



Physiological and Pharmaceutical Study of Cardiovascular Disease in Patients with Type 2 Diabetes Mellitus

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Abbreviations

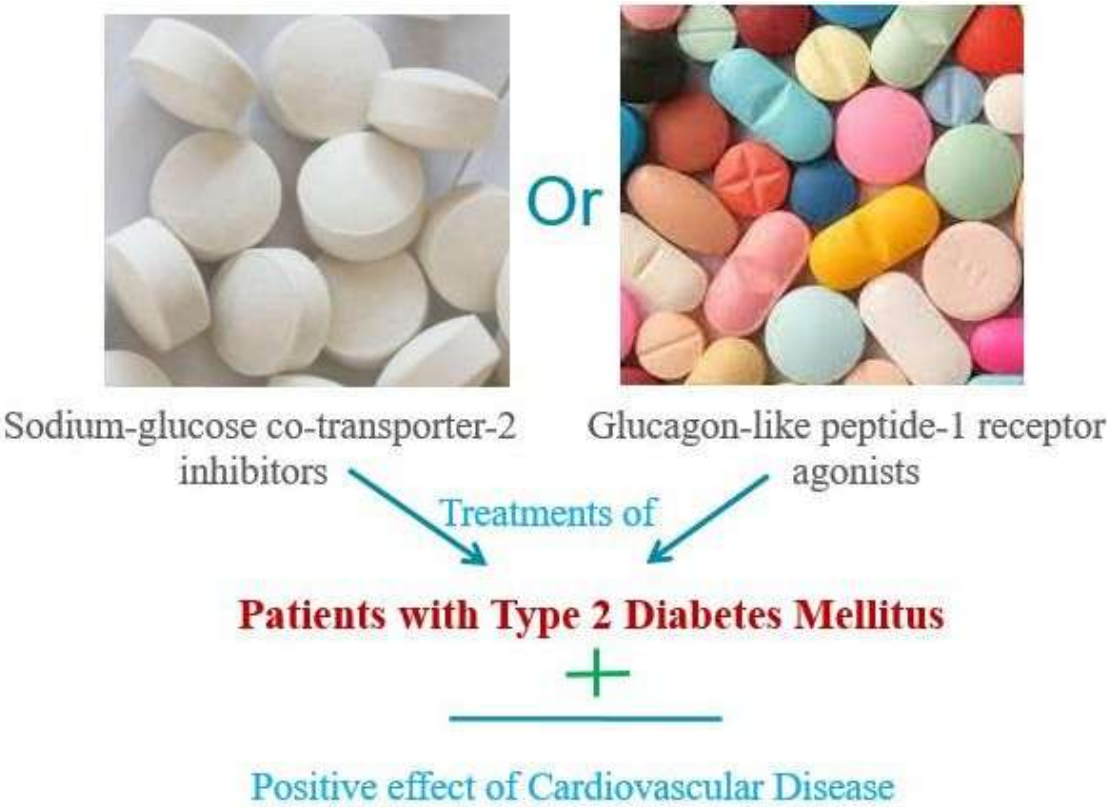
AGi	Alpha-glucosidase inhibitor
CV	Cardiovascular
CVD	Cardiovascular disease
BMI	Body mass index
AsCVD	Atherosclerotic cardiovascular disease
IDF	International Diabetes Federation
GFR	Glomerular filtration rate
GLA	Glucose-lowering agent
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
IQR	Interquartile range
T2D	Type 2 diabetes



SGLT2	Sodium glucose co-transporter 2 inhibitor
TZD	Thiazolidinedione

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Graphical abstract





Abstract

Drug interactions have been studied by different group of researchers, in which they have used a number of living organisms like humans and animals to reduce or inhibit risk of side effect of drug disease interaction and enhance action of drugs.

The present study was aimed to investigate the link of cardiovascular disease (CVD) including atherosclerotic CVD (AsCVD), into patients with type 2 diabetes (T2D) that use sodium-glucose co-transporter-2 inhibitors (SGLT2is) or glucagon-like peptide-1 receptor agonists (GLP-1 RAs) as well as to provide more information about the incidence of CVD in T2D patients. The current study included 422 patients with T2D have diagnosed in Erbil, Kurdistan, Iraq, during their attended to secondary care facilities. T2D patients were with the median age 66 years and median diabetes duration 13.3 years. Our results observed that the percentage of AsCVD was 27.2% of all cases of CVD. The coronary heart disease recorded the highest percentage (20.8%) followed by carotid artery disease (12.1%). Biguanides was the most common prescribed medication with percentage (74.2%) to treat the majority of patients (75.9%). The results also showed that patients with CVD were required higher rates of SGLT2is and lower rates of GLP-1 RAs) as compared to patients without CVD corresponding to the percentage (16.9% and 14.5% versus 14.8% and 15.1%, respectively). The major objective of this research was to investigate the dual functionality of drugs where they use for treatment of patients with Type 2 Diabetes, in addition these drugs show positive pharmacologically effect of patients with cardiovascular diseases.

Keywords

Cardiovascular disease, Diabetes type 2, Atherosclerotic, Heart disease medications, Drug interaction

1. Introduction

It is well known that heart failure, stroke, coronary artery disease, and peripheral artery disease are just a few of the disorders that fall under the umbrella term of cardiovascular disease (CVD), which affects the blood arteries and the heart. Drug development plays an important role in the field of the pharmaceutical formulations in order to introduce novel drugs which are pharmacologically effective for treatment of different diseases in living organisms and stable under physiological conditions.

Numerous variables, including obesity, smoking, diabetes, heredity, high cholesterol, high blood pressure, and a lack of physical activity, contribute to these illnesses ^{1,2}. Millions of people are affected by CVD each year, making it a significant cause of disability and mortality globally ^{3,4}. It is a significant factor in the burden of sickness on the planet, accounting for around one-third of all fatalities worldwide. People can make lifestyle changes, such as frequent exercise, eating a nutritious diet, stopping



smoking, and managing risk factors including high blood pressure and cholesterol, to reduce their risks of having CVD ⁵.

Indeed, insufficient insulin secretion by pancreatic-cells and the inability of insulin-sensitive tissues to respond to insulin are the two main causes of type 2 diabetes mellitus (T2DM), a common metabolic illness ^{6,7}. To meet metabolic requirements, the production and activity of insulin must be precisely regulated, and this entails controlling the molecular processes in charge of insulin synthesis, release, and tissue response. Any flaw in these processes could lead to metabolic dysregulation, which would help T2DM develop. Insulin-resistant cells are found in those with T2DM, and these cells are less able to respond to insulin's signals to take up glucose from the bloodstream ⁷⁻⁹. As a result, blood glucose levels rise, which over time can lead to a number of health issues, including damage to blood vessels, nerves, kidneys, and eyes. Risk factors for (T2DM) include a number of ethnicities, a family history of the disease, obesity, and inactivity. Increased hunger and thirst, frequent urination, hazy vision, weariness, and slowly healing wounds are all signs of T2DM ^{10,11}. T2DM patients are more likely to experience heart failure, peripheral arterial disease, coronary artery disease, stroke, and other cardiovascular illnesses (CVD). Inflammation, hyperglycemia, hypertension, endothelial dysfunction, insulin resistance, and dyslipidemia are among the factors that raise the risk of CVD in people with T2DM ¹².

For people with T2DM, early detection and good management of CVD risk factors are essential to reduce the chance of CVD complications and improve the outcomes. Individuals with diabetes have a two to three times higher risk of developing CVD than do adults without the condition, and CVD is the leading cause of early death in this population ¹³. Acute coronary syndrome risk is the same for diabetic individuals who have never had a myocardial infarction as it is for non-diabetic patients who have experienced previous myocardial infarctions ^{14,15}. In Kurdistan, T2D affects more than three million individuals, and its incidence has been rising as a result of a number of causes, including an aging population, higher obesity rates, and worse socioeconomic level. The micro- and macrovascular consequences of type 2 diabetes (T2D) are associated with a higher risk of illness, a lower quality of life, and disability ^{16,17}. According to the World Health Organization (WHO), CVD, which accounts for 42%



of all fatalities worldwide, is the main cause of mortality for people with T2D ¹⁸. To lower the incidence of CVD in patients with T2D, international guidelines advise the use of diabetes medications with established cardiovascular benefits, such as sodium-glucose co-transporter-2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) ^{19,20}. Thus, the present study was aimed to explore the benefit use of these medication to CVD for people with T2D in region of Kurdistan-Iraq.

2. Methods

Data were obtained from Kurdistan Regional Government's Directorate of Planning and Ministry of Health. The protocol for the study was first approved by the center's ethics committee (Hawler Medical University-College of Pharmacy- Ph-Ec-080522-664).

2.1. Study population

Along with general practitioners, the National Healthcare System in Kurdistan-Iraq has a wide network of experts who provide diabetes care and management. Up to 500,000 diabetes individuals, or a sizable portion of the T2D community, are seen in such clinics. The CAPTURE study only took individuals from secondary care locations as a result. Because the estimated prevalence of CVD in Kurdistan can be calculated with a precision of 2-3 % points using a target sample size of 800, the results from this sample can be used for determining the T2D population being treated at secondary care facilities in Kurdistan and Iraq.

A 120-day window to enroll was provided by their physicians to adults over the age of 20 who had been diagnosed with T2D at least 180 days before giving informed consent. Type 1 diabetes (T1D) and known congenital cardiac diseases or anomalies were the exclusion criteria ²¹.



2.2 Data collection

Information was acquired during a typical visit to the Laila Qasim and Cardiac Center-Erbil from the patients' medical records. After collecting blood sample, participants were questioned about any information found to be missing from the medical record, and the code "participant referred" was added.

Aortic disease, heart failure, cardiac arrhythmia, and established CVD have all been studied by researchers (such as AsCVD, cerebrovascular disease, coronary heart disease [CHD], peripheral artery disease, or carotid artery disease). Patients were divided into groups based on whether or not they had developed CVD (CVD group) (No CVD group). In addition to current GLAs and CV medicines, demographic and clinical data, including the existence of comorbidities, were obtained (such as retinopathy and neuropathy).

2.3 Objectives/endpoints of the study

The CAPTURE study analysis's main goal was to ascertain the prevalence of cardiovascular disease (CVD) among Kurdish T2D patients. The secondary goal was to describe how these individuals were using CVD and glucose-lowering medications.

2.4 Statistical analysis

In particular for the Kurdish community, the study sought to determine the prevalence of several subtypes of cardiovascular disease (CVD), including AsCVD, and offer their estimated prevalence with a 90 % confidence interval (CI). The study also offered descriptive data to contrast various groups, including those between the Kurdish sample and the worldwide sample, as well as between the CVD group and the No CVD group.



3. Results

3.1 Study population

The CAPTURE research enrolled 3400 T2D patients between December 3, 2019, and September 30, 2022, of whom 904 were drawn from 15 Kurdish secondary care facilities. There were participants from 12 different nations. The demographic and clinical characteristics of the Kurdish population are shown in Table 1. The median age was 69 years (with a range of 63 to 76 years between the quartiles), the median duration of diabetes was 11.2 years (with a range of 5.6 to 17.8 years), and the median HbA1c level was 8%. 22.6 percent of patients had an estimated glomerular filtration rate (eGFR) of less than 59 mL/min/1.73 m², and 36.8 % of the population was female. In addition, the majority of the patients 74.8% had a history of hypertension. Obesity is characterized by a body mass index (BMI) of 25 kg/m² or more, and it was present in certain patients.



Characteristic	Study population N = 904		By CVD status			
			CVD n = 312		No CVD n = 488	
	n	Data	N	Data	n	Data
Female	904	322 (38.9)	312	97 (33.3)	488	213 (42.8)
Age, years	904	69 [62–75]	312	73 [64–73]	488	66 [62–72]
Diabetes duration, years	904	14.2 [4.9–19.6]	312	13.6 [4.9–18.4]	488	11.7 [6.3–15.9]
HbA1c, %	802	8.0 [5.5–6.9]	311	7.8 [6.8–7.8]	488	7.6 [6.9–7.1]
HbA1c, mmol/mol	802	51.0 [46.5–61.9]	311	52.4 [46.0–63.0]	488	53.0 [47.5–63.0]
FPG, mmol/L	733	7.7 [6.8–8.6]	293	7.8 [6.4–8.6]	446	8.4 [6.6–8.7]
Body weight, kg	904	76.3 [43.0–154.0]	317	78.8 [51.2–153.0]	488	77.0 [48.0–175.0]
BMI, kg/m ²	904	25.4 [26.3–34.5]	315	28.5 [24.6–31.2]	488	28.3 [25.1–32.5]
Systolic blood pressure, mmHg	904	140 [110–130]	321	140 [125–145]	488	140 [120–140]



Characteristic	Study population N = 904		By CVD status			
			CVD n = 312		No CVD n = 488	
	n	Data	N	Data	n	Data
Diastolic blood pressure, mmHg	248	72 [75–85]	312	74 [71–79]	488	83 [70–80]
Total cholesterol, mmol/L	722	5.1 [3.8–5.2]	273	4.0 [3.4–4.5]	460	4.4 [3.7–4.9]
LDL cholesterol, mmol/L	644	2.3 [1.8–2.6]	266	2.3 [1.6–2.5]	433	2.6[1.8–2.8]
HDL cholesterol, mmol/L	706	1 [1.1–1.4]	265	1.4 [1.0–1.4]	438	1.4 [1.0–1.5]
Non-HDL cholesterol, mmol/L	255	3.2 [2.4–3.4]	118	2.70 [2.0–3.0]	161	2.9 [2.5–3.9]
Triglyceride, mmol/L	708	1.6 [1.0–1.9]	280	1.44 [1.0–1.9]	466	1.87 [1.0–1.9]
eGFR, mL/min/1.73 m ²	644		255		428	
>89 (normal)		246 (37.5)		82 (33.7)		168 (42.6)
>59–89		276 (38.6)		106 (38.1)		182 (44.3)
≤59		155 (20.8)		76 (20.8)		74 (17.8)
Albuminuria	644		243		400	
Normal–mildly increased		467 (77.3)		161 (68.8)		313 (76.8)
Micro- and macroalbuminuria		177 (24.3)		82 (33.2)		90 (21.8)
Retinopathy	904		322		488	
Yes		96 (11.0)		41 (12.9)		53 (12.0)
Nephropathy	904		312		488	
Yes		136 (15.2)		76 (11.9)		62 (16.0)



Characteristic	Study population N = 904		By CVD status			
			CVD n = 312		No CVD n = 488	
	n	Data	N	Data	n	Data
Neuropathy	904		312		488	
Yes		88 (13.0)		44 (16.7)		42 (9.2)

The n (percent), median [interquartile range], and mean standard deviation are the three forms of data that are discussed in this paragraph. It also shows that no statistical techniques were used to examine any variations between the CVD and No CVD groups. Among the terminology used are body mass index, cardiovascular disease, estimated glomerular filtration rate, fasting plasma glucose, and glycated hemoglobin. LDL stands for low-density lipoprotein, whereas HDL stands for high-density lipoprotein. CVD incidence AsCVD prevalence made up the majority of the predicted overall CVD prevalence in the CAPTURE Kurdistan, which was 36.8 % of the Iraqi population (32.8%).

It is significant to remember that a person may have multiple diagnoses, and those diagnoses are not exclusive. There were no statistical comparisons of the various illness subtypes and diagnoses in the study. CHD was the most prevalent type of CVD among the Kurdish study participants, followed by carotid artery disease (12.8%), cardiac arrhythmia and conduction abnormalities (8.0%), and cerebrovascular disease (5.8%). In addition, heart failure affected 4.6% of patients, the majority of whom exhibited symptoms (3.8%).

The most prevalent CHDs in the Kurdish group were myocardial infarction (12.4%) and prior revascularization procedures (11.8 %). The two most prevalent types of cerebrovascular illness were ischemic stroke (3.6 %) and transient ischemic attack (2.6 %). Claudication (1.8%), asymptomatic peripheral arterial disease (1.8%).



3.2 Characteristics of the study population stratified by CVD status

In this investigation, individuals with CVD were more likely to be male (69.7% vs. 54.8%), older (median age 69 [IQR: 64-78] vs. 66 [IQR: 64-78] years), and have less functional kidneys (68.1% vs. 61% with an eGFR of 88 mL/min/1.72 m2) than non-CVD patients. Additionally, there were greater incidences of nephropathy (23.1% vs 12.0%) and neuropathy in the CVD group compared to the No CVD group in terms of the prevalence of microvascular effects (15% vs 8.5%). Additionally, the CVD group had a higher prevalence of a history of hypertension, microalbuminuria, and macroalbuminuria compared to the No CVD group (26.0 % vs 18.8 %, 7.1 % vs 3.3 %, and 85.5 percent% vs 70.8 %, respectively).

.3 GLA use in the study population

Table 2 displays the prevalence of various GLAs in the CAPTURE Kurdistan-Iraq population. Two oral GLAs were administered to the majority of patients (84%): biguanide (metformin; 77.1%) and dipeptidyl peptidase-4 inhibitor (DPP-4i; 19.6 %). The least frequently used drugs were glinides, thiazolidinediones, and alpha-glucosidase inhibitors (2.4 %, 2.2 %, and 2.5 %, respectively). In contrast to the CVD group, the No CVD group utilized biguanides, DPP-4is, sulphonylureas, glinides, TZDs, and AGis more frequently. Insulin was widely used, especially in the group with CVD (42% vs. 31.9 %).

Table 2: shows the distribution of GLA use by CVD status in the CAPTURE Kurdistan-Iraq population.

Empty Cell	Total (N = 904)	No CVD (n = 488)	CVD (n = 312)	AsCVD (n = 260)
GLAs	703 (86.3)	452 (83.0)	247 (83.3)	208 (88.1)
Biguanide	646 (72.2)	452 (70.8)	214 (72.4)	182 (74.6)
DPP-4i	158 (19.9)	117 (20.8)	52 (15.6)	46 (14.3)
SGLT2i	142 (15.6)	74 (13.8)	61 (21.4)	55 (23.4)
SU	84 (12.4)	54 (15.8)	29 (9.8)	24 (8.8)



Empty Cell	Total (N = 904)	No CVD (n = 488)	CVD (n = 312)	AsCVD (n = 260)
TZD	22 (2.4)	14 (4.2)	6 (1.2)	5 (1.1)
AGi	21 (2.6)	14 (3.8)	6 (1.4)	5 (1.2)
Glinide	19 (2.1)	12 (2.4)	5 (1.8)	3 (3.1)
GLP-1 RA	127 (16.8)	84 (16.2)	45 (15.5)	36 (14.7)
Insulin	288 (36.2)	166 (31.9)	136 (40.3)	124 (40.2)

The information reported in this study is expressed as percentages and is not weighed. Additionally, statistical comparisons of differences between subgroups were not made.

The terms AsCVD and AGi stand for atherosclerotic cardiovascular disease and alpha glucosidase inhibitor, respectively. Cardiovascular disease (CVD), dipeptidyl peptidase-4 inhibitor (DPP-4i), glucose-lowering agent (GLA), glucagon-like peptide-1 receptor agonist (GLP-1 RA), sodium-glucose co-transporter-2 inhibitor (SGLT2i), and sulphonylurea (SU) are all abbreviations for the same compound.

SGLT2i and GLP-1 RA medicines, which are known to have cardiovascular advantages, were prescribed to 15.8% and 16.8% of patients, respectively, in the population evaluated in CAPTURE Kurdistan-Iraq. Compared to the No CVD group, the CVD group used SGLT2i treatment more frequently (21.2% vs. 13.6%, respectively), while the CVD group used GLP-1 RA medicine a little less frequently (15.5% vs 16%, respectively). Similar dosages of SGLT2is and GLP-1 RAs were given to the AsCVD group and the CVD group as a whole.

3.4 Standard CV medication use in the study population

The CAPTURE Kurdish cohort also looked at how many people with T2D took common cardiovascular disease drugs, including as hypolipemic, antiplatelet, and anti-hypertensive therapy (Table 3). In general, 64.7% of patients received prescriptions for lipid-lowering medications (mostly statins), 72.0% received prescriptions for anti-hypertensive medications (mostly ACE inhibitors or angiotensin II receptor blockers),



44.0% received prescriptions for antiplatelet medications, 26.9% received prescriptions for diuretics, and 5.4% received prescriptions for anti-thrombotic medications. When compared to the No CVD group, all CVD drugs were taken more frequently in the CVD group.

Table 3: *shows the top CV drugs, stratified by CVD status, in the CAPTURE Kurdistan-Iraq population.*

Empty Cell	Study population N = 904	By CVD status	
		CVD n = 312	No CVD n = 488
Any CV medication			
Yes	732 (89.8)	303 (97.2)	407 (84.6)
Medications for hypertension or other CVD			
Any	590 (74.0)	276 (84.5)	329 (64.8)
Angiotensin II receptor blocker	230 (27.4)	98 (29.6)	145 (26.1)
Angiotensin-converting enzyme inhibitor	268 (31.2)	123 (36.1)	140 (27.0)
Lipid-lowering medication			
Any	528 (67.9)	235 (79.3)	283 (59.7)
Statin	496 (60.1)	233 (70.2)	264 (50.3)



Empty Cell	Study population N = 904	By CVD status	
		CVD n = 312	No CVD n = 488
Platelet aggregation inhibitor			
Any	356 (45.0)	206 (63.4)	154 (32.1)
Anti-thrombotic medication			
Any	46 (5.7)	42 (13.9)	5 (0.8)
Diuretic			
Any	236 (26.7)	128 (35.2)	106 (27.2)

We have n (%) data. Subgroup differences weren't statistically compared.



4. Discussion

According to the CAPTURE study in the Kurdish community, secondary care outpatient clinic patients with T2D had a predicted overall CVD prevalence of 36.9%, of which 86 % had AsCVD. Carotid artery disease and CHD were found to be important risk factors. The Kurdish cohort had only marginally greater odds of receiving a diagnosis of CVD or AsCVD overall (5% and 1.4% higher, respectively) when compared to the weighted prevalence values for the worldwide CAPTURE population²². Unpublished data also show that the prevalence of cardiovascular disease (CVD) and atherosclerotic cardiovascular disease (AsCVD) among Kurdistan-Iraq patients seeking secondary care was only marginally lower than the worldwide population (4.4 % and 1.0 % difference, respectively). In contrast to the overall CAPTURE population, the Kurdish cohort, however, had a larger proportion of patients with diseases like coronary heart disease, carotid artery disease, cardiac arrhythmia, peripheral artery disease, aortic disease, and heart failure. On the other hand, the Kurdish group had fewer patients with cerebrovascular illness. Comparing the Kurdish group to the worldwide CAPTURE population, the Kurdish group also had around twice as many patients with symptomatic heart failure and more than twice as many patients with atrial fibrillation, myocardial infarction, or prior revascularization procedures. Comparing the Kurdish group to the larger global CAPTURE population reveals distinct traits. These variations include a smaller proportion of females, a higher median age, and a higher proportion of hypertensive patients. These demographics may contribute to the greater prevalence of cardiovascular disease (CVD) and specific subtypes of CVD in Kurdistan-Iraq. A considerable percentage of T2D patients in Kurdistan-Iraq are treated through a network of secondary and tertiary diabetic care clinics thanks to the unique structure of the country's healthcare system. This could explain why some subtypes of CVD are more common in Kurdistan-Iraq than elsewhere in the world. When compared to primary care, diabetes care in Kurdistan-Iraq is associated with a lower overall death rate. This method of treating diabetes may have led to earlier and more frequent cardiovascular disease identification (CVD). Additionally, the network has been putting the AMD Annals Initiative into practice since 2006 in an effort to track patient



disease indicators and enhance clinical outcomes for T2D. This program might have contributed to the rise in CVD detection in Kurdistan-Iraq. Prior epidemiological studies that concentrated on CVD prevalence in T2D patients getting secondary care in Kurdistan-Iraq should be compared with the most recent data on the prevalence of CVD and its subtypes from the CAPTURE Kurdistan-Iraq project.

According to a directorate of planning in Ministry of Health, Kurdistan Regional Government between 2001–2006 titled Diabetes and Informatics, the prevalence of coronary heart disease (CHD) was reported to be 21.4% in the CAPTURE Kurdistan–Iraq population compared to 11 % in T2D patients. 21.6 % of T2D patients who participated in the Renal Insufficiency and Cardiovascular Events (RIACE) trial, which enrolled participants between 2004 and 2006, reported having severe acute CVD events. Patients in the RIACE research had an increased risk of cardiovascular disease development if they had long-term diabetes and impaired renal function (CVD) ^{23–25}. The Kurdish CAPTURE research, which focused on patients with an average diabetes duration of 10 years in 2019, looked at patients and found that those with an average diabetes duration of 20 years had a significant prevalence of CVD (35.5%).

According to a clinical record data analysis of the AMD Annals done in 2018, myocardial infarction, coronary revascularization, carotid revascularization, stroke, and peripheral revascularization were the most common CVD complications among T2D patients in Kurdistan-Iraq, with an overall prevalence of CVD of 32 % among those who had diabetes for more than 22 years ^{26,27}. Due to changes in the case mix resulting from the use of various data collection procedures at various sites, the prevalence of cardiovascular disease (CVD) and coronary heart disease (CHD) may differ between studies. The prevalence of CVD among T2D patients in Kurdistan-Iraq may have risen during the previous ten years as a result of an aging population and rising obesity rates. Nevertheless, local statistics from the CAPTURE experiment revealed that 16% of T2D patients were treated with GLP-1 RAs, compared to 11 % in the global cohort, and 15.8% were treated with SGLT2is, despite the high prevalence of CVD in Kurdistan-Iraq. In the CAPTURE trial, the Kurdish population, especially those with known cardiovascular disease, utilized more extra cardiovascular medications than people in other nations, including statins, acetylsalicylic acid, or antihypertensive therapies ^{27,28}.



Although national data from the AMD Annals Initiative, ARNO observatory, and other study-participating nations were compared to the CAPTURE project data in Kurdistan-Iraq, the usage of cardiovascular (CV) medications and glucose-lowering agents (GLAs) with established CV benefits was higher. However, the results show that their utilization is still insufficient and inconsistent with current national and international guidelines, given the considerable burden of CVD in Kurdistan-Iraq. Furthermore, although though the usage of SGLT2 inhibitors and GLP-1 receptor agonists was not particularly investigated in the CAPTURE investigation, it is likely that reasons other than their efficacy contributed to their less-than-ideal persistence. The emphasis on the substantial use of insulin therapy in patients with established CVD is highlighted in this line. It's unclear whether the high insulin use is the result of meticulous clinical assessment or clinical inertia. It is crucial to carry out additional research to examine this problem.

It should be emphasized that the CAPTURE project's Kurdish and international populations may have different rates of CVD and prescription drug use. These discrepancies might be influenced by variables including the research's setting, the healthcare system, a person's genetic make-up, their lifestyle, and screening procedures, which this study did not address. This study has a number of significant flaws, including the potential for ascertainment bias in the results since T2D patients who had signs of CVD may have been more likely than other T2D patients to seek medical assistance. Additionally, because this study was descriptive in nature, statistical variations across groups were not examined.

The study design did not specify any additional testing to verify diagnoses in cases where medical records were missing, which resulted in a limited amount of data that could be examined. Additionally, the correctness and completeness of patient medical records also had an impact on the results. The depth of our understanding of heart failure in this study is constrained by the paucity of information on echocardiography and heart failure with diminished or intact ejection fraction. It is important to note that because the Kurdish cohort only comprises patients who visited secondary care outpatient clinics, our results could not apply to all T2D patients. The cohort's racial makeup may not accurately reflect that of the entire Iraqi population; therefore, people of White



ancestry may benefit more from the findings. However, the CAPTURE data indicates that CVD, particularly AsCVD, affects more than one-third of T2D patients in Kurdistan-Iraq who sought treatment in secondary diabetic centers. Even though T2D patients in Kurdistan-Iraq have a high CVD prevalence, only a tiny portion of them are currently receiving treatment with GLAs that have been shown to have cardiovascular advantages.

5. Conclusion

This study was conducted on patients having type 2 diabetes (T2D) on their visit to Laila Qasim and Cardiac Center-Erbil (Kurdistan region). According to our results it was seen that the incidence of various cardiovascular diseases (CVDs) including AsCVD is more in T2D patients as compared to normal counterparts. Also the incidence of other CVDs like coronary heart disease, heart failure, aortic disease, cardiac arrhythmia, and cerebrovascular disease is more in the patients. The results showed that a small proportion of T2D patients are on those antidiabetic medications having a cardiovascular benefit effect (SGLT-2is and GLP-1RA), and this is opposite to the current recommendations issued by national and international organizations. In the other hand, a substantial number of the patients have CVDs, that's why our results emphasize on increasing the use of those anti-diabetic medications having cardiovascular benefit (SGLT-2is and GLP-1RA) in T2D patients with concomitant CVDs, and also in T2D patients without CVDs in order to reduce the risk of getting CVDs.



Acknowledgements

Many thanks to the Laila Qasim and Cardiac Center-Erbil

Disclosure and conflict of interest

The authors declare that they have no conflicts of interest.



References

- 1 Tsao CW, Aday AW, Almarzooq ZI *et al.* Heart Disease and Stroke Statistics—2022 Update: A Report From the American Heart Association. *Circulation* 2022; **145**: (8). doi:10.1161/CIR.0000000000001052.
- 2 Fuchs FD, Whelton PK. High Blood Pressure and Cardiovascular Disease. *Hypertension* 2020; **75**: (2)285–292.
- 3 Coronado F, Melvin SC, Bell RA *et al.* Global Responses to Prevent, Manage, and Control Cardiovascular Diseases. *Prev Chronic Dis* 2022; **19**220347.
- 4 Roth GA, Mensah GA, Johnson CO *et al.* Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019. *J Am Coll Cardiol* 2020; **76**: (25)2982–021.
- 5 Rippe JM. Lifestyle Strategies for Risk Factor Reduction, Prevention, and Treatment of Cardiovascular Disease. *Am J Lifestyle Med* 2019; **13**: (2)204– 212.
- 6 Reed J, Bain S, Kanamarlapudi V. A Review of Current Trends with Type 2 Diabetes Epidemiology, Aetiology, Pathogenesis, Treatments and Future Perspectives. *Diabetes, Metab Syndr Obes Targets Ther* 2021; **Volume 14**3567–3602.
- 7 Galicia-Garcia U, Benito-Vicente A, Jebari S *et al.* Pathophysiology of Type 2 Diabetes Mellitus. *Int J Mol Sci* 2020; **21**: (17)6275.
- 8 Li M, Chi X, Wang Y *et al.* Trends in insulin resistance: insights into mechanisms and therapeutic strategy. *Signal Transduct Target Ther* 2022; **7**: (1)216.
- 9 Ormazabal V, Nair S, Elfeky O *et al.* Association between insulin resistance and the development of cardiovascular disease. *Cardiovasc Diabetol* 2018; **17**: (1)122.
- 10 Artasensi A, Pedretti A, Vistoli G *et al.* Type 2 Diabetes Mellitus: A Review of Multi-Target Drugs. *Molecules* 2020; **25**: (8)1987.
- 11 Kyrou I, Tsigos C, Mavrogianni C *et al.* Sociodemographic and lifestyle-related risk factors for identifying vulnerable groups for type 2 diabetes: a narrative review with emphasis on data from Europe. *BMC Endocr Disord* 2020; **20**: (S1)134.
- 12 De Rosa S, Arcidiacono B, Chiefari E *et al.* Type 2 Diabetes Mellitus and Cardiovascular Disease: Genetic and Epigenetic Links. *Front Endocrinol (Lausanne)* 2018; **9**. doi:10.3389/fendo.2018.00002.
- 13 Joseph JJ, Deedwania P, Acharya T *et al.* Comprehensive Management of Cardiovascular Risk Factors for Adults With Type 2 Diabetes: A Scientific Statement From the American Heart Association. *Circulation* 2022; **145**: (9). doi:10.1161/CIR.0000000000001040.
- 14 Cui J, Liu Y, Li Y *et al.* Type 2 Diabetes and Myocardial Infarction: Recent Clinical Evidence and Perspective. *Front Cardiovasc Med* 2021; **8**. doi:10.3389/fcvm.2021.644189.
- 15 Jensen ES, Olesen KKW, Gyldenkerne C *et al.* Cardiovascular risk in patients with and without diabetes presenting with chronic coronary syndrome in 2004– 2016. *BMC Cardiovasc Disord* 2021; **21**: (1)579.
- 16 Hayfron-Benjamin C, van den Born B-J, Maitland - van der Zee AH *et al.* Microvascular and macrovascular complications in type 2 diabetes Ghanaian residents in Ghana and Europe: The RODAM study. *J Diabetes*



-
- Complications* 2019; **33**: (8)572–578.
- 17 Armengol GD, Hayfron-Benjamin CF, van den Born B-JH *et al.* Microvascular and macrovascular complications in type 2 diabetes in a multi-ethnic population based in Amsterdam. The HELIUS study. *Prim Care Diabetes* 2021; **15**: (3)528–534.
 - 18 Ma C-X, Ma X-N, Guan C-H *et al.* Cardiovascular disease in type 2 diabetes mellitus: progress toward personalized management. *Cardiovasc Diabetol* 2022; **21**: (1)74.
 - 19 Patorno E, Htoo PT, Glynn RJ *et al.* Sodium–Glucose Cotransporter-2 Inhibitors Versus Glucagon-like Peptide-1 Receptor Agonists and the Risk for Cardiovascular Outcomes in Routine Care Patients With Diabetes Across Categories of Cardiovascular Disease. *Ann Intern Med* 2021; **174**: (11)1528– 1541.
 - 20 Marx N, Husain M, Lehrke M *et al.* GLP-1 Receptor Agonists for the Reduction of Atherosclerotic Cardiovascular Risk in Patients With Type 2 Diabetes. *Circulation* 2022; **146**: (24)1882–1894.
 - 21 Alyousif SMM, Aldokhel FT, Alkhanbashi OK *et al.* The Incidence of Congenital Heart Defects in Offspring Among Women With Diabetes in Saudi Arabia. *Cureus* 2021. doi:10.7759/cureus.14225.
 - 22 Darabi Z, Najafi F, Safari-Faramani R *et al.* Controlled direct effect of psychiatric disorders on cardiovascular disease: evidence from a large Kurdish cohort. *BMC Cardiovasc Disord* 2020; **20**: (1)501.
 - 23 Zhang R, Mamza JB, Morris T *et al.* Lifetime risk of cardiovascular-renal disease in type 2 diabetes: a population-based study in 473,399 individuals. *BMC Med* 2022; **20**: (1)63.
 - 24 Bueno Junior CR, Bano A, Tang Y *et al.* Rapid kidney function decline and increased risk of heart failure in patients with type 2 diabetes: findings from the ACCORD cohort. *Cardiovasc Diabetol* 2023; **22**: (1)131.
 - 25 Penno G, Orsi E, Solini A *et al.* Renal hyperfiltration is independently associated with increased all-cause mortality in individuals with type 2 diabetes: a prospective cohort study. *BMJ Open Diabetes Res Care* 2020; **8**:(1). doi:10.1136/bmjdr-2020-001481.
 - 26 Prevalence of type 2 diabetes associated complications ion Kurdistan Region Iraq.
 - 27 Mala Ahmed N, Dauod A, Sulaiman K. Perception of cardiovascular diseases among women attending primary health care centers in Erbil city, Iraq. *Zanco J Med Sci* 2022; **26**: (1)1–12.
 - 28 Abdulah DM, Miro SS. Prevalence and correlated factors for chronic total occlusion in patients with coronary artery disease in Iraqi Kurdistan. *Ann Clin Biomed Res* 2022; **3**: (1). doi:10.4081/acbr.2022.170.

