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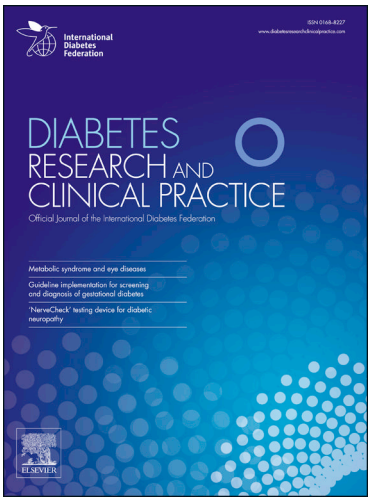

The right place for Sulphonylureas today

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PII: S0168-8227(19)31159-3
DOI: https://doi.org/10.1016/j.diabres.2019.107836
Reference: DIAB 107836

To appear in: *Diabetes Research and Clinical Practice*

Received Date: 21 August 2019
Accepted Date: 22 August 2019

Please cite this article as: D.R. Webb, M.J. Davies, J. Jarvis, S. Seidu, K. Khunti, The right place for Sulphonylureas today, *Diabetes Research and Clinical Practice* (2019), doi: https://doi.org/10.1016/j.diabres.2019.107836

The right place for Sulphonylureas today

Part of review the series: Implications of recent CVOTs in Type 2 Diabetes Mellitus

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Key Words: Sulphonylureas, Cardiovascular Outcomes, Glucose lowering, medicines management

Abstract

The place of Sulphonylurea based insulin secretagogues in the management of Type 2 diabetes appears as controversial today as it was fifty years ago. Newer therapies are associated with less hypoglycaemia and weight gain than Sulphonylureas but currently cost more and lack assurances which come with long-term exposure. Emergence of recent CVOT data for SGLT-2 inhibitors and GLP-1 receptor agonists is likely to influence therapeutic choices and guidance is now supportive of their earlier use in cases at high risk of cardiovascular disease. Meta-analyses of Sulphonylurea trials have failed to indicate a consistent effect (positive or negative) on cardiovascular disease or mortality, although are limited by the relative scarcity of studies directly reporting these outcomes. The CAROLINA trial is reassuring in demonstrating cardiovascular safety for the Sulphonylurea Glimepiride when compared directly with the DPP-4 inhibitor Linagliptin, suggesting either of these agents would be relatively safe second line options after Metformin in the majority of patients. This review provides a balanced assessment of available Sulphonylurea treatments in the context of current cardiovascular outcome trial data (CVOT) data and hopefully assists informed decision making about the place of these drugs in contemporary glucose lowering practice.

Introduction

Regarded as glucose lowering stalwarts by some and dubious cardiotoxins by others, no class of diabetes drug has divided opinion more than the Sulphonyurea based insulin secretagogues [1]. Introduced as Tolbutamide and Chlorpropamide in the 1950s, the staying power of this class in its various forms is undisputed. Over the last forty years stereochemical changes to the moiety housing the biologically active sulphonamide ring have successively improved the pharmacological properties of more modern second and third "generation" drugs and have probably contributed to this classes longevity [2]. Due to a likely combination of trusted efficacy, cost and practicality, Glicazide, Glibencamide and Glimepiride remain among the most widely prescribed drugs on the planet [3]. Yet as will be discussed, concerns around the cardiovascular safety of Sulphonylureas have never been entirely resolved and these drugs are universally acknowledged to cause hypoglycaemia and weight gain. The advent of the Cardiovascular Outcome Trial (CVOT) era is a significant and possibly watershed moment in the natural history of Sulphonylureas, as all newly introduced glucose lowering therapies have clear evidence of cardiovascular safety at least, and some have significant beneficial effects on these important patient centred outcomes. Pharmaceutical companies perhaps understandably wanting to see a return on the huge costs of bringing their products to market, avidly promote the beneficial properties of new treatments without necessarily directly comparing them with older agents. Until this year published CVOT data incorporating a Sulphonylurea as the subject of a placebo or comparator controlled trial was extremely limited with only the TOSCA.IT trial reporting no difference in incidemt CV events between sulphonylurea use and the thiazolidinedione Pioglitazone after 57 months of follow up [4]. It could be argued that the sheer quantity of CVOT data now for other drugs other than sulphonylureas makes objective assessment a challenge and the choice of second line medication after Metformin too complicated even for the specialist. By focusing upon cardiovascular safety, glucose lowering potential and hypoglycaemia risk this review attempts to provide an up to date perspective on the place of Sulphonylurea therapy in clinical practice. It will specifically consider the implications of new CVOT data on prescribing and also briefly discuss the emerging role of personalised medicine in support of pharmacotherapeutic decision making in Type 2 diabetes.

Cardiovascular safety concerns of Sulphonylureas: from UGDP to CAROLINA

It is now more than 40 years since publication of the University Group Diabetes Program (UGDP), where an association between incident cardiovascular death and the use of the first generation Sulphonylurea Tolbutamide (drug compared to placebo 26 versus 10 cases $p<0.005$) prompted the United States Food and Drug Administration (FDA) to impose a blanket "black box" warning on all Sulphonylureas [5]. These drugs stimulate insulin release by binding to the SUR cell membrane receptor and inhibiting ATP-sensitive K+ influx channels on the pancreatic beta-cell [6]. It is proposed that transient ischaemia induced opening of myocardial and vascular smooth muscle ATP-sensitive K+ channels has a protective effect through reduced cardiac afterload and peripheral vasodilation, a phenomenon referred to as Ischaemic preconditioning. Non-selective binding and SUR based closure of myocyte ATP-sensitive K+ channels is therefore potentially deleterious and Sulphonylurea effects on preconditioning have been proposed as an explanation for the results of UGDP [7]. Sulphonylureas appear to have a range of affinities for different SUR receptor isoforms, resulting in significant within class variation in their ability to interfere with ATP-sensitive K+ channel activity [8].

Over twenty years later the main randomisation analysis of the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that Sulphonylureas reduce medical complications of Type 2 diabetes without any evidence of the harm observed in UGDP [9]. Moreover, repeated meta-analyses of Sulphonylurea clinical trial data have subsequently tended to show no consistent association with MACE (Major Adverse Cardiovascular Event) outcomes, whilst acknowledging the general heterogeneity of available data and/or inclusion of studies not specifically designed to evaluate these outcomes (Table 1) [10-14]. In one study MACE risk estimate was not increased (OR 1.08, 95% CI 0.86–1.36; p=0.52), and the authors suggested that longer-term cardiovascular outcome studies were necessary to fully assess cardiovascular safety of Sulphonylureas [12]. Another used a network analysis to indicate that the risk of all-cause and cardiovascular mortality was lower with Gliclazide and Glimepiride than with

Glibenclamide (all-cause mortality for Gliclazide 0.65, 95% CI 0.53-0.79) [14]. Of all the Sulphonylurea trials included, only Glipizide was associated with an increased risk of all-cause mortality (OR 1.68, 95% CI 1.06–2.66) and cardiovascular mortality (2.1, 95% CI 1.09–3.72), whereas neither Gliclazide and Glimepiride were associated with an increased all-cause mortality (0.92, 95% CI 0.49–1.72) or cardiovascular mortality (1.94, 95% CI 0.86–4.39). Evidence from meta-analyses of studies that were limited to new-generation Sulphonylureas and those with robust methodological quality indicate no convincing association between all-cause mortality or cardiovascular mortality and Sulphonylurea use in people with Type 2 diabetes [13].

Observational data is generally consistent with these findings. In a French registry study of patient outcomes following myocardial infarction, mortality was significantly lower in people with diabetes previously treated with Sulphonylureas compared to those on other oral medication, insulin or no medication [15]. Arrhythmia and ischaemic complications were also less common in the Gliclazide group and Glimepiride groups. Conversely, other researchers using the Swedish National Diabetes register observed that second-line treatment with Dipeptidyl peptidase-4 (DPP-4) inhibitors and Thiazolidinediones was associated with reduced mortality risk compared with Sulphonylureas [16]. Others have found both increased and decreased risk of cardiovascular events and death associated with Sulphonylureas [17,18].

As suggested earlier, the availability of longer-term high quality CVOT evidence assessing named agents within the Sulphonylurea class is extremely limited. The results of the CAROLINA (Cardiovascular Outcome study of Linagliptin versus glimepiride in patients with Type 2 diabetes) study were recently reported at the American Diabetes Association 2019 [19, 20]. This unique trial assessed the cardiovascular safety and glucose lowering efficacy of the DPP-4 inhibitor Linagliptin over a six year period. Compared with Glimepiride, Linagliptin demonstrated similar overall effects on HbA1c% and importantly a MACE primary outcome of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. Linagliptin was associated with a lower risk of hypoglycaemia and no weight gain compared with the Sulphonylurea. Importantly the absolute risk of a severe episode of hypoglycaemia on Glimepiride was small (NNT approximately 99 to prevent 1

severe episode of hypoglycaemia). CAROLINA could be interpreted as proof that both DPP-4 inhibitors and Sulphonylureas are safe and effective glucose lowering drugs, with the latter being vindicated as an established less expensive second line option after Metformin [19]. DPP-4 inhibitors have demonstrated their cardiovascular safety but have not demonstrated a significant reduction in MACE outcomes within the four CVOTs published to date, involving nearly 50,000 people with Diabetes.

Future guidance is likely to attach increasing importance to the ability of glucose-lowering therapies to address cardiovascular co-morbidities associated with Type 2 diabetes. Medications that have evidence of efficacy in high risk cases for example obesity, existing heart disease and microalbuminuria, are likely to be promoted in this role. The lack of this in the case of Sulphonylureas and some may argue DPP4i is beginning to affect some prescribing behaviours and may have major implications for these drugs.

What can the major glucose lowering trials tell us about Sulphonylureas?

It is more than fifty years since the Framingham heart study connected Type 2 diabetes, then still commonly referred to as NIDDM (Non-Insulin Dependent Diabetes) with premature death from cardiovascular causes, leading researchers to confidently predict that strict management of hyperglycaemia would improve outcomes for this burgeoning "new" disease [21]. A number of randomised controlled trials followed which were specifically designed to test this hypothesis. UKPDS, ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR controlled examination) and ACCORD (Action to Control Cardiovascular Risk in Type 2 Diabetes) are examples, which despite amassing over 160,000 person years of follow up subsequently failed to demonstrate that intensive glucose lowering has a major short-term impact on cardiovascular disease mortality [9,22-24]. In the case of ACCORD, the aggressive glucose lowering algorithm that was used in particularly high cardiovascular disease risk patients was surprisingly associated with an increased risk of death. Longer term observational follow up of these studies has also yielded somewhat unpredictable results with some suggesting a so-called "legacy effect" or a benefit with respect to cardiovascular disease outcomes well

after conclusion of the trial, and others reporting no benefit at all from intensive glucose control [25-28].

Although not designed as drug efficacy trials the results of these highly influential studies has led to intense speculation about not only the safety of intensive glucose lowering in this complex multifaceted disease but also the overall effectiveness of therapeutics used to manage it at the time. Whilst examining the use of treatment regimens, rather than specific pharmacotherapies, importantly over 50% of patients in the intensive arms of these studies took either subcutaneous insulin or Sulphonylurea based drugs. It has been suggested that recognised (and possibly unrecognised) adverse effects of these still ubiquitous therapeutics could nullify or in selected patients actually reverse the likely modest beneficial effect accrued from glucose lowering on important cardiovascular outcomes.

As discussed in other papers in this series, since these trials the introduction of new therapies with alternative glucose lowering properties and a lower risk of clinically important adverse effects has markedly changed the therapeutic landscape. Some of these new therapies have significant and relatively rapid beneficial effects on major adverse cardiovascular events in certain population groups [29-34]. As a result prescribing patterns in the United Kingdom and around the world maybe changing, especially around second and third line therapeutic choices after Metformin. However, the position of Sulphonylurea based drugs as an important option in most consensus guidance remains and these drugs are undoubtedly still an extremely popular, established choice for many clinicians. Latest evidence appears to support the view that modern generation Sulphonylureas are safe/neutral from a cardiovascular disease perspective, carry a higher risk of hypoglycaemia than newer treatments and result in modest weight gain [19].

Cardiovascular outcome trials and future direction of glucose lowering guidance

In response to concerns about the cardiovascular safety of diabetes drugs, in 2008 the US Food and Drug Administration issued a directive that clinical trials of new agents should include outcome data to demonstrate they are not associated with increased cardiovascular risk [35]. Unlike Sulphonylureas, whose introduction to clinical practice

predate these requirements, newer drugs have been or are being tested in this way as a mandatory pre-requisite to gaining regulatory approval. This level of scrutiny provides additional reassurance that a new therapy is not going to increase cardiovascular risk, or if the study design allows for enough power, it can also sometimes demonstrate cardiovascular benefit. This has recently been shown to dramatic effect in the EMPA-REG OUTCOME (Empagliflozin cardiovascular outcome and mortality in type 2 diabetes), CANVAS (Canagliflozin cardiovascular assessment study), LEADER (Liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results), HARMONY (Albiglutide and cardiovascular outcomes in patients with Type 2 diabetes and cardiovascular disease), REWIND (Dulaglutide and cardiovascular outcomes in type 2 diabetes) and SUSTAIN-6 (Trial to evaluate cardiovascular outcomes with Semaglutide in subjects with type 2 diabetes) phase three CVOTs, where highly relevant cardiovascular mortality benefits were demonstrated for the SGLT-2 inhibitors Empagliflozin and Canagliflozin and the Glucagon Like Peptide-1 receptor agonists (GLP-1 RA) Liraglutide and Semaglutide in people with or at high risk of pre-existing cardiovascular disease [29-34]. Such results are extremely powerful, providing clinicians with long sought-after knowledge that the glucose-lowering therapies they are advising for their patients are firstly safe and secondly may have a beneficial effect on cardiovascular disease. Since completion of these trials other GLP-1RAs and SGLT-2 inhibitors have been or are being tested in CVOTs, adding to the encouraging evidence base for both these new classes [36-38]. There is also safety data available for the DPP-4 inhibitors, with four trials indicating that Linagliptin, Sitagliptin, Saxagliptin and Alogliptin are non-inferior to placebo in MACE defined primary CVOTs [39-42]. This new evidence is influencing recommendations for the management of Type 2 diabetes from organisations such as the EASD/ADA [43]. These recommendations advocate the use of newer agents such as SGLT-2 inhibitors and GLP-1RAs earlier in the treatment pathway for Type 2 diabetes, especially in people with pre-existing cardiovascular disease. The use of SGLT-2 inhibitors is particularly recommended in groups with heart failure and CKD.

Glucose lowering potency and glycaemic durability of Sulphonylurea therapies

The basic premise of Type 2 diabetes management is to maintain plasma glucose in a range that reduces the risk of complications whilst simultaneously avoiding

hypoglycaemia and excessive weight gain. Because its primary cellular defects of pancreatic beta cell dysfunction and target cell resistance typically worsen over time, multiple interventions are usually required to minimise progressive hyperglycaemia once a diagnosis of Type 2 diabetes is made. The timing and extent of treatment intensification is largely determined by the ensuing metabolic compromise and requires careful consideration of the relative merits and risks of available glucose-lowering pharmacotherapy. Current EASD/ADA and ACE/AACE guidance recommends individualised thresholds for the addition and titration of second and third line glucose lowering therapies when mutually agreed targets are not achieved with Metformin alone or risks of progressive CVD, CKD and heart failure are significant [43,44]. Over the last ten years options for intensification have increased considerably and many clinicians have access to a rapidly expanding array of drugs. Whilst greater choice is generally positive, more options do however demand greater knowledge and awareness amongst those charged with supporting Type 2 diabetes management decisions particularly around second and third line choices. It is therefore not difficult to see how "tried and tested" drugs such as Sulphonylureas may be preferred, especially if they are cost-effective or their glucose lowering efficacy compared with newer agents remains competitive. Unfortunately, despite the need for additional treatment, there is often a significant delay in sequential intensification of any kind. Although the drivers of this "therapeutic inertia" are not entirely understood, it is conceivable that anticipated side effects, hypoglycaemia risk or the additional monitoring burden of proposed medication choices play an important role [45]. It is therefore worth considering glucose lowering potency, durability and hypoglycaemia risk when considering Sulphonylurea based therapies.

Glycaemic Efficacy

By stimulating endogenous insulin secretion Sulphonylureas improve glycaemic control when used as monotherapy or in combination therapy including with insulin. Table 2 summarises published Meta-analyses of randomised controlled trials reporting mean HbA1c reduction with Sulphonylureas versus placebo, comparator agents or other members of the class [11, 46-49]. For example, Hirst *et al* in a systematic review of 31

double-blind randomised placebo controlled trials (including 3,956 patients) with median duration of 16 weeks (range 3 weeks to 3 years), found that Sulphonylurea monotherapy lowered HbA1c concentration by 1.5%, by 1.6% when added to other oral glucose-lowering therapy (Metformin or Troglitazone), and by 0.5% compared with insulin [47]. Trial data also suggests that there is little difference in glucose lowering efficacy between first, second and third generation Sulphonylureas [46]. Similar reductions in HbA1c were also found in a systematic review of 27 randomised controlled trials (involving 11,198 patients in total and each trial lasting at least 3 months) comparing different drug classes, including Sulphonylureas, Thiazolidinediones, and DPP-4 inhibitors, added to maximally titrated or tolerated metformin in patients with inadequate glycaemic control. In a large retrospective analysis of 'real-world' effects of second-line therapies after Metformin, both DPP4 inhibitors and Sulphonylureas demonstrated reductions in Hba1c of the magnitude described in meta-analyses of trial data (6 month adjusted change in Hba1c for Metformin plus Sulphonylurea -1.09% and for Metformin and DPP4 inhibitors -1.02%) [50]. For Sulphonylureas specifically, the weighted mean difference in HbA1c% from baseline was 0.79% (95% CI –0.90 to 0.68; $p<0.05$) identical to DPP-4 inhibitors and only marginally inferior to Thiazolidinediones and GLP-1RAs [48]. Indeed, when considering glucose lowering in isolation, even the GLP-1RA and SGLT-2 inhibitor classes do not demonstrate convincing superiority over modern generation Sulphonylureas, although it would be naïve to overlook the clear differences in weight and hypoglycaemia. Whilst direct comparisons are lacking, meta-analyses of available placebo controlled clinical trials suggest that pooled mean reductions in HBA1c% for GLP-1RAs (0.6-1.2%), SGLT-2is (0.6-0.9%) and Sulphonylureas (0.5-1.5%) are similar whether they are used as dual, triple or insulin add-on therapy [46-49]. Observational data from the United Kingdom national diabetes audit, an annually collected repository of primary care practices registering one hundred or more patients with Type 2 diabetes (over 1.5 million people), has shown that new therapies appear to be having a modest impact on the proportion achieving target HbA1c% levels [510].

Glycaemic Durability

Since the late 1990s it has been postulated that Sulphonylurea mediated insulin secretion does little to slow or may even accelerate beta-cell failure. Evidence for this

comes from observational studies linking extended Sulphonylurea use with more rapid loss of beta cell function and glycaemic control than other agents and *in vitro* experiments in islet cells suggesting that prolonged use of sulphonylureas may be toxic to beta-cells by inducing cellular apoptosis [52, 53]. There is some evidence that Thiazolidinediones, GLP1-RAs and SGLT2 inhibitors have a more durable effect on HbA1c than sulphonylureas [54-56]. More recently, it has been proposed that Sulphonylurea induced sustained closure of K+ ATP membrane channels results in insulin secretory failure without beta-cell death. Differing binding affinities could explain why certain Sulphonylureas (e.g. Gliclazide) appear not to be associated with accelerated functional beta cell decline in this scenario. Conversely, falling plasma insulin concentration and rising HBA1c% over time was largely unaffected by treatment allocation in the UKPDS study, whether diet, metformin or Sulphonylurea based [9] and a recent study concluded that Sulphonylureas when introduced as second line therapy resulted in a longer duration of insulin independence than other regimens [57]. Evidence supporting the beta cell "burn out" hypothesis remains quite weak and this whole area remains in need of further research. The results of studies such as GRADE (Glycaemia Reduction Approaches in Diabetes: A comparative effectiveness study) should assist in addressing this knowledge gap [58]. GRADE aims to compare commonly used diabetes medications (including Sulphonylureas) over time and is examining glucose trajectories and treatment failure. At present it is not possible to establish whether modern generation Sulphonylureas demonstrably exacerbate background beta cell decline in patients with Type 2 diabetes. In summary, Sulphonylureas are potent glucose-lowering therapies whose short-term clinical efficacy appears similar to newer agents. The evidence that they accelerate beta cell decline or expedite the need for insulin therapy in patients with Type 2 diabetes is inconclusive.

Hypoglycaemia and weight gain

Sulphonylureas have been part of treatment algorithms for Type 2 diabetes since their introduction in the 1950s, because as discussed, in the short term they reliably reduce plasma glucose. The most frequently encountered and clinically important side effects of Sulphonylureas are hypoglycaemia and weight gain. These by-products of glucose

independent insulin secretion have always been an area of major concern for clinicians and patients alike but notably are not major features of new diabetes drugs such as DPP-4 inhibitors, GLP-1RAs and SGLT-2 inhibitors. Hypoglycaemia is probably the most feared adverse effect of diabetes treatment and contributes significantly to both patient distress and therapeutic inertia. The importance of low blood glucose has taken on new meaning over the last ten years as it has become increasingly linked to cardiovascular mortality and some of the deleterious pro-inflammatory responses more traditionally associated with hyperglycaemia [59]. Both high and low HbA1c are linked to all-cause mortality and cardiovascular disease, and recent meta-analyses suggest that hypoglycaemia may nullify benefits accrued by the effort of intensive glucose-lowering [60, 61]. The ACCORD trial demonstrated increased cardiovascular death with an intensive glucose lowering regimen targeting an HBA1c of less than 6.0% [23]. Unsurprisingly, severe hypoglycaemic episodes occurred more frequently in the intensively managed group and were identified as a risk factor for mortality in secondary analyses of the trial. Like UKPDS and ADVANCE it is not possible to unpick the role of individual therapies in the complex glucose lowering algorithms of ACCORD, or even whether hypoglycaemia is the reason for its surprising outcome. However, since its publication, drugs with the capacity to cause hypoglycaemia have been on the decline. For example, there has been a significant reduction in Sulphonylurea use in the US, UK and other European countries over the last ten years as clinicians and patients opt for therapies with less propensity for hypoglycaemia and weight gain [4, 62-64]. Although all Sulphonylureas can cause hypoglycaemia it appears that some may carry a higher risk than others (Table 2 [46-49]). Differences in chemical structure and pharmacodynamic properties between Sulphonylureas probably explain the variation in hypoglycaemia risk. Conventional and network meta-analyses of trial data has shown differential effects of Sulphonylureas, with Glibenclamide, generally being associated with a higher risk of hypoglycaemia compared with Gliclazide, Glimepiride and Glipizide. However, what must be considered is that risk of severe hypoglycaemia is relatively small [20]. Further evidence in support of the notion that severe hypoglycaemia is relatively rare amongst Sulphonylureas comes from a recent UK-based observational study. Dunkley et al, 2019 [65] analysed prospectively collected event diaries and reported that whilst hypoglycaemia of any description was significantly more common, the incidence of

severe episodes in patients taking Sulphonylureas, Metformin and incretin-based therapies was similar.

Cost effectiveness

Expenditure on treatments for Type 2 diabetes has spiralled over the last decade. In the UK the National Health Service spend on diabetes drugs surpassed a billion pounds in 2017/18, up 73% since 2007 [66]. It is estimated that one in twenty general practitioner (GP) prescriptions now relate directly to diabetes with new "on patent" drugs being amongst the main cost drivers.

Rapid widespread access to more expensive agents coupled with significant geographical variation in prescribing are beginning to raise concerns over sustainability and equity of access. Continued exponential rise in treatment costs is predicted as the number of people with diabetes together with the number of available treatments dramatically increase.

According to current British National Formulary (BNF), a conservative estimate of the difference in price between the most and least expensive listed glucose lowering medication is between £800-900 per annum, if prescribed at maximum licenced dose [67]. Given such marked variation it is not difficult to see how clinicians challenged to work within budget are likely to choose the cheapest option, especially if the only unit of assessment is a modest difference in glucose lowering efficacy. Some of the previously described advantages of newer agents such as reduced weight gain, reduced hypoglycaemia, reduced progression to CKD and reduction in heart failure are undoubtedly important but possibly more difficult to factor into an overall assessment of cost effectiveness. Unsurprisingly, most studies published in this area are somewhat open to bias and tend to evaluate more expensive products, rather than cheaper generic therapies such as Metformin and Sulphonylureas. It is now clear that analyses looking beyond HbA1c% in isolation are needed to confidently differentiate glucose lowering drugs on the basis of cost. It is hoped that in the future we will see well designed studies that can develop models to assess the true estimation of cost effectiveness of all medications allowing medications to be targeted at those more likely to benefit. Until

then, the high costs of newer agents will mean that Sulphonylureas will remain prima facie a highly cost effective option.

The future? Using personalised medicine to target the beta cell

It is increasingly understood that inherited variation in beta cell K+ sensitive ATP channel functionality probably contributes to the development of diabetes in some patients [68]. It is well known that Sulphonylureas bind with varying affinity to the SUR component of this channel, setting in motion a chain of events resulting in glucose-independent insulin exocytosis.

Carriers of common variants of genes encoding the SUR and Kir 6.2 components of the K+ sensitive ATP channel are at high risk of diabetes presumably because the beta cell is less responsive to ATP induced closure and membrane depolarisation in the face of rising plasma glucose concentration [69, 70]. It is hypothesised that under these circumstances the administration of Sulphonylurea, potentially at a fraction of the dose currently used in clinical practice, may restore insulin sensitivity and provide a more targeted treatment. Certainly this approach has already been used to dramatic effect in neonatal diabetes mellitus, where 50% of cases are caused by activating mutations of the K+ sensitive ATP channel or the SUR receptor [71]. Understanding the relative contribution of inherent beta cell dysfunction to the overall pathogenesis of Type 2 diabetes at a patient level will help personalise treatment approaches and suggests that Sulphonylureas will still have a role to play in future treatment algorithms.

Conclusion

Sulphonylurea based insulin secretagogues are under scrutiny and an increasing number of pharmacologics compete for position in Type 2 diabetes management algorithms that are placing more emphasis on co-morbidities and diverse patient groups. Whilst broadly similar in their ability to lower plasma glucose in the short term, GLP1-RAs and SGLT-2 inhibitors do offer important additional benefits in selected patients. These new classes have the advantage of lower rates of hypoglycaemia and are not associated with weight

gain, all have undergone strict cardiovascular safety testing before being approved for use and some have been shown to improve mortality through mechanisms independent of glucose lowering. Whilst some ongoing uncertainties with certain newer treatments may impact their future use, novel pleiotropic properties which improve “hard outcomes” in Type 2 diabetes is something which Sulphonylureas and other older drugs have never and possibly will never demonstrate. With consensus guidance rapidly shifting towards the earlier use of individualised treatments with evidence of cardiovascular or chronic kidney disease benefit the use of Sulphonylureas, especially in cases at high risk of events is likely to decline. It is also likely that Sulphonylurea use will be affected by newer agents coming off patent and becoming more affordable to the mass market. Sulphonylureas have survived the test of time however, successfully beating off challenges from some quite formidable rivals in the past, and their continued stolid popularity amongst prescribers suggests we would be ill advised to write them off just yet. We finally have MACE outcome safety data for Glimepiride, which is reassuring and preliminarily research in the rapidly emerging field of personalised medicine suggests that drugs directly targeting beta cell insulin exocytosis may continue to have an important role in the management of Type 2 diabetes.

Conflict of interest

The authors declare no conflict of interest.

Funding

The authors received no funding from an external source.

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Table 1 Summary of RCT Meta-analyses reporting associations between all cause and cardiovascular Disease mortality and Sulphonylurea use

	Description	No. of trials	Duration	Number of subjects (age range)	Main outcomes
Bain S *et al.* (2017) [10]	SUs vs. placebo or any antihyperglycaemic drug	82	24 wks-15 years	NA (44-67 yrs)	HR Death (all cause) +1.26 (+1.10 to +1.44) CV death +1.46 (+1.21 to +1.77) MI vs. DPP-4i +2.54 (+1.74 to +6.57)
Ganji AS *et al.* (2007) [11]	Glibenclamide monotherapy vs. other oral secretagogues¥ or insulin	21 (12 vs. oral¥, 3 vs. insulin)	4 wks – 5 years	7,047 (NA)	RR vs. other oral secretagogues¥ CV event: +0.84 (+0.56 to +1.26) Death: +0.87 (+0.70 to 1.07)
Monami M *et al.* (2013) [12]	SU vs. non-SU therapy reporting mortality* / MACE events‡	62* / 30‡	Mean 70 wks	NA (mean age 56.6 yrs)	OR MACE SU vs. Comparator +1.08 (+0.86 to +1.36) OR Death (all cause) SU vs. Comparator +1.22 (+1.01 to +1.49) OR CV death SU vs. Comparator +1.40 (+0.87 to +2.26) No differences between SUs
Rados DV *et al.* (2016) [13]	RCTs of 2nd / 3rd generation SUs vs. non-SU reporting mortality/ MACE events	47	52 wks - 3 years	37,650 9mean age 57.3 yrs)	OR Death (all cause) SU vs. Comparator +1.12 (+0.96 to +1.30) OR CV Death SU vs. Comparator +1.12 (+0.87 to +1.42)
Simpson SH *et al.* (2015) [14]	RCTs reporting all-cause, or cardiovascular mortality for SUs	18	NA	1,632 (NA)	RR of death cf. index Glibenclamide +0.65 (+0.53 to +0.79) Gliclazide +0.83 (+0.68 to +1.00) Glimepiride +0.98 (+0.80 to +1.19) Glipizide +1.34 (+0.98 to +1.86) Chlorpropamide

RCT: Randomised Controlled Trial. HR: Hazards Ratio, RR: Relative Risk, OR: Odds Ratio, SU: Sulphonylurea, NA: Not available from manuscript

Table 2 Summary of RCT Meta-analyses reporting glycaemic efficacy (HBA1c% reduction) and relative risk of hypoglycaemia with Sulphonylurea therapy compared with placebo or comparator glucose lowering agents

	Description	Number of trials	Duration	Number of subjects (age range)	HBA1c (%) difference SU vs. other (95 CI)	Hypoglycaemia relative risk SU vs. other (95 CI)
Chan SP et al. (2015) [46]	Gliclazide vs. oral insulinotropic drugs	9 (5 directly comparing other Sus*)	13-104 wks	3,461 / 1,117* (55-72 yrs)	-0.11% (-0.19 to -0.03) / -0.12% (-0.25 to +0.01)*	No significant difference Less severe hypo with gliclazide cf. glimepiride or glibenclamide
Ganji AS et al. (2007) [11]	Glibenclamide monotherapy vs. other oral secretagogues or insulin	21 (12 vs. oral¥, 3 vs. insulin)	4 wks – 5 years	7,047 (NA)	-0.13% (-0.52 to +0.26)¥	+1.52 (+1.21 to +1.92) with Glibenclamide vs. other oral secretagogue
Hirst JA et al. (2013) [47]	Any SU add-on vs. placebo or comparator	31	12-156 wks	3,956 (34-66 yrs)	-1.51% (-1.78 to -1.25) vs. Placebo (monotherapy) -1.62% (-2.24 to -1.00) vs. placebo or comparator	+2.41 (+1.4 to + 4.1) with SU versus combined placebo and comparator
Phung OJ et al. (2010) [48]	Non-insulin glucose lowering drugs added to metformin	27 Mixed treatment comparison	18-52 wks	11,198 (53-62 yrs)	SU: -0.79% (-1.15 to -0.43) DPP-4i: -0.79% (-0.94 to -0.63) GLP-RA: -0.99% (-1.19 to -0.78)	SU: +2.63 (+0.73 to +9.13) DPP-4i: +0.67 (+0.3 to +1.5) GLP-RA: -0.94 (+0.4 to +2.1)
Schopman JE et al. (2014) [49]	Any SU or insulin vs. incretins	25 (22 for Sus)	16-114 wks	6,500 (53 – 65 yrs)	Not analysed	10.1% (7.5 – 13.8) taking SU had a hypo event (0.8% had a severe hypo. Glimepiride worse than gliclazide