# Evolution of Sulfonylureas: Commentary on Developmental Process and Initial Trials

**Manoj K Srivastava[1], Ghanshyam Agarwal[2], Sanjeev R Phatak[3], Alok Modi[4], Mahesh Babu[5], Anjan Roy[6], V Mohan[7]**

**Abstract**

In the last few decades, the options of pharmacotherapies for the management of patients with type 2 diabetes mellitus (T2DM) have increased dramatically. Among them, the sulfonylureas (SUs) are one of the oldest and most commonly used antihyperglycemic agents for the treatment of T2DM.The use of SUs in the treatment armamentarium of diabetes mellitus has evolved, over past few decades. Sulfonylureas have emerged from being a mere antihyperglycemic agent to frontrunners in the field of precision medicine. Here we will discuss developmental process of SUs, the initial trials of SUs and the place of SUs in the precision diabetes medicine.

## History of Sulfonylureas

The evolution of sulfonylureas predates World War II, to the period when efforts were being made to combat bacterial infections. The history of the SUs began in 1937 with the observation of the hypoglycemic activity of synthetic sulfur compounds by Ruiz *et al*. Five years later, in 1942, Marcel Jabon *et al.* discovered that some patients developed severe hypoglycemia while being treated with p-amino-sulfonamide-isopropylthiodiazole for typhoid. In August 1946, Lobatieres *et al*. confirmed that sulfa drugs were responsible for the stimulation of insulin secretion by pancreatic islet β cells. In the 1950s, the first SU, viz. tolbutamide, was marketed in Germany. This was followed by the introduction of the other first-generation agents: chlorpropamide, acetohexamide, and tolazamide. The next advancement in SU therapy occurred with the release of more potent second-generation agents such as glipizide, glyburide and glibenclamide in 1984.[1] Glibenclamide was known as HB 419 a combined research product of Hoechst and Boehringer Mannheim.[2] The third-generation SU agent glimepiride, referred to as a 'modern sulfonylurea,' was approved in 1995 (Figure 1).[1]

## Classification of SUs

Sulfonylureas are classified based on the hierarchy of development as conventional and modern SUs. According to the mechanism of action, SUs are classified as short-, intermediate-, and long-acting. Sulfonylureas are also classified as first, second and third generation SUs based on their date of release (Table 1).[3,4]

## Developmental Process of SUs: From Glycemic Control Durability to Precision Medicine

### Early Cardiovascular Concerns in UGDP Era (1970–1980)

The findings of the University Group Diabetes Program (UGDP) raised concerns about the cardiovascular safety of certain sulfonylureas. Conventional SUs inhibits mitochondrial adenosine triphosphate sensitive potassium $K_{ATP}$ channels in cardiac myocytes and, thereby, impair ischemic preconditioning—contributing to an increased risk of cardiovascular events. Modern SUs offers myocardial protection by preserving ischemic

**Table 1: Classification of SUs[3,4]**

| | |
|---|---|
| **Classification based Molecules on generation** | |
| First-generation | Tolbutamide, chlorpropamide |
| Second-generation | Glipizide, glibenclamide, gliclazide |
| Third-generation | Glimepiride |
| **Classification based on hierarchy of development** | |
| Conventional | Tolbutamide, glibenclamide |
| Modern | Glimepiride, gliclazide MR, glipizide MR |
| **Classification based on mechanism of action** | |
| Short-acting | Tolbutamide |
| Intermediate-acting | Glipizide, gliclazide |
| Long-acting | Glibenclamide, glimepiride, glipizide MR, gliclazide MR |

SUs: Sulfonylureas

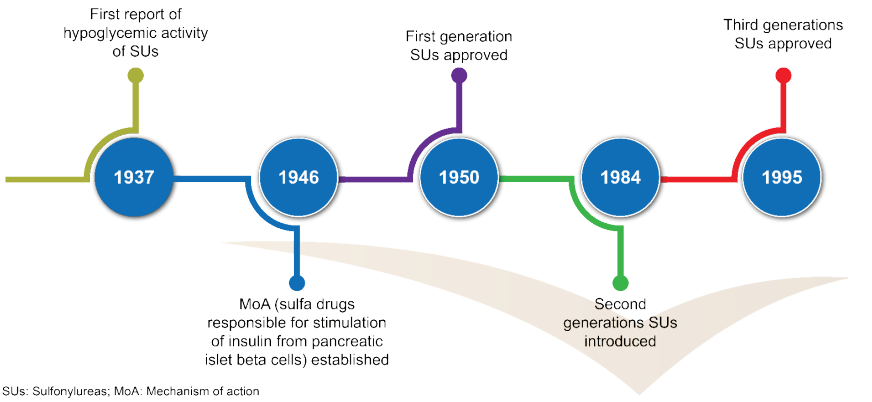


**Fig. 1: Timeline of major events in evolution of SUs**

[1]Senior Consultant and Diabetologist, Manasvi Diabetes Clinic, Indiranagar, Secretory UPDA (Uttar Pradesh Diabetes Association) Lucknow, Uttar Pradesh; [2]Consultant Endocrinologist, R.P. Diabetic Center, Lucknow, Uttar Pradesh; [3]Consultant Diabetologist, Vijayratna Diabetes Diagnosis and Treatment Center, Ahmedabad, Gujarat; [4]Consultant Diabetologist Jupiter Hospital and Medical Director Kevalya Hospital, Mumbai, Maharashtra; [5]Senior Consultant Diabetologist, Meenakshi Mission Hospital and Research Centre, Madurai, Tamil Nadu; [6]Medical Affairs, Diabetes and Cardiovascular, Sanofi India Ltd.; [7]Chairman and Chief Diabetologist, Dr. Mohan's Diabetes Specialities Centre, Chennai, Tamil Nadu

preconditioning and are, thereby, associated with fewer CV side effects compared to conventional SUs.[5,6]

### Reassurance on Glycemic Durability from Large Landmark Trials (1998–2009)

The United Kingdom Prospective Diabetes Study (UKPDS) confirmed that intensive blood-glucose control by either sulfonylureas or insulin resulted in a 25% risk reduction in microvascular complications. The findings of the ADVANCE (Action in Diabetes and Vascular Disease: PreterAx and DiamicronMR controlled examination) trial further strengthened the findings from UKPDS study and showed improved microvascular benefits especially in diabetic nephropathy in people treated with modern SUs and consolidated the use of modern SUs for the management of T2DM.[7,8]

### Utility of SUs in Cardiovascular Outcome Trials (CVOT) (2008–Present)

Rosiglitazone, a thiazolidinedione, was approved for use in T2DM based on its ability to control glycemic levels. Study conducted by Nissen *et al*., reported that rosiglitazone was associated with significant increase in myocardial infarction (odds ratio 1.43[95% confidence interval, 1.03 to 1.98; p=0.03] and borderline risk of death from cardiovascular causes (1.64 [95% CI, 0.98 to 2.74; p=0.06]).[8]

In the wake of the rosiglitazone controversy, the United States Food and Drug Administration (USFDA) mandated and issued a directive that clinical trials on all new diabetes drugs should include cardiovascular outcomes studies, to demonstrate that they are not associated with an increased cardiovascular risk. Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA IT) study showed that the incidence of cardiovascular events was similar with sulfonylureas (mostly glimepiride and gliclazide) and pioglitazone as add-on treatments to metformin. Pointing on the CV safety of glimepiride.[9] Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA), have proved the CV safety of modern SUs. Data from the recent CAROLINA trial indicate the CV safety of glimepiride by not exposing patients to an increased risk of CV events (3 and 4-point MACE) and resolve the decades-long controversy stoked by the UGDP trial.[10,11]

### Stepping into the Era of Precision Medicine

Precision Medicine is defined as an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment and lifestyle for each person.' Diabetes mellitus is a heterogeneous condition, and a personalized approach to its treatment will facilitate more accurate treatment and better prevention compared to the routine, standard-of–care approach. Monogenic forms of diabetes such as maturity-onset diabetes of the young (MODY) and neonatal diabetes are associated with unique mutations and require personalized treatment approach.[12]

Modern SUs such as glimepiride have been proven to be effective for the treatment of diabetes mellitus involving genetic mutations.[13] Treatment with SUs has resulted in discontinuation of insulin therapy in 90% of patients diagnosed with neonatal diabetes.[13] Sulfonylureas have been found to be effective for the management of MODY 1 and 3. Sulfonylureas are making an entry into the era of personalized medicine; they could be considered examples of classic precision medicine for the management of diabetes.[14-21]

### Conclusion

Sulfonylureas have evolved over the years, and presently constitute an important pillar for the treatment of diabetes mellitus. Modern sulfonylureas such as glimepiride possess unique characteristics such as effective glycemic control, cardiovascular safety and are now at the forefront in precision medicine.

### Conflict of Interest:

AR is an employee of Sanofi India. All other authors report no conflicts of interest.

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### Authorship

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