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YEDITEPE UNIVERSITY
INSTITUTE OF HEALTH SCIENCES
DEPARTMENT OF PHARMACOECONOMICS AND
PHARMACOEPIDEMIOLOGY

COST-EFFECTIVENESS OF DIPEPTIDYL PEPTIDASE-4 INHIBITORS VERSUS SULFONYLUREAS AS A SECOND LINE THERAPY ADDED TO METFORMIN IN THE TREATMENT OF TYPE 2 DIABETES MELLITUS IN TURKEY: A PHARMACOECONOMIC STUDY

MASTER THESIS

YIGIT YAMAN, B Pharm

Istanbul-2019

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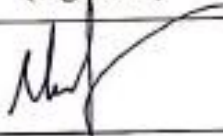YIGIT YAMAN, B Pharm

SUPERVISOR
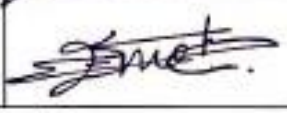Prof. Dr. Meriç Köksal Akkoç
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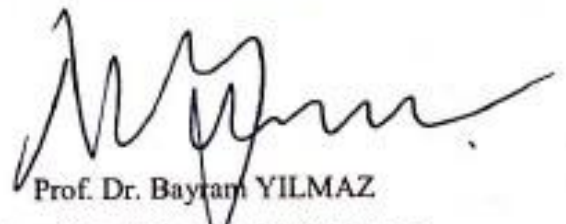
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APPROVAL

This thesis has been deemed by the jury in accordance with the relevant articles of Yeditepe University Graduate Education and Examinations Regulation and has been approved by Administrative Board of Institute with decision dated 16.07.2019..... and numbered ..2019/12-14

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DECLARATION

I declare that during the preparation of this thesis, from planning to its writing, I have not involved in non-ethical actions and this thesis is prepared with my own work. All information in this thesis is obtained in accordance with academic and ethical rules. I have given reference for all of the information and comments not obtained from this thesis and I did not have any actions that may result in the violation of patent or copyrights.

05.07.2019

Yiğit Yaman

DEDICATION

I dedicate this thesis to my wife Gül Elvan Özkaya Yaman.

ACKNOWLEDGEMENTS

This thesis has been prepared with great effort. My advisors Prof. Dr. Meriç Köksal Akkoç and Dr. Emel Mashaki Ceyhan have given me all the support that I have needed throughout the preparation of this thesis. It is a great honor to be their master's student and I am willing to take our scientific collaboration forward.

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LIST OF SYMBOLS AND ABBREVIATIONS

3P-MACE	3-Point Major Adverse Cardiovascular Events
AACE	American Association of Clinical Endocrinologists
ACE	American College of Endocrinology
ADA	American Diabetes Association
CAD	Coronary Artery Disease
CBA	Cost Benefit Analysis
CEA	Cost Effectiveness Analysis
CKD	Chronic Kidney Disease
CMA	Cost Minimization Analysis
COI	Cost of Illness
CUA	Cost Utility Analysis
CV	Cardiovascular
CVD	Cardiovascular Disease
DED	Diabetic Eye Disease
DPP4i	Dipeptidyl Peptidase-4 Inhibitor
EASD	European Association for the Study of Diabetes
ESRD	End-stage Renal Disease
GDM	Gestational Diabetes Mellitus
GIP	Glucose-dependent Insulinotropic Polypeptide
GLP-1 RA	Glucagon-like Peptide-1 Receptor Agonist
H_bA1_c	Hemoglobin A1$_c$
HF	Heart Failure
HHF	Hospitalization for Heart Failure
IDF	International Diabetes Federation
IGT	Impaired Glucose Tolerance
IHD	Ischemic Heart Disease
MET	Metformin
MI	Myocardial Infarction
NPH	Neutral Protamine Hagedorn
PAD	Peripheral Artery Disease
RCT	Randomized Clinical Trial
QALY	Quality-Adjusted Life-Years

SGLT2i	Sodium-Glucose Cotransporter 2 Inhibitor
SU	Sulfonylurea
SUT	Health Implementation Directive
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TUIK	Turkish Statistical Institute
TZD	Thiazolidinedione
WHO	World Health Organization

ABSTRACT

Yaman, Y. (2019). Cost-effectiveness of dipeptidyl peptidase-4 inhibitors versus sulfonylureas as a second line therapy added to metformin in the treatment of type 2 diabetes mellitus in Turkey: a pharmacoeconomic study. Yeditepe University, Institute of Health Science, Department of Pharmacy, MSc thesis, Istanbul.

Type 2 Diabetes Mellitus (T2DM) is a serious public health problem with a major cause of morbidity and mortality. As the population ages, the prevalence of T2DM continues to increase which leads to the development of new treatment technologies and medicines. Thus the health expenditures to treat T2DM is augmenting accordingly. As a result, in today's world, regulatory health authorities should develop strategies to address this staggering economic burden by introducing systematic cost-effectiveness evaluation among most recent innovative oral antidiabetics (OADs) with older treatment options while safeguarding the timely access of patients to optimum treatments. This study aimed to assess the cost-effectiveness of an innovative OAD class, dipeptidyl peptidase-4 inhibitors (DPP4is), with an older OAD class, sulfonylureas (SUs), as 2nd line therapy added to metformin in T2DM in Turkey. An event driven cost-effectiveness model developed with a 1 year time horizon with health care payer's perspective. Target T2DM population for the analysis calculated with data from literature. Direct costs of drug acquisition, screening, laboratory testing and costs of efficacy parameters included events of hypoglycemia, microvascular and macrovascular complications calculated. Incremental cost-effectiveness ratio was calculated as TL 2.779,82. Because the ICER value is below the ICER threshold of TL 45.463 per QALY gained, DPP4is estimated to be a cost-effective treatment alternative compared with SUs for the treatment of patients with T2DM.

Key words: Cost-effectiveness analysis, dipeptidyl peptidases, pharmacoeconomics, sulfonylurea compounds, type 2 diabetes mellitus

ABSTRACT (Turkish)

Yaman, Y. (2019). Türkiye'de Tip 2 Diyabet tedavisinde metforminden sonra ikinci basamakta Dipeptidil peptidaz-4 inhibitörlerinin sülfonilürelere kıyasla maliyet-etkililiği: Farmakoekonomik Çalışma. Yeditepe Üniversitesi Sağlık Bilimleri Enstitüsü, Eczacılık ABD., Master Tezi. İstanbul.

Tip 2 diyabet, sebep olduğu mortalite ve morbidite nedeniyle önemli bir sağlık problemidir. Nüfusun yaşlanmasıyla birlikte tip 2 diyabetin prevalansı artmaya devam edecek ve bunun sonucunda yeni tedavi teknolojilerinin ve ilaçların geliştirilmesini sağlayacaktır. Bu sebeple, tip 2 diyabetin tedavisi için ayrılan sağlık harcamaları artmaktadır. Artmakta olan bu ekonomik yük nedeniyle karar verici otoriteler, en güncel yenilikçi oral antidiyabetik ürünleri eski kuşak tedavi seçenekleriyle kıyaslayan maliyet-etkililik değerlendirmelerini hayata geçiren ve hastaların optimum tedavi seçeneklerine zamanında erişmesini garanti altına alan stratejiler geliştirmelidir. Bu çalışma, yenilikçi oral antidiyabetik sınıfı olan dipeptidil peptidaz-4 inhibitörlerinin (DPP4i) daha eski bir sınıf olan sulfonilürelere kıyasla, Türkiye'de tip 2 diyabet tedavisinin 2. basamağında metformine ek olarak, maliyet-etkililiğini değerlendirmeyi amaçlamaktadır. Olaya dayalı, 1 yıl süreli ve geri ödeme kurumu perspektifine dayanan bir maliyet-etkililik modeli oluşturulmuştur. Analiz için hedeflenen tip 2 diyabet hasta popülasyonu, literatürden elde edilen veriler kullanılarak hesaplanmıştır. Analiz kapsamında; ilaç, tahlil, ilaç yan etkisi ve hastalığa bağlı mikrovasküler ve makrovasküler komplikasyon maliyetlerini kapsayan direkt maliyetler değerlendirilmiştir. İlave maliyet-etkililik oranı 2.779,82 TL olarak hesaplanmıştır. Bu değer, Türkiye 2018 kişi başı gayri safi milli hasıla değeri ve aynı zamanda ilave maliyet-etkililik eşiği olan 45.463 TL'nin altında olduğu için DPP4i'ler sülfonilürelere kıyasla Türkiye'de tip 2 diyabet tedavisinin 2. basamağında metformine ek olarak maliyet-etkili bulunmuştur.

Kilit sözcükler: Dipeptidil peptidazlar, farmakoekonomi, maliyet-etkililik analizi, sülfonilüre bileşikleri, tip 2 diabetes mellitus

1. INTRODUCTION and PURPOSE

1.1. Background

Diabetes is a chronic disease that is associated with the most common causes of morbidity and mortality worldwide. The 8th Diabetes Atlas Study of International Diabetes Federation (IDF) estimated that 424,9 million of people worldwide are diabetic in 2017 (1). Diabetes is characterized as the state of hyperglycemia, presence of high blood sugar, due to the lack of or inadequate production of the hormone insulin which is responsible from the balance of blood glucose levels. The most common forms of diabetes are; type 1 diabetes (T1DM) in which the immune system is often activated to destroy the cells in the pancreas responsible for producing insulin. The second type is type 2 diabetes (T2DM) which is characterized by insulin resistance as the body does not fully respond to insulin. If the Diabetes Mellitus (DM) is untreated properly and timely, the hyperglycemia can result in microvascular complications resulting damage to eye, kidney and nerve systems and macrovascular complications resulting in cardiovascular disease (CVD) complications. Therefore, a healthy diet, exercise, lifestyle modifications and pharmacological treatments are crucial to improve health related outcomes of patients with diabetes in order to prevent or slow the progression of complications, early morbidity and mortality (2).

T2DM is considered one of the new epidemics of the twenty-first century with an increasing prevalence rates. Aging of the population, sedentary lifestyle and obesity are among the main factors that increase the risk of T2DM. According to IDF, 8.8% of prevalence of diabetes in 2017 is expected to grow to 9.9% by 2045, equating a total of 628,6 millions of diabetic patients (1).

The projected increase in prevalence of T2DM could result in a significant increase in healthcare expenditures. IDF has estimated the global overall cost of treating T2DM for the year 2017 to be $850 billion dollars, which is projected to grow by 8% for the year 2045 (1). In Turkey, the cost of diabetes is estimated as 10 billion TL in 2012 with a +18% of growth versus previous year. In addition, in 2012, 22.6% of the Turkish national healthcare budget was allocated to treat diabetes and its complications (3). Due to this staggering economic burden of diabetes in healthcare expenditures, decision

makers focus on the develop of new healthcare policies in order to increase disease awareness, level of education for patients and improve health related outcomes.

It is well known that the economic impact of T2DM is substantial in healthcare budgets, however there is a lack of pharmacoeconomic studies which aims to estimate the economic impact of using innovative antidiabetic treatments such as the comparison of new OADs to older class of OADs. In a cost conscious society with escalating healthcare costs and limited healthcare resources, there is a need to evaluate the comparative added value of newer generation medicines compared to older generations for a particular disease or disorder in order to allocate the necessary resources efficiently and ensure optimal decision making processes. Accordingly, this study aims to provide a cost-effectiveness analysis for newer generation OADs in comparison to older generation OADs at 2nd line of treatment of T2DM in Turkey.

1.2. Problem Statement

T2DM is a complex, progressive disease increasing the risk of morbidity and mortality resulting a heavy economic burden on healthcare system. Up-to-date several studies such as Turkish Diabetes Epidemiology Study (TURDEP I and II), International Diabetes Management Practices Study (IDMPS) and Patient-based study on the Adherence of physicians to guidelines for the management of type 2 diabetes in Turkey (ADMIRE) performed to investigate the epidemiology of T2DM in Turkey. According to these studies; the prevalence, of DM, frequency of complications, prognosis of the disease, the diagnosis rate and treatment success outcomes were identified in the Turkish population (4-7). However, there is lack of scientific data to assess the economic impact of T2DM in Turkey. In addition, there are no pharmacoeconomic studies comparing more innovative treatment options with traditional treatments in the management of T2DM in Turkey which could provide data for the policy and decision makers. To date, there are no cost-effectiveness studies comparing innovative OADs, Dipeptidyl peptidase-4 inhibitors (DPP4is), with older OADs, Sulfonylurea (SUs), in treatment of T2DM patients not controlled with metformin (MET) in Turkey.

1.3. Purpose of The Research

This dissertation assessed direct costs including medicine, monitoring and adverse events for DPP4is and SUs by employing an event driven analysis for the year 2018. The purpose of this dissertation was to compare the innovative treatment options such as DPP4is with SUs at T2DM patients uncontrolled with MET in Turkey by using a cost-effectiveness analysis. In addition, this dissertation aimed to possible provide policy and decision-makers in Turkey with a comprehensive cost-effectiveness overview regarding these treatment options. Thus the objectives of this study were; to provide an in-depth cost-effectiveness analysis of DPP4is compared to SUs for the T2DM patients not controlled with MET monotherapy in Turkey and to provide decision-makers a cost-effectiveness overview for the DPP4is in comparison to SUs as a 2nd line therapy after MET in Type 2 diabetes in Turkey.

The hypothesis of this dissertation is that DPP4is are a cost-effective treatment option with better patient treatment compliance outcomes compared to SUs for the treatment of patients with T2DM not controlled with MET monotherapy in Turkey.

1.4. Significance of The Study

This dissertation is the first study of its kind to evaluate the incremental cost effectiveness between DPP4is versus SUs as a 2nd line therapy added to MET in patients with T2DM in Turkey. With the escalating health care costs, there is an increasing demand to demonstrate the cost-effectiveness of newer technologies as well as new medications, especially in diabetes and cardiovascular (CV) medicines. The provision of these cost and resource utilization estimates could be an important input in determining the cost-effectiveness of newer technologies and medications. In addition, the results could also help in conducting sensitivity analyses around the estimates from a clinical trial and in supporting pricing and reimbursement decisions. For example, sensitivity analyses using the estimates from this study would better reflect the "real world" costs relative to the costs obtained from a clinical trial.

In addition, the results of the literature review in this dissertation provided an in-depth analysis of the most recent diseasemanagement patterns in T2DM in Turkey in comparison to the global ones as well as established a strong insight with regards to the practical implementation of the use of OADs in Turkey.

2. LITERATURE REVIEW

2.1. Epidemiology of Type 2 Diabetes Mellitus

The burden of diabetes is high and it is increasing steadily worldwide due to the rise in the prevalence of obesity and unhealthy lifestyles. According to the estimates of IDF, there was 424,9 million people with diabetes in 2017 globally and it is expected to rise to 629 million by 2045 (1). T1DM and T2DM are the two major forms of diabetes and diabetes prevalence of T2DM is 9 times more than the prevalence of T1DM. Although the underlying cause of the two forms of diabetes is different, their progression may result in macrovascular and microvascular complications. Macrovascular complications are diseases of the large blood vessels such as coronary artery disease, stroke and peripheral arterial disease. Whereas, microvascular complications affect small blood vessels leading damage to eyes (retinopathy), to kidneys (nephropathy) and to nerves (neuropathy). All these factors reduce quality of life and life expectancy of patients with T2DM, thus increasing the costs of treating diabetes and its complications. Therefore, T2DM creates a heavy burden on healthcare system that the policy makers should focus on (2).

According to a global study performed during 2017 by IDF on the epidemiology of diabetes in different continents, the prevalence of diabetes in Europe is projected to be 8,8% in 20-79 years of age, equaling 58.0 million diabetes patients of whom 22,0 million of them remain as undiagnosed. While Europe has the second-lowest diabetes prevalence among other continents, some countries in Europe such as Turkey has high rates of prevalence compared to other countries. The prevalence rate of diabetes is estimated as 12,1% for Turkey, equaling a diabetic population around 6,7 million (1)

2.2. Clinical Background of Type 2 Diabetes Mellitus

2.2.1. Development of Type 2 Diabetes Mellitus

T2DM is characterized as the presence of hyperglycaemia which is the state of increased levels of glucose in bloodstream. This condition is resulted mainly due to an alteration in the physiological production process of the hormone insulin leading inadequate levels in the body. Moreover, this situation also triggers additional

mechanisms that decrease the effective use of insulin by the body (2). Insulin is produced in the β cells of pancreas and it plays a key role by enabling the transport of glucose that is present in the blood to the cells of the body. Transported glucose is the main source of energy for the cells. Therefore, lack of insulin creates a state of stress within cells for the needed glucose uptake. This situation further increases the levels of glucose in the bloodstream leading to higher levels of glucose called hyperglycaemia. The presence of high levels of glucose in the bloodstream can cause damage to macrovascular and microvascular systems leading to the development complications affecting the eye, kidney, nerve and vascular system in the body which is responsible from the increased risk of morbidity and mortality observed with diabetic patients. However, appropriate management of diabetes can delay or prevent these complications (2).

The most common types of diabetes are T1DM, T2DM and gestational diabetes mellitus (GDM). T1DM, known as juvenile diabetes, is a type of diabetes in which immune system destroys the insulin producing β cells in pancreas leading to inadequate or no production of insulins. T1DM is mainly diagnosed during the early childhood and thus insulin replacement treatments are crucial to prevent morbidity and early mortality. T2DM is the most prevalent type of diabetes, characterized by the inability of body to respond insulin effectively, a state which is referred as insulin resistance. T2DM is mainly diagnosed in middle-aged adults with >40 years of age. GDM is another type of diabetes which a woman without diabetes develop the disease during pregnancy. It is mainly diagnosed during the last three months of pregnancy and this type of diabetes often disappears after giving birth (2).

To diagnose diabetes, World Health Organization (WHO) states certain criteria that is based on the levels of elevated glucose in bloodstream. Diabetes is often diagnosed when fasting plasma glucose is ≥7.0 mmol/L or two hours plasma glucose is ≥11.1 mmol/L after 75g oral glucose loading test or any random blood glucose ≥11.1 mmol/L or hemoglobin A1$_c$ (H$_b$A1$_c$) ≥6.5%. Impaired glucose tolerance (IGT) should be diagnosed when fasting plasma glucose is 6.1-6.9 mmol/L or two-hours plasma glucose is ≥7.8 <11.1 mmol/L after 75g oral glucose loading test. Impaired fasting glucose (IFG) should be diagnosed when fasting plasma glucose is <7.0 mmol/L or two-hours plasma glucose is <7.8 mmol/L after 75g oral glucose loading test (8).

The symptoms of T2DM are; increased thirst, tiredness, recurrent infections, fatigue, delay in wound healing time, need to urine more often and weight loss. In 1 out of 2 T2DM patients may also present without symptoms, therefore nearly 50% of patients

with T2DM is undiagnosed. During this undiagnosed stage, harmful effects of hyperglycaemia to the vascular system and organs may lead to complications. Therefore, complications of diabetes such as renal failure, foot ulcer, infection or change in vision may already be present in newly diagnosed patients with T2DM. To date, the causes of T2DM are not clearly understood but there is relation with being overweight, increased age and family history (9).

The cornerstone of T2DM treatment is the transformation of the current lifestyle of the patient by taking necessary steps for a healthier lifestyle including regular exercise, reducing alcohol intake, cessation of smoking, following a healthy diet consisting of low glycaemic load foods and weight control plans that includes steps for weight reduction if feasible. If attempts to change lifestyle are not adequate to control blood glucose levels, oral antidiabetic (OAD) medications are prescribed in order to manage glycaemic control. MET is the first line OAD globally with a long history of experience in this condition of more than 60 years. If treatment with MET monotherapy is not adequate to reach the target $HbA1_c$ levels, combination therapies can be used such as; dipeptidyl peptidase-4 inhibitors (DPP-4is), glucagon-like peptide-1 receptor agonists (GLP-1 RAs), sodium-glucose cotransporter 2 inhibitors (SGLT2is), sulphonylureas (SUs), thiazolidinediones (TZDs) and insulin together with MET where indicated. Insulin injections are prescribed mainly at higher baseline $HbA1_c$ levels in a combination with other OADs or when OADs are unable to control hyperglycaemia to target $HbA1_c$ levels (9-11). Beyond the control of hyperglycemia, it is critical to take necessary steps to minimize the risk of macrovascular and microvascular complications.

2.2.2. Factors Impacting Type 2 Diabetes Mellitus

2.2.2.1. Age

Higher rates of prevalence is observed in patients with increased age in T2DM. Possible reasons for this relation can be; the development of glucose intolerance in the elderly which increases the risk of developing the disease for patients with increased age, decrease in insulin sensitivity leading insulin resistance, loss of the quantity of β cells and decrease in their functional capacity due to the effects of aging (12). According to the results of 8th Atlas of IDF in 2017, global diabetes prevalence increases starting from the

ages of 40 with an 8% and shows the highest prevalence at the age of 65-79 with 18% (1).
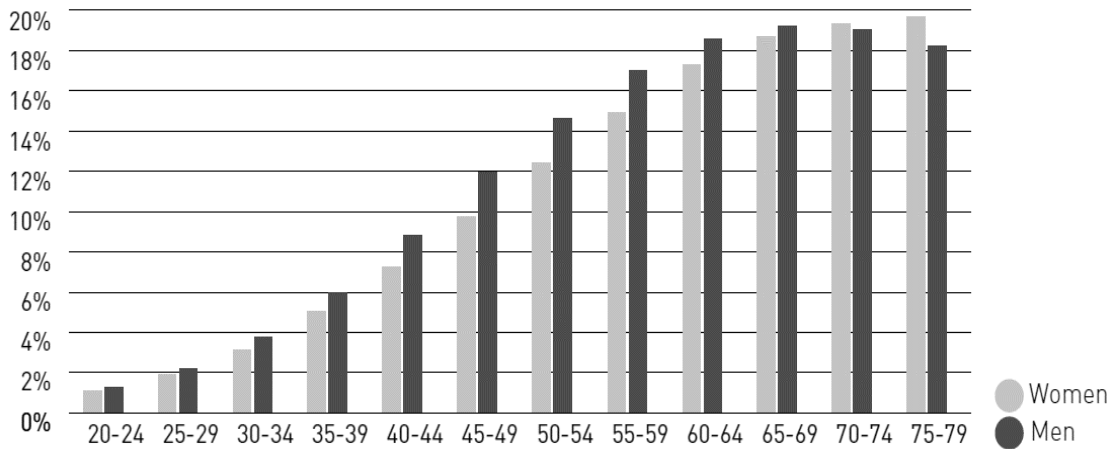
Figure 1.1. Prevalence of Diabetes by Age and Sex (1).

According to a national analysis performed by SSI (National Security Institute) in 2012 to identify the percentage of diabetic patients according to their age distribution in Turkey; 2% of diabetic patients are in the range of 0-24 years of age, 14% are at 25-45 years of age, 52% 46-64 years of age and 32% is >65 years of age. The highest number of diabetic patients are at the age of 46-64 representing more than half of the Turkish diabetic patient population (3). These data clearly suggest that with advancing age, the prevalence of T2DM increases substantially and age became an important risk factor.

2.2.2.2. Gender

Several studies have suggested gender differences as a risk factor and variance in treatment outcomes both for T2DM and its complications. According to these studies, reaching the target glycaemic goals is harder with women compared to men with T2DM (13). In addition, the risk of developing CV complications is higher for women with T2DM compared to men with T2DM, however the risk of developing microvascular complications is higher for men compared with women. Limited data suggest that the mortality risk is higher for women compared with men in T2DM (14,15). The mortality risk due to cardiovascular disease (CVD) increases three-fold for men with T2DM, whereas four-fold higher risk remains for women (15, 16). In summary, there is still

limited data to reach a conclusion about the effect of gender on the prognosis and treatment outcomes of T2DM. Thus, further clinical trials are required to specifially identify this relation and evaluate gender differences and impact on DM.

2.2.2.3. Ethnicity

Ethnicity is another factor which may have effect on the rate of prevalence, prognosis and response to medications in the management of T2DM. According to the report of Centers for Disease Control and Prevention in 2017, the prevalence rate differs among ethnic groups. While lowest prevalence was observed for non-Hispanic whites among different ethnic groups have the with 6.8-8.1%, American Indian or Alaskan Natives have the highest prevalence among ethnic groups in US with 14.9-15.3% during 2013-2015 (17).
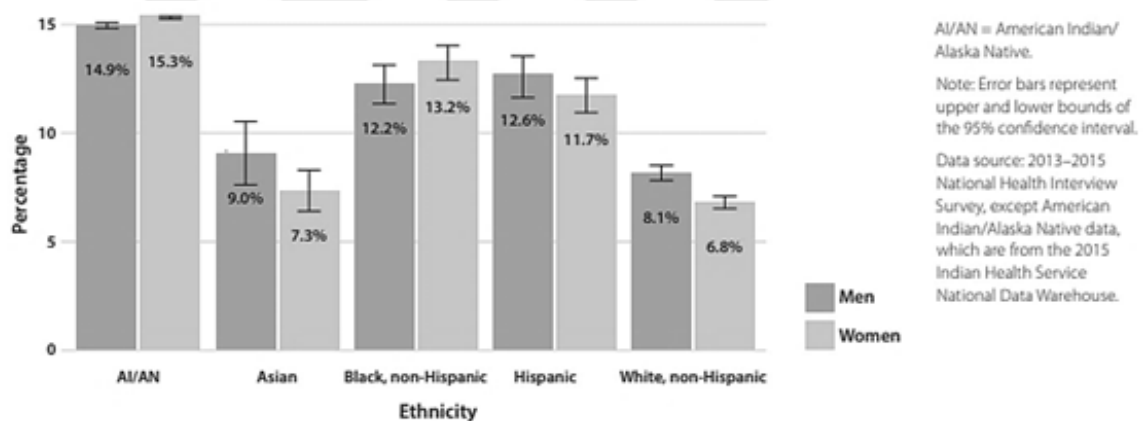
Figure 1.2. Prevalence of Diabetes by Ethnicity and Sex (17)

In the UK Prospective Diabetes Study (UKPDS), insulin resistance was found to be the highest in patients with South Asians ethnicity and Caucasians was the second ethnic group with highest insulin resistance. (18). In addition, limited studies highlight the effect of ethnic differences on T2DM related complication risk. End stage renal disease (ESRD), defined as the condition when kidneys are stopped working and dialysis or a kidney transplant necessary for survival, was more common among patients with T2DM for African American, Hispanic and Asian origin (19).

2.2.2.4. Comorbidities

T2DM can lead to serious complications which may results in hospitalizations and increased risk of mortality. Diabetes is one of the most common causes of CVD, nerve damage leading to diabetic foot related amputations and kidney. GDM increases the risk of maternal and fetal complications during pregnancy. Limited data shows wide variance of in diabetes-related complications between countries (1).

There are two types of complications in T2DM management. The first type of complications are acute complication where the damaging effects of the disease state starts immediately and necessary action should be taken to avoid from the harm of the situation such as hypoglycaemia, hyperglycaemic hyperosmolar state (HHS), diabetic ketoacidosis (DKA) and seizures. The second type of complications are chronic complications, which are progressive conditions leading to decrease in quality of life, increased morbidity and mortality such as microvascular complications (nephropathy, neuropathy and retinopathy) and macrovascular complications (coronary artery disease (CAD), peripheral artery disease (PAD) and diabetic foot) (1).

Disease awareness is low in diabetes, therefore patients with T2DM may have developed complications, however they can be unaware of the seriousness of the disease state. When the complications were not treated with optimum care with a timely manner, the negative impact on the health related outcomes increases substantially. Therefore, screening activities are important approaches to detect diabetic patients with comorbidities. (20). T2DM requires a personalized treatment plan including patient education about appropriate diet, exercise, and weight control, monitoring and appropriate use of medications for T2DM and diabetes related complications management.

2.2.2.4.A. Cardiovascular Diseases

50% of patients with T2DM die because of CVD. Hyperglycemia increases activity of the coagulation system, thus creating a risk of the formation of blood clotting. T2DM is also associated with high blood pressure and cholesterol levels, which lead to increased risk of CV complications such as CADs, myocardial infarction (MI), PADs and congestive heart failure (HF). CVDs are a collection of disorders such as CAD and PAD (1).

It is estimated that 14-47 per 1,000 diabetic patients in 50-69 years of age experience a CVD event annually. Among these, 2-26 per 1,000 are CAD events while 2-18 per 1,000 are strokes (1). The risk of having a CVD in patients with T2DM increases 2-3 times more than patients without T2DM (21). Increased age is highly related with increased prevalence of CVD increases and higher event rates are observed for low-middle income countries (22).

CVD creates a substantial burden on diabetes related health care expenditures. According to a US study, CVD complication of T2DM is responsible from 20% of inpatient days and 15% of physician office visits (23). 1 out of 4 inpatient costs of T2DM resulted due to a CVD event and 15% of doctor office visit costs are related to CVD (24). Other indirect costs are; increased absenteeism, loss in labor force and decreased productivity.

Preventing CV events reduce the risk of morbidity and mortality risk, thus decreasing the economic burden that can result from MI or stroke. Up-to-date scientific data demonstrated that intensive glycemic control combined with CVD management shows a relative risk reduction of 53% in 3-Point Major Adverse Cardiovascular Events (3P-MACE); reduction in the combined outcome of death from CV causes, nonfatal MI, nonfatal stroke, revascularization and amputation in T2DM (25). Blood glucose self-management, adoption of healthy diet, exercising regularly, weight management and appropriate use of antidiabetics, antihypertensives, statins and aspirin are important measures for the prevention of CVD events in T2DM.

2.2.2.4.B. Diabetic Nephropathy

Chronic kidney disease (CKD), which is present in patients in T2DM mainly referred to as diabetic nephropathy. According to studies, up to 40% of people with diabetes may develop CKD during their lifetime and 19% of them belong to the latter stages, stage ≥3 (26). Patients with diabetes are under ten times more risk compared to patients without diabetes and kidney dysfunction leading failure are mainly occurred as a result of T2DM. 12-55% of ESRD cases attributable to diabetes (27). Progression to kidney failure starts with the induction of hyperfiltration due to high blood glucose leading damage to nephrons (28).

Literature reveals that CKD has a high share in the economic burden of T2DM. The costs increase exponentially depending on the severity of kidney disease. For

example, according to a study in US, while mean annual medical cost of diabetic patients without nephropathy is USD 4,573, for diabetic patients with nephropathy annual medical cost increase by 50% reaching USD 6,826. Moreover, among patients with ESRD those not on dialysis experienced annual mean costs of USD 10,322, while for those on dialysis the cost increases 2.8 times fold (29).

Prevention and management of CKD in T2DM is also associated with CVD, therefore control of both hypertension and hyperglycaemia is important. Screening for the presence of albumin in the urine, known as albuminuria, should be done every year since diagnosis of T2DM and renin-angiotensin aldosterone (RAAS) system blockers should also be initiated with antidiabetic medications proven to have renal benefits, SGLT2is and GLP1 RAs, to the optimal management of CKD in patients with T2DM.

The ideal strategy to decrease the health care expenditure involves taking necessary steps to prevent T2DM in the first place and for patients with prevalent kidney diseases, early management strategies should be taken to delay the progression of kidney disease. In order to do achieve this, tight management of hyperglycemia, blood pressure and healthy lifestyle modifications should be followed with a regular monitoring by healthcare professionals.

2.2.2.4.C. Diabetic Retinopathy

Diabetic eye disease (DED) occurs as a result of chronic high blood glucose which cause damage, leakage and blockage in the retinal capillaries leading to loss of vision. DED includes; diabetic retinopathy (DR), glaucoma and diabetic macular edema (DME). DME is an advanced form of complication involving damage to the eyes (30). Retinopathy risk is increased among patients with T2DM and 1 in 3 patients living with T2DM have DR and 1 in 10 develop an advanced stage of the disease leading to vision loss. According to International Association on the Prevention of Blindness (IAPB), the prevalence of DR in patients with T2DM is 35% and 7.6% of patients with T2DM are diagnosed with DME globally (30, 31).

DED has a high burden on healthcare budget and patient's quality of life. DME and DED limits the daily activities of patients (31). According to the cost of illness studies, the cost of DR increased from 200 to 233 €; while the cost of DME increased from 705 to 4,200 € in Spain from 2007 to 2014 (32, 33).

DED is mainly asymptomatic in its early stages, therefore diabetic patients need to screening on a regular basis. The primary prevention for DED is to have a proper diabetes management including intensive glycemic control, lifestyle modification, healthy diet and appropriate use of antidiabetic medications if needed. These measures can help about the prevention about the onset of DR by 76% and its progression by 54%. Moreover, intensive glycaemic control in T2DM can improve the health status of the eye system (26, 34).

2.2.2.4.D. Diabetic Neuropathy

Neuropathy is a common complication of diabetes which occurs due to the damaging effect of hyperglycemia to the nerves throughout the body. Nerve damage can cause ulceration, serious infections which can lead to lower-limb amputations (35). Diabetic foot is a chronic complication that result in the formation of lesions in the deep tissues and peripheral vascular diseases in the lower limbs. The prevalence of diabetic neuropathy is estimated to be 16 to 66% (36). T2DM increases the amputation risk of patients by 10 times. The annual incidence of foot ulceration among diabetic patients is 2% and 1% of diabetic patients suffer from lower-limb amputation (37).

Foot complications have a significant impact on healthcare expenditures related to diabetes. 1/3 of costs related to diabetes estimated to be foot ulcers. The cost of care for diabetic patients with foot ulcers 5.4 times higher compared to those without foot ulcers and the treating higher grades of foot ulcers estimated to be 8 times higher compared to those with lower grades (38). In order to prevent from diabetic foot complications, intensive glycaemic control which estimated to reduce amputation risk by 35% compared to less intensive glycaemic management, regular feet examination, use of appropriate footwear and management of possible ulceration timely are among the important factors to consider (39).

2.3. Optimal Management of Type 2 Diabetes Mellitus

Optimal management of T2DM is a multifactorial approach consisting of lifestyle management, physical exercise, weight control, smoking cessation, diabetes education and the use of antidiabetic medication if needed. The aim is to lower hyperglycaemia in order to alleviate symptoms of T2DM and reduce long-term diabetes related complication

risk. Studies have shown that intensive glycemic control especially in the early stages of the disease reduces the onset and progression of microvascular complications (26). T2DM patients with poorer glycemic control have shown greater absolute risk reduction (ARR) compared to those with near the target blood glucose levels (10). However, the ARR of intensive glucose control on macrovascular complications is less certain and ACCORD study have shown that for a specific group of T2DM patients intensive glycemic control below the target glucose levels can even increase macrovascular event risk. According to American Diabetes Association (ADA), target $HbA1_c$ for T2DM should be around 53 mmol/mol (7%) or less and this value should be revised depending on the patient profile (9).

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality in patients with T2DM and studies showed the necessity of managing ASCVD risk factors (40). With ASCVD risk management approaches consisting stringent control of blood glucose, blood pressure and lipid levels including the use of newer generation antidiabetic medications with proven CV benefit, SGLT2is and GLP1 RAs, in selected group of T2DM patients, reductions in ASCVD events and mortality benefit observed as early as the first couple of years after the initiation of the therapies (41, 42).

2.3.1. Diagnostic Testing

Blood glucose control is primarily assessed with the $HbA1_c$ test, which reflects average blood glucose levels of the past 2-3 months. This laboratory test is also the main test to detect blood glucose levels in randomized clinical trials. Regular self-monitoring of blood glucose (SMBG) is widely used for self-management and medication adjustment purposes particularly in individuals taking insulin. In patients with T2DM using only OADs, routine glucose monitoring have minor clinically significant benefit and this should be considered to lessen the added examination costs related to disease (9).

2.3.2. Pharmacological Treatment

Several long-term, randomized, multicentered clinical trials such as UKPDS, The Action to Control Cardiovacular Risk in Diabetes (ACCORD), Glucose control and vascular complications in veterans with type 2 diabetes (VADT), Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes (ADVANCE), performed

to better understand the optimum treatment goals in T2DM management (26, 43, 44, 45). Evidence from these clinical trials suggest the importance of determining individualized glycemic goals depending on the individual patient profile. According to ADA/EASD 2018 consensus guideline recommendations about the optimal management of T2DM, adults with recent T2DM onset and no clinically significant CVD, HbA1c level of <7.0% should be targeted and broader HbA1c range can be considered for the elderly and for patients under high risk for hypoglycemia. Initially, MET stated as the first line antidiabetic medication for T2DM when target glycemic levels could not be achieved despite necessary lifestyle modification, healthy diet and physical exercise measures have taken (11). T2DM patients not achieving glycemic goals with MET, selection of 2nd line antidiabetic medication should be based on patient's therapeutic goal, age, presence of comorbid conditions (ASCVD, CKD, HF), risk of hypoglycemia and weight gain, treatment limitations, adverse effects and costs of each medication. In line with these factors, ADA/EASD guidelines prioritizes SGLT2is and GLP1 RAs among other agents as a 2nd line therapy after MET for T2DM patients with established ASCVD or CKD and for patient having the need to lose weight (11).
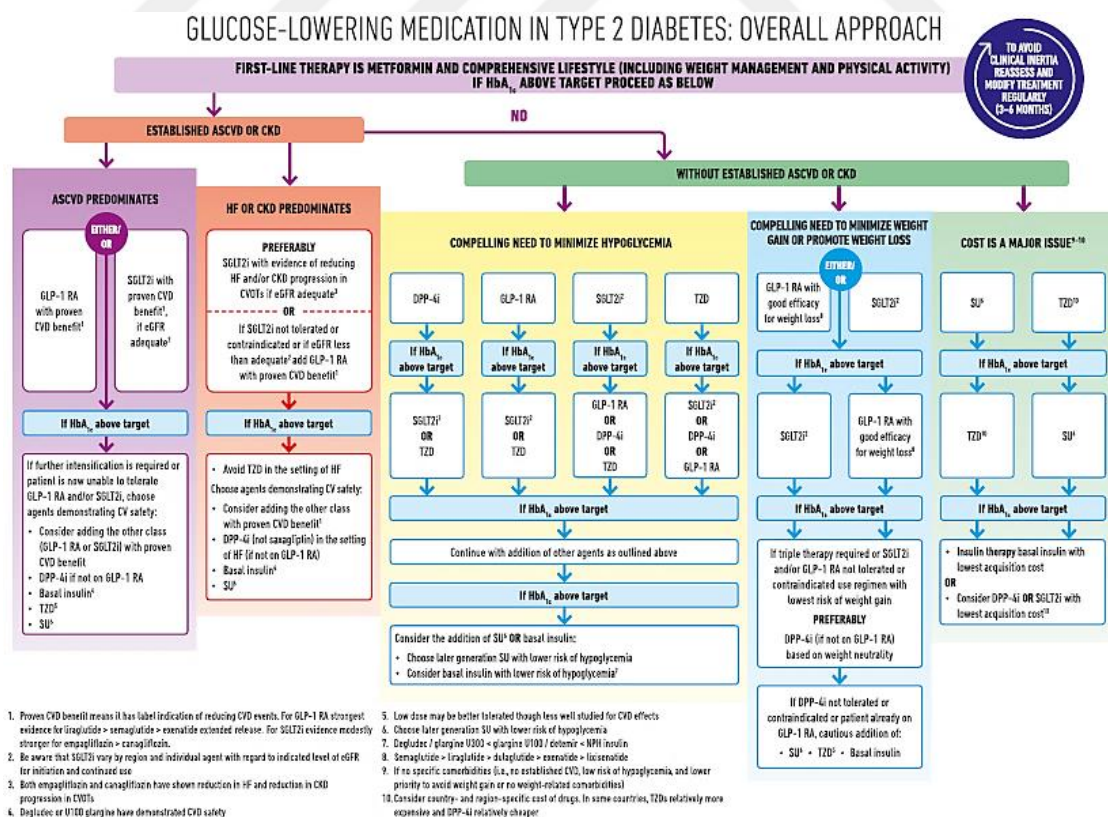
Figure 1.3. T2DM Management Algorithm of ADA and EASD Guidelines (11).

American Association of Clinical Endocrinology and American College of Endocrinologists, AACE/ACE, and guidelines in 2018 suggest a similar algorithm compared to ADA/EASD guidelines (10). In AACE/ACE consensus guidelines, H_bA1_c goal of ≤6.5% recommended for patients without concurrent illness and at low risk of hypoglycemia risk and >6.5% for patients with concurrent illness and at risk of hypoglycemia. In addition, this guideline prioritizes certain treatment classes in T2DM algorithm based on the efficacy, safety and added benefits of these classes. At 2nd line of treatment after MET, GLP-1 RAs, SGLT2is and DPP4i are the top 3 antidiabetic classes recommended based on up-to-date clinical evidence, whereas SUs remains to be the last choice of treatment with a "use with caution" sign due to increased risk of hypoglycemia, weight gain and possible risk of CV risk with older generation within this class (10).
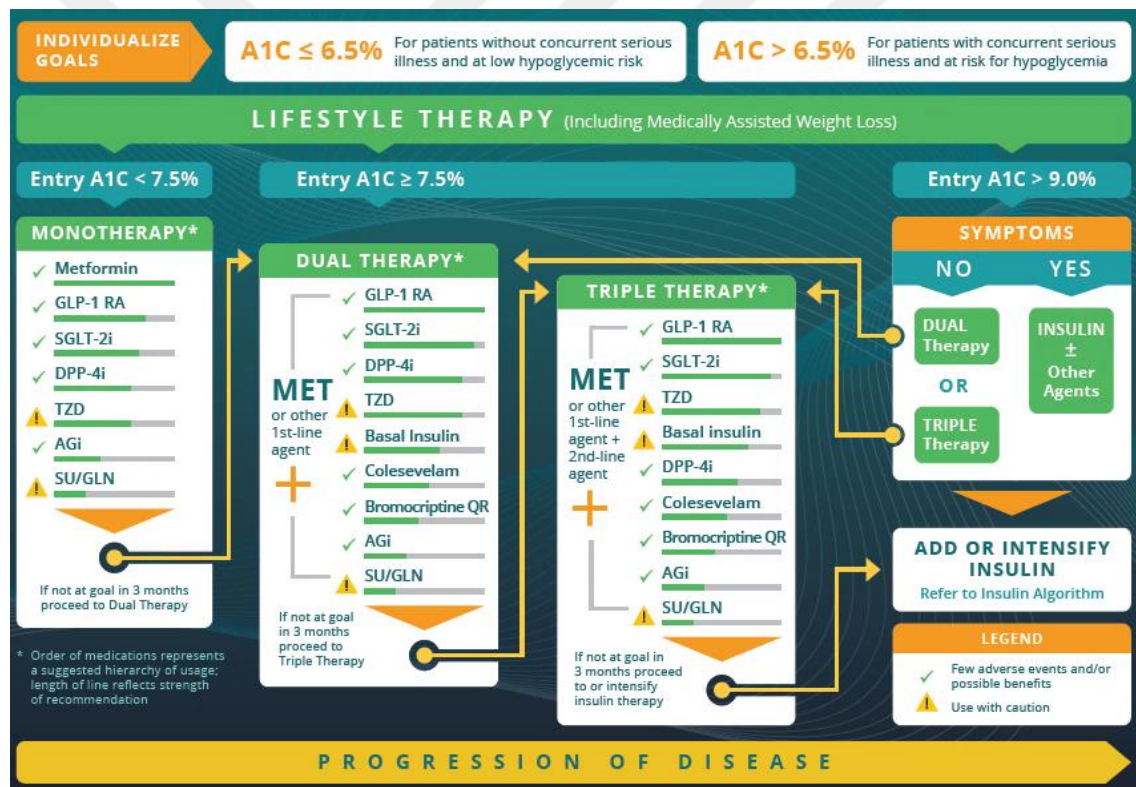
Figure 1.4. T2DM Management Algorithm of AACE and ACE Guidelines (10).

Regardless of the pharmacological treatment selected, lifestyle modifications, weight control, healthy diet and patient education are important factors and patients must be followed regularly to ensure glycemic goals are achieved and maintained.

2.3.2.1. Metformin

MET is an oral medication that reduces plasma glucose by multiple mechanisms which could not be clearly identified up-to-date. It is can be administered either once daily or twice a day. Dosage of MET starts at 500 mg once or twice a day with meals and should be increased as tolerated to a target dosage of 1,000 mg twice a day. Doses above 2,000 mg are have little additional benefit in terms of efficacy and have poorer tolerability (11). The most common side effects with MET is gastrointestinal symptoms which are dose dependent. MET dose should be reduced for patients with eGFR is <45 mL min^{-1} [1.73 m]^2 and the use of MET should be stopped when eGFR is <30 mL min^{-1} [1.73 m]^2 (46). Advantages of MET are; high efficacy of lowering H_bA1_c, high safety profile, low cost, minimal hypoglycemia risk and weight loss which makes it the first-line medication for management of T2DM. Some studies also suggested a benefit for preventing CVD and lower the risk of CV events in selected T2DM populations (26). MET should be omitted in the setting of severe illness, vomiting, or dehydration due to the increased risk of developing lactic acidosis in these conditions (11).

2.3.2.2. Dipeptidyl Peptidase-4 Inhibitors

DPP4is exert glucose lowering effects by inhibiting DPP4 enzyme which is responsible from the breakdown of the incretin hormones; GLP1 and glucose-dependent insulinotropic polypeptide (GIP). This action stimulates glucose-dependent insulin secretion and suppresses glucagon secretion. DPP4is have; modest H_bA1_c lowering properties, low risk of hypoglycemia, high safety profile and weight-neutral (11). All DPP4is except linagliptin, are excreted by the kidneys; therefore, dosage needs to be adjusted for patients with renal dysfunction. All DPP4is are administered orally once daily except vildagliptin which is administered twice a day. Clinical trials demonstrated that DPP4is have been shown to have neutral effects on cardiovascular outcomes. Although, an increased risk of hospitalization for heart failure was observed with saxagliptin and alogliptin in their cardiovascular outcome trials (CVOT), SAVOR and EXAMINE respectively, linagliptin and sitagliptin proved to have neutral in terms of risk of hospitalization for heart failure in CARMELINA and TECOS CVOTs (47-50). In addition, with CARMELINA trial, linagliptin proved long term safety both in CV and renal outcomes. An important advantage with this group of antidiabetics is the ability to

combine with all other antidiabetic medications except GLP-1 RAs due to presence of a similar mechanism of action. Although a causative association with the development of pancreatitis has not been established with DPP4is, it should be taken with care.

2.3.2.3. Glucagon-like Peptide 1 Receptor Agonist

GLP-1 RAs stimulate insulin secretion and reduce glucagon secretion in a glucose-dependent manner, improve satiety, and promote weight loss. Structural differences among GLP-1 receptor agonists affect duration of action, and their formulation and dosing may affect efficacy for glucose-lowering and weight reduction as well as side effect profile and cardiovascular effects (11). Dulaglutide, exenatide extended-release, and semaglutide are administered once weekly. Liraglutide and lixisenatide are administered once daily, and exenatide is available in a twice-daily formulation. All GLP-1 RAs in the market are administered as subcutaneous injection, however an oral form of semaglutide is in the development process. GLP-1 RAs have high anti-hyperglycaemic efficacy; semaglutide once weekly having the greatest efficacy, followed by dulaglutide and liraglutide, exenatide once weekly, exenatide twice daily and lixisenatide being the least effective among the class (11). All GLP-1 RAs promote weight loss between 1.5kg to 6.0kg over the duration of 30 weeks period and have minimal risk for hypoglycemia. In LEADER[42] trial with liraglutide and in SUSTAIN 6 trial with semaglutide, these agents demonstrated to improve CV outcomes (52). However, in SUSTAIN 6 trial with Semaglutide, an increased risk of retinopathy complications observed which is explained to occur due to the rapid improvement of glycemic control with semaglutide (52). The most common side effects of GLP-1 RAs are gastrointestinal side effects; nausea, vomiting and diarrhea. GLP-1 RAs are associated with increased risk of gallbladder events, however not a direct relation is found in terms of increasing risk for pancreatitis, pancreatic cancer or bone disease (11). Due to their high efficacy, low hypoglycemia risk, weight loss effect and proven CV and renal benefit in selected T2DM populations, GLP-1 RAs are among the prioritized antidiabetic class along with SGLT2is for the treatment of T2DM according to up-to-date clinical evidence.

2.3.2.4. Sodium-Glucose Cotransporter 2 Inhibitor

SGLT2is are administered orally and reduce plasma glucose by enhancing urinary excretion of glucose. Therefore, efficacy of these medications is dependent on renal function and the use of SGLT2 inhibitors are not recommended at an eGFR below 45 mL min^{-1} [1.73 m]^2. These medications are of high efficacy in lowering glucose in the setting of normal renal function, promotes weight reduction and blood pressure and have a low risk for hypoglycemia (11). Empagliflozin and canagliflozin have demonstrated CV and renal benefits in T2DM for patients with established ASCVD in EMPA-REG and CANVAS CVOTs (41, 53). Side effects for this class includes; genital infections, diabetic ketoacidosis, dehydration and orthostatic hypotension that caution should be taken when SGLT2is are used in combination with diuretics, renin angiotensin aldosterone system blockers and/or insulin (11). In addition, an increased risk for lower-limb amputations and bone fractures observed in CANVAS trial with canagliflozin (53). Due to their high efficacy, low hypoglycemia risk, weight loss effect, proven CV and renal benefit observed especially with empagliflozin in selected T2DM populations and convenient once daily oral administration, SGLT2is are among the prioritized antidiabetic class along with GLP-1 RAs for the treatment of T2DM according to up-to-date clinical evidence.

2.3.2.5. Sulfonylureas

SU are administered orally and lower hyperglycemia by stimulating insulin secretion from pancreatic β cells. They have; high glucose-lowering efficacy, however lack durable effect on glycemic control, risk of hypoglycemia creates a necessity of dose titration and weight gain which can lead to treatment failure (11). Long term efficacy and safety of SUs are investigated in UKPDS and ADVANCE CVOTs, which demonstrated safety in terms of CV outcomes and reductions in microvascular complications (26, 45). Members of the SU class also have some differences in terms of their safety profile. For example; glibenclamide has a higher risk of hypoglycemia compared to glipizide, glimepiride, and gliclazide (54). Adverse CV outcomes with an older generation SU, tolbutamide, raised concerns about the possible risk of SUs in terms of CV safety (10). However, there is no head-to-head CVOT trial comparing newer class of antidiabetics with SUs up-to-date. In 2019, the results of CAROLINA trial, which investigates the long term CV safety of linagliptin compared with glimepiride in T2DM on top of standard of

care (51). Caution should be taken for the use of SUs especially for diabetic patients at high risk of hypoglycemia, older patients and patients with CKD. Due to efficacy and safety profile combined with their low cost and wide availability worldwide, SUs are recommended in current diabetes guidelines as the latest line of diabetic medications except from insulin. It seems to be a reasonable choice when cost is an important consideration.

2.3.2.6. Thiazolidinedione

TZDs are oral medications that have high anti-hyperglycaemic efficacy with proven glycemic durability, increase insulin sensitivity and HDL cholesterol. According to PROACTIVE CVOT, pioglitazone demonstrated reduction in CV outcomes in patients with T2DM however a moderate risk of increase in hospitalization of HF may be a concern (55). On the other hand, a meta-analysis done in 2007 showed a possible increase in MI risk with rosiglitazone and in Europe, the European Medicines Agency (EMA) recommended in 2010 that rosiglitazone should be suspended because the benefits no longer outweighed the risks (56). Among the side effects of TZDs are; fluid retention, weight gain, HF, bone fracture and bladder cancer. Due to its lower safety profile, TZDs are recommended for selected patients mainly to benefit from increase in insulin sensitivity with this class (11).

2.3.2.7. Insulin

Insulin is the most potent glucose lowering agent. However, risk of hypoglycemia and weight gain are the two most important factors with this class. In UKPDS trial, 7-15% of insulin-treated patients experienced at least 1 episode of hypoglycaemia annually and 1-2% of patients have a severe hypoglycemia episode which may lead to fatal ventricular arrhythmias needing urgent medical assistance (26). When initial of insulin to the T2DM management decided, a single daily dose of basal insulin should be added to the regimen and dosage should be adjusted at regular and fairly short intervals to achieve the targeted glycemic goal (9).

Basal insulin analogs are preferred over neutral protamine Hagedorn (NPH) insulin because of the effect of basal insulin of providing flat serum insulin concentration for 24 hours or longer and they possess lower risk of hypoglycemia compared to NPH.

Glargine U300 and degludec U100 and U200 have more prolonged effects than glargine U100 and detemir. Randomized clinical trials (RCT) have reported equivalent glucose lowering efficacy with lower rate of severe or confirmed hypoglycemia compared to glargine U100 and detemir insulin (11). Moreover, in the DEVOTE CVOT, CV outcomes for insulin degludec and insulin glargine were equivalent (57). On the other hand, premixed insulins associated with higher risk of hypoglycemic events compared to basal and basal-bolus regimens. For basal insulin using patients with T2DM who are not at target glycemic goals, GLP1 RAs, SGLT2is, or DPP4is can be added to the regimen which enhance further glucose reductions and minimize weight gain and the risk of hypoglycemia (9-11). These patients may also require mealtime insulin to cover postprandial hyperglycemia. Prandial insulin can be added to the treatment when daily dose of basal insulin is greater than 0.5 U/kg. Main approach is to follow stepwise addition of prandial insulin to basal insulin (9). For these patients, SMBG is necessary to evaluate the effects of the treatment and adjust the dosage if necessary.

Due to being the most potent antidiabetic class having side effects of increased hypoglycemia and weight gain, initiation of insulin regimen is recommended for T2DM patients with >9 H_bA1_c in combination with other antidiabetic medications according to up-to-date diabetes guidelines (10). Before initiating an insulin therapy patient's motivation, cardiovascular and end-organ complications, age, general well-being, risk of hypoglycemia, health status and costs of the treatment should be considered.

2.3.4. Economic Burden of Type 2 Diabetes Mellitus

T2DM creates significant economic impact in healthcare systems. According to the 8th Diabetes Atlas of IDF, healthcare expenditure for treating diabetes worldwide is growing from USD 232 billion in 2007 to USD 727 billion in 2017 for those aged 20-79 years (1).
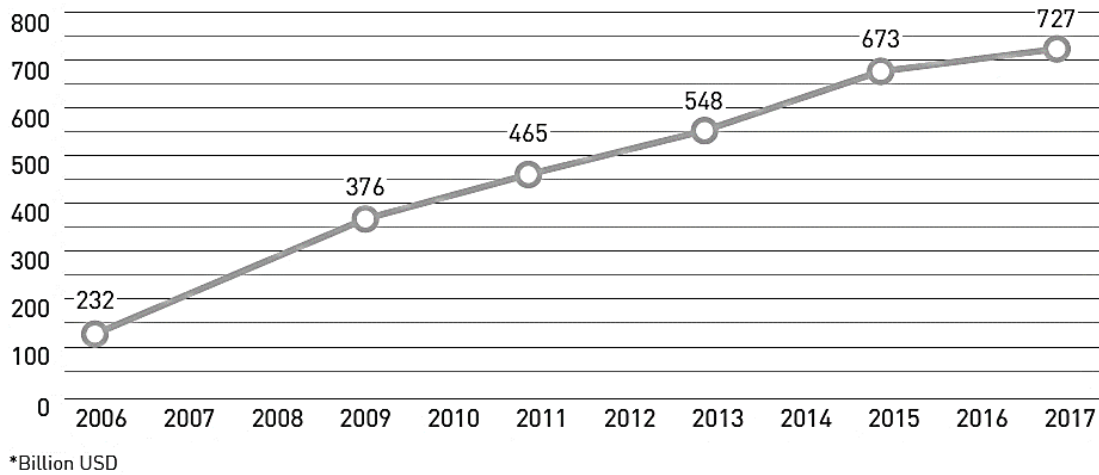
Figure 1.5. Diabetes Related Healthcare Expenditure (1).

In 2017, IDF estimates the total healthcare expenditure on diabetes will reach USD 727 billion for patients aged 20-79 years, which represents an 8% increase compared to the 2015 estimate (1). When using the expanded age group of 18 to 99 years, the costs totaled USD 850 billion and economic burden of diabetes is expected to continue to its growth. It is projected that the healthcare expenditure on diabetes will reach USD 776 billion by 2045 for patients aged 20-79 years which represents a 7% growth and reach USD 958 billion for patients aged 18-99 years (1).
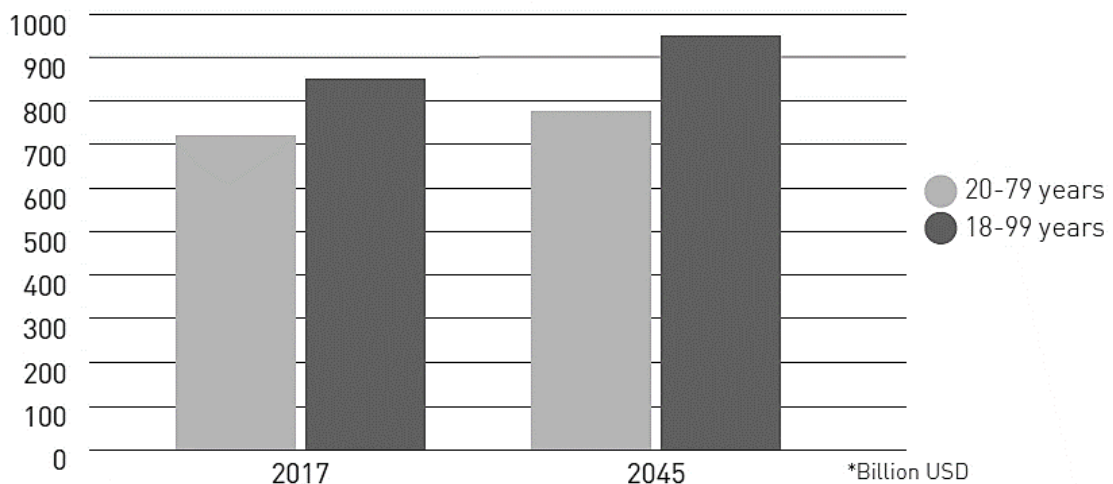
Figure 1.6. Diabetes Related Healthcare Expenditure in 2017 and 2045 (1).

According to IDF's study in 2017, the highest expenditures on diabetes were observed in US, China and Germany with USD 351,3 billion, 62,8 billion, 44,1 billion respectively. Moreover, healthcare expenditures vary greatly among countries mainly due to the number of T2DM population and average cost of treatment per person. US has the highest yearly diabetes cost per person with USD 11,638 and Central African Republic has the lowest expenditure per person with USD 29. In addition, The North American and Caribbean region has the highest expenditure on diabetes with USD 383 billion corresponding to 52% of the total amount spent globally and second highest expenditure on diabetes estimated as the European region with USD 166,4 billion corresponding to 23% of the total global spending (1).

Expenditure on diabetes has a heavy burden on healthcare budgets globally. 16.6% of total healthcare budget of Middle East and North African region was allocated to diabetes, followed by 14% with North American and Caribbean region and the lowest proportion of healthcare budget spent estimated to be the African region with 6% (1).
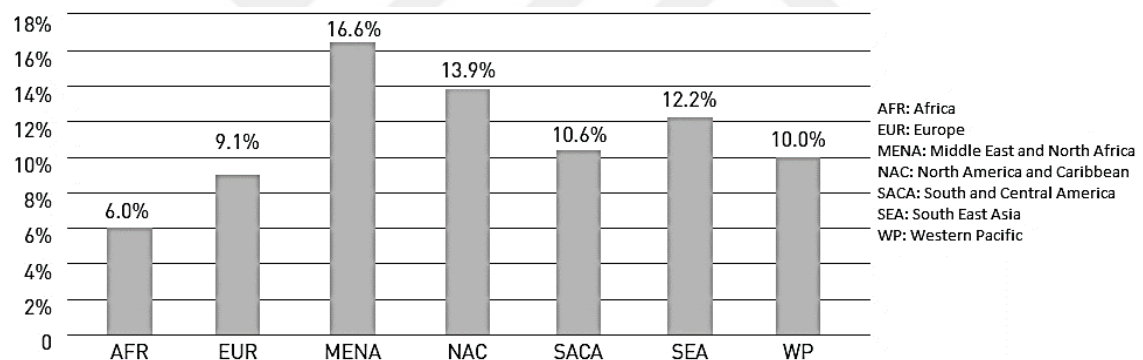
Figure 1.7. Proportion of Diabetes in Total Healthcare Expenditures (1).

According to a national report of SSI in Turkey, treating diabetes resulted nearly 10 billion TL in 2012. In addition the costs are increasing rapidly with an 18% growth compared to previous years. While the proportion of diabetes related expenditures in national healthcare budget was ~16% in 2008, it reached ~23% in 2012. Moreover, the majority of the costs of diabetes accounted from diabetes related complications with a 74% which creates the need of optimizing diabetes treatment to improve outcomes and lessen the burden of disease (3).

In order to address this alarming situation, governments initiated several multidisciplinary approaches to increase awareness of T2DM in the society and

conducted patient education campaigns to facilitate the early diagnosis rate and improve compliance rate. Due to the prevalence of diabetes which increased substantially in Turkey within the past 10 years, the Turkish government launched a Diabetes Control Program in 2015 (3). This program was a 5 years plan containing patient education programs, improvement in healthcare infrastructure, optimizing monetary and human resources to increase the coverage rate for diabetic patients. In addition to these measure, timely access to newer generation of OADs and innovative treatments was considered to improve the outcomes of the disease and lessen the national burden (3).

2.3.5. Reimbursement Practices for Antidiabetics of SSI in Turkey

The healthcare system in Turkey is divided into three parts which are; primary, secondary and tertiary healthcare institutions. Primary healthcare institutions includes health stations, health centers, maternal and infant care and family planning centers that exist in each district in each province in Turkey. Secondary healthcare institutions include state hospitals and tertiary healthcare institutions including research and training hospitals and university hospitals. Referrals from secondary to tertiary healthcare institutions are possible based on the emergency criteria and in case of needs for intensive care services (58).

Turkey's General Health Insurance scheme ensures a full and equal access to health care services for all Turkish citizens and mandates to have medical insurance coverage under the national reimbursement system. The national health care reimbursement system criteria and conditions are published by the SSI periodically under the scope of the 2013 Health Implementation Directive (SUT) which outlines the reimbursed healthcare interventions and treatments for general health insurance beneficiaries.

According to the latest updates in July 5th 2018 update to the SUT of 2013, there are differences in the reimbursement conditions for antidiabetic classes. While the reimbursement conditions including authorized health care professionals (HCPs), healthcare institutions, report duration and special conditions are fully reimbursed for older generation antidiabetics such as SUs and MET, newer generations may have restricted reimbursement conditions (59). For example, prior to the SUT published on October 7th 2016, DPP4is could only be reimbursed if they are prescribed by specialists

in tertiary healthcare institution. However, with an update in the SUT on October 7th 2016, specialists in all healthcare institutions authorized to prescribe DPP4is.

Another example could be provided as prior March 21th 2018 update in SUT, SGLT2is reimbursed by the prescription of all specialists, however, after the March 21th 2018 update in SUT, SGLT2i reimbursement restricted to only endocrinologist prescriptions. With the December 28th 2018 update for the SUT, SGLT2is reimbursement changed again from only endocrinologist prescription to cover the prescription of all specialists. These reimbursement policies of SSI slows the timely access of newer medications for the patients seeking new therapy options (59).

To-date reimbursement conditions of SUs and DPP4is are summarized in the below table including latest updates of December 28th 2018 SUT. Two major differences between the classes can be identified which are only endocrinology and internal medicine specialists are authorized to initiate an outpatient healthcare report for DPP4is whereas all physicians can initiate an outpatient healthcare report for SUs. Secondly, there is special condition for reimbursement for DPP4is which is a DPP4i can be prescribed for patients with insufficient glycemic control under maximum tolerated doses of MET and/or SU (59).

Table 1.1. Reimbursement Criteria of OAD Classes in Turkey (59).

		MET	SU	DPP4i
Outpatient Without Report	Reimbursement Condition	Reimbursed	Reimbursed	Reimbursed
	Authorized HCPs for Prescription	All Physicians	All Physicians	Specialists of Endocrinology or Internal Medicine
Outpatient With Report	Reimbursement Condition	Reimbursed	Reimbursed	Reimbursed
	Authorized Healthcare Institutions	All Institutions	All Institutions	All Institutions
	Authorized HCPs for Report Initiation	All Physicians	All Physicians	Specialists of Endocrinology or Internal Medicine
	Authorized HCPs for Prescription based on the Report	All Physicians	All Physicians	All Physicians
	Duration of the Report	2 years	2 years	2 years
Inpatient Reimbursement		Reimbursed by Healthcare Institution	Reimbursed by Healthcare Institution	Reimbursed by Healthcare Institution
Special Conditions for Reimbursement		None	None	Prescribed for patients with insufficient glycemic control under maximum tolerated doses of MET and/or SU

2.6. Pharmacoeconomic Analysis

Pharmacoeconomics is a scientific discipline which identifies, measures and compares the value of treatment strategies or pharmaceutical drugs to another in a given healthcare system and society. There are several different methods used in pharmacoeconomics; cost effectiveness analysis (CEA), cost-utility analyses (CUAs), cost benefit analysis (CBA), cost minimization analysis (CMA) and cost of illness analysis (COI) (60).

CEA offers a standardized means of comparing both the costs and outcomes of two different interventions or treatments. A single clinical outcome used to measure the effectiveness and incremental cost effectiveness ratio (ICER) calculated to reveal additional costs incurred to achieve greater clinical benefit (60). CUA is a similar analysis compared to CEA in which both costs and outcomes of two or more interventions compared. The main difference is that in CUA, health outcomes are obtained from patient data and are converted to quality-adjusted life-years (QALYs). This approach would be useful to compare the costs among different conditions or disease areas. CBA is an alternative tool for CEA and CUA, in which both benefits and costs are expressed in monetary units. It allows to calculate the net benefit for each intervention in monetary units. Willingness-to-pay (WTP) is the most widely agreed method to valuate health outcomes. CBA based on WTP provides strong evidence about the opportunity costs of health interventions. CMA is used to compare the cost of interventions with equivalent efficacy and safety. For example, drugs within the same therapeutic class having equivalent efficacy and safety profile with different costs. COI studies estimate the economic impact of a disease by calculating direct and indirect costs related to the management of the disease in a defined setting for a specified period (60).

Among these pharmaco-analysis tools, CEA is found to be the most suitable method to compare the cost and outcomes of two different OAD classes, newer generation DPP4i class with an older generation SU class, in the treatment of a chronic condition, T2DM.

3. MATERIALS and METHODS

This dissertation assess the cost effectiveness of two different antidiabetic classes as a 2nd line therapy for patients with T2DM in Turkey in 2018. In addition, the study has an aim of providing the current reimbursement policy of SSI for these antidiabetic classes.

In order to achieve these aims, several methods have been utilized throughout the dissertation. Thus an extensive literature review was done to identify the current pharmacological treatment options and disease management algorith in T2DM. In addition, the SSI reimbursement conditions and prescription criteria of the different oral antidiabetic classes and a pharmacoeconomic literature review were summarized to determine the burden of T2DM both globally and in Turkey. Moreover, an in-depth cost effectiveness analysis was performed to compare the cost and effectiveness of DPP4is and SUs as a 2nd line of treatment after MET in Turkey in 2018.

3.1. Cost-Effectiveness Model

A cost-effectiveness model was developed in Microsoft Excel 2016 software which has two states. First state is the 1st line of therapy state in T2DM management, in which patients were under the treatment of MET monotherapy. From literature, 67,1% of T2DM patients observed to be under treatment with MET monotherapy as a 1st line of therapy (61). Therefore, 67,1% of the target population was assumed to be in the 1st line of therapy state. Patients could remain in the first state or transition to the second state. Second state is the 2nd line of therapy state, in which either a DPP4i or a SU is added to patients uncontrolled with MET therapy. From literature, 17,0% of patient with T2DM who are under MET therapy initiate a 2nd line therapy after 2 years. Therefore, 17,0% of patients in the first state transited to the second state either by addition of a DPP4i treatment, stated as MET+DPP4i, or a SU treatment, stated as MET+SU. Model duration was 2 years, as a result only 1 transition occurred from the first state to the second state. It assumed that both first state and the number of patients transited to second state complete their cycles at the same period of 1 year time horizon.
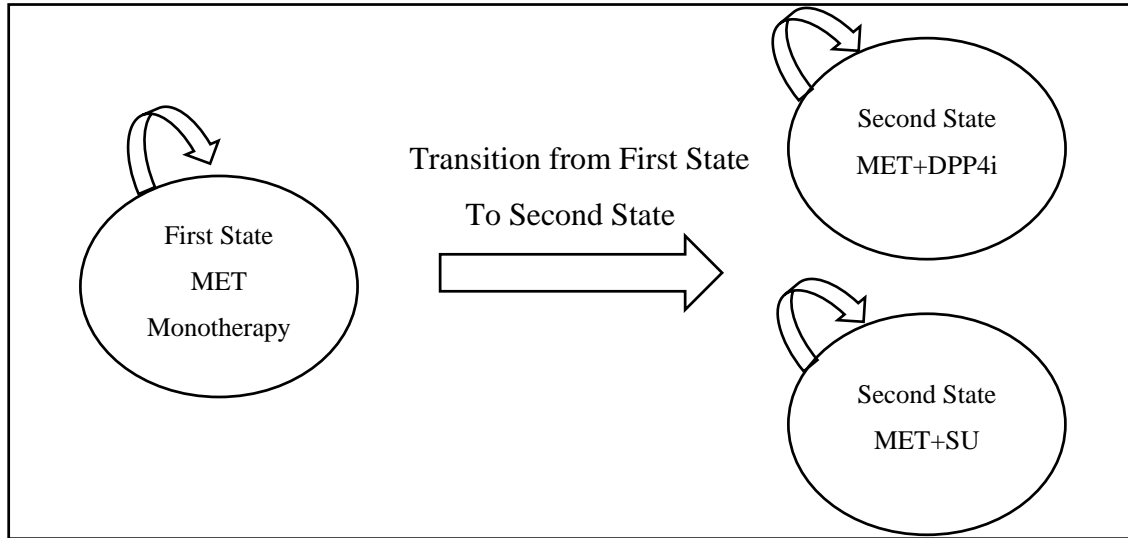
Figure 1.8. Cost-Effectiveness Model Diagram

3.2. Analytic Perspective

Economic evaluations in this analysis performed from the health care payer's perspective. Only direct costs of medications, screening and examination costs and costs of complications from payer's perspective were evaluated. Therefore, the outcomes of this analysis provide valuable data for decision makers.

3.3. Target Population

In order to calculate the target population for the cost-effectiveness analysis, T2DM population of Turkey in 2018 projected by using several data were gathered from the literature and rational assumptions were made accordingly. Thus as per the Turkish Statistical Institute (TUIK) data, population projection for individuals with ≥20 years of age is found as 56.3 Million for 2018 (62). The 8th Diabetes Atlas of IDF, estimated a diabetes prevalence of 12,8% for individuals ≥20 years of age in Turkey with 90% of diabetes cases are T2DM and a diagnosis rate of 61,8% (1). While the diagnosis rate shows the percentage of patients diagnosed with the disease, the rest of the population is mainly not diagnosed due to the absence of symptoms or are not aware about the disease. With these data, it is possible to project a T2DM population of 6.5 Million people of 4.0 Million are diagnosed. In addition, drug treatment rates shows the percentage diagnosed

individuals who are under antidiabetic medications. An epidemiological study conducted in Turkey to better understand T2DM showed drug treatment rate as 85,5% in Turkey, leading to a target population of 3.4 million patients with T2DM under antidiabetic medications (5). (Table 1.2.)

Table 1.2. T2DM Population in Turkey

Turkish T2DM Population	Data	Reference
Turkish Population in 2018	81.867.223	TUIK 2018 (62).
Population with ≥20 years of age	56.260.624	TUIK 2018 (62).
Diabetes Prevalence Rate	12,8%	8th IDF Atlas, 2017 (1).
T2DM/T1DM Ratio	90,0%	8th IDF Atlas, 2017 (1).
Diagnosis Rate	61,8%	8th IDF Atlas, 2017 (1).
Drug Treatment Rate	85,5%	TURDEP II Study, 2013 (5).
T2DM Population	6.481.224	Calculated.
Diagnosed T2DM Population	4.005.396	Calculated.
T2DM Population on Anti-diabetic Medications	3.424.614	Calculated.

3.4. Time Horizon

The cost-effectiveness analysis performed with a 1 year life horizon.

3.5. Direct Costs and Health Related Outcomes

3.5.1. Cost of Drug Acquisition

Cost of medications are calculated by gathering the retail price of available SUs and DPP4is published by the report of Turkish Medicines and Medical Devices Agency (TITCK) on 19th of february 2018 (63). After the deduction of the SSI Mandatory discounts for each form of product, the reimbursed price is obtained. The Defined Daily Dose is the daily consumption of a defined compound which determined by world health organization (WHO). Considering the Defined Daily Doses and Reimbursed prices for each form of products, the daily costs for each form of SU and DPP4i were determined.

Target CE population is assumed to consume MET, SU or DPP4i for 365 days duration for the year 2018.

Costs of medications in 2nd line of therapy were calculated for MET, DPP4i and SU therapies. There are different molecules and several brands available in the Turkish market for MET, DPP4i and SU with varying daily costs. Due to the availability of different molecules for both DPP4i and SU treatment classes and availability of several brands for those molecules with high variance among daily costs for the payer, average price method used to represent the unit cost of each treatment class; MET, DPP4i and SU, instead of taking the least costly product within each treatment class. Average daily cost for a brand in each treatment class from the payer's perspective in 2018 is calculated firstly by obtaining the reimbursed price for each form of brand in three different treatment classes. In order to find the reimbursement price, which is the cost of a brand in for the payer per box, retail box price of each form of brand taken from TITCK multiplied by the mandatory discount rate of the payer demanding from the manufacturer in order to include a form of that brand in Turkish reimbursement list. Because each form of brand may have different pack size and amount of active pharmaceutical ingredient, daily defined dose for each molecule is obtaned from WHO. Daily defined dose represents the daily aomunt of ideal consumption of a given active pharmaceutical ingredient (compound) in order to treat a given disease. In order to calculate the Net Daily Cost of each antidiabetic brand, calculated reimbursement price is divided by the number of tables in that form. Then this calculated price per tablet multiplied by the ratio of daily defined dose for the compound in that specific brand over the amount of active pharmaceutical ingredient in that brand per tablet.

Moreover, specific brands from each available compouns in treatment classes selected to represent the cost of treatment class, named as the average price method. MET analyzed by taking the averages of only 1000mg and 500mg forms of MET brands (MATOFIN, GLUCOPHAGE, GLUKOFEN, GLIFOR and DIAFORMIN) due to the defined daily dose of 2000mg. Average daily cost for a SU analyzed by taking the averages of all available SU molecules with its least costly form, GLIBEN, AMARYL 2mg from, EFIKAS MR and GLUCOTROL XL 10mg form. Average daily cost for a DPP4i analyzed by taking the averages of all available DPP4i brands, JANUVIA, ONGLYZA, TRAJENTA and GALVUS. Two brands of DPP4i fixed dose combination with MET available in Turkish market were not considered in this study due to high variance in cost and lack of all available DPP4i fixed dose combinations.

Table 1.3. Cost Analysis of DPP4is and SUs in Turkey

OAD Class	Brand	Compound	Form	Retail Price/Box (TL, including VAT)	Mandatory Discount (%)	Reimbursed Price/Box (TL)	Defined Daily Dose (mg)	Net Daily Cost (TL, Payers perspective)
MET	MATOFIN	Metformin	850mg 100 tablets	15,51	10%	13,96	2000	0,33
	MATOFIN	Metformin	1000mg 100 tablets	20,56	13%	17,89	2000	0,36
	MATOFIN	Metformin	1000mg XR 100 tablets	20,56	10%	18,50	2000	0,37
	MATOFIN	Metformin	500mg XR 100 tablets	13,18	4%	12,65	2000	0,51
	GLUCOPHAGE	Metformin	1000mg 100 tablets	20,40	12%	18,03	2000	0,36
	GLUCOPHAGE	Metformin	850mg 100 tablets	20,16	10%	18,14	2000	0,43
	GLIFOR	Metformin	1000mg 100 tablets	20,56	10%	18,50	2000	0,37
	GLIFOR	Metformin	850mg 100 tablets	19,36	17%	16,03	2000	0,38
	DIAFORMIN	Metformin	1000mg 100 tablets	20,56	10%	18,50	2000	0,37
	DIAFORMIN	Metformin	850mg 100 tablets	18,52	14%	16,02	2000	0,38
	GLUKOFEN	Metformin	1000mg 100 tablets	20,56	10%	18,50	2000	0,37
	GLUKOFEN	Metformin	850mg 100 tablets	20,56	14%	17,78	2000	0,42
SU	GLIBEN	Glibenclamide	5mg 100 tablets	7,51	0%	7,51	10	0,15
	AMARYL	Glimepiride	6mg 30 tablets	8,43	10%	7,59	2	0,08
	AMARYL	Glimepiride	4mg 30 tablets	7,15	0%	7,15	2	0,12
	AMARYL	Glimepiride	3mg 30 tablets	7,15	6%	6,72	2	0,15
	AMARYL	Glimepiride	2mg 30 tablets	6,23	0%	6,23	2	0,21
	AMARYL	Glimepiride	1mg 30 tablets	7,15	0%	7,15	2	0,48
	GLIMAX	Glimepiride	4mg 30 tablets	7,15	0%	7,15	2	0,12
	GLIMAX	Glimepiride	3mg 30 tablets	7,15	0%	7,15	2	0,16
	GLIMAX	Glimepiride	2mg 30 tablets	6,34	0%	6,34	2	0,21
	GLIMAX	Glimepiride	1mg 30 tablets	7,15	0%	7,15	2	0,48
	EFIKAS MR	Gliclazide	60mg 60 tablets	17,44	10%	15,70	60	0,26
	DIAMICRON MR	Gliclazide	60mg 60 tablets	20,56	10%	18,50	60	0,31
	BETANORM MR	Gliclazide	60mg 60 tablets	20,56	10%	18,50	60	0,31
	GLUCOTROL XL	Glipizide	10mg 20 tablets	18,15	10%	16,34	10	0,82
	GLUCOTROL XL	Glipizide	5mg 20 tablets	12,31	0%	12,31	10	1,23
DPP4i	JANUVIA	Sitagliptin	100mg 28 tablets	98,84	41%	58,32	100	2,08
	ONGLYZA	Saxagliptin	5mg 28 tablets	104,91	41%	61,90	5	2,21
	TRAJENTA	Linagliptin	5mg 30 tablets	118,33	41%	69,81	5	2,33
	GALVUS	Vildagliptin	50mg 56 tablets	134,02	41%	79,07	100	2,82

3.5.2. Cost of Screening and Examination

Physician examination costs and screening for the evaluation of treatment effects and disease prognosis were also calculated for both DPP4is and SUs at the 2nd line of therapy after MET. From a 2017 CEA on Diabetes in Turkey in a tertiary healthcare clinic (64), the average cost of screening and examination for a diabetic patient was identified and this value inflated in line with the guidance of US Health Services Research GDP method (65). The GDP per capita data for 2017 and 2018 were obtained from TUIK which was TL 38.680 and TL 45.463 respectively and the related screening and examination cost of 2017 is inflated, by using the ratio of the GDP of 2018 to GDP of 2017, to calculate the cost of screening and examination for a diabetic patient in 2018 (66). This value multiplied with the target second-line therapy for DPP4is and SUs to calculate the total screening and examination costs.

3.5.3. Cost of Complications

The other important parameter to consider was difference in terms of complication costs of MET+DPP4i compared to MET+SU. Therefore, the outcomes of ENDURE trial were used to conduct the analysis since ENDURE trial was a randomized, international study involving 2.639 patients comparing the efficacy and safety profile of alogliptin versus glipizide as an add-on therapy to MET (67). Differences among treatment effects for the two different 2nd line therapies, DPP4is and SUs, as an add-on to MET for T2DM treatment were; H_bA1_c lowering effects, -0.75% for DPP4i compared with -0.70% for SU; change in BMI (kg/m^2), -0.54 for DPP4i compared with 0.51 for SU; minor hypoglycemia not resulting in hospitalization, 1.28% for DPP4i compared with 21.86% for SU. These values from this study are used in this thesis to calculate the treatment effects among different groups. Moreover, a pharmacoeconomic study based on the outcomes of ENDURE trial revealed cost-effectiveness of alogliptin compared to glipizide as a 2nd line therapy after MET in patients with T2DM (68). Annual event rates for diabetes related macrovascular and microvascular complications with MET+DPP4i and MET+SU treatment groups are taken from this study. Difference in the number of event rates for a specific complication between MET+DPP4i and MET+SU for the year 2018 in Turkey found by subtracting the annual event rate of that complication for MET+DPP4i from MET+SU based on the data of ENDURE study. Because there is lack

of national clinical data for annual diabetes related complications for antidiabetic treatments in Turkey and ENDURE study is an international study, event rates taken from ENDURE study assumed to reflect the Turkish clinical setting. Annual event rate difference of all diabetes related complications between MET+DPP4i and MET+SU calculated with the same method. In order to calculate the cost occurring for a specific diabetes related complication, annual event rate of that complication from ENDURE study for each treatment group is taken and these figures are multiplied by the number of 2nd line T2DM target population calculated for 2018 in Turkey. In this way, number of events occurred for each complication both for MET+DPP4i and MET+SU groups are found. Annual direct costs of each complication calculated by multiplying the target 2nd line T2DM population and the acute and ongoing cost of that complication in Turkey for 2018. Overall complication cost for both MET+DPP4i and MET+SU calculated by adding all complication costs for that treatment group. In order to find the incremental cost of diabetes related complications between two treatment options, overall complication costs were subtracted from one treatment group to another (68).

Table 1.4. Annual Event Rate of Complications Between The Two Groups (68).

Complications	Annual Event Rate MET+SU (%)	Annual Event Rate MET+DPP4i (%)	Annual Event Rate Difference MET+SU vs MET+DPP4i (%)
Myocardial Infarction	18,42	17,63	0,79
Angina	13,72	13,06	0,66
Peripheral Vascular Disease	19,26	18,79	0,47
Stroke	7,66	7,53	0,13
Heart Failure	15,72	15,19	0,53
Microalbuminuria	41,25	40,88	0,37
Macroalbuminuria	14,80	14,48	0,32
Peritonal Dialysis	4,86	4,66	0,20
Background diabetic retinopathy	29,62	29,35	0,27
Proliferative diabetic retinopathy	2,56	2,48	0,08
Cataract extraction	13,09	13,08	0,01
Macular oedema	25,47	25,19	0,28
Peripheral neuropathy	72,80	72,49	0,31
Ulcer	41,90	41,57	0,33
Amputation	19,53	19,43	0,10
Major hypoglycaemia	0,54	0,00	0,54

A COI study performed in Turkey during 2010 revealed both acute and ongoing costs of managing T2DM complications (69). By using the acute cost and ongoing annual cost from this study, total annual cost for a diabetes related complication item was calculated. Total annual costs of 2010 were inflated in line with the guidance of US Health Services Research GDP method (65). GDP per capita data for 2010 and 2018 were taken as a reference from TUIK which is TL 15.860 and TL 45.463 respectively and the ratio of the GDP of 2018 to GDP of 2010 is reflected to 2010 complication costs to find the total annual cost of complications for the year 2018.

Table 1.5. Annual Cost of Diabetes Related Complications in Turkey (69).

Complications	Acute Cost (TL, 2010 year)	Ongoing Annual Cost (TL, 2010 year)	Inflated Acute Cost (TL, 2018 year)	Inflated Ongoing Annual Cost (TL, 2018 year)	Total Annual Cost (TL, 2018 year)
Peripheral Vascular Disease	4.356	1.443	12.487	4.136	16.623
Stroke	3.799	805	10.890	2.308	13.197
Heart Failure	3.697	759	10.598	2.176	12.773
Myocardial Infarction	2.163	1.519	6.200	4.354	10.555
Macroalbuminuria	1.597	2.017	4.578	5.782	10.360
Angina	1.928	1.157	5.527	3.317	8.843
Peritonal Dialysis	N/A	1.939	N/A	5.558	5.558
Proliferative diabetic retinopathy	1.606	N/A	4.604	N/A	4.604
Macular oedema	1.606	N/A	4.604	N/A	4.604
Ulcer	1.362	183	3.904	525	4.429
Peripheral neuropathy	497	542	1.425	1.554	2.978
Amputation	800	41	2.293	118	2.411
Cataract extraction	390	172	1.118	493	1.611
Microalbuminuria	140	383	401	1.098	1.499
Diabetic retinopathy	137	N/A	393	N/A	393
Major hypoglycaemia	87	N/A	249	N/A	249

3.5.4. Calculation of Quality Adjusted Life Years

In order to quantify the health effects of the two groups of treatments, QALYs are calculated. It is possible to calculate QALYs by multiplying quantity of years in life with a specificied utility value.

There are no specific utilities estimates in Turkey for T2DM and its complications. Utility decrements related with complications were therefore obtained from the UKPDS

study (26). The utility value for a patient with T2DM was taken as 0,780 and the utility decrements for each complication were obtained from the literature: ischemic heart disease (IHD), 0,090, non-fatal MI, 0,055; congestive HF, 0,108; non-fatal stroke, 0,164; lower limb amputation, 0,280; blindness, 0,07426; renal failure, 0,37927; symptomatic hypoglycemia, 0,0142; severe hypoglycemia, 0,04728; and weight loss (per unit loss in BMI), 0,0171 (26).

Table 1.6. Individual Utility Decrements (26)

Event Disutilities	Utility Decrement
IHD	0,090
MI	0,055
Congestive HF	0,108
Stroke	0,164
Blindness	0,074
ESRD	0,263
Amputation	0,280
Ulcer	0,059
Symptomatic Hypoglycaemia	0,014
Major Hypoglycaemia	0,047
Decrease in BMI unit	0,017

With the defined utilizes per event for 1 year in life, incremental QALYs obtained from the ENDURE study which was 0.14 between MET+DPP4i vs MET+SU (68).

3.5.5. Calculation of Incremental Cost Effectiveness Ratio

ICER is calculated as the incremental total costs between MET+DPP4i group compared with MET+SU group divided by incremental QALYs between MET+DPP4i group compared with MET+SU group. The resulted ICER value was then compared with an ICER threshold value. Thus when the ICER value is below three times of the ICER threshold, the medication is considered to be a cost-effective alternative to the compared medication. According to the WHO guidance, in order to calculate the ICER based on GDP per capita, the ICER threshold was calculated based on the per capita GDP in Turkey for 2018 which was TL 45.463 (70).

3.6. Inflation and Discounting

Costs of diabetes related complications in Turkey for 2010 was inflated in line with the guidance of US Health Services Research GDP method and complication costs for 2018 calculated by multiplying the ratio of per capita GDP of 2018 which is TL 45.463 divided by the GDP of 2010 which is TL 15.860 in Turkey (65). On the other hand, because of the 1 year time horizon of the model, expenses and health related outcomes were not discounted.

3.7. Literature Review

A literature review is a method which aims to include a methodological and theoretical contributions to an existing knowledge. The use of this method was crucial in this dissertation since there is very limited literature which assess the burden of T2DM in Turkey and there is no pharmacoeconomic study which compares a newer generation treatment option with a traditional treatment in the management of T2DM in Turkey to provide evidence based data for the decision makers. Therefore, an extensive literature review was performed using various sources of information and published local and global data including; current treatment guidelines, burden of the disease, current practice of physicians on T2DM, cost effectiveness analysis performed in different countries with regards to T2DM management as well as comparison studies and the implementations in Turkey and global.

4. RESULTS

4.1. Cost-Effectiveness Outcomes

The cost effectiveness evaluation considered the differences in costs of preferring either a DPP4i or a SU as a 2nd line therapy added to MET for T2DM in Turkey in 2018. Cost of preferring a DPP4i as a 2nd line therapy after MET for 1 year period resulted a total drug acquisition cost of TL 318,5 Million, whereas preferring a SU as 2nd line therapy after MET resulted a total drug acquisition cost of TL 86,4 Million. Incremental drug acquisition cost for preferring a DPP4i compared to SU projected to be TL 232,1 Million as a 2nd line therapy for uncontrolled patients with T2DM who were under MET monotherapy. Cost of screening and examination for two groups are equal with a yearly cost of TL 93,3 Million, having an incremental cost difference of 0. Cost of preferring a DPP4i as a 2nd line therapy after MET resulted a total diabetes related complication cost of TL 5,2 Billion and the total diabetes related complication cost with a SU increased to TL 5,3 Billion, leading an incremental cost difference of TL 108,1 Million between two 2nd line therapy groups. In detail, incremental cost difference between DPP4i groups compared to SU group calculated as TL 78,3 Million for macrovascular and TL 29,8 Million for microvascular complications. Moreover, incremental cost of major hypoglycaemia estimated to be TL 427.801. As a total, cost of preferring a DPP4i as a 2nd line therapy after MET in T2DM management projected an additional cost of TL 123,6 Million compared to preferring a SU as 2nd line therapy after MET.

Table 1.7. Incremental Cost Between The Two Groups

Cost Items	Cost of MET+ DPP4i (TL)	Cost of MET+SU (TL)	Incremental Cost (TL, DPP4i vs SU, 2nd line therapy, Add-on to MET)
Drug Acquisition	318.571.654	86.435.309	232.136.345
Screening & Examination	93.343.701	93.343.701	0
Total Diabetes Related Complications	5.196.543.751	5.304.624.027	-108.080.276
Macrovascular Complications	2.515.368.953	2.593.630.677	-78.261.724
Myocardial Infarction	591.104.665	617.592.055	-26.487.390
Stroke	315.688.369	321.138.500	-5.450.131
Heart Failure	616.355.458	637.860.948	-21.505.490
Peripheral Vascular Disease	992.220.462	1.017.039.175	-24.818.713
Microvascular Complications	2.681.174.798	2.710.993.350	-29.818.552
Retinopathy	72.882.984	74.389.756	-1.506.772
Neuropathy	685.838.621	688.771.577	-2.932.956
Nephropathy	671.212.997	683.506.024	-12.293.027
Diabetic Macular Edema	368.385.051	372.479.843	-4.094.792
Cataract	66.937.941	66.989.117	-51.176
Diabetic Foot Amputation	148.797.997	149.563.813	-765.816
ESRD	82.279.570	85.810.882	-3.531.312
Ulcers	584.839.636	589.482.337	-4.642.701
Other Costs (Major Hypoglycaemia)	0	427.801	-427.801
TOTAL COSTS	5.563.655.696	5.440.027.428	123.628.269

Furthermore, the health related efficacy outcomes for IHD, non-fatal MI, congestive HF, non-fatal stroke, lower limb amputation, blindness, renal failure, symptomatic hypoglycemia, severe hypoglycemia and weight loss (per unit loss in BMI) estimated to be higher in MET+DPP4i group with a total QALY of 9,86 compared with MET+SU group having a total QALY of 9,72. This leads an incremental difference of 0.14 QALYs favoring MET+DPP4i versus MET+SU group.

Despite the increased drug acquisition costs, DPP4is resulted in greater predicted lifetime QALY gains with an ICER of MET+DPP4i compared to MET+SU calculated as TL 2.779,82.

Table 1.8. Incremental Cost Effectiveness Ratio Calculation

Incremental Cost Effectiveness Ratio Calculation		
ICER =	$\dfrac{\textbf{Cost MET+DPP4i - Cost MET+SU}}{\textbf{Net Effects MET+DPP4i - Net Effects MET+SU}}$	
ICER =	$\dfrac{\textbf{17.514 - 17.125}}{\textbf{9,86 – 9,72}}$	= 2.779,82 TL / QALY
ICER of 2.779,82 is lower than ICER threshold of 45.463. Cost-effectiveness of DPP4is compared to SUs.		

Since this value was below the ICER threshold of TL 45.463 which is the per capita GDP in Turkey in 2018, DPP4is represent a cost-effective treatment alternative to SU at 2nd line of therapy as an add-on to MET in patients with T2DM (66).

5. DISCUSSION and CONCLUSION

5.1. Discussion

Due to the climbing prevalance of T2DM in Turkey, effective management strategies to lessen the burden of the disease on healthcare budget became an important point of consideration for the payers as well as policy makers. Diabetes related costs could further exacerbatewhen the preferred antidiabetics medications lack sustainable efficacy and have a low adverse event profiles. Therefore, the cost-effective treatments with favorable adverse event profiles can be the preferred choice in order to lessen the burden of T2DM in Turkish healthcare budget.

This dissertation provides a pharmacoeconomic analysis to reveal the cost-effectiveness of DPP4is compared to SUs as 2nd line therapy after MET in the management of T2DM in Turkey. Clinical efficacy and safety datas for the economic analysis were taken from a RCT of alogliptin compared to glipizide as an add-on therapy after MET and health related outcomes were gathered from UKPDS utility datas. It is estimated that addition of a DPP4i after MET as a 2nd line therapy is associated with an increased glycemic sustainability, fewer adverse events and improved quality of life. These factors resulted higher costs of diabetes related complications for SUs compared to DPP4is. When total direct costs and QALYs compared between DPP4is versus SUs, incremental cost-effectiveness ratio was calculated as TL 2.779,82. This figure reflects that in order to gain 1 unit of QALY with a DPP4i compared to a SU after MET as a 2nd line therapy in T2DM, an additional treatment cost of TL 2.779,82 should be spend per patient. Because the ICER value is below the ICER threshold of TL 45.463 per QALY gained, DPP4is estimated to be a cost-effective treatment alternative compared with SUs for the treatment of patients with T2DM.

Literature suggests that DPP4is are cost-effective compared to SUs in different setting including, UK, Germany and Portugal when added to MET in the management of T2DM (68, 71, 72). In Turkish setting, although the drug acquisition cost of preferring a DPP4i compared to a SU is more expensive as a 2nd line of therapy, costs of managing diabetes related complications and adverse events was significantly lower. Thus, the overall cost effectiveness analysis of the DPP4i in comparison to SU classes resulted in a positive outcome.

When up-to-date diabetes guidelines were observed such as AACE and ACE consensus guidelines in 2018, DPP4is recommended prior to SUs in the algorithm of T2DM management due to its sustainable efficacy and favorable adverse event profile including low risk of hypoglycemia and weight neutral. Therefore, timely access of such newer medications is crucial both to improve the health realted outcomes of the patients and to decrease the burden of the disease. However, the reimbursement policies of SSI which slows the entrance of newer medications by restricing the reimbursement conditions compared to older generation such as specific authorized specialties for prescription or authorization of prescription only in selected healthcare institutions, partially approving or not approving the reimbursement of newer diabetic medications such as GLP1 RAs, SGLT2is and DPP4is may results in higher overall costs of T2DM in Turkey.

This study had the importance of being the first analysis which provides the total number of T2DM patients under antidiabetic in 2018, analyzed up-to-date optimal management of T2DM with latest guidelines and revealed the reimbursement conditions for newer generation of antidiabetics versus older generation and evaluated the cost-effectiveness of DPP4is compared to SUs in the treatment of T2DM in Turkey.

5.2. Limitations

The cost effectiveness analysis method used in this dissertation is a basic analysis model performed with taking consideration of several assumptions that excludes the continuous effect of clinical progression of the disease. Therefore, the results should be interpreted within the scope of the provided assumptions taking into consideration some limitations.

This thesis assumed a definite target of 2nd line patient population where the rest of the population was neglected which affects the patient population and therefore the overall costs of every cost item. In addition, it was assumed that the target population was at age ≥ 20 years old and the data from the analysis does not have the power to generalize to other ages.

Because of the lack of studies that provide the disease characteristics of Turkey, needed data obtained from international trials. Treatment effects such as change in H_bA1_c, hypoglycaemia, change in weight in terms of BMI, macrovascular and microvascular complication rates obtained from a study from United Kingdom with limited time

horizon. Utility scores were obtained from an international study UKPDS in which newer generation antidiabetics such as DPP4is were not used. Depending in all of these factors, the results found in this study might have when projected

Fixed dose combination forms of DPP4is and SUs were out of scope of this thesis. In addition, indirect costs were not considered in the study. Self-monitoring costs were also excluded in the study. These factors might also have an effect on the cost of two treatment groups.

Future research can investigate the cost-effectiveness by including both direct and indirect costs related with these treatment groups via detailed pharmacoeconomic models with lifetime horizon to better reflect the overall cost-effectiveness of these treatments.

In spite of these limitations, this thesis has the importance of being the first pharmacoeconomic analysis which compares newer generation antidiabetics with older generation antidiabetics in T2DM management in Turkey.

5.3. Implications for Future Research

This dissertation provides a first in literature perspective in Turkey towards the cost-effectiveness for a newer class of antidiabetic medication with an older class. Due to the lack of available scientific data representing the Turkish population, event rates of complications, utility scores for QALY calculations and the cost of complications for the 2018 in Turkey were gathered from the different publications and implemented in the thesis to provide a perspective in the setting of Turkey.

For future research, an up-to-date COI analysis should be performed to obtain more precise estimates of the costs of complications in Turkey. In addition, the outcomes of the CAROLINA study which is a CVOT comparing the CV safety of linagliptin versus glimepiride in patients with T2DM, which will be published in 2019 should be taken to calculate the incremental difference among event rates of complications between DPP4is and SUs. Moreover, a Markov Model based on UKPS data in T2DM should be developed with defined health states and a time horizon.

With the use of these more current data reflecting the cost and health related efficacy measures in Turkey and a developed Markov Model would result in better estimates of CEA between DPP4is and SUs as a second-line of therapy can be made to provide valuable insight for decision makers.

5.4. Conclusion

The use of DPP4is might be associated with improved outcomes compared to SUs at a cost that would likely be considered acceptable in the Turkey. DPP4is are projected to have a sustainable efficacy combined with a favorable tolerability profile and a cost-effective treatment compared to SUs as 2nd line of therapy option after MET in the management of T2DM. DPP4is answers some of the unmet medical needs in the treatment of T2DM gain compared to SUs such as minimizing the risk of hypoglycaemia and weight control. This generated a lower overall incidence of diabetes related complications, resulting in an ICER within the cost-effectiveness threshold for the Turkish healthcare system setting.

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Education

Degree	Department	The name of the Institution Graduated From	Graduation year
Master	Business Administration	**Bahcesehir University**	2018
University	Pharmacy	**Yeditepe University**	2012
High school	-	**American Robert College**	2005

Al All the grades must be listed if there is more than one (KPDS, ÜDS, TOEFL; EELTS vs),

Languages	Grades (#)
English	-
German	-

Work Experience (Sort from present to past)

Position	Institute	Duration (Year - Year)
Diabetes Senior Product Manager	Boehringer Ingelheim Co.	2019-2019
Diabetes Product Manager	Boehringer Ingelheim Co.	2017-2019
Diabetes Regional Medical Manager	Boehringer Ingelheim Co.	2016-2017
Key Hospitals Manager	CSL Behring Co.	2015-2016
Sales Representative	Servier Pharmaceuticals Co.	2013-2015
Assistant Production Manager	Turkish Military Pharmaceutical Plant	2013-2014
Jr. Product Manager	Servier Pharmaceuticals Co.	2012-2013

Computer Skills

Program	Level
Microsoft Office	Excellent
Adobe Photoshop	Average

*Excellent , good, average or basic

Scientific works
The articles published in the journals indexed by SCI, SSCI, AHCI

-

Articles published in other journals

-

Proceedings presented in international scientific meetings and published in proceedings book.

-

Journals in the proceedings book of the refereed conference / symposium

-

Others (Projects / Certificates / Rewards)

Several Rewards in Pharmaceuticals Business field about accomplishments in Sales, Marketing and Medical Affairs.