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Original article

Physicians' choices in the first- and second-line management of type 2 diabetes in the Kingdom of Saudi Arabia

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ABSTRACT

Objectives: The DISCOVER study is a global, prospective, three- year- observational (non-interventional) study that was conducted in 37 countries throughout the world including Saudi Arabia and aimed to assess variations in treatment patterns and therapeutic outcomes in type 2 diabetic patients. The current manuscript is reporting data of DISCOVER study across different health sectors of various provinces in the Kingdom of Saudi Arabia.

Methods: In this study, 519 Saudi type 2 diabetics, non-insulin users, aged 18 years or older, initiating second line therapy, were selected from nine health institutes, in four out of five provinces in Saudi Arabia. Data was collected at baseline (initiation of 2nd line therapy) by the treating physician using an electronic case report form (eCRF) via a web-based data capture system. Each selected subject was asked to complete four self-administered questionnaires.

Results: The mean age of the studied population was 52.4 ± 11 years. Among the subjects selected from the nine medical centers, 55% were men, with almost 65% between the ages of 46 and 65 years. The oral agent used as 1st line in the majority of patients was metformin, prescribed in 89.2% of the study cohort. In the second line, sitagliptin was the most frequently used, at 61.8%. followed by gliclazide, glibenclamide, and glimepiride at 35.6%, 13.1%, and 12.7%, respectively.

Conclusion: Metformin, with or without sulfonylureas, is the most commonly prescribed first-line treatment for patients with type 2 diabetes, managed either in governmental institutions, or in the private sector. The most common second line drugs were DPP4 inhibitors, mainly sitagliptin, followed by the third and second generation of sulfonylureas. Drug affordability was not an issue, since the vast majority of the patients received medication free of charge.

1. Introduction

The management of patients with type 2 diabetes relies on many factors, including the physician's knowledge, institutional practice, and on national and international management guidelines. Physicians' choices in drug selection are affected by their experience, drug efficacy, safety, tolerability, availability and by patient-satisfaction (Zafar et al., 2015).

The consensus statement of the American Diabetes association (ADA), and the European Association for the Study of Diabetes

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(EASD) guidelines recommend metformin in conjunction with lifestyle modification as a first-line treatment option for type 2 diabetic patients (Davies et al., 2018). However, in some countries, such as the United States, and Italy, about 40% of patients received an initial oral antidiabetic (OAD) agent, rather than metformin (Berkowitz et al., 2014; Desai et al., 2012; Rafaniello et al., 2015).

Treatment intensification through introduction of second-line glucose lowering agents is recommended if glycemic control is not achieved within 3 months of initial therapy (Inzucchi et al., 2015). There are several second-and subsequent-line therapies that could be used for treating type 2 diabetic patients, however, there is no clear consensus on the optimal treatment regimen among those patients (Nathan et al., 2009). Since the majority of diabetic patients are treated by primary health care physicians (Davidson, 2010), studies on drug utilization patterns are needed, to discover actual prescription patterns among type 2 diabetics. It will also provide an insight into the different patient, physician, and system level factors that are responsible for the lack of timely treatment initiation, and intensification.

As a part of a multinational study DISCOVER study was conducted in 37 countries, including four different provinces of the Kingdom of Saudi Arabia, aiming to describe the patterns of management, and the clinical status, of type 2 diabetic patients starting second line oral antidiabetic drugs, either as monotherapy, or in combination. This study also aims to evaluate the effect of management on patients' outcomes, including: glycemic control, incidence of both, microvascular and macrovascular complications, and hypoglycemic episodes.

2. Methods

2.1. Study design and participants

In this manuscript we are reporting the data of the enrolled 519 Saudi type 2 diabetic, who were non-insulin users, aged 18 years or older, switching over to second line therapy, were selected from nine health institutes, in four out of five provinces in Saudi Arabia. Out of the selected cohort, 15 patients were excluded: 10 patients withdrew their consent, 2 lost of follow up, and 1 had missing data. Two more patients were excluded for other reasons as shown in Fig. 1.

The participating medical institutes were classified into three sectors: the first was the Ministry of Health (MOH) sector that included the King Salman bin Abdul-Aziz Hospital (76 patients), the Prince Mutaib bin Abdul-Aziz Hospital (93 patients), the Aseer General Hospital (60 patients), and the Al-Thager Hospital (24 patients). The second sector included non-MOH hospitals, namely, the University Diabetes Center (62 patients), the King Khalid University Hospital (66 patients), and the Armed Forces Hospital in the southern region (101 patients). The third sector was the private health sector, where patients were recruited from the Saudi German hospital (24 patients), and The International Medical Center (13 patients). All patients consented to be enrolled in this study.

This study was reviewed and approved by the Institutional Review Board, College of Medicine, King Saud University, for the university hospitals, by the Institutional Review Board of King Fahad Medical City for the MOH hospitals, and the International Medical Center Ethics Committee for the International Medical center, and the Armed Forces Hospital, southern region. The Saudi German Hospital Local Ethics Committee reviewed and approved the study, for the Saudi German Hospital.

2.2. Data collection

Data were collected by the treating physician using an electronic case report form (eCRF) via a web-based data capture system. Data were immediately saved to a central database, and all eCRFs were checked to ensure that they were completed appropriately. Demographic data including the age, gender, health insurance, social history, educational level, and working status was collected during the initial visit. All anthropometric measurements, including the height, weight, and waist circumference, were retrieved from the medical chart, or measured, during this initial visit. The systolic and diastolic blood pressure was measured in sitting position, using the hospital's electronic sphygmomanometer. The medical history of type 2 diabetes, the presence of comorbidities, and information on non-diabetes related medications, were also collected. The metabolic parameters, including glucose, glycosylated hemoglobin (HbA1c), lipids, and uric acid, were collected from the patients' charts.

Each selected subject was asked to complete four self-administered questionnaires, which included the Medical Outcomes Study Questionnaire Short Form 36 health survey version 2 (SF-36 v.2), (Guermazi et al., 2012) which is used to measure general health status across eight domains: vitality, physical function, body pain, general health perceptions, physical function, emotional function, social function, and mental health. Scores range from 0 to 100, 0 indicating the less favorable health status and 100 the most favorable one. The second questionnaire used, was the revised Hypoglycemia Fear Survey (HFS-II), (Gonder-Frederick et al., 2011) a 33-item survey using five-point Likert scales (score range 0–132), which was used to assess the behavior, and worries, relating to the fear of hypoglycemia. The respondents rank the responses on a 5- point Likert scale from 0 (never) to 4 (always). Higher scores indicate increased fear of hypoglycemia. The third questionnaire was a seven-item questionnaire, that was used to assess patients lifestyles, categorized as unhealthy, intermediate, healthy, or very healthy, based on questions related to smoking, alcohol intake, physical activity, and diet. The two-item questionnaire related to health avoidance due to cost, was the fourth questionnaire. For each patient, the treating physician was asked four questions, related to the patients' first–and second-lines of therapy. The question included the: nature of changes made in patients' first-line therapy, the reasons for change of first-line therapy, the name of the class or classes of drugs prescribed for second-line therapy, and the products that the physician prescribed as second-line therapy and reasons for choosing the second-line therapy.

A total of 519 Saudi type 2 diabetic patients were enrolled, of which 354 (68.2%) were from the MOH sector, and 128 (24.7%) from the non-MOH governmental sector. The remaining 37 (7%) were from private sectors. After excluding 15 patients, only 504 patients completed the baseline evaluation.

2.3. Statistical analysis

Descriptive and frequency analyses were used to assess clinical and demographic data in all participants, and different subcategories. Categorical data are presented as numbers and percentages. Mean (standard deviation [SD]) values, median (interquartile range [IQR]) values are reported, when appropriate. Data from each domain of the SF-36 were analyzed for the descriptive statistics of mean with standard deviation, median with interquartile range. All statistical analysis was performed using the SAS statistical software system (SAS institute, Inc, Cary, NC).

3. Results

The mean age of the selected subjects from the nine medical centers was 52.4 ± 11 years. A total of 55% were men and more than 64.6% of the study population was between the ages of 46 and 65 years. Most of the patients lived with their families and

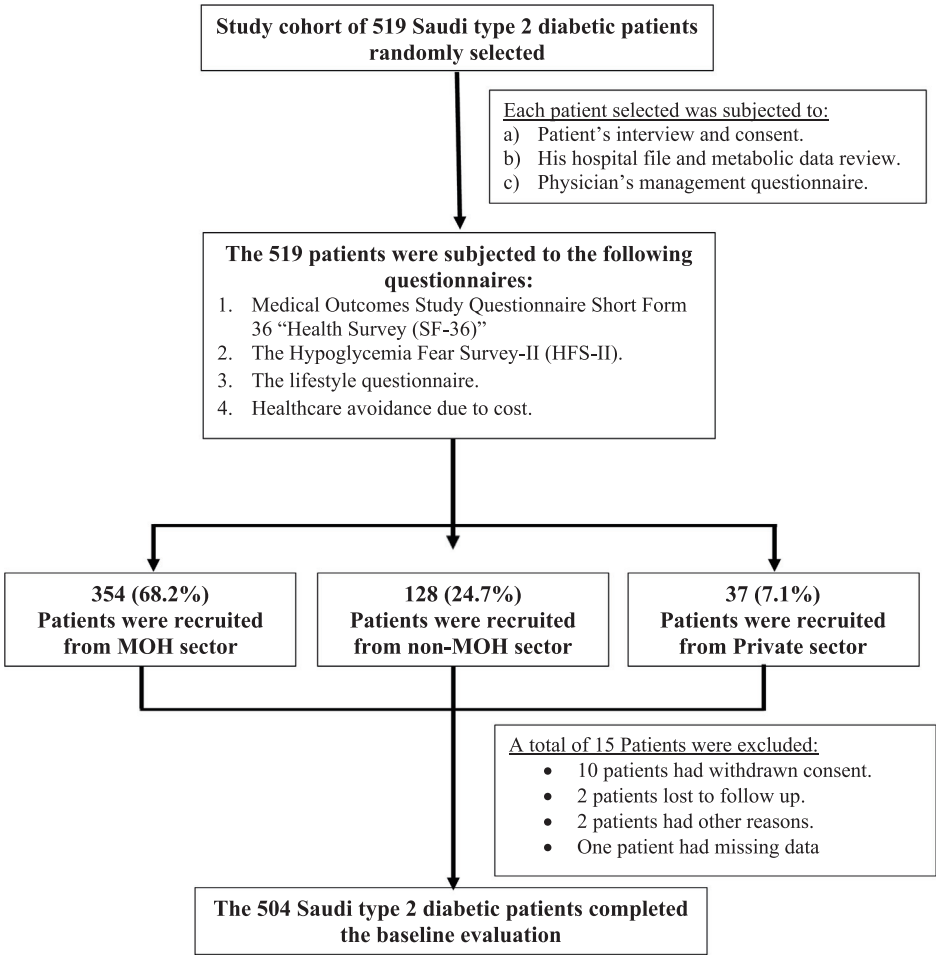


Fig. 1. Study Flow chart.

had either primary or secondary educational level. A total of 92.6% were managed by public (governmental) health institutes. Among the study cohort, around 40% were employed, and the rest were unemployed, or retired; 20% had a current or past history of smoking tobacco, and 2% were either or former alcohol drinkers. The mean body mass index (BMI) was 31.9 ± 6.6 kg/m^2, and the mean duration of diabetes was 6.4 ± 5.2 years.

The metabolic control of the study cohort, as shown in Table 1. The mean HbA1c level was 8.8 ± 1.7%, with fasting blood glucose (FBG) levels of 186.9 ± 65.5 mg/dL. The mean total cholesterol levels were 190 ± 52.7 mg/dL, while the mean level of triglycerides was 190.7 ± 160.5 mg/dL. The mean LDL-cholesterol levels were 112 ± 35.7 mg/dL.

Coronary artery disease was found in 7.3% of the cases, with 1.5% reporting previous episodes of acute myocardial infarction, and a history of angina in 2.3%, while 0.8% had developed atrial fibrillation, and 1.5% complained of congestive heart failure. A total of 3.3% of the cardiac patients were managed with Percutaneous Coronary Intervention (PCI), of which 52.9% required stent placement, and 0.6% were surgically managed with coronary artery bypass surgery (CABG).

Transient ischemic attack was reported in 0.8% of the studied cohort, while 2.3% had strokes, mainly of an ischemic nature. Only two patients (0.4%) required carotid stents. None of the studied patients had a history of diabetic foot, or amputation. Diabetic nephropathy and retinopathy were noted in 0.6% and 3.9% of the cases, respectively. Neuropathy was reported in 11.4%, which was mostly peripheral neuropathy; while 6% complained of erectile dysfunction.

Table 2 demonstrates the frequency of use of different oral antidiabetic drugs as first-line therapy. Metformin was the most commonly used oral agent, being prescribed in 89.2%. Among sulfonylurea group, gliclazide was the most prescribed, at 21.6%, followed by glibenclamide at 18.9%. Glimepiride, glipizide and glyclopyramide were the least frequently prescribed sulphonylureas. Among the dipeptidyl peptidase 4 (DPP4) inhibitors, sitagliptin, vildagilptin, and saxagliptin were the most frequently prescribed, at a frequency of 6.2%, 1.9%, and 1.2% respectively. Linagliptin was not used as a first-line drug. Pioglitazone was the only thiazolidinedione drug prescribed as a first-line, at rate of 0.4%. Other oral antidiabetic agents, like alpha glucosidase inhibitors, and meglitinides were not prescribed as a first-line (see Table 3).

In the second line, sitagliptin was most commonly prescribed either alone or as an addition to the previous treatment at 61.8%, followed by gliclazide at 35.6%, and glibenclamide, at 13.1%. Glimepiride was the least prescribed with 12.7% of the studied population. The use of insulin as a second line, whether basal, or premixed, was noted in less than 8% of cases.

In terms of drug availability and restrictions, metformin had 100% availability, without any restrictions, while the availability of sulphonylureas was varied. Availability was more than 90% for gliclazide, glibenclamide, and glimepiride, with no restrictions for gliclazide. Glibenclamide, and glimepiride were slightly restricted. More restrictions were noted with both glipizide, and glycopyra-

Table 1
The mean (±SD) and percentage of clinical and metabolic characteristics of the study cohort at the baseline.

Variable	Value
Number of participants	504 (100%)
Mean age ± SD (years)	52.4 ± 11.0
<25 years	3 (0.5%)
25–45 years	127 (24.5%)
46–65 years	335 (64.6%)
>65 years	54 (10.4%)
Gender (Men/Women)	284/235 (1.2:1)
Private health insurance	25 (5.2%)
Public /governmental	452 (92.6%)
Mixed	8 (1.6%)
Smokers	103 (20.0%)
Alcohol drinker	10 (2.0%)
Living alone	7 (1.5%)
Illiterate	91 (18.6%)
Primary (1–6) years of education	111 (22.7%)
Secondary (7–13) years of education	173 (35.5%)
University or higher education (>13 years)	113 (23.2%)
Employed	187 (38.9%)
Self-employed	18 (3.7%)
Unemployed	194 (40.3%)
Retired	82 (17.0%)
Height (cm)	16.2 (±9.6)
Weight (Kg)	83.4 (±17.6)
Waist circumference (cm)	104.1 (±14.4)
BMI (Kg/m^2)	31.9 (±6.6)
Systolic blood pressure (mmHg)	133.7 (±17.5)
Diastolic bold pressure (mmHg)	79.2 (±10.9)
Diabetes duration (years)	6.4 (±5.2)
HbA1c (%)	8.8 (±1.7)
FPG (mg/dL)	185.9 (±65.5)
RBG (mg/dL)	227.0 (±79.2)
PPG (mg/dL)	256.2 (±78.5)
HDL Cholesterol (mg/dL)	44.0 (±11.5)
LDL Cholesterol (mg/dL)	112.0 (±35.7)
Total Cholesterol (mg/dL)	190.0 (±52.7)
Triglycerides (mg/dL)	190.7 (±160.5)
Albumin/creatinine ratio (mg/g)	45.3 (±62.6)
Serum creatinine (mg/dL)	1 (±1.2)
Urinary albumin (mg)	51.3 (±90.9)
Uric acid (mg/dL)	4.7 (±1.3)

mide, and they were less available. Except for sitagliptin, which had almost 100% availability with only one case of restrictions, the DPP4 inhibitors were not available in almost 30% of the institutions. There were some restrictions on the availability of thiazolidinediones, and pioglitazone, in particular was widely available. Alpha-glucosidase inhibitors were not available in about 15% of the institutions which is the same case for rapiglinides and both were not restricted in more than 80% of cases. The GLP-1/incretin mimetics were largely non-restricted and were available in more than 60% of the institutions. Various types of insulin were widely available with no restriction for use.

Fig. 2 shows the pattern of first-line treatment, monotherapy with metformin was used in 47% of the cases, while sulfonylureas and DPP-4 inhibitors were prescribed alone in 7.5% and 0.6%, respectively. Combinations of biguanides with other oral agents were variable, with the highest number of combinations with sulphonylureas at a rate of 36.3%, followed by DPP4 inhibitors, at 4.4%. For triple therapy, biguanides were mostly combined with sulphonylureas and DPP4 inhibitors, in 3.1%. Fixed dose combinations with sulphonylureas were being taken by 2.7%. Combinations of sulfonylureas and thiazolidinediones were less common, with the prescription rates of fixed dose combinations being 0.6% and 0.2%, respectively.

Fig. 3 represents the percentage different oral hypoglycemic drugs combination used as a second line management according to their subgroups. Monotherapy with biguanides (usually metformin) was used in 2.2% as second line therapy. Combinations of biguanides with sulfonylureas and with DPP4 inhibitors in the second line, was noted in 4.6%, and 16.6%, respectively. Sulfonylureas were used alone in 8.7%, and in combination with thiazolidinediones in 0.6% of the patients. The DPP4 inhibitors were the most frequently used oral agent as a second line at a rate of 29.5%. These agents were also used as combinations with both, metformin, and sulfonylureas in 14.9%. Triple therapy in the second line, constituting of metformin, sulfonylureas, and thiazolidinediones, was noted in 0.2%. Alpha-glucosidase inhibitor were chosen as a single second line oral agent in 0.6%. In general, monotherapy versus triple drug,

Table 2
Frequency of different oral hypoglycemic drugs registered in Saudi Arabia used as a first- or second-line management in addition to their availability or restriction.

Medication classes	Drug name	Management choice		Drug availability and restriction		
		First lineNumber (%)	Second line Number (%)	Not restricted Number (%)	Restricted Number (%)	Not available Number (%)
Biguanides	Metformin	463 (89.2)	475 (91.5)	519 (1 0 0)	0 (0)	0 (0)
Sulfonylurea	Gliclazide	112 (21.6)	185 (35.6)	518 (99.8)	1 (0.2)	0 (0)
	Glibenclamide (Glyburide)	98 (18.9)	68 (13.1)	510 (98.3)	1 (0.2)	8 (1.5)
	Glimepiride	32 (6.2)	66 (12.7)	473 (91.1)	1 (0.2)	45 (8.7)
	Glipizide	3 (0.6)	12 (2.3)	330 (63.3)	1 (0.2)	188 (36.2)
	Glyclopyramide	1 (0.2)	1 (0.2)	341 (65.7)	0 (0)	178 (34.3)
DPP-4 inhibitors	Sitagliptin	32 (6.2)	321 (61.8)	518 (99.8)	1 (0.2)	0 (0)
	Veldagliptin	10 (1.9)	24 (4.6)	371 (71.5)	1 (0.2)	147 (28.3)
	Saxagliptin	6 (1.2)	38 (7.3)	402 (77.5)	2 (0.4)	115 (22.2)
	Linagliptin	Not used	1 (0.2)	329 (63.4)	1 (0.2)	189 (36.4)
Thiazolidinedione/ glitazones	Pioglitazone	2 (0.4)	23 (4.4)	517 (99.6)	1 (0.2)	1 (0.2)
	Rosiglitazone	Not used	1 (0.2)	330 (63.6)	0 (0)	189 (36.4)
Alph-glucosidase inhibitors	Acarbose	Not used	5 (1.0)	440 (84.4)	2 (0.2)	77 (14.8)
Meglitinides/Glinides	Repaglinide	Not used	3 (0.6)	443 (85.4)	0 (0)	76 (14.6)
Incretin mimetics/GLP1	Exenatide	Not used	2 (0.4)	327 (63.0)	1 (0.2)	191 (36.8)
	Liraglutide	Not used	2 (0.4)	427 (82.3)	1 (0.2)	91 (17.5)
Insulin	Premix Insulin	Not used	15 (2.9)	517 (99.6)	2 (0.4)	0 (0)
	Basal Insulin	Not used	29 (5.6)	518 (99.8)	1 (0.2)	0 (0)
	Basal/Bouls insulin	Not used	2 (0.4)	518 (99.8)	1 (0.2)	0 (0)

The following drugs were not included since they were not available either in the institution or the Saudi market: Albiglutide, Alogliptin, Anagliptin, bromocriptine, canagliflozin, colesevelam, dapagliflozin, dulaglutide, empagliflozin, exenatide QW, gemigliptin, gliquidone, glisoxepide, lixinatide, lobeglitazone, miglitol, mitiglinide, nateglinide, teneligliptin, tolbutamide, vildagliptin, voglibose.

Table 3
Results of the Medical Outcomes Study Questionnaire Short Form 36 and the Hypoglycemia Fear Survey-II surveys.

Score parameter	Score result Mean (±SD)	Score result Median (IQR)
Medical Outcomes Study Questionnaire Short Form 36 "Health Survey (SF-36)"		
Physical function	48.5 (±8.4)	49.9 (44.1–55.7)
Role physical	48.5 (±8.5)	49.4 (39.5–75.1)
Bodily pain	50.6 (±9.2)	50.6 (41.9–60.9)
General health	52.2 (±7.8)	53.1 (46.4–58.8)
Vitality	51.9 (±7.3)	52.8 (47.4–58.3)
Social function	49.2 (±8.4)	51.8 (41.9–56.7)
Role emotional	44.9 (±11.6)	48.0 (32.7–55.6)
Mental health	47.8 (±9.4)	47.8 (40.4–55.2)
Physical component	51.0 (±7.0)	51.9 (47.0–56.0)
Mental component	47.4 (±9.1)	48.6 (40.9–54.4)
The Hypoglycemia Fear Survey-II "HFS-II"		
Behaviors	7.2 (±11.6)	0.0(0.0–11.0)
Worries	6.4 (±11.9)	0.0(0.0–7.0)
Behaviors and worries	13.0 (±21.5)	0.0(0.0–17.0)

and four drug therapy were found in 3%, 2.6%, and 1.1%, respectively. Monotherapy of insulin was chosen as a second line in 8.7% of the cases (see Fig. 4).

The main reason for switching over from first-line anti-diabetic medication was the lack of efficacy, in 93.5%; the next most common reason being weight gain at 5.7%. The physician's preference and occurrence of hypoglycemic events, contributed for 4.6% and 2.4% of the changes, respectively. Adverse events, tolerability issues, and drug interactions contributed to 2.1% of reasons for switching from first to second line. In rare instances, convenience issues, or patients' requests were the reasons fro changing first-line anti-diabetic medication (Appendix A).

For physicians, the reasons that directed them for switching to second line were mostly for better efficacy in 71.6% or better tolerability in 30.8%, while 20.3% were looking for a beneficial effect on weight. and 17% were aiming to reduce the risk of hypoglycemia. Drug convenience and comfort were the reason for prescription modification in 1.8% of subjects. Patients requested second line

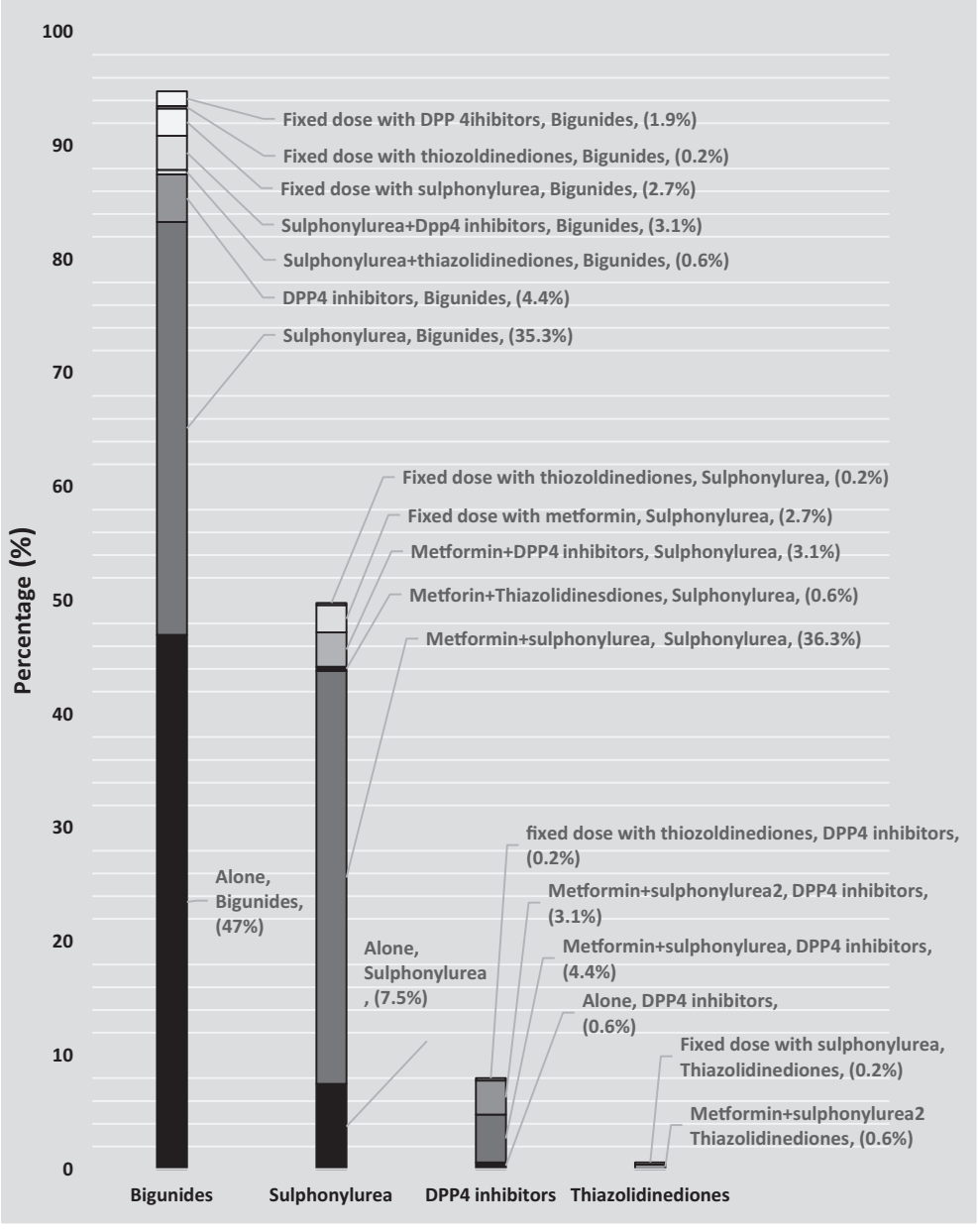


Fig. 2. The percentage of different oral hypoglycemic drugs used as a first line management according to their classes.

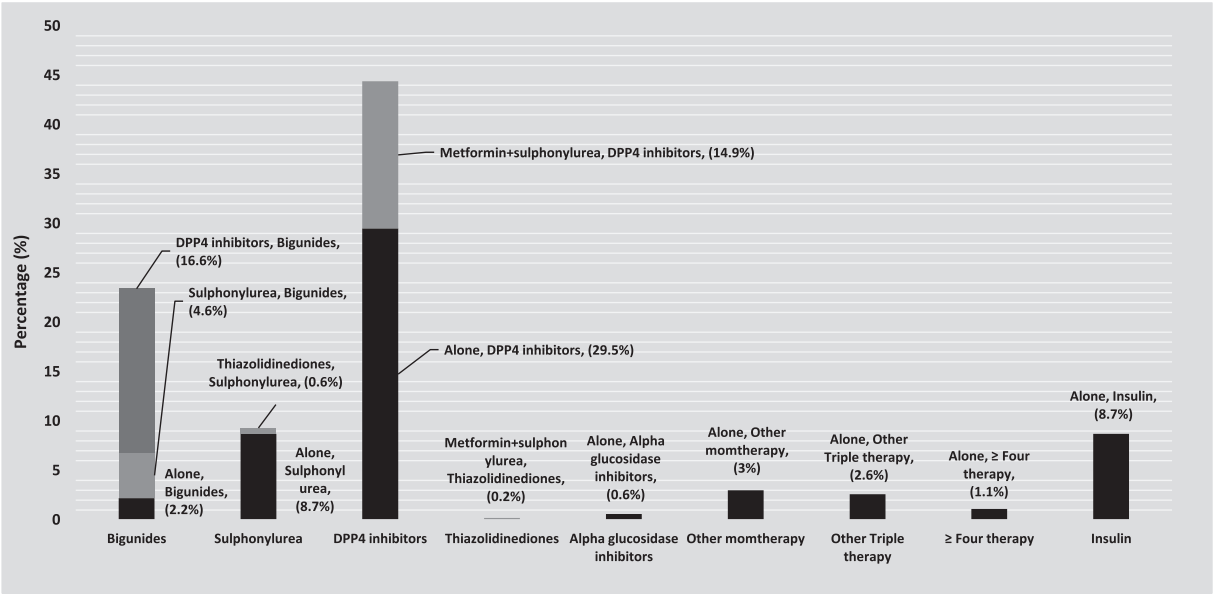
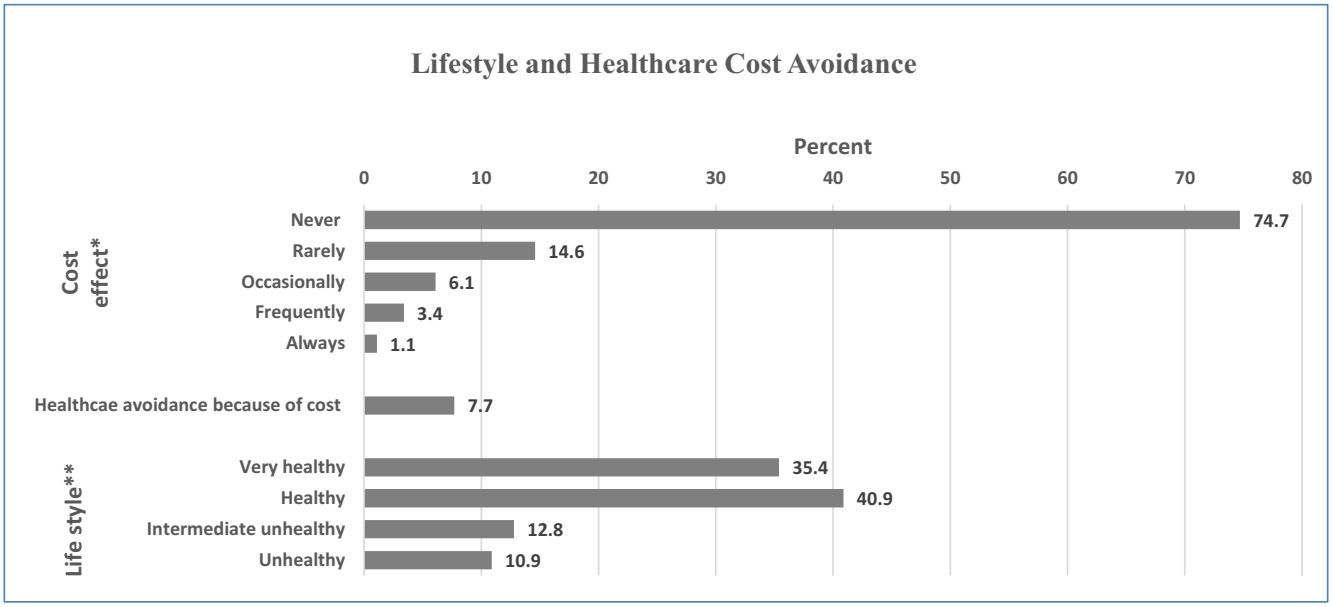


Fig. 3. The percentage different oral hypoglycemic drugs combination used as a second line management according to their subgroups.



*In the past year, how often have you not taken a medication that your doctor prescribed because of the cost?
**Using the following score: (0-2) unhealthy, (3) intermediate unhealthy, (4-5) healthy, (6-7) very healthy.

Fig. 4. The Lifestyle and Healthcare Cost Avoidance survey results in the study cohort at the baseline.

medications in 1.5%, while 0.8% and 0.2% had an access or affordability reasons i respectively.

The Medical Outcomes Study Questionnaire using short form-36 (SF-36), revealed the scores for all items including: physical, social, and mental mean scores were scoring between 44% and 52%, which was similar to the median score. The Hypoglycemia Fear Survey–II demonstrated a mean score of 7.2 ± 11.6 for behavior, and 6.4 ± 11.9 for worries, increasing to 13 ± 25, for both. The lifestyle scoring showed 40.9% to be healthy, and 35.4% to be very healthy. The current study assesses the health care cost avoidance score in the total selected cohort where it was 7.7%.

4. Discussion

The DISCOVER study program aims to describe type 2 diabetes management patterns, and both first, and second line glucose lowering therapy choices in routine clinical practice, in 38 countries across the globe. Saudi Arabia contributed to 3.2% of the total study population. The selected sample from Saudi Arabia presented in this study represented the normal distribution of type 2 diabetic patients in this community (Al-Rubeaan et al., 2013), with respect to gender, age groups, geographical areas (rural and urban), and health sectors (private or public,), varying only in terms of drug

availability, and adherence to management guidelines. Since health care is mostly free in this country (Walston et al., 2008), more than 90% of the patients were managed with the medications available in different governmental health institutions (Davies et al., 2018). This might have affected the choice of both, first and second line drugs, as shown in the results section.

The selected cohort had a mean duration of diabetes of six years, and a mean HbA1c level of 9%, which is higher than that reported from Germany, but almost similar to that from the UK (Khunti et al., 2018).[14] Among the patients studied, the rate of both cardiovascular and cerebrovascular complications were lower than the values reported among type 2 diabetic patients in this community (Al-Nozha et al., 2004). This was also true for both, diabetic nephropathy, and retinopathy (Abu El-Asrar et al., 1999; Alwakeel et al., 2008). This could be due to underdiagnosis of these complications, owing to the lack of proper screening, or due to errors in documentation or different population characteristics. Additionally, the shorter mean duration of diabetes may have contributed to the lower rates of both micro- and macrovascular complications.

The most commonly used oral agent in the first-line was metformin, either alone in about 50% of the cases, or in combination, particularly with a sulfonylurea. This trend was similar to that reported from countries like India and the United States (Boccuzzi et al., 2001; Das et al., 2011). This could be due to the fact that metformin and sulfonylurea are known for their low prices and availability and been recommended as first line medications in both ADA and EASD guidelines. (Davies et al., 2018). Sulfonylureas were the second most commonly used drugs as a first-line choice. Prescription rates in combination with metformin approached 50%. They were also prescribed as a single oral agent in 10%. Although similar trends were observed in most clinical studies, particularly in Europe (Overbeek et al., 2017), researchers from Taiwan have reported sulfonylurea as the most commonly prescribed drug in their country, followed by biguanides (Maguire et al., 2014). In Saudi patients, the DPP4 inhibitors are mainly used as a combined oral therapy with metformin, or with metformin and sulphonylurea, almost 10%. It is used as a single oral agent in less than 1%. These are similar to the observed in the United Kingdom, and Spain, where the use of DPP4 inhibitors reaches up to 9%. However, this was less than the rate of 27%, reported from France (Overbeek et al., 2017). Possible reasons could have been the late availability of DPP4 inhibitors in the Saudi market. Thiazolidinediones are the least frequently used oral agents, either alone, or in combination with metformin and sulphonylurea. This is in accordance with the decreased worldwide trend of the use of thiazolidinediones, especially after the global withdrawal of rosiglitazone, and subsequent negative impression about the whole class.

Compared to other countries, our findings show that first line management using metformin alone is less than what has been observed from other countries (Maguire et al., 2014). This could be explained by the fact that most of our recruited patients were from tertiary centers that usually receive referred and more advanced cases. This could also be due to a higher use of sulphonylurea and metformin combinations, which were higher than what has been observed in other countries. The practice of prescribing sulphonylurea in higher percentage in Saudi Arabia could be a result of its wide availability at governmental institutions being produced locally and for its low price compared to other oral agents. This could also be exaggerated by physicians following the local guideline adopted in the Kingdom.

In the second line, DPP4 inhibitors, either alone, or in combination with metformin or sulphonylurea, were the most commonly prescribed drug. This trend was also observed in France, where the use of DPP4 inhibitors as a second line medication was reported in 41% cases in the second line (Overbeek et al., 2017). This could be due to the strong marketing, drug availability, high tolerability and the promising effects of this new class as a second line. Biguanides, alone, or in combination with sulfonylurea or DPP4 inhibitors were most prescribed in the second line in our cohort. Sulphonylureas, either in monotherapy or in combinations with thiazolidinediones are the third most prescribed second line class, this is contrary to the findings in other countries, where sulfonylureas are the commonly used second choice (Chiang et al., 2006). However, this pattern could be suitable for the Saudi population, which is known for higher rates of obesity, and consequently, higher insulin resistance. This would explain the physicians' intention to enhance insulin secretion using DPP4 inhibitors, which are associated with lower rates of hypoglycemia and weight gain, compared with sulfonylureas (Dicker, 2011).

In a national survey that was conducted to assess how doctors choose medication to treat type 2 diabetes, total of 886 specialists and general physicians who were members of either the Society of General Internal Medicine or the American Diabetes Association were assessed. The three major considerations were found to be patients' health status, the extent of HbA1c elevation, and patients' weight (Grant et al., 2007). In the current study, the reasons for changing first-line antidiabetic medication are mainly lack of efficacy, or secondary failure of oral medication in achieving the target HbA1c levels. Weight gain, as a result of fluid retention, was found to be the reason for change of pioglitazone (thiazolidinediones). Physician preference and hypoglycemic events were less frequent reasons to change first-line therapy. Reasons related to drug accessibility, and affordability were not frequent as more than 90% of the study population comprised patients from governmental institutions providing free healthcare. Change in first-line medication owing to issues related to drug interactions, contra-indications, or patients' preferences were least reported.

When choosing second line medication, seeking for an effective drug was found to be the most frequent reason, followed by tolerability, and weight management benefits. Around 20% switched to second line therapy in order to reduce the risk of hypoglycemia. It has been observed that patients in healthcare plans with lower out-of-pocket costs were generally less likely to receive newer second-line medication classes, such as DPP4s, glucagon like peptide-1 (GLP1s), and sodium-glucose cotransporter-2 inhibitors (SGLT2s), and were more likely to receive cheaper drugs or those that have been on the market for longer (Ackermann et al., 2017). However, in this study, lack of access, and high cost were not frequent reasons for switching to second line therapy.

The Medical Outcome Questionnaire SF-36 in its short form indicated similar average scores for physical function, body pain, and vitality as that of social function, and mental health. These findings will be reassessed during subsequent visits and will be compared with findings from other countries. Since all selected patients were type 2 diabetic patients, the HFS-II score for hypoglycemia was expected to be low, as both patients' behavior and worries, were not expected. The lifestyle and healthcare avoidance questionnaire revealed that around 80% of subjects were very healthy or healthy, and that only around 8% had avoided healthcare because of costs. In more than 70% of cases, cost was not a reason for poor compliance to medication, because of the free health care system in the Kingdom of Saudi Arabia (Gonder-Frederick et al., 2011).

4.1. Strengths and limitations

The main limitation of this study is that the diagnosis of the complications was based on the judgment of the investigator. This may have led to misclassification, underestimation, or overestimation of complication rates. Another limitation of the study was the

reliance on the patients' medical records, which show the prescription rather than the compliance to medication. The records were used with the assumption that the patients had complied with the prescribed medication. Conversely, the main strength of this study was the use of a standardized case report form, which facilitated consistent data collection. The study data relied on a large representative cohort since it included patients from different health sectors, in different regions in the Kingdom.

5. Conclusion

In conclusion, patients with type 2 diabetes managed either in governmental institutions, or in the private sector, were using metformin more frequently as first-line treatment, with or without sulfonylureas. DPP4 inhibitors were less frequently used in the first-line. Meglitinides, GLP-1, and alpha-glucosidase inhibitors, were not considered as first-line therapy in the Kingdom of Saudi Arabia. The most commonly used second line drugs were DPP4 inhibitors, mainly sitagliptin. Sulfonylureas followed DPP4 inhibitors as the next most popular option. Most of the old and recent oral antidiabetic agents (OADs) were available in the Saudi market. Drug affordability was not an issue, since the vast majority of the patients receiving free medication. The main reasons for choice of OADs were better efficacy, and benefits in weight management.

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Declaration of Competing Interest

The authors of this manuscript have no conflicts of interest to declare.

Appendix A. The frequency results of reasons for changing first line anti-diabetic medications or selecting second line therapy.

Reasoning	Reasons for changing first line anti-diabetic medications Number (%)	Reasons for selecting second line medications Number (%)
Efficacy	507 (93.5)	388 (71.6)
Weight effect	31 (5.7)	110 (20.3)
Physician preference	25 (4.6)	–
Hypoglycemic events	13 (2.4)	92 (17)
Side effects /tolerability/ drug interactions	11 (2.1)	167 (30.8)
Access reasons / Affordability	1 (0.2)	5 (0.8)
Patient request	1 (0.2)	8 (1.5)
Convenience	1 (0.2)	10 (1.8)
Others	–	25 (4.6)

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