Some Doubts About the Mantra on the Deleterious Cardiovascular Effects of Sulfonylureas

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Patients with type 2 diabetes are at increased mortality risk, mainly because of cardiovascular disease (1). On the basis of the evidence that a pharmacological approach against hypertension, dyslipidemia, and hyperglycemia is needed to tackle this devastating clinical outcome (2), such patients are usually aggressively treated. In the U.S., prescribed retail pharmaceutical spending accounted for approximately half of the annual diabetes cost, which approximated $100 billion in 2013 (3). How long will we be able to cope with such a burden, especially considering it is likely to increase over the next decades (4)? Under this scenario, it is both ethical and smart to pay attention to the costs.

In treating hyperglycemia we are facing a tendency, partly driven by pressure from pharmaceutical companies, to abandon the old, well-known, and cheap sulfonylureas in favor of new and costly glucose-lowering molecules. One of the reasons given is that there is a deleterious effect of sulfonylureas on cardiovascular disease suggested by various observational studies but never proven by randomized clinical trials (5–7), the gold standard approach for addressing similar issues. Unfortunately, as sulfonylureas entered the market long before the U.S. Food and Drug Administration request of cardiovascular risk assessment for novel antidiabetes drugs to be approved (8), an adequately powered cardiovascular trial on sulfonylurea therapy is not available. One should, therefore, wonder if the mantra of cardiovascular deleterious effects of this class of drugs is destined to last forever.

Recently, genetic studies have been appropriately designed to get deeper insights on on-target drug pleiotropic effects, such as that of GLP-1 agonists on cardiovascular outcomes (9) or that of statins on the risk of type 2 diabetes (10). Along this line, the study by Emdin et al. (11) in this issue of *Diabetes* adds important, and somehow reassuring, evidence on the cardiovascular effect of sulfonylureas. The common p.A1369S nonsynonymous polymorphism in *ABCC8* (the gene encoding for SUR1, a component of the sulfonylurea receptor) was used as a naturally occurring model of SUR1 activation to test for an association with coronary heart disease (CHD) in 120,286 participants from the UK Biobank and in summary data from several previous genome-wide association studies. In addition, the authors investigated the association with type 2 diabetes and various cardiometabolic traits. Data obtained by this intelligent study design clearly show that the p.A1369S amino acid change, previously known *1*) to mimic in vitro the pharmacological effects of sulfonylureas by promoting closure of the ATP-sensitive potassium channel (12), *2*) to increase in vivo insulin secretion (13), and *3*) to protect from type 2 diabetes (13,14), was in fact associated with a reduced risk of CHD and a composite cardiovascular end point, including stroke, heart failure, and peripheral vascular disease (per allele reduction equal to 2% and 3%, respectively). Each copy of the p.A1369S variant was also associated with a 7% lower risk of type 2 diabetes, thus replicating previous findings (13). This makes it possible to calculate that per 10% reduction in type 2 diabetes risk the *ABCC8* p.A1369S variant exerts a 4% reduction on CHD risk. Such a relationship is very similar to that reported for a missense variant in *GLP1R*, encoding the GLP-1 receptor, the specific target of GLP-1 agonists, which—notably, in our specific context—have been recently reported to be cardioprotective (15,16).

Although association studies cannot provide definite mechanistic evidences, one cannot avoid asking how *ABCC8* p.A1369S exerts such positive effect on cardiovascular outcomes. Considering that SUR1 is mostly expressed in brain, pancreatic (α, β, and δ), and other neuroendocrine cells (17), it is unlikely that *ABCC8* p.A1369S acts directly on the vasculature and heart.

By referring to previous studies addressing the role of genetic predisposition of diabetes on the risk of CHD (18), Emdin et al. (11) suggest that the cardioprotective effect of p.A1369S variant is based on more than just diabetes risk reduction. Although this is an intriguing possibility, it remains truly impossible to determine whether and to what

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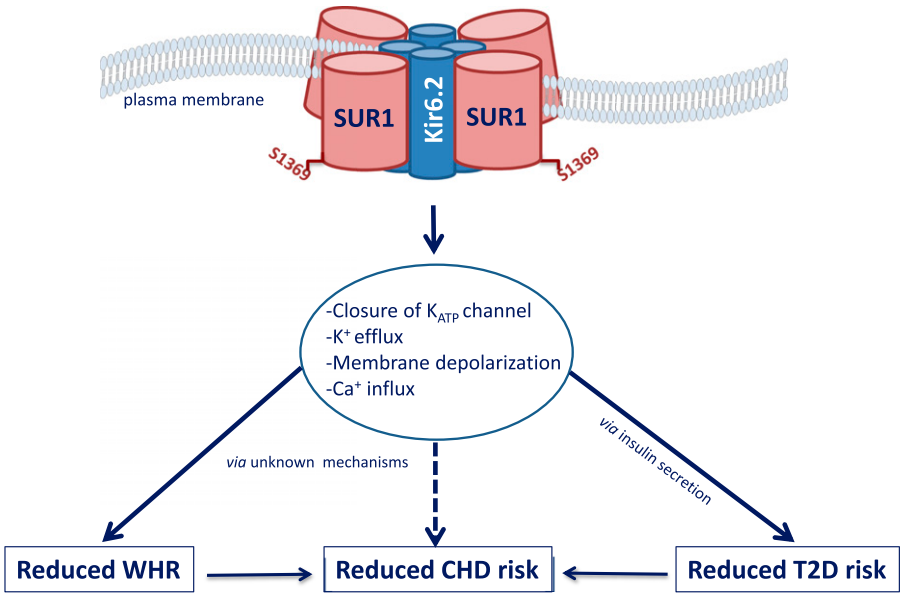

Figure 1—Pleiotropic effects of naturally occurring SUR1 gain-of-function amino acid change on cardiometabolic traits. The ATP-sensitive potassium channel is composed by SUR1, encoded by *ABCC8*, and the selective potassium pore Kir6.2, encoded by *KCNJ11*. The SUR1 p.A1369S is a gain–of-function amino acid change, which mimics in vitro the effects of sulfonylureas by promoting the closure of ATP-sensitive potassium channel (12) that ensues in increasing potassium efflux, cell membrane depolarization, calcium influx and promoting insulin exocytosis in pancreatic β-cells. In humans, the p.A1369S variant has been associated with enhanced glucose-induced insulin secretion (13) and reduced risk of type 2 diabetes (13,14). Emdin et al. (11) showed that the SUR1 p.A1369S variant is also associated with lower risk of CHD. The intimate biology underlying this association is not known. One possibility is that the SUR1 p.A1369S variant affects the risk of CHD, at least partly, via its protective effect on type 2 diabetes, a major cardiovascular risk factor. It is also possible that the reduced risk of CHD is a consequence of the unexpected and difficult-to-understand reduced abdominal adiposity shown by carriers of SUR1 p.A1369S. Finally, SUR1 is mostly expressed in brain, pancreatic, and neuroendocrine cells (17), which are unlikely to be involved in shaping cardiovascular risk. However, it cannot be entirely excluded that part of p.A1369S cardioprotective effect is mediated by low, though physiologically relevant, expression of SUR1 in other tissues. T2D, type 2 diabetes; WHR, waist-to-hip ratio.

extent the two favorable outcomes are independent or, conversely, somehow interwoven. An alternative hypothesis comes from data on adiposity measures, with the p.A1369S variant being associated with an expected increased BMI (6,7) but also an unexpected lower BMI-adjusted waist-to-hip ratio, an established marker of reduced risk for both type 2 diabetes and CHD (19). Whether a favorable nonabdominal fat accumulation has played a role on the cardioprotective effect of *ABCC8* p.A1369S and whether such an effect is observed also under sulfonylurea treatment are questions that remain unanswered. A schematic view of possible pleiotropic effects of the p.A1369S gain-of-function amino acid change on cardiometabolic traits is shown in Fig. 1.

As Emdin et al. (11) admit and clearly discuss, their study has some limitations. First, although the effect of *ABCC8* p.A1369S on CHD has been tested in the general population, the cardiovascular effect of sulfonylureas, if any, would occur in patients with diabetes, who are aggressively treated and intrinsically prone to CHD. Investigating the association between *ABCC8* p.A1369S and CHD among patients with diabetes is the only way to understand whether the encouraging finding of Emdin et al. is extendable to type 2 diabetes. Second, the length and degree of SUR1 stimulation are very different depending on whether it is due to *ABCC8* p.A1369S or to exogenous sulfonylurea administration, with the former being lifelong and mild and the latter initiating in adult life and being definitively more dramatic. For example, in patients with type 2 diabetes, treatment with sulfonylureas is a main cause of severe hypoglycemic episodes, which are believed to increase cardiovascular risk (20). The genetic tool used to recapitulate sulfonylurea-mediated SUR1 stimulation certainly does not capture this drug side effect. Third, it cannot be totally excluded that sulfonylureas also have off-target (i.e., not mediated by SUR1) cardiovascular effects, which, by definition, cannot be replicated by a genetic variant affecting SUR1.

In all, although the above-mentioned limitations call for caution in interpreting and generalizing the reported results, the study by Emdin et al. (11) does question the mantra of sulfonylureas as burdened by cardiovascular side effects, a relevant issue for the entire diabetes community.

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