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Original article

Prevalence of cardiovascular events among patients with type 2 diabetes in the west region of Saudi Arabia

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ABSTRACT

Background: Diabetes mellitus (DM) remains a concern globally and particularly in Saudi Arabia, where its prevalence is continuously increasing among the Saudi population. DM is known to increase the risk of cardiovascular disease (CVD), which can progress significantly if DM is poorly controlled.
Aim: Determine the prevalence of cardiovascular events among patients with type 2 diabetes (T2DM) in the west region of Saudi Arabia, and additionally the use of antidiabetic agents with cardiovascular benefits (ADc) in T2DM patients with cardiovascular events (CVEs).
Method: A retrospective cohort study was conducted among all patients with T2DM who presented to the diabetic center of Prince Mansour Military Hospital (PMMH), Taif city, between the 1st of January and 30th of June 2021. Data extracted from patient medical records included demographics, home medications, medications used to treat T2DM, lab results, and ECG data. Descriptive statistics were used to analyze and compare the results. The study was approved by the Research and Ethics Committee of Medical Services General Directorate, Armed Forces Hospitals, Taif region.
Result: A total of 349 patients with T2DM were recruited and included in the final analysis. Of this study population, 132 patients had experienced at least one cardiovascular event while 54 were considered to be at risk of future cardiovascular events due to having risk factors for cardiovascular diseases above and beyond the presence of diabetes. A subgroup analysis was conducted to examine HbA1c% among all groups; interestingly, all were similar, with $p > 0.05$. Of all diabetic patients with CVEs, only 34.8 % were on at least one anti-diabetic agent known to have cardiovascular benefits; the remainder were on other anti-diabetic agents. A similar analysis was conducted on diabetic patients with risk of CVEs, of which only 13 % were on at least one anti-diabetic agent having known cardiovascular benefits; the remainder were on other anti-diabetic agents.
Conclusion: The prevalence of CVEs among T2DM patients in Saudi Arabia is very close to the global prevalence, but ADcs are underutilized in this population. Tighter glycemic control is warranted to help rein in and reduce the CVE incidence among patients with T2DM.

1. Introduction

According to data from the World Health Organization (WHO) on the prevalence of diabetes mellitus (DM), Saudi Arabia ranks second highest in the Middle East and seventh globally, with an estimated diabetic population of 7 million and a pre-diabetic population of around 3 million (Akbar et al., 2003, Al-Shammary 2007, Ahmed et al., 2013, Al Dawish et al., 2016, Al Slail et al., 2016). Notably, DM is associated with poor general health and lower quality of life, along with high mortality, high morbidity, and vascular complications (Fox et al., 2007, Leon and Maddox 2015). In partic-

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ular, DM increases the risk of cardiovascular disease (CVD), which can refer to numerous problems pertaining to the heart and blood vessels, including atherosclerosis, arrhythmia, heart attack, heart valve problems, heart failure, stroke, and cerebrovascular disease. CVD is also the primary cause of morbidity and mortality in diabetes patients, for whom the risk of cardiovascular death is about threefold greater for each risk factor than it is among people without diabetes (Fox et al., 2007, Al Slail et al., 2016, Pushkin et al., 2019).

For patients with type 2 diabetes (T2DM), in any given age group, the overall risk of CVD mortality is more than double that of non-diabetic patients (Akbar et al., 2003, Fox et al., 2007, Laakso 2010). The same is true for specific cardiovascular events such as stroke, coronary heart disease (CHD), myocardial infarction (MI), angina pectoris, and sudden death (Laakso 2010). For example, one study of death rates due to cardiovascular causes found that among patients with a history of MI, those with T2DM had a death rate of 42.0 %, while the rate in non-diabetic patients was 15.9 %; meanwhile, among patients with no prior MI, the death rates were 15.9 % for diabetic patients and 2.1 % for non-diabetics (Einarson et al., 2018). According to the American Diabetes Association, the main risk factors for coronary artery disease (CAD) that can and should be controlled are uncontrolled hypertension, uncontrolled cholesterol and high triglycerides, poor glycemic control, smoking, obesity, and insufficient physical activity (2020). Patients having diabetes in combination with one or more of these risk factors are more likely to experience cardiovascular events. Conversely, controlling these risk factors may avoid or delay the development of heart and blood vessel disease, and is especially important for patients with diabetes.

To the best of our knowledge, despite the high prevalence of diabetes in Saudi Arabia, no study exists concerning the prevalence of cardiovascular events among Saudi patients with type 2 diabetes. Existing studies have only considered the prevalence of cardiovascular risk factors (Akbar et al., 2003, Al Slail et al., 2016). The objectives of this study are to investigate the prevalence of cardiovascular events (CVEs) in patients with type 2 diabetes attending Prince Mansour Military Hospital, and to investigate the association of this prevalence with use of anti-diabetic medication.

2. Patients and methods

2.1. Study design

We conducted a retrospective cohort study among diabetic patients (30–90 years old) who presented to the diabetic center of Prince Mansour Military Hospital (PMMH), which specializes in the management of diabetic patients. The study used a single cohort design in light of the fact that at the time of recruitment, the study hospital was the only tertiary care and designated hospital for all diabetic patients' visits in the region. The study was approved by the Research and Ethics Committee of Medical Services General Directorate, Armed Forces Hospitals, Taif region (REC.T.2020–08-478).

2.2. Data source

Data extracted from patients' medical records and through face-to-face interviews included demographics, medications used to treat diabetes (including agents with cardiovascular benefits [ADcs] such as: empagliflozin, canagliflozin, dapagliflozin, ertugliflozin, dulaglutide, liraglutide, semaglutide, and saxagliptin), any other related or unrelated medications, dosing and frequency of medications, comorbidities including cardiovascular and non-cardiovascular diseases, lab electrolytes, and ECG data. Exclusion criteria included: non-Saudi, non-diabetic patient, gestational diabetes mellitus (GDM), type 1 diabetes mellitus (T1DM), and latent autoimmune diabetes in adults (LADA). A form developed in-house on the basis of previous studies was used to collect study data. Reference notes were taken on the hospital's protocols for managing T2DM, including national and international guidelines. All applicable measures were employed to ensure data integrity and privacy: assignment of numeric identifiers to participants, password protection of the database, and restriction of access to selected personnel having signed confidentiality agreements.

2.3. Sample size & sampling technique

Each year, approximately 2891 patients with T2DM visit the diabetic center clinics in PMMH. The prevalence of CVD in diabetic patients is assumed to be 32.2 %, consistent with the systematic review of worldwide evidence conducted by Einarson et al. (2018). The sample size needed to achieve 95 % confidence, accepting an error of 5 %, was determined to be 339 using the Roasoft online sample size calculator (Raosoft)Raosoft, 2020. To compensate for non-respondents and incomplete responses, a total of 350 patients were recruited for the study. The study sample was recruited over a one-year period, with patients selected each day from the diabetic center clinics in PMMH. All patients were available in light of the inclusion and exclusion criteria, based on the total number visiting each clinic daily.

2.4. Statistical analysis

Data analysis was carried out with SPSS (IBM® SPSS® Statistics 27) (Ji et al., 2020; IBM Corp. Released, 2020) and GraphPad Prism (RRID:SCR_002798) (Zhou et al., 2020). Data are presented as mean (SD) if continuous and n (%) if categorical. Univariate characteristics were summarized by means of descriptive statistics such as absolute counts and percentages. The *t*-test was used to determine the statistical significance of differences, taking $p < 0.05$ as the threshold.

3. Results

3.1. Study population and characteristics

From January 1, 2021 to June 30, 2021, 349 patients with type 2 diabetes were recruited; data from all of those patients were included in the final analysis. Patient characteristics are summarized and presented in Table 1. The mean age of participants was 62 years with standard deviation 12.2 years. Male patients accounted for 43 % of the study population. Hypertension and hyperlipidemia were experienced by around 53 % and 70 % of patients, respectively; in addition, nearly 66 % of patients were on metformin, while around 44 % were on insulin therapy. Lastly, the mean HbA1c% of patients was 8.9 % with standard deviation 2.1 %.

3.2. Prevalence of cardiovascular events in the study population

Of the study population, 132 patients (37.8 %) had experienced at least one cardiovascular event while 54 (15.5 %) were considered to be at risk of future cardiovascular events due to having risk factors for cardiovascular diseases above and beyond the presence of diabetes (Fig. 1). A subgroup analysis was conducted to examine HbA1c% among all groups; interestingly, all were similar, with $p > 0.05$ (Fig. 2).

Table 1
Patient Demographics.

Characteristics	No	%
Age (years), median (SD)	62 (12.2)	
Gender (male)	152	43
Co-morbidities		
Hypertension	187	53.5
Hyperlipidemia	244	69.7
Heart Failure with Reduced Ejection Fraction	2	0.5
Heart Failure with Preserved Ejection Fraction	1	0.2
Myocardial Infarction	1	0.2
Angina	2	0.5
CKD	12	3.4
Medications		
Metformin	231	66
Atorvastatin	19	5.5
Perindopril	84	24
Aspirin	140	40
Bisoprolol	25	7.14
Indapamide	48	13.7
Valsartan	30	8.5
Cholecalciferol	3	0.8
Vitamin B	7	2 %
Fenofibrate	22	6.2 %
Empagliflozin	24	6.8 %
Liraglutide	27	7.7 %
Furosemide	4	1.1 %
Pantoprazole	11	3.14 %
Insulin Glulisine	96	27.42 %
Valsartan	31	8.8 %
Vildagliptin	84	24 %
Insulin	62	17.17 %
Amlodipine	51	14.5 %
Spironolactone	8	2,2%
Glargine	155	44.2 %
Lab	**Mean (SD)**	
Hb1A1c (%)	8.9 (2.1)	
Potassium (mEq/L)	4.4 (0.5)	
Magnesium (mEq/L)	0.9 (0.7)	
Sodium (mEq/L)	137.2 (4.3)	
Calcium (mEq/L)	2.1 (0.5)	
High Density Lipoprotein (mg/dL)	47.7 (17)	
Low Density Lipoprotein (mg/dL)	78 (63.5)	
Total Cholesterol (mg/dL)	167 (44.6)	
Triglyceride (mg/dL)	66.6 (61.6)	
Creatinine Clearance (mL/min)	88.6 (73)	
Albumin/Urea (mg/day)	103.6 (209)	

3.3. Use of anti-diabetic agents in patients with or at risk of cardiovascular events

Of all diabetic patients with CVEs, only 46 (34.8 %) were on at least one anti-diabetic agent known to have cardiovascular benefits; the remainder were on other anti-diabetic agents (Fig. 3**, A**). Further analysis was conducted to compare those groups in terms of glycemic control, upon which no difference in HbA1c% was observed between the two groups ($p > 0.05$; Fig. 3**, B**).

A similar analysis was conducted on diabetic patients with risk of CVEs, of which only seven (13 %) were on at least one anti-diabetic agent having known cardiovascular benefits; the remainder were on other anti-diabetic agents (Fig. 4**, A**). Glycemic control was likewise analyzed, and yielded no difference in HbA1c% between the two groups ($p > 0.05$; (Fig. 4**, B**).

4. Discussion

In terms of diabetes prevalence, Saudi Arabia ranks second highest in the Middle East and seventh globally, with an estimated diabetic population of 7 million and a pre-diabetic population of around 3 million (Akbar et al., 2003, Al-Shammary 2007, Ahmed et al., 2013, Al Dawish et al., 2016, Al Slail et al., 2016)**.** Patients

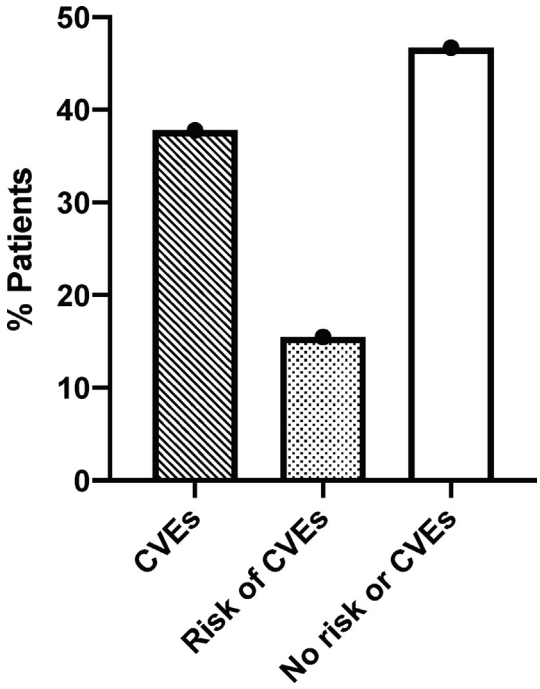

Fig. 1. Breakdown of diabetic patients with or without CVEs or risk of CVEs. Those with CVEs represented 37.8% of all patients, those with risk of CVEs represented 15.5%, and those with neither CVEs nor risk of CVEs represented 46.7%.

with diabetes mellitus are at increased risk of cardiovascular events (CVEs); however, despite the elevated prevalence of T2DM, the prevalence of CVE development in Saudi Arabia is not well known. This study aimed to determine the prevalence of CVEs among diabetic patients and to investigate their association with the use of anti-diabetic agents.

Our study population had a median age of 62 years, and 37.8 % had experienced at least one CVE. Interestingly, this proportion is very close to the prevalence of CVEs in several other populations. Einarson et al. estimated the global prevalence of CVD among adults with T2DM by reviewing literature published within the prior ten years (2007–March 2017) (Einarson et al., 2018). Their analysis included data from 57 articles for a total sample size of around 4,549,481 T2DM patients. Of the included patients, 52.0 % were male and 47.0 % were obese; the mean age was 63.6 ± 6.9 y ears old; and the mean T2DM duration was 10.4 ± 3.7 years. The authors found cardiovascular disease to impact 32.2 % of T2DM patients. Cardiovascular events commonly reported within that group included atherosclerosis (29.1 %; 4 studies, N = 1153), coronary heart disease (21.2 %; 42 studies, N = 3,833,200), heart failure (14.9 %; 14 studies, N = 601,154), angina (14.6 %; 4 studies, N = 354,743), myocardial infarction (10.0 %; 13 studies, N = 3,518,833), and stroke (7.6 %; 39 studies, N = 3,901,505). Overall, CVD was found to account for 50.3 % of deaths among T2DM patients, primarily driven by coronary artery disease and stroke; as such, it is the major cause of mortality in this population.

Numerous studies have demonstrated several anti-diabetic agents to have benefits for diabetic patients with CVEs, including the analogs of glucagon-like pepide 1 (GLP1) liraglutide (Marso et al., 2016, Gupta et al., 2017, Sattar et al., 2017, Nauck and Quast 2021) and semaglutide (Sattar et al., 2017, Nauck and Quast 2021)) and the SGLT2 inhibitors empagliflozin (Zinman et al., 2015, Fitchett et al., 2016, Sattar et al., 2017, Špinar et al., 2021) and canagliflozin (Neal et al., 2017, Sattar et al., 2017)). Therefore, it is strongly recommended to start diabetic patients having CVEs or CVE risk on one of these approved agents. In our

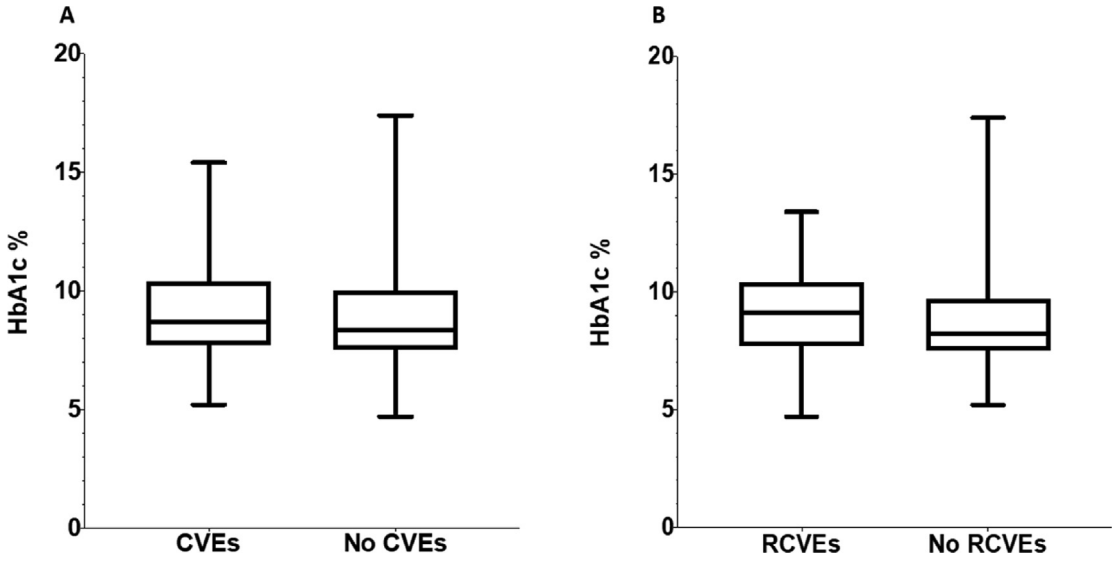

Fig. 2. HbA1c% among diabetic patients included in the study. (A) Box plot of HbA1c% among diabetic patients with CVEs and those without ($p > 0.05$). (B) Box plot of HbA1c% among diabetic patients with risk of CVEs (RCVEs) and those without ($p > 0.05$).

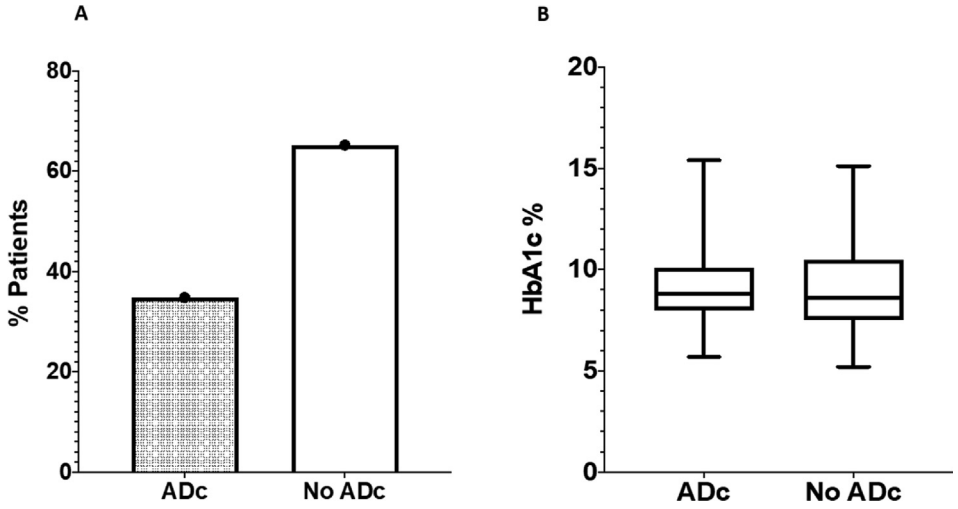

Fig. 3. Medication and glycemic control among diabetic patients with CVEs. (A) Percentage of patients with CVEs who were on anti-diabetic therapy with known cardiovascular benefits (ADc). (B) Box plot of HbA1c% values according to ADc grouping, showing no significant difference between the two groups ($p > 0.05$).

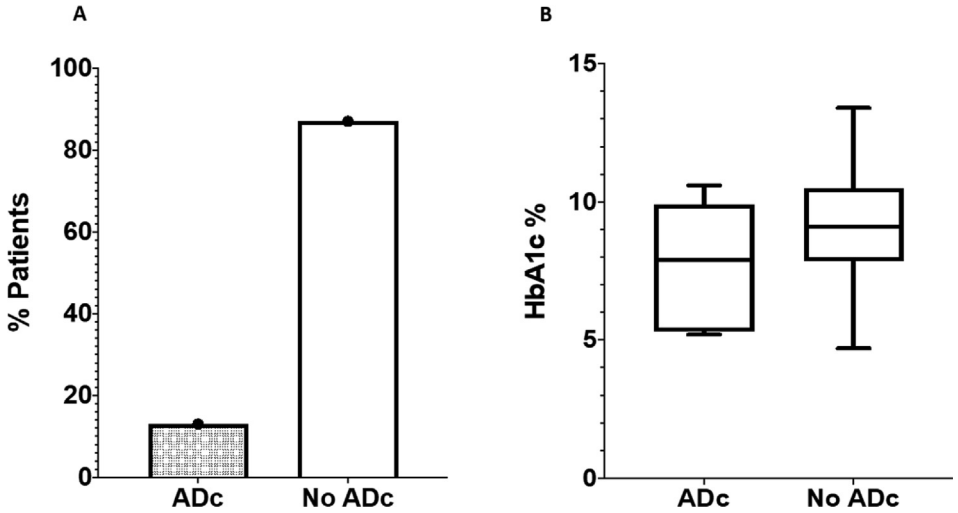

Fig. 4. Medication and glycemic control among diabetic patients with risk of CVEs. (A) Percentage of patients at risk of CVEs who were on anti-diabetic therapy with known cardiovascular benefits (ADc). (B) Box plot of HbA1c% values according to ADc grouping.

study, only 34.8 % of diabetic patients with CVEs and 13 % of those at risk of CVEs were on least one ADc. These low percentages might be attributed to several factors, including unavailability of some of these agents due to high expenses or to medication shortages resulting from the COVID-19 outbreak crisis. Another potential explanation is clinician preference in trying older agents that they are more accustomed to working with, as there is no data showing benefits in Saudi patients specifically. Increasing clinician awareness of these agents' benefits in this population as increased evidence becomes available would definitely help patients in optimizing management of their disease and gaining benefits relating to CVEs.

As this study was conducted during the COVID-19 pandemic, it was subject to limitations in patient access that hindered prospective data collection. Other limitations include its design as a single cohort study, the focus on a constrained population, the finite duration, the use of retrospective data, and the fixed composition of that data both in terms of demographic and clinical variables and due to recording only definite outcomes. A more inclusive study is merited to expand on the results of this work and generate conclusive evidence as to how the management of T2DM patients with CVEs is impacted by demographic and clinical variables.

In conclusion, the results of this study demonstrated the prevalence of CVEs in Saudi patients with T2DM to be close to the global prevalence. Additionally, the study revealed an underuse of ADcs in the clinical setting at the study center. Future studies with larger sample sizes are warranted to prove the benefits of CVEs for patients with T2DM in Saudi Arabia so as to encourage clinicians to optimize therapy and provide patients with the maximum possible clinical benefits. Lastly, more focus should be directed to T2DM patients at risk of CVEs to aid their glycemic control and prevent CVEs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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