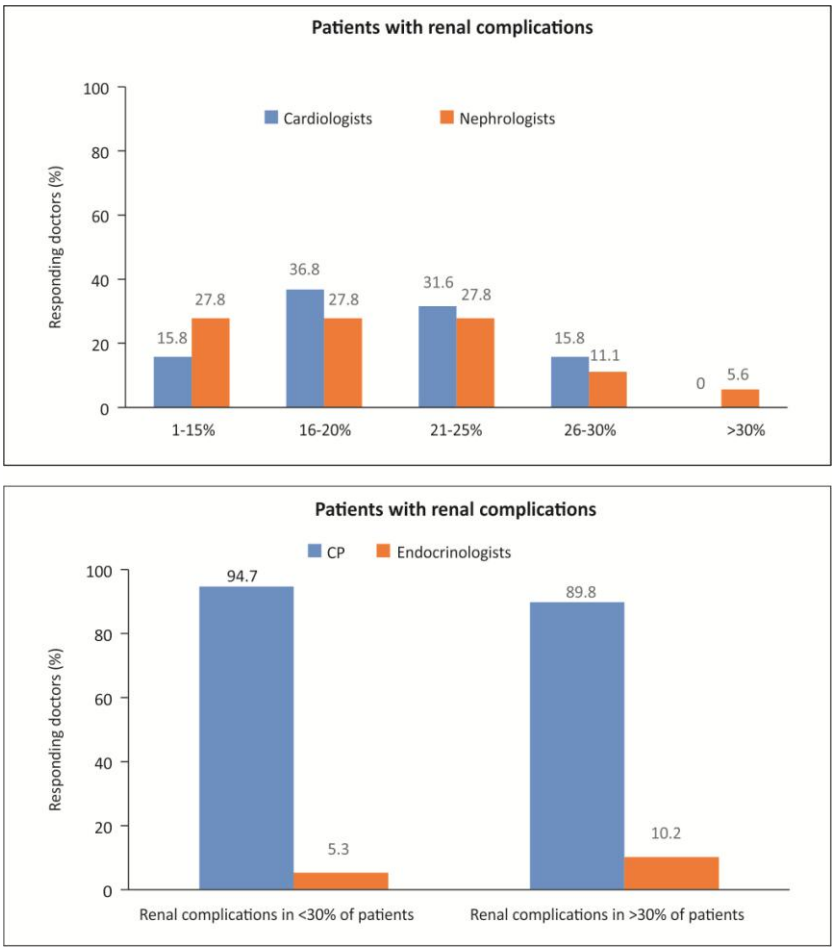


Figure 3: Responses of doctors regarding proportion of their patients requiring combination therapy

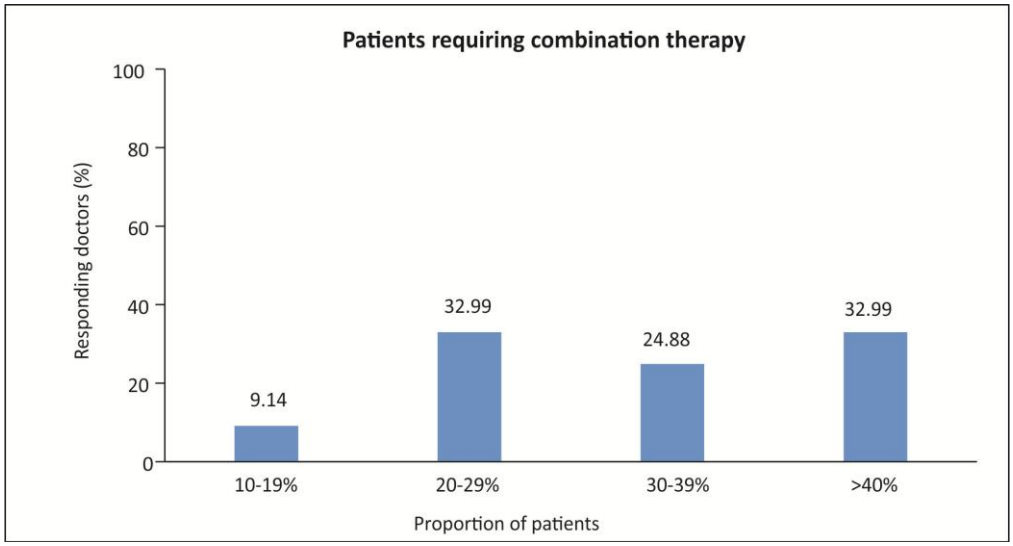


Figure 4: Responses of the doctors for the HbA1c level at which they prescribe combination therapy

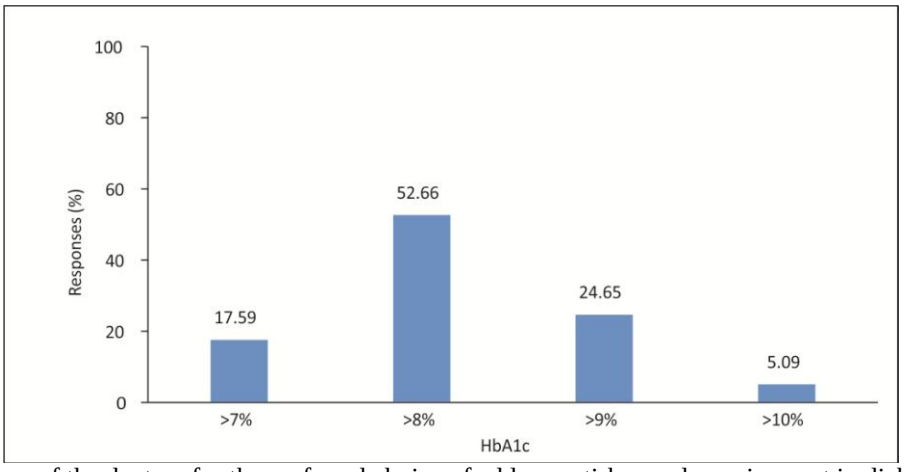
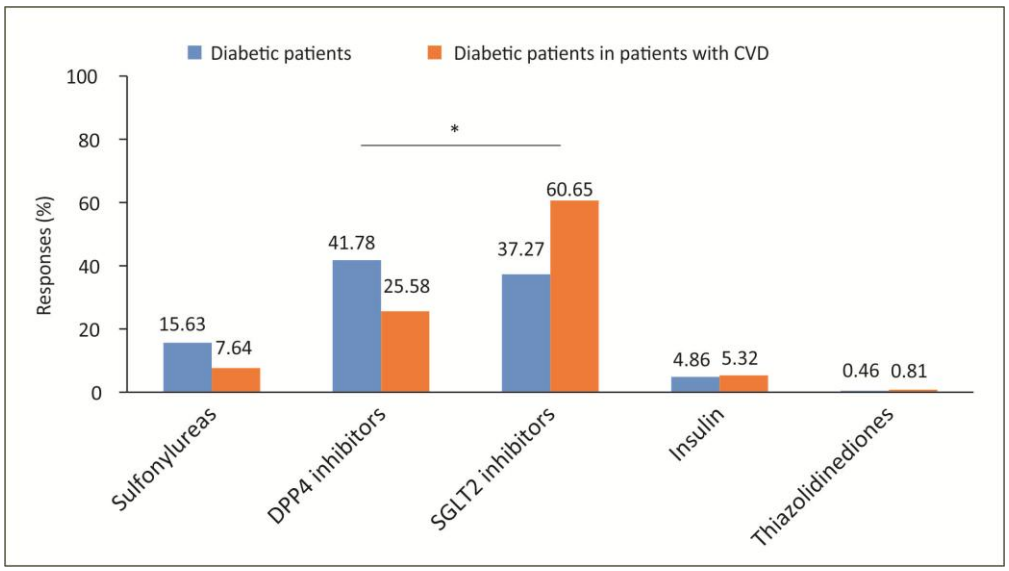


Figure 5: Responses of the doctors for the preferred choice of add-on anti-hyperglycemic agent in diabetic patients, and diabetic patients at risk of complications



* χ^2 = 79.3664, p<0.00001 for the comparison of SGLT2 inhibitors and DPP4 inhibitors being prescribed to T2Dm patients and T2DM patients with risk of CVD

Figure 6: (A) Comparison of preferred add-on drug class among consulting physicians and endocrinologists (B) Comparison of preferred add-on drug class among consulting physicians in patients with and without co-morbid cardiovascular disease (B) Comparison of preferred add-on drug class among endocrinologists in patients with and without co-morbid cardiovascular disease

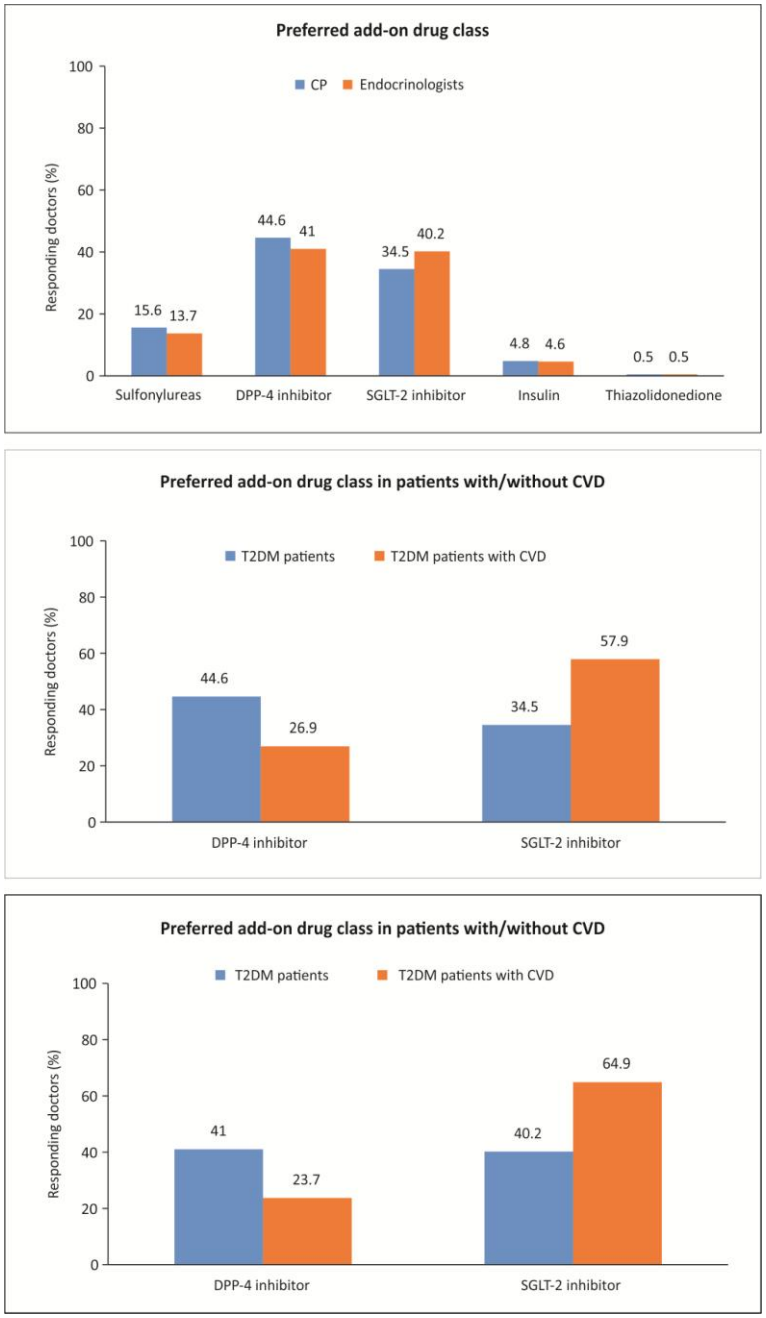


Figure 7: Preferred drug in the classes of (A) SGLT2 inhibitors (B) DPP4 inhibitors

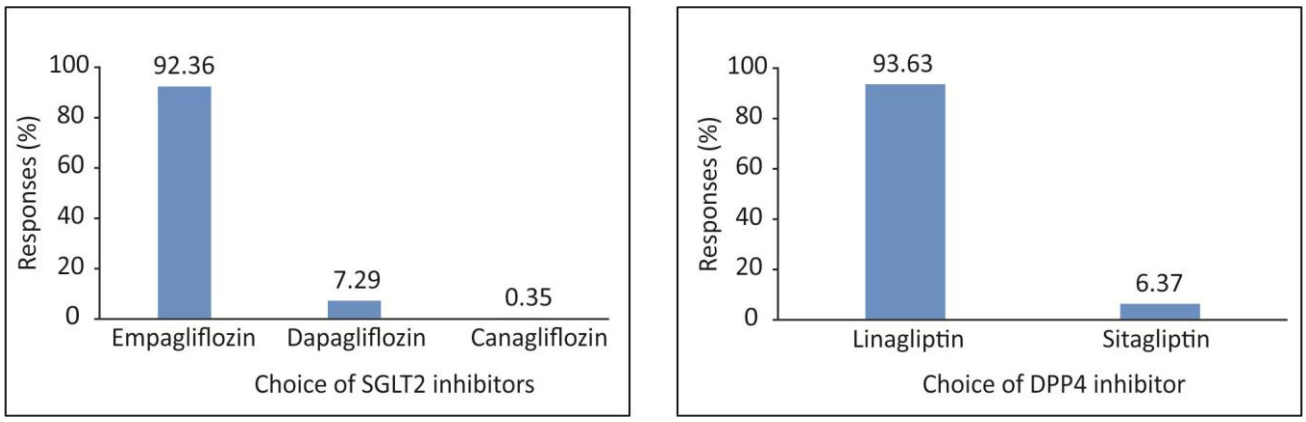
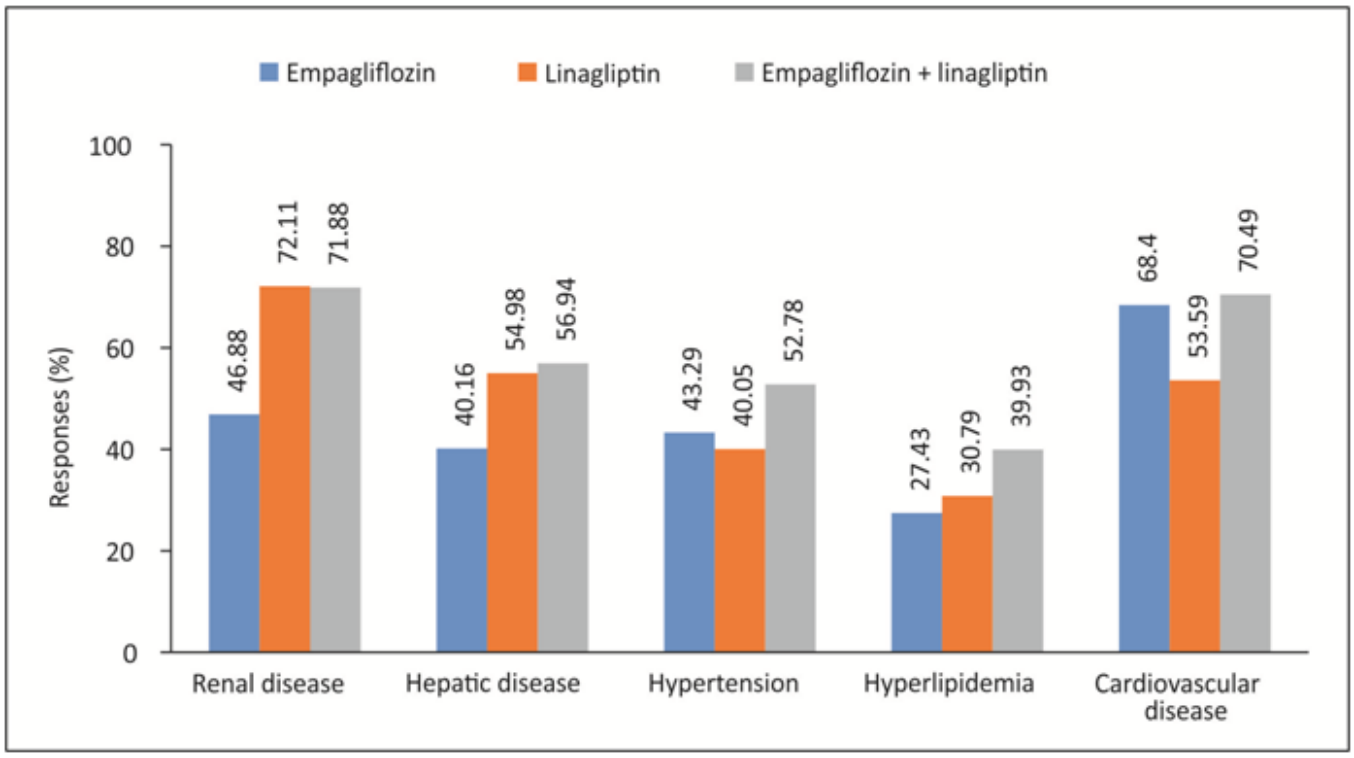


Figure 8: Co-morbidities for which empagliflozin, linagliptin, and empagliflozin plus linagliptin are considered useful



Total number of response is high because multiple responses were permitted for this question

Figure 9: Preference of linagliptin for patients with co-morbid renal disease, and empagliflozin for patients with co-morbid CVD

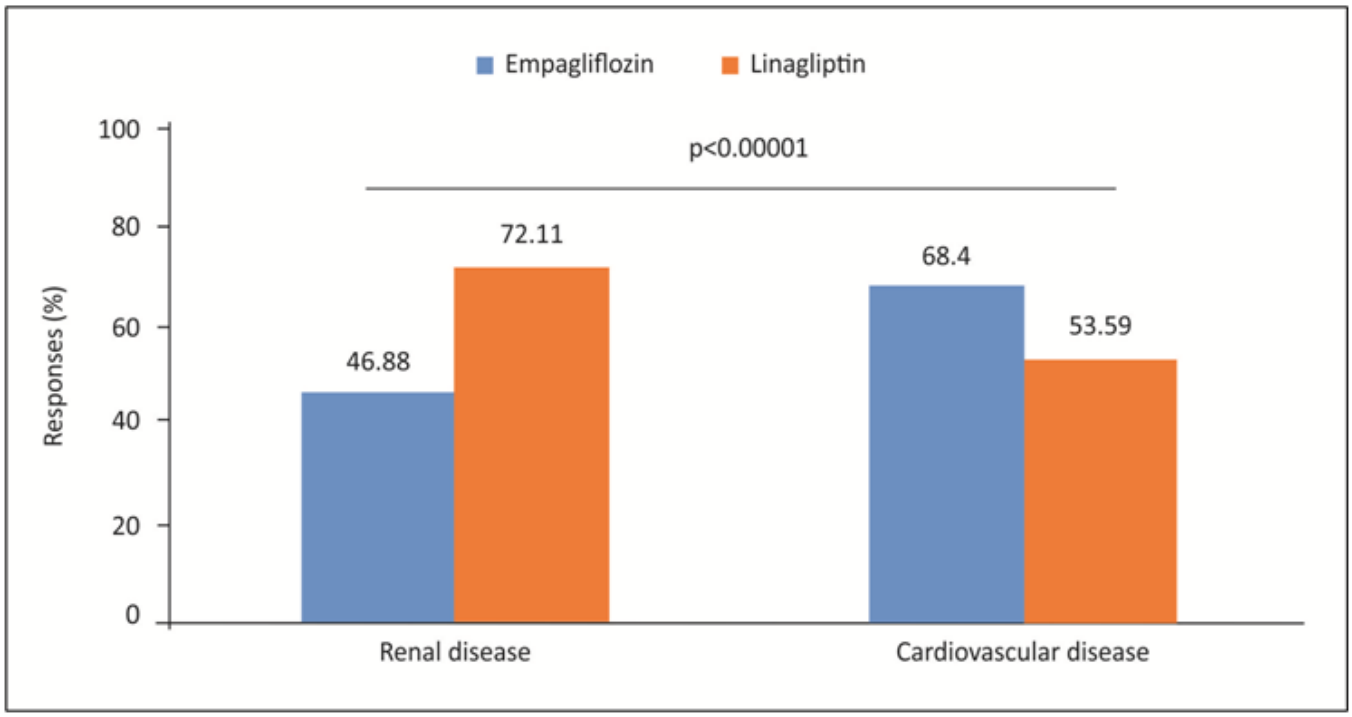


Figure 10: Prescribing practice for the combination of empagliflozin and linagliptin (A) No. of drugs used before prescribing he combination (B) Disease duration before prescribing the combination (C) HbA1c at initiation of the combination

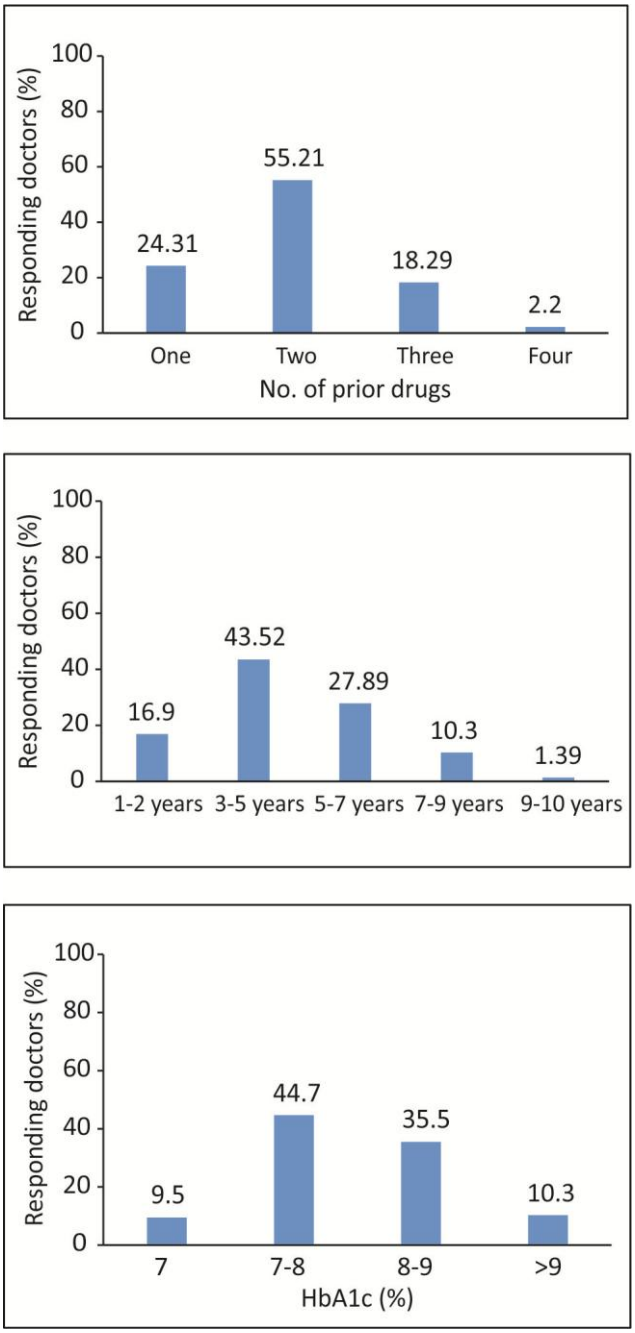


Figure 11: Comparison of the prescribing practice of consulting physicians and endocrinologists for the combination of empagliflozin and linagliptin (A) No. of drugs used before prescribing he combination (B) Disease duration before prescribing the combination (C) Age at initiation of the combination