Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i4.5371

A REAL WORLD SAFETY STUDY ON DAPAGLIFOZIN, A PRELIMINARY ACTIVE SURVEILLANCE IN A TERTIARY CARE SETTING

Dr.Padmaja Shetty K[1*], Dr.Pratibha Nadig[2], Dr. Prashanth Kumar M[3], Ms. Tanya Tanaaz[4], Ms. Shruthi Hari[5], Ms. Ananya[6]

[1*]Assistant Professor, Department of Pharmacology, Dr Chandramma Dayananda Sagar Institute f Medical Education and Research, Dayananda Sagar University, padmajaalva@gmail.com Contact no- 9448862850

[2] Professor & HOD, Department Of Pharmacology, Dr Chandramma Dayananda Sagar Institute Of Medical Education and Research, Dayananda Sagar University, pratibha.nadig@gmail.com Contact no- 9901961964

[3] Professor & HOD, Department Of Physiology, Dr Chandramma Dayananda Sagar Institute Of Medical Education and Research, Dayananda Sagar University, drprashanthkumar@gmail.com Contact no- 9448015663

[4]Pharm D student, College of Pharmaceutical Sciences, Dayanada Sagar University

[5] Pharm D student, College of Pharmaceutical Sciences, Dayanada Sagar University

[6] II MBBS Student, Dr Chandramma Dayananda Sagar Institute Of Medical Education and Research, Dayananda Sagar University

***Corresponding author**: Dr Padmaja Shetty K.
Assistant Professor, Department of Pharmacology, Dr Chandramma Dayananda Sagar Institute Of Medical Education and Research, Dayananda Sagar University, E-mail: padmajaalva@gmail.com, padmajashetty.cdsimer@dsu.edu.in, Contact no- 9448862850

Abstract:

Background: Dapaglifozin, a popular SGLT 2 inhibitor is frequently used as a single or add on therapy in type 2 diabetes mellitus. With its efficacy established through extensive clinical trials, our study aims to collect preliminary safety data on dapaglifozin through active surveillance.

Material and Methods: The safety profile of dapaglifozin was evaluated in 100 patients aged > 18 years either on mono or add on dapaglifozin treatment for a duration of > 2 weeks. The safety data was collected on CRF after obtaining consent for a duration of 4 months from April 2022- July 2022 at a tertiary care hospital. The primary outcome was the proportion and frequency of AEs, causality and severity assessment of AEs. Secondary outcome delineated the association between sociodemographic and dapaglifozin characteristics with safety data.

Result: On analysis of safety data of 100 patients, mean age was 57.65 $\pm$ 12.23 years with male preponderance (57%) with average BMI – 27.75 $\pm$ 2.42. About 39% adverse events were reported, of which the most common AEs were increased fatiguability (28.2%)(unexpected), hypoglycemia (17.9%), dapa specific adverse events such as genital tract infections (12.8%) and UTI (12.8%), gastro intestinal adverse events (~10-17%) and backpain- 9.09%. With 93% on add on therapy,

higher dose(10mg) and duration of administration (218.7 days) were significantly associated with adverse events.

Conclusion: Widespread clinical application of dapaglifozin among diabetics/nondiabetics have been associated with the need for vigilance on the safety data. The real life dapaglifozin safety data collected here contribute to the global incidence and watchlist.

Keywords: dapaglifozin, Adverse events, hypoglycemia, genital tract infections, UTI, Indian population

Introduction:

Sodium glucose transporter 2 (SGLT2) inhibitors initially introduced as oral hypoglycemiac agents were later also found to exhibit reduction in sympathetic activity, oxidative stress, cardioprotection, renoprotection, weight loss and lowering of blood pressure. Their unique insulin independent mechanism of action targeted the high capacity sodium glucose transporters located in the early portion of proximal convoluted tubules of the kidney leading to glycosuria. This property has been used in order to attain euglycemic control either alone or in combination regimen. [1,2,3]

Of the several FDA approved SGLT2 inhibitors, dapaglifozin was the first in the class antidiabetic agents.[4,5] Dapaglifozin is used either in monotherapy or in combination with other antidiabetic medications/insulin at any stage of type 2 diabetes mellitus.[5] Dapaglifozin is used at a dose of 5mg to a maximum of 10mg/ day for adequate glycemic control. Several randomized controlled trials have shown noninferiority of dapaglifozin in comparison to other antidiabetic agents. The therapeutic role of dapaglifozin has been expanded to many other non diabetic conditions as well.[6]

Several randomized controlled trials have studied the efficacy and provided a comprehensive list of adverse events profile of dapaglifozin. Dapaglifozin in single/dual/ triple therapy has shown greater glycemic control with respect to HbA1c levels and weight reduction. [7]

The increasing popularity of SGLT2 inhibitors for various indications also draws our attention towards safety data. The most common adverse events reported are hypoglycemia, genital tract infections, urinary tract infections, backache, dryness of mouth, gastrointestinal adverse events such as nausea, vomiting, constipation.[5,8,9]

Despite the safety and efficacy of dapaglifozin proved through RCTs, real world data/observational studies have shown varying incidence and severity of adverse events such as urinary tract infections, genital tract infections and more serious adverse events such as fournier's gangrene, ulcers/ non healing wounds.[5] Hence this preliminary real world safety surveillance aims to determine the frequency, association and severity of dapaglifozin safety data among Indian diabetic population where its usage has risen substantially.

Materials and methods:

Review of outpatient and ward case sheet prescription by the clinical pharmacists, 130 patients on dapaglifozin were screened for the study, of which 18 patients did not agree to participate in the study and 12 patients did not meet the study criteria.

The study size of 100 diabetic patients met the study criteria of >18 years of age, both gender, on dapaglifozin for >2 weeks, either alone or in combination at a dose of 5mg or 10mg . Study was conducted from April 2022- July 2022 at a tertiary care setting after obtaining written informed consent. Type-2 diabetic patients who were on dapaglifozin for more than 2 weeks but had to discontinue treatment were also included in the study. Patients with contraindications to dapagliflozin such as hypersensitivity reactions, stopped dapaglifozin within 2 weeks, patients on dapaglifozin for conditions other than type 2 diabetes, pregnant women were excluded from the study.

For this active surveillance, the CRF for direct patient interviews was designed to include sociodemographic, clinical, medication related data and a set of 12 adverse drug reactions of

dapaglifozin as listed on FDA-PI, SmPC and other real time clinical studies. For telephonic interviews a set of 10 validated questionnaires comprising of the above 12 ADRs were included.
The study was designed and conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines and was conducted after obtaining instituitional ethics committee approval (CDSIMER/MR/0019/IEC/2021). The adverse events thus collected were assessed for frequency, severity, duration, causality, seriousness of reactions and association of risk factors with ADRs.
The primary outcomes included the proportion, frequency and types of AEs reported. Causality and severity assessment of adverse events(AE) and association of AE with sociodemographic, clinical and dapaglifozin characteristics were included as secondary outcomes.
WHO causality assessment score was used to measure the relationship between dapaglifozin and AEs as definite=3, probable=2, possible=1 and unlikely=0 while Hartwig's severity score classified the severity of AEs as mild=1, moderate=2 and severe=3.

Statistical analysis: A preliminary sample size of 100 was calculated for this study derived from previous real time data. Descriptive and inferential statistical analysis has been carried out in the present study. Continuous measurements are presented as mean $\pm$ SD and categorical measurements are presented in number/percentages (%).
A multivariate logistic regression was performed to assess the relation between adverse event and the explanatory variables: gender, age, address, employment status, BMI, education, socioeconomic status and comorbidities. Data were checked for multicollinearity with the Belsley-Kuh-Welsch technique. Heteroskedasticity and normality of residuals were assessed respectively by the Breusch-Pagan test and the Shapiro-Wilk test. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed with Microsoft Excel and the Statistical Package for Social Sciences (SPSS) version 27.

Result:

Patient demographic and clinical characteristics:

Patient demographics and clinical characteristics details are as shown in table 1. The study included patients aged 57.65$\pm$12.23 years with male preponderance(57%). Clinical evaluation showed patients with BMI 27.75 $\pm$ 2.42 and systolic blood pressure was 128.27 $\pm$13.3mm Hg and diastolic blood pressure : 80.22$\pm$9.9 mm Hg.

Table 1: Sociodemographic and clinical characteristics (n=100)

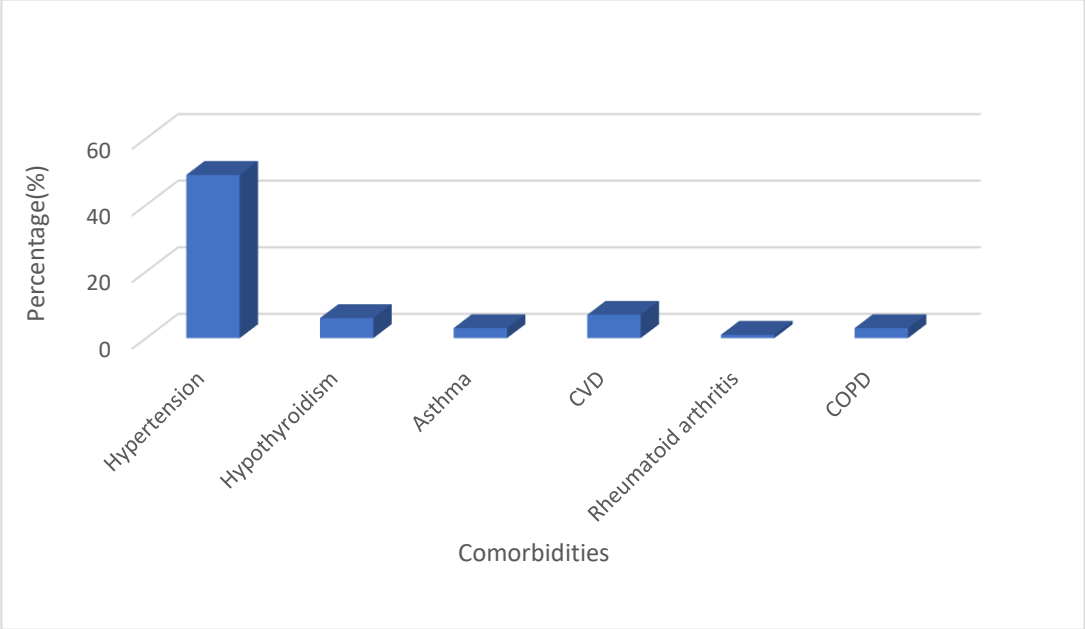
Sociodemographic & clinical characteristics	%
Age in Years	
• 18-30	5.0
• 31-45	16.0
• 46-65	56.0
• Above 65	23.0
Gender	
• Male	57.0
• Female	43.0
BMI	
• <25	77
• >25	23
Address	
• Rural	55.0
• Urban	45.0
Education	
• Educated	76
• Uneducated	24
Socioeconomic status	
• Upper middle	33.0

• Lower middle	37.0
• Upper lower	30.0
Employment status	
• Employed	45
• Unemployed	55
Blood pressure	
• <120/80 (Normal)	63.0
• 120-139/80-89 (Prehypertension)	23.0
• 140-159/90-99(Stage 1 HTN)	12.0
• >160/100 (Stage 2 HTN)	2.0
Presence of Comorbidities	55

At the time of enrolment in the study, laboratory examination showed FBS -150.5±49.12mg/dl, PPBS- 250.94+92.04 mg/dl with mean HbA1C as 9.56±2.29 % and serum creatinine levels-0.88 ±0.21mg/dl.

Among the study population with comorbidities (55%) (Bar Chart 1) the most common comorbidities observed were hypertension (49%), coronary heart disease (7%), asthma (3%), COPD (3%), rheumatoid arthritis (1%) and hypothyroidism (6%).

Bar Chart 1: Frequency distribution of comorbidities (n=100)



Dapaglifozin use and concomittant medications :

Considering the dapaglifozin related characteristics : 7% were taking dapa as single drug while 66% were on 10mg dose, 93% were add on therapy. Most of the patients (57%) included in this study have been on dapaglifozin for an average duration of 218.7 days (Table 2).

Table 2: Real Time Dapaglifozin utilisation characteristics(n=100)

Dapaglifozin characteristics	**%**
Dapa(single/ combi)	
• Single	7.0
• Adds on	93.0
Combination	
• No	2.0
• Single	6.0
• 2 drugs	29.0
• 3 drugs	61.0
• > 3	2.0

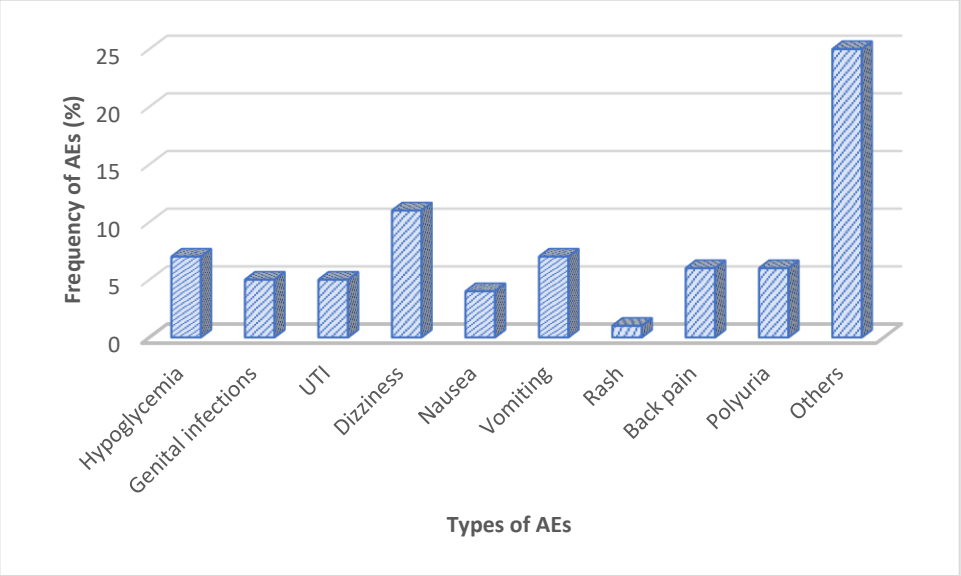
Dapa dose	
• 5mg	34.0
• 10mg	66.0
Duration	
• 1-6 months	57.0
• 7-12 months	21.0
• 1-2 yr	16.0
• 2-5 year	6.0
Personal history	
• No	89.0
• Smoking	4.0
• Alcohol	6.0
• Tobacco	1.0
Concomitant medications	
• No	44.0
• Yes	56.0

Around 56% of patients were on concomitant medications, of which 69.6% were on antihypertensive medications, 35.7% were on anticoagulants and antiplatelets drugs, 46.4% were on other medications such as statins, thyronorm, alprazolam, salbutamol, ambroxol, formoterol and budenoside, clopidogrel, thyronorm, antibiotic doxycycline, Vitamin B supplements, hematinics etc.

Adverse events(AE) profile among patients:

The frequency of AEs reported among patients is as shown in Bar Chart 2. 39% of patients on dapaglifozin presented with AEs. The most common AEs reported for dapaglifozin were fatiguability (28.2%) (unexpected), hypoglycemia (17.9%), dizziness(28.2%), polyuria (15.38%), backpain (9.09%), genital infections (12.8%), urinary tract infection (12.8%), nausea (10.2%), vomiting (17.9%), rash (2.56%), constipation (7.69%)(unexpected), dryness of mouth (5.12%), headache (2.56%)(unexpected), weight loss(2.56%), sleeplessness (2.56%)(unexpected), palpitations (2.56%)(unexpected), pain abdomen (5.12%), loss of appetite (2.56%)(unexpected), wound/ulcer (2.56%), chills (2.56%) and chest pain (2.56%)(unexpected).

Bar Chart 2: Frequency distribution of adverse events



Treatment was not changed for 29% of AEs reported, while in 12% cases, treatment with the suspected drug was withheld, but no treatment was given to manage AE. In 6% AEs, treatment with suspected drug was withheld/ discontinued and other treatment was given to manage AEs.

Causality assessment by WHO Probability Scale showed that 57% had possible and 22% had probable relationship to AEs. As per Hartwig's severity score assessment, 63%`of AEs were mild while 16% were moderate. There were no serious AE(SAEs) reported.

Association of sociodemographic factors and clinical characteristics with AEs:
As shown in Table 3, multivariate analysis showed that lower BMI (OR=0.8, [0.64 ; 1.0], p= 0.046) was associated with higher rates of adverse events while the socioeconomic status, employment status, education, gender, age , address and presence of comorbidities were not associated with the AEs incidences.

Table 3: Association between demographic variables & rate of adverse events:

	Odds Ratio	**p-Value**
Rate of adverse events	293.2 [0.686 ; 125252.96]	0.066
Age		
Risk for each 1-unit increase	0.999 [0.958 ; 1.04]	0.958
Address		
Reference: rural	1.1 [0.368 ; 3.31]	0.861
Employment status	0.793 [0.222 ; 2.83]	0.72
BMI		
Risk for each 1-unit increase	0.799 [0.641 ; 0.996]	0.046 *
Education	**0.902[0.251;3.24]**	0.875
Socioeconomic status		
Reference: lower middle		
	1.14 [0.36 ; 3.62]	0.821
	0.506 [0.155 ; 1.65]	0.259
Comorbidities		
	2.06 [0.799 ; 5.31]	0.135
Gender		
Reference: M	0.994 [0.277 ; 3.57]	0.993

* p<0.05** p<0.01*** p<0.001**** p<0.0001

In multivariate analysis (Table 4), > 1 year duration of administration of dapaglifozin (OR=4.66, [1.58 ; 13.75], p= 0.0053) and concomitant medications (OR=0.32, [0.13 ; 0.81], p= 0.016)were associated with higher rates of AE.

Table 4: Association of dapaglifozin data to rate of AEs

	Odds Ratio	**p-Value**
Intercept		
	0.873 [0.47 ; 1.62]	0.668
Dapa dose		

	Odds Ratio	p-Value
Reference: 10mg		
	0.532 [0.202 ; 1.4]	0.202
Duration		
Reference: <1 year		
	4.66 [1.58 ; 13.75]	0.00527 **
Concomittant medications		
Reference: Yes		
	0.321 [0.127 ; 0.809]	0.016 *

* p<0.05** p<0.01*** p<0.001**** p<0.0001

Multilogistic regression analysis showed that the most common AEs like hypoglycemia, UTI , GI disturbances showed a positive trend of incidence towards duration of dapaglifozin administration while fatiguability was significantly associated with higher dose of dapaglifozin (10mg)($p<0.05$).

Discussion:

Amongst the various SGLT2 inhibitors, dapaglifozin has been one of the commonly used antidiabetic agents in Indian population at a dose of 5mg/10mg/day. In the recent days, its use has also been expanded towards management of heart failure, chronic kidney disease, myocardial infarction, fatty liver diseases, weight loss, dyslipidemia.[10,11,12]

Sociodemographic and clinical characteristics observed in study by Jung-Fu Chen et al was similar to that observed in our study including mean age (57.65$\pm$12.23yrs), male preponderance (57%) with BMI (27.75 $\pm$ 2.42)($p<0.05$). More than half of our study population had comorbidities(55%), most common being hypertension(49%) similar to the study.[13]

In this study the real time dapaglifozin utilisation showed majority of study population on multiple antidiabetic medications while 66% were on highest dapaglifozin dose/day for effective blood glucose control. This was also associated with 56% of study population on concomitant medications to improve morbidity and mortality status. AE frequency of our study was similar to the study done by Brooks A.M et al where single and multidose phase I studies reported 21% and 37% of AEs while safety data analysis from phase II/III studies done by Serge Jabbour showed $\geq$1 AEs in 60% of cases.[14,15]

Most common AEs reported in this study were classified as expected such as dapaglifozin specific adverse events such as urinary tract infections (UTI)(12.8%), genital tract infections(GTI)(12.8%), hypoglycemia(17.9%), gastrointestinal tract infections such as nausea, vomiting, pain abdomen, weight loss and unexpected AEs included increased fatiguability, palpitation, loss of appetite, chest pain. The expected AEs reported is similar to review article by Sohita Dhillon [16] and research study done by Guo L[17] et al, where hypoglycemia was ~14% while genital and urinary tract infections were ~5%. While the clinical practice experience study done by Anitha A P et al showed hypoglycemia, GTI, UTI, hypotension, increased risk of breast and bladder cancer and increased uric acid levels.[18] DECLARE TIMI 58 clinical trial and study by Martha K Nicholson showed higher frequency of genital tract infections among women (13.2 %) which is similar to our study.[19]

Questionnaire based surveillance focused on the subjective AEs which included the increased incidence unexpected events such as increased fatiguability, constipation, loss of appetite, weight loss, palpitation, chest pain. These AEs affected the routine activity, medication adherence among the patients. Focusing on subjective AEs are important to identify and report AEs as well as provide timely assistance to help patients adhere to treatment.[20]

Increased rate of dapa specific adverse events such as hypoglycemia, UTI and genital tract infections were significantly ($p<0.05$) associated with factors such as increased duration (>1 yr) and higher dose (10mg) of dapaglifozin administration, concomitant medications and increased BMI (>25). More than half of the study population showed mild AEs and possible relationship with

dapaglifozin. Study by Amit Varshney[21] has shown good safety profile of dapaglifozin when administered in Indian population.

Despite absence of SAEs, our study has shown that 6% of AE cases discontinued treatment similar to study by jabbour at al.[15] The most common adverse events reported in our study which resulted in discontinuation of treatment were increased fatiguability, hypoglycemia and genital tract infections which affected their quality of life.[22]

The study focused on active surveillance to collect AEs through direct patient interviews which significantly showed association with reasons for discontinuation of treatment. Dapaglifozin related AEs reported can be added to the global watchlist. However, the study also presents with the limitation of a smaller sample size and was confined to a smaller geographical distribution. Hence more detailed multicentric study should be carried out to track the safety profile of SGLT2 inhibitors due to its increasing popularity,

Conclusion: Safety data in this preliminary study on real time dapaglifozin utilisation has shown incidence similar to global reporting. The increased incidence of unexpected adverse events which had serious implication on patient's day to day activity and medication adherence needs more surveillance on field.

References:

1. Nelinson DS, Sosa JM, Chilton RJ. SGLT2 inhibitors: a narrative review of efficacy and safety. J Osteopath Med. 2021 Feb 1;121(2):229-239. doi: 10.1515/jom-2020-0153. PMID: 33567084.
2. Fadiran O, Nwabuo C. The Evolution of Sodium-Glucose Co-Transporter-2 Inhibitors in Heart Failure. Cureus. 2021 Nov 8;13(11):e19379. doi: 10.7759/cureus.19379. PMID: 34925982; PMCID: PMC8654149.
3. Jaehyun Lim, Soongu Kwak, You-Jung Choi et al. Differing Efficacy of Dapagliflozin Versus Empagliflozin on the Risk of Incident Atrial Fibrillation in Patients With Type 2 Diabetes: A Real-World Observation Using a Nationwide, Population-Based Cohort. Journal of the American Heart AssociationVol. 13, No. 3. e030552 https://doi.org/10.1161/JAHA.123.030552
4. Padda IS, Mahtani AU, Parmar M. Sodium-Glucose Transport Protein 2 (SGLT2) Inhibitors. [Updated 2023 Jun 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK576405/
5. Saeed MA, Narendran P. Dapagliflozin for the treatment of type 2 diabetes: a review of the literature. Drug Des Devel Ther. 2014 Dec 10;8:2493-505. doi: 10.2147/DDDT.S50963. PMID: 25525338; PMCID: PMC4267514.
6. Hsia DS, Grove O, Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. Curr Opin Endocrinol Diabetes Obes. 2017 Feb;24(1):73-79. doi: 10.1097/MED.0000000000000311. PMID: 27898586; PMCID: PMC6028052.
7. Sahay, R.K., Giri, R., Shembalkar, J.V. et al. Fixed-Dose Combination of Dapagliflozin + Sitagliptin + Metformin in Patients with Type 2 Diabetes Poorly Controlled with Metformin: Phase 3, Randomized Comparison with Dual Combinations. Adv Ther 40, 3227–3246 (2023). https://doi.org/10.1007/s12325-023-02523-z
8. Filippatos TD, Liberopoulos EN, Elisaf MS. Dapagliflozin in patients with type 2 diabetes mellitus. Ther Adv Endocrinol Metab. 2015 Feb;6(1):29-41. doi: 10.1177/2042018814558243. PMID: 25678954; PMCID: PMC4321869.
9. Fda.gov. [cited 2024 Feb 12]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202293s020lbl.pdf
10. Zargar AH, Trailokya AA, Ghag S et al. Current Role of Dapagliflozin in Clinical Practice. J Assoc Physicians India. 2021 Sep;69(9):11-12. PMID: 34585897.
11. Gupta M, Rao S, Manek G et al. The Role of Dapagliflozin in the Management of Heart Failure: An Update on the Emerging Evidence. Ther Clin Risk Manag. 2021 Aug 12;17:823-830. doi: 10.2147/TCRM.S275076. PMID: 34408424; PMCID: PMC8367215.
12. Bailey CJ, Gross JL, Hennicken D et al. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-

week trial. BMC Med. 2013 Feb 20;11:43. doi: 10.1186/1741-7015-11-43. Erratum in: BMC Med. 2013;11:193. PMID: 23425012; PMCID: PMC3606470.
13. Chen JF, Peng YS, Chen CS, et al. Use and effectiveness of dapagliflozin in patients with type 2 diabetes mellitus: a multicenter retrospective study in Taiwan. Peerj. 2020 ;8:e9998. DOI: 10.7717/peerj.9998. PMID: 33240585; PMCID: PMC7678460.
14. Brooks AM, Thacker SM. Dapagliflozin for the treatment of type 2 diabetes. Ann Pharmacother. 2009 Jul;43(7):1286-93. doi: 10.1345/aph.1M212. Epub 2009 Jul 7. PMID: 19584379.
15. Jabbour S, Seufert J, Scheen A et al. Dapagliflozin in patients with type 2 diabetes mellitus: A pooled analysis of safety data from phase IIb/III clinical trials. Diabetes Obes Metab. 2018 Mar;20(3):620-628. doi: 10.1111/dom.13124. Epub 2017 Oct 26. PMID: 28950419; PMCID: PMC5836959.
16. Dhillon S. Dapagliflozin: A Review in Type 2 Diabetes. Drugs. 2019 Jul;79(10):1135-1146. doi: 10.1007/s40265-019-01148-3. Erratum in: Drugs. 2019 Dec;79(18):2013. PMID: 31236801; PMCID: PMC6879440.
17. Guo L, Wang J, Li L et al. A multicentre, prospective, non-interventional study evaluating the safety of dapagliflozin in patients with type 2 diabetes in routine clinical practice in China (DONATE). BMC Med. 2023 Jun 14;21(1):212. doi: 10.1186/s12916-023-02906-7. PMID: 37316847; PMCID: PMC10268430.
18. Anitha AP, Balasubramanian S, Ramalingam AG at al. An exploration of the experience of dapagliflozin in clinical practice. Future Sci OA. 2022 Nov 1;8(8):FSO816. doi: 10.2144/fsoa-2022-0038. PMID: 36457541; PMCID: PMC9704035).
19. Martha K Nicholson, Randa Ghazal Asswad & John PH Wilding(2021). Dapagliflozin for the treatment of type 2 diabetes mellitus – an update, Expert Opinion on Pharmacotherapy, 22:17, 2303-2310, DOI: 10.1080/14656566.2021.1953471
20. Liu L, Suo T, Shen Y, Geng C,et al. Clinicians versus patients subjective adverse events assessment: based on patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). Qual Life Res. 2020 Nov;29(11):3009-3015. doi: 10.1007/s11136-020-02558-7. Epub 2020 Jun 20. PMID: 32564293.
21. Varshney A, Rawat R. Comparison of safety and efficacy of dapagliflozin and empagliflozin in type 2 diabetes mellitus patients in India. Rev Assoc Med Bras (1992). 2023 Aug 14;69(8):e20230090. doi: 10.1590/1806-9282.20230090. PMID: 37585983; PMCID: PMC10427181.
22. Cahn A, Raz I, Bonaca M, Mosenzon O et al. Safety of dapagliflozin in a broad population of patients with type 2 diabetes: Analyses from the DECLARE-TIMI 58 study. Diabetes Obes Metab. 2020 Aug;22(8):1357-1368. doi: 10.1111/dom.14041. Epub 2020 Apr 27. PMID: 32239659.