

Sulfonylurea Glimepiride: A Proven Cost Effective, Safe and Reliable War Horse in Combating Hyperglycemia in Type 2 Diabetes

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Abstract

Recently, a debate has been raised regarding the place and the role of sulfonylureas (SU) amongst the armamentarium of drugs available for treatment of hyperglycemia in subjects with type 2 diabetes mellitus. With the advent of new drugs, SUs are being relegated and denigrated by some authorities contrary to present recommendations by various organizations e.g. American Diabetes Association, European Association for the Study of Diabetes and International Diabetes Federation. In this article, the advantages of SUs over the new agents in terms of their well established and proven better efficacy as well as their short term and long term (over 50 years) safety based on extensive literature data are documented. Moreover, lower costs of SUs render them to be far more cost effective when compared to new agents and therefore make them affordable in many regions of the world. Additionally, SUs are probably the initial drugs of choice in lean subjects with prediabetes and type 2 diabetes because they are the most effective secretagogues and major pathophysiologic mechanism of altered glucose metabolism in lean subjects is the decline in insulin secretion and not rising insulin resistance. Furthermore, SUs are also the most cost effective 2nd line agents in obese subjects with type 2 diabetes on lapse of glycemic control while receiving metformin. Finally, with progression of the disorder, the most cost effective combination of 2 oral agents in conjunction with basal insulin remains to be metformin and SUs. Many studies have documented a significantly greater extra pancreatic effect of glimepiride in comparison to other SUs probably because of its unique property in enhancing insulin sensitivity in conjunction with its ability to stimulate both 1st and 2nd phase insulin secretion. These characteristics may contribute to its greater efficacy with lesser hypoglycemia when compared with other SUs. Lack of hypoglycemic effect of metabolites of glimepiride may also be responsible for lesser hypoglycaemia. Moreo-

ver, metabolism of glimepiride performed partially by the liver and partially by the kidneys may render it suitable and adaptable to be administered safely in subjects with hepatic or renal dysfunction as well as elderly. Finally, the documentation of its pleiotropic effects in lowering of cardiovascular surrogate markers, improving thrombotic milieu by reducing platelet aggregation factors along with improvement in glycemic control and its preferential binding to SU receptors on the pancreatic beta cells rather than myocardium may be responsible for providing better cardiovascular outcomes in comparison to other SUs and thus make it a better choice amongst SUs in subjects with or without presence of cardiovascular disease. Additionally, once daily administration because of lasting efficacy for 24 hours based on its half life is likely to enhance compliance on the part of patients and assist in attaining and maintaining desirable glycemic control. Therefore, SUs still deserve to be major players in management of hyperglycemia in subjects with type 2 diabetes mellitus and glimepiride may be the best choice amongst SUs because of its long term record regarding efficacy and safety in diverse population of subjects with type 2 diabetes mellitus.

Keywords

Type 2 Diabetes, Sulfonylureas (SU)

1. Introduction

“Sulfonylurea” (SU) debate was recently published in Journal “Diabetes Care” [1] [2]. Ganuth [2] affirms that newer agents are as effective as SUs although premarketing clinical trials have documented markedly greater lowering of A1c from baseline level (25% - 30%) by older drugs, sulfonylureas and metformin in drug naïve subjects in comparison to many newer agents (Table 1) as well as SGLT 2 inhibitors (7% - 12%) [3]-[16]. In fact in UKPDS [17]-[19]) SUs, glibenclamide and chlorpropamide were more effective in all comers, and obese and non-obese subjects when compared with metformin in obese subjects (Table 1). The greater efficacy of sulfonylureas in comparison to newer drugs, e.g. DPP4 inhibitors or GLP1 analogs in drug naïve subjects may be attributed to their ability to lower both the fasting and postprandial plasma glucose by stimulating both 1st and 2nd phase postprandial insulin secretion whereas DPP4 inhibitors and GLP1 analogs stimulate only the 1st phase insulin secretion and thus are devoid of much effect on fasting plasma glucose levels [20]-[26]. In fact, the major alternative mechanism of lowering post prandial glycemia by DPP4 inhibitors is documented to be via decrease in glucagon secretion rather than enhancement of insulin release by beta cells [27]-[40]. Moreover, postprandial glycemia is closely correlated to fasting plasma glucose [41]. Therefore, SUs lower post prandial glycemia to a greater degree when compared with DPP4 inhibitors and GLP 1 analogs. Furthermore, the decline in fasting plasma glucose induced by SUs results in superior efficacy in lowering overall diurnal glycemia with a greater reduction in HbA1c as described previously [11]. Finally, Glimepiride induces a rise in both 1st and 2nd phase postprandial insulin secretion as well as improvement in insulin sensitivity and therefore appears to be more effective than other SUs [11] [26].

In contrast, an equal or greater lowering of HbA1c by newer agents compared to SUs and even metformin in subjects with prolonged duration of diabetes described by Genuth [2] may be attributed to several reasons. Many

Table 1. UKPDS: glycemic control (median HbA1C) and median change (r) in body weight (BWKG) over ten years [17]-[19].

Treatment	Median HbA1C	Median r BW
Chlorpropamide	6.7	5.1
Glyburide	7.2	+4.2
Insulin	7.1	+6.0
Metformin	7.4	+3.0
Conventional	8.0	+2.5

published clinical trials have compared the efficacy of the maximum daily dose of newer agents: DPP4 inhibitors, GLP1 analogs and SGLT2 inhibitors with either a minimally effective or submaximal recommended daily dose of SUs [27]-[40] [42]-[46]. The reason for administration of SUs in a minimally effective or sub maximal daily dose, e.g. glimepiride, 1 - 6 mg in these comparative trials may be explained by the selection of subjects with average baseline HbA1c between 8% and 8.5% prior to initiation of drugs because the maximal daily dose of newer agents is established to lower HbA1c by 10% - 15% whereas the maximum daily dose of glimepiride is documented to lower HbA1c by approximately 25% [11] and therefore a much lower than the maximum daily dose is adequate to obtain a comparable reduction in HbA1c. Moreover, many of these recent comparative clinical trials are conducted by using generic SU, e.g. glimepiride probably with variable bioavailability and variable efficacy. Also, many of these studies are conducted in “clinical trial mills” with same cadre of subjects in their collective databases as recently documented [47] [48]. Thus, recycling of the same subjects hopping from one trial to another may have skewed the “real and accurate” comparative efficacy [48]. Finally, reduced efficacy of older drugs in these “comparative efficacy” trials when compared to the efficacy documented in their “premarketing” trials may be attributed to “drug receptor interaction”. Previous long term or repeated exposure is likely to induce “down regulation” as well as decreased affinity of the receptors of older drugs resulting in decreased efficacy whereas lack of exposure causes “up regulation” and maximal affinity of the receptors for the newer agents at their initiation with consequential maximum efficacy. Therefore, the optimal and appropriate methodology is the comparative trials in drug naïve subjects with the drugs being used either as monotherapy or as a second line agents added to metformin as designed in the ongoing “Grade” trial [49]. Finally, even if the similar efficacies of newer agents are factual, as suggested by Ganuth [2], as per his own admission, SUs are less expensive, thus rendering them to be distinctly more cost effective than newer agents.

2. Discussion

Long term safety of SUs especially in terms of cardiovascular outcomes and all cause mortality has been questioned in several epidemiologic studies mostly through registry data [50]-[53]. However, all these studies are retrospective in nature. Moreover, the other risk factors such as the degree of glycemic control, lipid profiles, duration of diabetes, age of the patients and presence of hypertension and other complications including autonomic neuropathy and renal dysfunction may have impacted these results and hence conclusions. In contrast, the prospective clinical trials have established long term safety of SUs regarding cardiovascular outcomes including occurrence of congestive heart failure as well as all cause mortality [54]-[62]. In fact, UKPDS showed that SUs specifically glibenclamide and chlorpropamide lowered the rate of both micro and macrovascular complications in the original trial as well as during the follow up period of 10 years described as a “Legacy Effect” [17] [18] [56]. Moreover, newer SUs, glipizide, glyclazide and glimeperide are documented to be as or more effective and safer than glibenclamide in terms of cardiovascular outcomes in several studies with glimeperide being the leader [61] [63]-[67]. The superiority of glimeperide over other SUs may be attributed to its ability to improve several surrogate cardiovascular risk markers [67]-[75]. Unfortunately though, lack of increase or decrease in cardiovascular outcomes has become the standard of cardiovascular safety as documented in recent trials with newer agents [15] [16] [76]-[84] rather than lowering of these outcomes with improvement in glycemic control as was documented in UKPDS and Advance studies [17] [18] [55]-[57]. Moreover, the period of observation for safety for newer agents is comparatively markedly shorter when compared with the studies with SUs.

Other valid concerns regarding SUs are their role in induction of hypoglycemia and weight gain. Severe hypoglycemia as defined by diabetes organizations is documented to be extremely rare with SUs [56] [57] [85]-[91]. Non severe hypoglycemia did occur even in metformin treated subjects in UKPDS as well, although the occurrence was significantly lower in comparison to subjects receiving SUs [18]. Similarly, in UKPDS, weight gain was documented in all groups of subjects over a period of 10 - 15 years including obese subjects treated with metformin [17] [18]. Both the occurrences of hypoglycemia and weight gain appeared to be dependent on the degree of long term glycemic control and were greater with better glycemic control in both non obese and obese subjects treated with SUs in comparison to obese subjects receiving metformin (**Table 2**); metformin was not used in nonobese subjects in this study [17] [18]. Moreover, newer SUs, glipizide, glyclazide and glimeperide are documented to be safer in terms of hypoglycemia in comparison to glibenclamide used in UKPDS [55] [57] [90] [91].

Thus, newer SUs, glipizide, glyclazide and glimeperide are documented to be as or more effective and safer in terms of both hypoglycemia and cardiovascular outcomes in several studies with glimeperide being the leader

Table 2. Comparison of efficacy in drug naïve subjects with type 2 diabetes mellitus [11].

Drug	Dose mg/day	Pre-RX HbA1C %	Post-RX HbA1C %	r HbA1C %	r% HbA1C
Glipizide	20	8.8	7.1	1.7	19
Glimepiride	8	9.1 (13.2)	6.7 (7.6)	2.4 (5.6)	26 42
Metformin	2550	8.4	7.0	1.4	16
Avandia	8	8.5	7.3	1.2	14
Actos	45	10.0	8.1	1.9	19
Prandin	12	8.5	7.8	0.6	7
Starlix	360	8.3	7.6	0.8	10
GLP1 analogs	Variable	8.2	6.8	1.4	15
Gliptins	Variable	8.0	7.2	0.8	10

[61] [63]-[75] [87] [90] [91].

In contrast, long term efficacy and safety of newer drugs remains to be established. In fact, SGLT 2 inhibitors possess much lesser efficacy with far greater costs and undesirable adverse effects when compared to SUs. The undesirable adverse effects of SGLT2 inhibitors include dehydration and orthostatic hypotension due to persistent glycosuria resulting in elevations in serum urea nitrogen, creatinine, potassium with an occasional manifestation of severe hypercalcemia and hypernatremia [15] [16] [92]. Moreover, hypercalciuria as well as uricosuria accompanying glycosuria in presence of dehydration may facilitate formation of renal calculi [93]. Another recent report documented increased prevalence of fractures and osteoporosis with use of these agents and attributed this finding to rise in PTH and FGF 23 [94]. We believe that a simple pathophysiology for increase in osteoporosis and fractures is hypercalciuria and phosphaturia accompanying glycosuria induced by these drugs. Additionally high prevalence of genitourinary sepsis secondary to persistent glycosuria should not be acceptable because of a consequential decline of quality of life as well as the cost of management of these infections. Furthermore, glycosuria with resultant polyuria or pollakiuria is likely to induce a decline in quality of life even without occurrence of genitourinary infections especially in elderly men with prostatism and postmenopausal women with urinary incontinence, the population with the highest prevalence of type 2 Diabetes. In fact, the major precipitant in induction of DKA in many of the subjects reported in the recent caution by the U.S Food and Drug Administration (FDA) and European Medicine Agency (EMA) was urinary sepsis [95] [96], a frequent manifestation in subjects with uncontrolled hyperglycemia because of concurrent presence of immunosuppression. The onset of ketoacidosis may also be attributed to increased lipolysis induced by elevated plasma glucagon levels required to promote hepatic glucose production to compensate for glycosuria [97]. The rise in plasma glucagon is also well established to facilitate lipolysis with onset of ketonemia and consequential ketonuria as documented in several recent clinical trials using these agents [15] [16] [98]. FDA also noted that many of these subjects manifested ketoacidosis without hyperglycemia as documented in another recent report [99]. Serum lipase and amylase concentrations were not determined in these subjects in spite of the presence of symptoms, e.g. nausea, vomiting and abdominal pain indicative of acute pancreatitis which has been reported in several case studies [100]-[102]. Therefore, it is likely that Euglycemic Ketoacidosis described in these subjects [95] [96] [99] may be in fact “Kabadi Syndrome of Pancreatic Ketoacidosis” induced by markedly elevated circulating lipase concentration [103]-[106] of acute pancreatitis, the diagnosis which was probably missed in these subjects [99]. Moreover, a pathophysiologic mechanism is also implicated in occurrence of Ketoacidosis on administration of SGLT2 inhibitors [107]-[109]. However, manufacturers of these drugs refute the significance of these reports by FDA and EMA based on the retrospective analysis of pre marketing clinical trials [110] [111]. The lack of significant occurrence of Ketoacidosis in these trials as compared to the other data may be explained by the fact that the participating subjects were healthier because of their selection bias based on several inclusion and exclusion criteria when compared with the population of subjects with type 2 Diabetes in clinical practice. Moreover, the opinions of investigators conducting these clinical trials require scrutiny [111]. Finally, rise in serum LDL and increase in serum viscosity secondary to dehydration is likely to induce a hypercoagulable

milleu with increased susceptibility for macrovascular events, e.g. strokes documented in even short term studies with Canagliflozin [15] [16] [112]. Finally, outcomes of the long term exposure of the genitourinary tract to hyperglycemic hyperosmolar urine are unknown although the increased prevalence of bladder cancer has been reported in early clinical trials using Depagliflozin [113]-[115]. I believe that constant presence of sugar, the most efficient fuel for cell growth may have promoted growth of bladder cancer in situ and rendered it to be manifested rather than initiating the onset. Therefore, the safety of these agents is questionable in the short term and remains to be established in the long term.

In UKPDS, SUs, glibenclamide and chlorpropamide delayed beta cell failure in more subjects and for a longer period of time in both non obese in comparison to subjects treated with conventional(diet and exercise) program as well as obese subjects in comparison to obese subjects treated with Metformin (**Figure 1** and **Figure 2**) [17] [18]. This interesting finding may be attributed to improvement in beta cell function from 50% at diagnosis to 80% by the end of 1st year by SUs (**Figure 3**) [116]. In contrast, beta cell function continued to decline in subjects receiving metformin [116]. I believe that progressive beta cell failure is reversible and not universal as documented on attaining and maintaining weight loss following long term life style intervention as well as bariatric procedures [117]-[124]. Moreover, persistent progressive beta cell failure may be secondary to fibrosis of islets caused by microvascular disease analogous to other microvascular complications of diabetes, e.g. retinopathy, nephropathy and neuropathy [125] [126]. Therefore, sustained, prolonged and permanent preservation of desirable glycemic control is likely to delay onset of beta cell failure similar to the other microvascular complications as demonstrated in recent “Origin” trial [127] [128]. We have recently documented better efficacy of Glimperide in delaying progression to diabetes for a longer period of time and in fewer lean subjects without occurrence of hypoglycemia in comparison to treatment with metformin in obese subjects with prediabetes [129]. The efficacy of glimepiride may be attributed to the decline in insulin secretion being the major pathophysiologic mechanism in onset of impaired glucose tolerance and type 2 diabetes in lean subjects [130]. In the same study, we observed similar improvements in lipid pattern and other cardiovascular surrogate markers with no deaths and CV outcomes in both lean and obese groups with prediabetes [67].

I believe that improvements in lipids and CV surrogate markers by both drugs, glimepiride and metformin described in this and several other studies are likely to be induced by improvement in functioning of cells and tissues by enhanced entry of glucose, the most effective fuel. In contrast, long term efficacy and safety of newer drugs remains to be established.

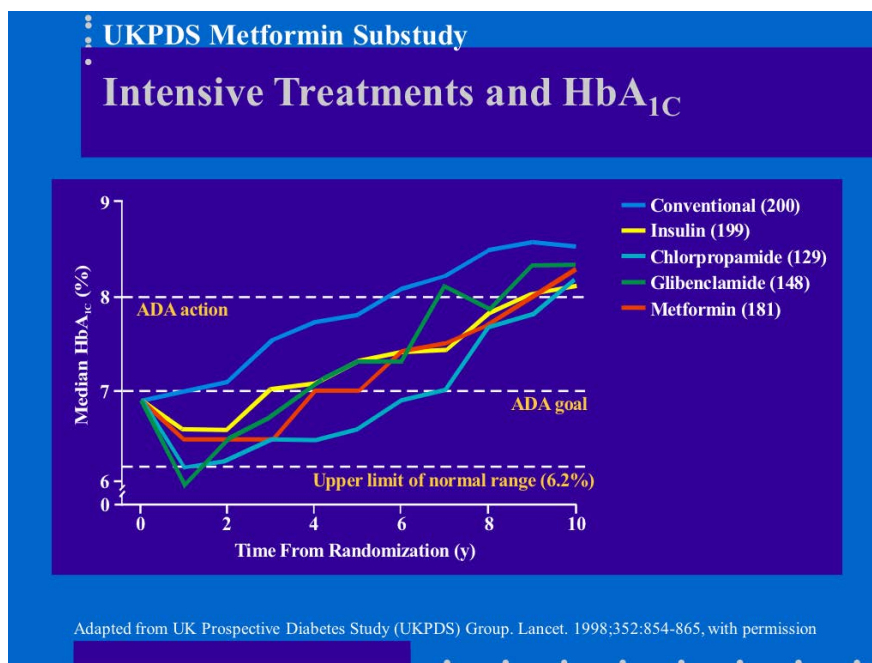


Figure 1. Maintenance of A1c < 7% for longer duration in subjects treated with SUs in comparison to metformin in UKPDS [17] [18].

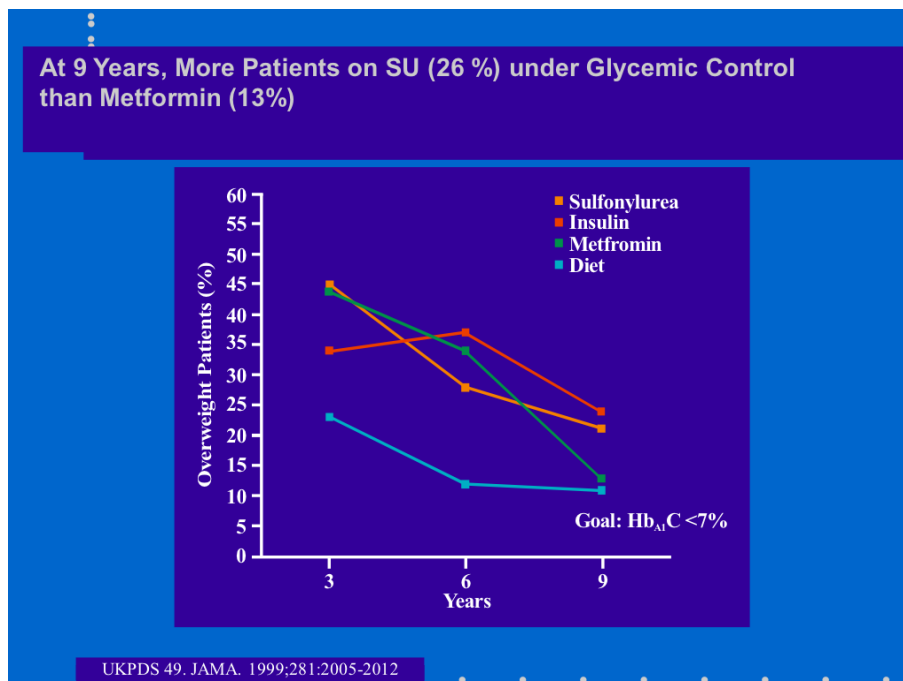


Figure 2. More subjects treated with SUs with desirable glycemic goal (7%) in comparison to metformin or conventional (diet and exercise) at 9 years [17] [18].

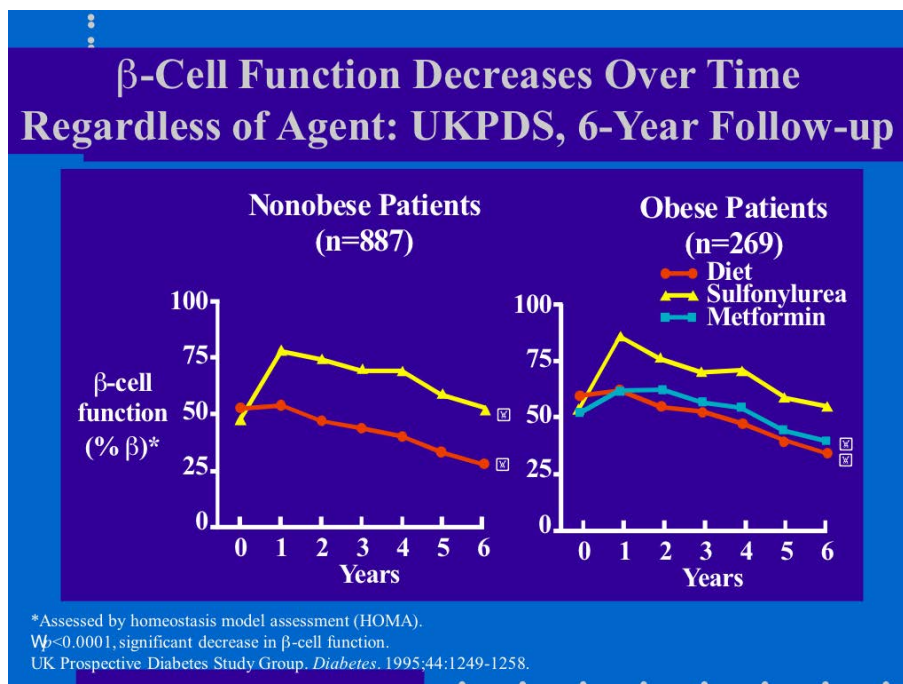


Figure 3. Greater beta cell function at 6 years in non obese subjects treated with SUs in comparison to conventional (diet and exercise) and in obese subjects in comparison to metformin [116].

Finally, therapy with SUs by themselves, especially gliclazide or with metformin when administered concurrently with basal insulin has been shown to be more cost effective when compared with combination of basal insulin with any other drug e.g. glitazones, DPP4 inhibitors or GLP1 analogs as a single agent. This outcome may be attributed to lower cost of SU and metformin as compared to other drugs including glitazones, DPP4 in-

hibitors and GLP1 analogs [11] as well as the lower daily dose of insulin required to achieve desirable glycemic control [85]-[87] [131]-[158]. In fact, adjunctive administration of both glimepiride and metformin is documented to lower daily insulin dose, basal type as well NPH or premixed insulins more than when these drugs are used alone [134]-[142]. The lower the daily dose, the lesser the number of peaks of insulin, lower is the hypoglycemic events and lesser the weight gain [134]-[144] [157] [158]. Finally a recent study also documented significantly longer delay for requirement of addition of insulin with SUs when compared with DPP4 inhibitors and GLP1 analogs [159].

In the final analysis, SUs have stood the test of time for over 50 years in terms of efficacy and safety whereas the long term efficacy and safety of newer drugs remain to be established. Moreover, SUs are thought to provide and maintain the better quality of life when compared with newer agents [159] and are distinctly far more cost effective than newer agents.

3. Conclusion

Therefore, SUs must remain as 1st line agents especially in management of non-obese subjects with type 2 diabetes since the dominant pathophysiologic mechanism is the decline in insulin secretion in this population [130]. Moreover, SUs remain the 2nd line most cost effective viable oral option in obese subjects on the lapse of glycemic control while receiving metformin since the addition of newer drugs is less likely to achieve the desirable glycemic goal of 6.5% - 7.0% due to their documented lesser efficacy in several studies [11]. Finally, in many regions of the world with markedly rising prevalence of diabetes e.g. Asia, Africa and South America with countries like China and India leading the pack [160], SUs remain the drugs of choice either as a 1st line drug in nonobese population and 2nd line agent in obese subjects with type 2 diabetes because of their well established efficacy, safety and mainly affordability in these regions and countries.

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