Association of Sulfonylureas in the treatment of Type 2 Diabetes and Cardiovascular risk

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

School Of Pharmacy
BRAC University
December 2023

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

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Ethics Statement

This study does not involve any kind of animal or human trial

Abstract

Type 2 diabetes mellitus has a great impact on worldwide. It is a disease which is getting more common day by day. There are many medications available to treat type 2 diabetes. Among those medications sulfonylureas has shown some excellent efficacy and results, so that it is getting more popular as an anti-diabetic drug to treat type 2 diabetes. There are various generations of sulfonylureas like first generation, second generation. This anti diabetic drug mainly works by inhibiting insulin release from the pancreatic beta cell. But along with the benefits of sulfonylureas there is a concern about the cardiovascular risk associated with this drug. In this paper, the role of sulfonylureas has been briefly discussed how it is beneficial for the type 2 diabetic patients. Duration of action, working mechanisms of sulfonylureas have also been discussed. Some assuring results has been shown related to the cardiovascular risk of the sulfonylureas.

Keywords: Diabetes mellitus, Type 2 diabetes, sulfonylureas, cardiovascular risk

Dedication

Dedicated to my parents

Acknowledgement

First and foremost, I would like to start by thanking Allah SWT Almighty for His infinite blessings and compassion. All praise to Him for blessing me with the enormous patience, strength, and help needed to finish this project. I would like to show gratitude to my supervisor, Luluel Maknun Fariha (Lecturer, School of Pharmacy, BRAC University), whose devoted participation and oversight in every step has helped me to effectively complete this project. I thank her for her precious advice and patient conduct whenever I encountered difficulty throughout this stage. I also want to show gratitude to our honorable Professor and Dean, Dr. Eva Rahman Kabir (School of Pharmacy, BRAC University).

Finally, in every step of my life, I want to thank my parents for their continuous support and motivation to work harder. Without their prayers and unconditional love, I do not think I would have come so far.

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List of Acronyms

WHO	World Health Organization
DM	Diabetes mellitus
T2DM	Type 2 diabetes mellitus
UKPDS	United Kingdom Prospective Diabetes Study
SU	Sulfonylurea
TZD	Thiazolidinedione

Chapter 1

Introduction

1.1 Background

Chronic hyperglycemia is known as metabolic disorder which occurs by the shortage of insulin secretion or it can be caused by reduced insulin action (Antar et al., 2023). Insulin have different important roles like it works similarly like an anabolic hormone, it also affects the metabolism of lipids, proteins, carbohydrates (Antar et al., 2023). Insulin resistance is the primary cause of the metabolic abnormalities linked to diabetes, which primarily impact among the tissues such as the liver, skeletal muscles, the adipose tissue (Antar et al., 2023). The symptoms may vary according to the type and duration of diabetes (Antar et al., 2023). Some individuals with diabetes, especially those having type 2 diabetes in its early stages, may not exhibit any symptoms (Antar et al., 2023). Without adequate care, uncontrolled diabetes can cause a number of consequences including coma, disorientation, and, in rare instances, death from untreated nonketotic hyperosmolar syndrome or ketoacidosis (Antar et al., 2023).

According to the WHO, 422 million of people have diabetes worldwide and each year 1.5 million people dies due to diabetes. The WHO reported that 8.5% of the population ages 18 and over had diabetes in 2014. In 2019, because of diabetes 1.5 million deaths were occurred, 48% among them were before the age of 70 (Antar et al., 2023). Diabetes-related standard mortality rates increased by 3% in the years between 2000 and 2019 and the death rate linked with diabetes increased by 13% in nations with lower middle-class incomes (Antar et al., 2023).

1.2 Types of Diabetes

Commonly diabetes is classified by two types and they are Type 1 and Type 2 diabetes (Petersmann et al., 2019). Besides that there is another type of diabetes which is called Gestational diabetes (Seferović et al., 2018). Type I diabetes which is known as autoimmune illness in this condition the body's immune system kills the cells that helps to produce insulin. Type II diabetes, which is more prevalent than type I, develops when the body does not react to the insulin produced (Khan et al., 2019). Before the start of abnormal insulin secretion, type 1 diabetes can be detected (Gnesin et al., 2020). The actual mechanism of type 2 diabetes is still unknown (Khan et al., 2019). Type 2 diabetes is influenced by both genetic and epigenetic factors (Filion et al., 2019). Obesity is one of the environmental factors that is linked to type 2 diabetes (Mohan et al., 2019). The management of type 2 diabetes mellitus requires changes in daily life and self-management abilities. Changes in eating habits are among the most important lifestyle adjustments and difficulties for diabetes patients (Chester et al., 2019). For many years, diabetic patients were advised to follow the standard portion-controlled carbohydrate diet. However, a variety of other diets are currently being evaluated in this group (Chester et al., 2019). The people with overweight or obese people having type 2 diabetes, the American Diabetes Association (ADA) suggests reducing calorie consumption using a hypocaloric diet to promote weight loss, which improves blood glucose levels (Chester et al., 2019). The American Diabetes Association also suggests a number of eating habits that are suitable for the maintenance of prediabetes and type 2 diabetes, such as the Mediterranean diet, dietary strategies to lower blood pressure, and plant-based diets. Leading MNT approaches for type 2 diabetes include calorie restriction and carbohydrate monitoring (Chester et al., 2019). Ketogenic diet is also recommended for the diabetic patients (Ipsen et al., 2020). Exercise and walking plays a vital role in the management of diabetes.

The manual measurement of blood sugar levels followed by daily subcutaneous insulin injections is the most famous Type 1 diabetes therapy method (Sharma et al., 2016). Instead of using standard injections, patients with difficult-to-control glucose levels may switch to insulin pumps, which offer the benefit of continually delivering tiny quantities of insulin subcutaneously (Akil et al., 2021). Metformin and lifestyle modification are well-established as the first-line treatments for type 2 diabetic mellitus (T2DM). But within a year of being diagnosed with T2DM, over half of those affected would need more antihyperglycemic drugs (Hedrington & Davis, 2019). Safety, effectiveness, tolerability, cost and ease of administration are the main considerations that healthcare professionals and patients must make when deciding whether to pursue second-line therapy (Varvaki Rados et al., 2016). Sulfonylureas (SU), dipeptidyl peptidase 4 inhibitors, thiazolidinediones, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, glucagon-like peptide receptor which is an agonist, and insulin are now among the second-line treatments for Type 2 diabetes mellitus (Hedrington & Davis, 2019). While SUs, TZDs, and insulin can all significantly improve glycemic control but they can also all lead to weight gain (Hedrington & Davis, 2019). Highly efficient peptide medications that imitate the incretin hormone (GLP-1) are known as GLP-1 receptor agonists (Hedrington & Davis, 2019). Glucose-lowering effects, a reduced risk of hypoglycemia, and weight reduction are further advantages of GLP-1 receptor agonists. Liraglutide has also been shown to have particular cardiovascular advantages. The group thus seems to be a desirable option for dual combination treatment in addition to metformin (Hedrington & Davis, 2019).

Sulfonylureas is the most commonly prescribed oral agents which is being used for the treating type 2 diabetes patients (Korytkowski, 2004). It is introduced nearly 50 years ago (Korytkowski, 2004). Since the introduction of the sulfonylureas it has been evolved through two generations. It is mainly effective for lowering the plasma glucose concentration level (Korytkowski, 2004). Sulfonylureas mainly triggers the release of insulin from the pancreatic

β cell (Rendell, 2004). Sulfonylureas occupy a particular position on the adenosine triphosphate sensitive potassium channels that causes the potassium channels to close and the calcium channels to subsequently open (Rendell, 2004). This activity is the outcome of the exocytosis of insulin (Rendell, 2004). There are some primary sulfonylureas like glyburide, gliclazide, glipizide which is being used worldwide for curing type 2 diabetes (Rendell, 2004). Compared to the other agents Glibenclamide has a higher rate of hyperglycemia (Rendell, 2004). Sulfonylureas gradually lose some of its efficacy after prolonged usage (Rendell, 2004). Hypoglycemia is sulfonylureas' main adverse effect. Theoretically, sulfonylureas might impair cardiac potassium channels, decreasing the heart's ability to respond to ischemia (Rendell, 2004). In addition to sulfonylureas, there are currently a variety of options for type 2 diabetes initial treatment. Thiazolidinediones and metformin have different effects on insulin sensitivity (Rendell, 2004). Disaccharidase inhibitors slow down the fast absorption of carbohydrates. Among the majority of type 2 diabetes patients, no single treatment seems to be able to achieve goal glucose levels (Rendell, 2004). Most patients having type 2 diabetes will continue to receive sulfonylureas, both as the main medication and as a component of a combination therapy (Rendell, 2004).

1.3 Cardiovascular risk

According to the UGDP, sulfonylureas therapy is related with cardiovascular effect (Younk et al., 2016). Their study shows that tolbutamide is correlated with cardiovascular mortality (Younk et al., 2016). Their review of different data proved that they failed to find any dissimilarity between the deaths which were linked with MI or diabetes correlated to sulfonylureas or the insulin therapy (Younk et al., 2016). At the same time potassium ATP channel, sulfonylurea receptor were found in cardiac myocytes (Younk et al., 2016). Some other research shows binding affinity between cardiac potassium ATP channel and glinides and sulfonylureas at the pancreas (Younk et al., 2016). This proves the correlation between the

insulin therapy and cardiovascular effects (Younk et al., 2016). The patients with acute myocardial infarction and the rate of early mortality were linked with sulfonylureas therapy (Younk et al., 2016). The UKPDS Insisted to use glyburide , chlorpropamide to imrove the glycemic control and to reduce mortality linked with diabetic conditions (Younk et al., 2016).

Chapter 2

2.1 Aim

This review aims to overview the use of Sulfonylureas and also to find out the efficacy, safety, the outcome of the everlasting use of sulfonylureas in the administration of type 2 diabetes and cardiovascular risk associated with the use of sulfonylureas.

2.2 Objectives

The objectives of this review are:

- To investigate the clinical pharmacology data about sulfonylureas and to provide an overview of the clinical studies conducted to determine the safety and efficacy of the sulfonylureas alone and in combination with metformin for the management of type 2 diabetes mellitus.
- To combine the existing knowledge about the mechanism of action, use and side effects of sulfonylureas for the management of type 2 diabetes.
- To find out currently used sulfonylureas to treat type 2 diabetes
- To find out the cardiovascular risk associated with the use of sulfonylureas

2.3 Rationale of the study

The rational of this study is to gather knowledge about the sulfonylurea which is an ant diabetic drug and to also know about the related cardiovascular risk. Sulfonylureas are the class of anti-diabetic drug which is being prescribed to maintain the blood glucose level. Various research and studies shows satisfying results that we can use this drug to treat type 2 diabetes. But they also warn us about the cardiovascular risk related to this drug as well. This report will enlighten us about the cardiovascular risk and will show us different data's and facts which will help us to understand about those risks. Along with the cardiovascular risk this study will also provide

us information about the different generation of sulfonylureas and will also show us which their efficacy as well.

Chapter 3

Methodology

All the details and information's in this study were gathered from various reliable references. Different journals, research articles, reviewed articles had been used. Moreover, some renowned and well known sources like Pubmed, Science Direct, Elsevier, Medscape, Google Scholar had been used to gather the information's. Relevant papers had been used to gather information's regarding the important keywords like Diabetes, type 2 diabetes, Sulfonylureas, cardiovascular risk etc. All the papers had been selected carefully to complete this review paper. All the tables and figures and data's were collected from the research articles. All the relevant information's were collected and summarized here in a precise way. To show respect to the original authors Mendeley software had been used for fair referencing.

Chapter 4

4.1 Mechanism action of Sulfonylurea

The sulfonylurea receptor: Sulfonylureas increase the release of insulin (Rendell, 2004). This improvement is physiological because it acts similarly to how insulin normally releases in response to glucose (Rendell, 2004). As a result, improvement in glucose level observed and also changes in insulin receptor levels (Rendell, 2004). The adenosine triphosphate sensitive potassium channels close as a result of the sulfonylureas' action at the β-cell membrane in pancreas (Rendell, 2004). The inactive potential of the membrane is lower than what is needed for the voltage gated activation of calcium channels when the potassium channels are open (Rendell, 2004). The amount of ATP produced by glycolysis increases as glucose enters the cell (Rendell, 2004). For the rise in ATP concentrations the ATP sensitive potassium channel closes (Rendell, 2004). Because of the closure of the potassium channel, the calcium channel opens which enhances exocytosis of insulin from storage granules (Rendell, 2004). The mechanism of action of sulfonylureas is to get connected with the ATP-sensitive potassium channel's sulfonylurea receptor subunit and cause channel closure (Rendell, 2004). The binding site for sulfonylurea comes in many forms: SUR 2A and SUR 2B are the vital modes in skeletal and cardiac muscle, among them SUR 1 is the predominant form in the β-cell membrane (Rendell, 2004). Excessive insulin release, or hyperinsulinaemic hypoglycemia of infancy, can result from mutations in the SUR gene (Rendell, 2004).

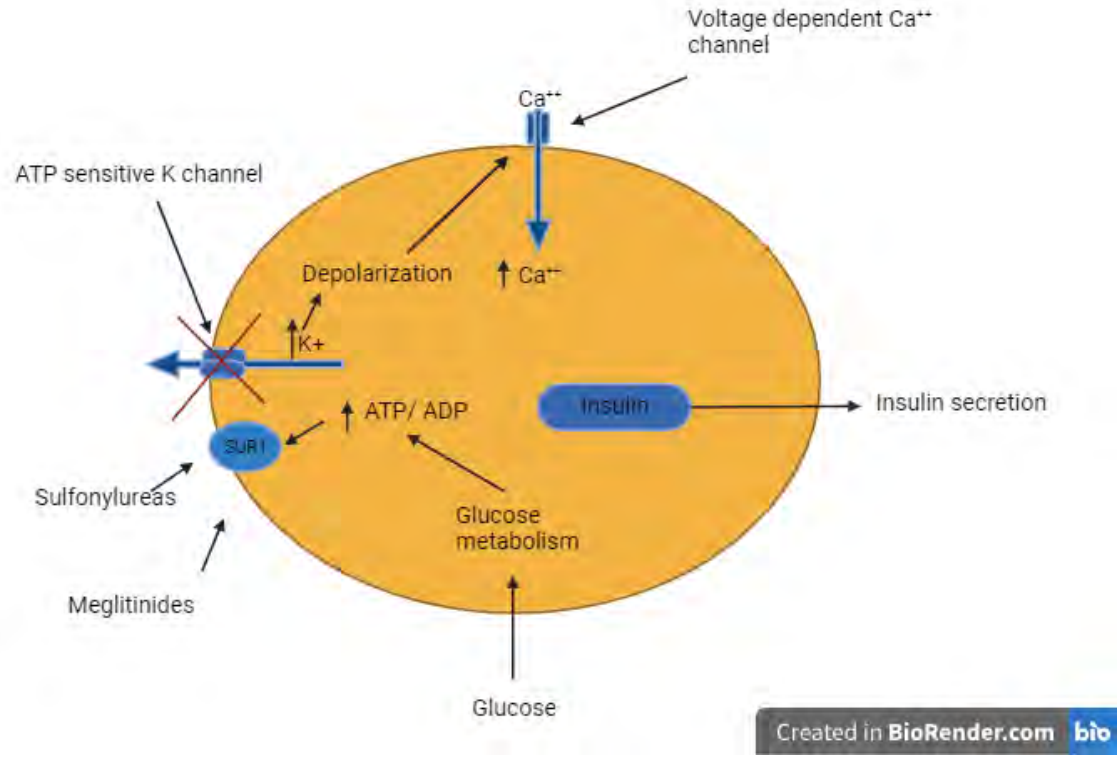

Figure 1 Mechanism of action of Sulfonylureas

4.2 Currently available sulfonylureas

Some first generation sulfonylureas are tolbutamide, chlorpropamide, tolazamide (Rendell, 2004). These first generation of sulfonylureas are successfully replaced by glyburide, glipizide, gliclazide which are known as second generation agents (K, 1998). Glimepiride is one of the most recent third generation sulfonylureas (Del Prato & Pulizzi, 2006). These newer generations are 20-50 times more potent and in comparison with the older agents they have longer biological action (Biederman et al., 2005). The newer generations have less undesirable effects such as reaction to hyponatremia, alcoholic beverages (Rendell, 2004).

4.3 First generation Sulfonylureas

First generation sulfonylureas are the class of drugs which are being used to treat type 2 diabetes (Rendell, 2004). They function by inducing the pancreatic beta cells to produce more insulin (Rendell, 2004). Insulin is a hormone that facilitates the absorption of glucose into cells, which helps control blood sugar levels (Rendell, 2004). The first generation sulfonylureas include:

- Tolbutamide: It was introduced in the early 1950s (Rendell, 2004). Its duration of action is shorter than the other generation of sulfonylureas (Rendell, 2004).
- Chlorpropamide: It has longer duration of action than the tobutamide (Rendell, 2004).

4.4 Second generation Sulfonylureas

These drugs were introduced after the first generation of sulfonylureas and they provide better duration of action, potency and they have low risk of hypoglycemia (Sola et al., 2015). Second generation of sulfonylureas include:

- Glyburide: One of the most widely utilized second-generation sulfonylureas is glyburide (Sola et al., 2015). Compared to first-generation sulfonylureas, it has a longer duration of action, which permits once-daily dosage in many circumstances (Sola et al., 2015). Glyburide acts by inducing the secretion of insulin from beta cells in the pancreas (Sola et al., 2015).

- Glipizide: Glipizide is a sulfonylurea of the second generation that acts more quickly than glyburide (Sola et al., 2015). In order to align with postprandial glucose spikes, it is frequently administered prior to meals (Sola et al., 2015). It increases the release of insulin, just as other sulfonylureas (Sola et al., 2015).

- Glimepiride: A more recent second-generation sulfonylurea with a longer half-life is glimepiride (Sola et al., 2015). It increases the production of insulin and is also given once a day (Sola et al., 2015). Compared to some other sulfonylureas, glimepiride is well-known for its potency and may have a decreased risk of hypoglycemia (Sola et al., 2015).

Table 1 Various generations of sulfonylureas

Molecules	**Generation**	**Dose (mg)**	**Duration of action**	**Activity of metabolites**	**Elimination rate**
Tolbutamide	First	500-2000 mg	Short 4.5-6.5 hour	Inactive	Urine (100%)
Glibenclamide	Second	2.5-15 mg	Intermediate to long 5-7 hour	Active till 10 hour	Bile (50%)
Gliclazide	Second	40-320 mg	Intermediate 10 hour	Inactive	Urine (65%)
Glipizide	Second	2.5-20 mg	Short to intermediate 2-4 hour	Inactive	Urine (70%)
Gliquidone	Second	14-180	Short 3-4 hour	Inactive	Bile (95%)
Glimepiride	Second	1-6 mg	Intermediate 5-8 hour	Active till 6 hour	Urine (80%)

4.5 Sulfonylureas in the management of type 2 diabetes

Monotherapy: Recently the purpose of managing type 2 diabetes is monotherapy with an antihyperglycemic agent (Khan et al., 2019). Insulin resistance and insufficient insulin are combined to form type 2 diabetes (Khan et al., 2019). Patients differ greatly in the relative significance of reduced insulin release and insulin resistance (Del Prato & Pulizzi, 2006). Among the non-obese patient the major problem is impairment of insulin secretion (Khan et

al., 2019). But for the obese patient insulin resistance is an important component (Khan et al., 2019). Patients who have type 2 diabetes always faces insufficient insulin secretion, regardless of how severe their insulin resistance may be (Rendell, 2004). Additionally, according to United Kingdom Prospective Diabetes Study data, there is an approximate 50% lack in pancreatic β-cell activity and insulin resistance in individuals having type 2 diabetes at the time of diagnosis (Rendell, 2004). Regardless of therapy, the later research showed a 4% annual decline in β-cell activity over time, but no change observed in case of insulin resistance (Rendell, 2004). Since the main damage in type 2 diabetes is insulin shortage, replacing the lost insulin must be a part of the treatment (Rendell, 2004). This objective can be achieved by increasing insulin secretion or by administering exogenous insulin (Rendell, 2004). The meglitinides and sulfonylureas are the two classes of drugs that have the ability to increase insulin secretion (Rendell, 2004). Currently, the sulfonylureas have some concern regarding the possible cardiac adverse effects (Rendell, 2004). According to the UKPDS, the cardiovascular outcomes of sulfonylureas, metformin, or insulin did not vary (Rendell, 2004). The extensive investigation into the sulfonylureas' mechanisms of action has improved our knowledge of the tissue specificity of different SUR agents (Rendell, 2004). Glimepiride, gliclazide, and glipizide extended-release at typical dosage seem to have less potential for interaction with the cardiac SUR than glibenclamide (Khan et al., 2019). Both hypoglycemia and bodyweight gain are risks associated with sulfonylureas (Rendell, 2004). The meglitinides acts at the SUR and shoes effects on the secretion of insulin like the sulfonylureas (Rendell, 2004). The meglitinides is advantageous than the sulfonylureas as it lessens the threat of hypoglycemia (Del Prato & Pulizzi, 2006). But the meglitinides drug have to be taken multiple times during the day which is one of the disadvantage of the meglitinides (Del Prato & Pulizzi, 2006). Clearly, meglitinides cause less hypoglycemia than sulfonylureas do; that being said, this is less of a problem when the patient has extremely elevated glucose levels (Rendell, 2004).

Meglitinides have higher price than the sulfonylureas. The meglitinides is advantageous to the elderly patient who have greater risk of hypoglycemia and the patients with renal impairment (Rendell, 2004). For curing type 2 diabetes there are other therapeutic alternatives as well. Metformin has shown great efficacy in treating obese patients with type 2 diabetes (Khan et al., 2019). Metformin decreases the hepatic gluconeogenesis (Khan et al., 2019). For the overweight patients with type 2 diabetes, metformin is a better option (Rendell, 2004). So in case of the obese patient metformin is likely to avoid further weight gain and for the people who have normal body weight the sulfonylureas is preferable as it helps in the regaining process of insulin secretion, which is considered as the major reason of type 2 diabetes (Rendell, 2004).

4.6 Combination therapy

Nowadays, metformin is often introduced as the initial adjuvant medication to sulfonylurea treatment (K, 1998). Acabose and miglitol, two disaccharidase inhibitors, work well when combined with sulfonylureas (Biederman et al., 2005). The combination of glibenclamide and miglitol works better against the hypoglycemia than the glibenclamide alone (Biederman et al., 2005). But when combined with sulfonylurea medication, metformin seems to have benefits over acarbose (Biederman et al., 2005). Insulin with sulfonylureas or metformin plus sulfonylureas reduced HbA1c levels around twice as much as acarbose plus sulfonylureas (Rendell, 2004). Compared to glibenclamide alone, metformin plus glibenclamide decreases HbA1c by 1.5% (Rendell, 2004). It is suggested that this combination can drop HbA1c levels more quickly and possibly with fewer side effects than either glibenclamide or metformin taken at their maximum dosages alone (Rendell, 2004). The combination of these two drugs, however, raises the possibility that cardiovascular mortality will be greater than taken each one alone (Rendell, 2004). Sulfonylureas and thiazolidinediones are also an effective combination which lowers HbA1c by 1- 1.4% (Rendell, 2004).

4.7 Combination of insulin with oral antihyperglycemic drug

Alongside the positive outcome of combination oral regimens, there has been a rise in the use of oral antihyperglycemic medications and insulin injections (Korytkowski, 2004). The incidence of hypoglycemia has been reduced when oral antihyperglycemic medications are used in conjunction with insulin glargine rather than NPH insulin (insulin suspension isophane) (Korytkowski, 2004). Patients suffering from type 2 diabetes who get insulin injections in addition to metformin, they observe a decrease in blood glucose levels and less weight gain than using the insulin itself (Korytkowski, 2004). Numerous trials have demonstrated the value of additional sulfonylureas in conjunction along with insulin for individuals with type 2 diabetes (Korytkowski, 2004).

4.8 Side effects of Sulfonylureas

Usually, Sulfonylureas are well tolerated (Sola et al., 2015). Hypoglycemia is the major side effects of sulfonylureas lile chlorpropamide and glibenclamide (Sola et al., 2015). But every sulfonylurea has the potential to induce hypoglycemia, because of taking excessive dosage (Sola et al., 2015). It is better to keep in mind that hypoglycemia can last for several hours and may need hospitalization (Sola et al., 2015). A 4-year prospective analysis of 14,000 type 2 diabetic patients over 65 years of age or older on various sulfonylurea medications revealed that severe hypoglycemia episodes were minimal (Sola et al., 2015). This incidence was higher among the patients who were taking glibenclamide and lower for the patients who were taking tolbutamide (Sola et al., 2015). For preventing hypoglycemia, it is better to begin treatment with sulfonylureas with low dose (Sola et al., 2015). By directly targeting β-cells, sulfonylureas enhance insulin secretion and cause progressive malfunction (Sola et al., 2015). Therefore, diabetes may get worse over time even with improved glucose control in the short term (Sola et al., 2015). This phenomenon is called secondary failure and this is the unavoidable destiny of all the hypoglycemic drugs, especially for the older sulfonylureas (Sola et al., 2015). The

incidence of hypoglycemia caused by sulfonylurea in the elderly is often undervalued and has varying reported frequencies (Sola et al., 2015). But in case of the new sulfonylureas like glipizide, glimepiride this risk is lower (Sola et al., 2015). Less aggressive treatment approaches can be used in the context of the "frail elderly," where the glycated haemoglobin target is raised upto 8.6% (Sola et al., 2015). The use of medications that increase the risk of longlasting hypoglycemia is not justified by this theory (Sola et al., 2015). Therefore, in the case of type 2 diabetes, sulfonylureas should be the second or third line drugs rather than as first line therapy due to the following conditions: liver disease, renal impairment, among the elderly patients (> 75 years) (Sola et al., 2015). Although it occurs less frequently than with insulin, weight gain is nearly always a side effect of sulfonylurea therapy (Sola et al., 2015). This undoubtedly has a negative impact, particularly when it comes to a chronic condition like diabetes mellitus when managing body weight may be the primary goal of treatment (Sola et al., 2015). Luckily, taking metformin simultaneously reduces the amount of gaining (Sola et al., 2015). Other rare adverse effects that might happen with any sulfonylurea including photosensitivity, exfoliative dermatitis including erythema multiforme, nausea (Sola et al., 2015).

Chapter 5

Results

Table 2 Randomized controlled trials that investigated the cardiovascular safety of sulfonylureas adapted from (Scheen, 2021)

RCTs	Sulfonylurea	Comparator	N SU/ Comparator	Follow up	CV Mortality	All Cause Mortality	Stroke	MACEs	MI
ADVANCE	Modified release Gliclazide	Standard treatment	5571/5569	5 years	0.88(0.74-1.04)	0.93(0.83-1.06)	1.02(0.85-1.24) Non lethal	0.94(0.84-1.06)	0.97(0.78-1.22)
CAROLINA	Gliclazide Glimepiride	Linagliptin	3010/3023	6.3 years	1.00(0.80-1.23)	1.10(0.94-1.28)	1.16(0.89-1.52)	1.02(0.88-1.19)	0.94(0.84-1.06)
UKPDS	Glibenclamide Clorpropamide	Diet alone Diet alone	615/1138 619/1138	11.1 years 11.1 years	NA NA	0.91(0.73-1.15) 1.02(0.82-1.27)	1.38(0.52-2.08) 1.01(0.65-1.58)	NA NA	0.78(0.60-1.01) 0.87(0.68-1.12)
TOSCA-IT	Glibenclamide Glimepiride	Pioglitazone	1493/1535	4.8 years	NA	0.91(0.62-1.33)	1.27(0.65-2.44) Non lethal	1.04(0.79-1.35)	1.15(0.65-2.08) Non lethal

ADVANCE: In this method, Gliclazide has been tested and was under observation up to 5 years. Related data were found which shows us the cardiovascular mortality rate, all-cause mortality rate, stroke rate, major advance cardiovascular events rate and the myocardial infarction rate.

CAROLINA: In this method, gliclazide and glimepiride were tested and was under observation up to 6.3 years. After the observation data were found regarding the cardiovascular safety.

UKPDS: Glibenclamide, chlorpropamide was under observation up to 11.1 years and tested which gave us satisfying data that there was no cardiovascular mortality and also for the major advance cardiovascular events.

TOSCA-IT: Again , glibenclamide and glimepiride were tested and the comparator was pioglitazone. In this test, there was no cardiovascular mortality as well.

Several meta-analyses summarized findings; two of them are shown in **Table 3.**

Table 3 Randomised controlled trials and observational studies that investigated the effects of sulfonylureas versus comparators on cardiovascular complications adapted from (Scheen, 2021)

References	Type of Studies	Mode of Comparison	CV Mortality	All Cause mortality	MACEs	MI	Stroke
Versus DPP-4is	RCTs+observational studies 7 RCTs	HR MH-OR	4.42(1.92-13.00) 1.50(0.49-4.52)	2.03(1.22-3.58) 1.40(0.74-2.65)	NA 1.85(1.20-2.87)	2.54(1.14-6.57) NA but NS	9.40(3.27-41.90) 4.51(1.60-12.66)
Versus Metformin	RCTs+observational studies 2-4 RCTs	HR MH-OR	1.38(0.90-2.16) NA	1.37(1.03-1.84) 1.29(0.80-2.13)	NA 0.95(0.34-2.70)	1.21(0.78-1.99) NA	1.40(0.92-2.22) NA

In this table, we can see the results of the randomized controlled trials which shows us the comparison of hazard ratio and odd ratio between metformin and dipeptidyl peptidase 4 inhibitors regarding the cardiovascular complexity.

Chapter 6

Discussion

Despite recent studies reporting favorable outcomes, but still there is ongoing disagreement over the Cardiovascular safety of Sulfonylureas following over 40 years (Scheen, 2021). The US UGDP (University Group Diabetes Program) results provide the first evidence against the CV safety of SUs (Scheen, 2021). Certainly compared to a placebo, there was a higher proportion of mortality associated with myocardial infarction while using a first-generation SU (tolbutamide); nonetheless, the trial was questioned from a statistical perspective because to its limited number of events and unsettling confounding variables (Scheen, 2021). At the end of the 1970s The United Kingdom Prospective Diabetes Study, or UKPDS, was designed to examine the benefit or risk ratio of stepping up glucose control with insulin or more modern SUs (chlorpropamide, glibenclamide/glyburide) (Scheen, 2021). Although positive outcomes with SUs in **Table 2** were documented, in the intensive group, the reduction in the frequency of CV events, particularly myocardial infarction, was not significantly correlated with the improvement in glucose control (Scheen, 2021). This finding was in contrast to a subset of obese individuals on metformin who had a substantial decrease in CV events (Scheen, 2021). Subsequently, a number of observational studies comparing various monotherapies revealed that patients with type 2 diabetes treated with SUs had a significantly higher risk of cardiovascular events and death than patients treated with metformin; this difference was more severe when gliptins were used as a treatment (Scheen, 2021). These results, together with other RCT findings, have helped developing doubt on the use of SUs in clinical practice, especially in patients who have a history of CV illness or who are at risk of developing such issues (Scheen, 2021). However, we have found reassuring results in **Table 2** regarding the use of sulfonylureas in the treatment of type 2 diabetes. First, ADVANCE demonstrated that gliclazide modified release glucose management was not linked to a higher rate of

cardiovascular events (Scheen, 2021). Second, the TOSCA-IT ("Thiazolidinediones Or Sulphonylureas and Cardiovascu-lar Accidents-Intervention Trial") study found that patients receiving pioglitazone, a medication that demonstrated some cardiovascular benefits in the PRO active ("PROspective pioglitAzone Clinical Trial In macroVascular Events") study, and SU (glibenclamide, glimepiride, or gliclazide) had similar incidence of CV events (Scheen, 2021). Third, the most recent and appealing trial, CAROLINA ("CARdiovascular Outcome study of LINAgliptinversus glimepiride in patients with type 2 diabetes") found no difference in the incidence of MACEs in patients at high CV risk with T2D treated with glimepiride (Scheen, 2021). For hypoglycemia the use of first generation sulfonylureas have higher risk and among the second geberation SUs, the use of glibenclamide is not recommended as discussed earlier (Scheen, 2021).

Chapter 7

Conclusion

Our study provides some important relationship between the use of sulfonylureas in the treatment of type 2 diabetes and cardiovascular risk. Some limitations of using sulfonylureas which varies among different age of patients have been discussed. The possible side effects of sulfonylureas are shown as well. Despite the limitations and side effects our study shows the evidence of the cardiovascular safety of the sulfonylureas. Some satisfying results has been showed which is the evidence about the efficacy of sulfonylureas in the treatment of type 2 diabetes. In future, more RCTs and long term prospective studies can be beneficial to find out the exact relationship between the sulfonylureas usage and cardiovascular outcomes. In conclusion, our study adds to the current discussion on the selection of the medications for the treatment of type 2 diabetes and enlightens us about the associated cardiovascular risk.

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