

## REVIEW

# Is impairment of ischaemic preconditioning by sulfonylurea drugs clinically important?

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In the UGDP study, published in the 1970s, a high incidence of cardiovascular mortality was found in patients treated with the sulfonylurea agent tolbutamide. Impaired ischaemic preconditioning is presumed to be the most important mechanism for the excess cardiovascular mortality observed. However, as tolbutamide has only a low affinity for cardiac sulfonylurea receptors, interference with ischaemic preconditioning seems unlikely to account for this excess mortality. Several smaller studies also failed to establish a definite link between sulfonylurea treatment before acute myocardial infarction and in-hospital mortality. However, when the myocardium becomes exposed to repeated or prolonged periods of ischaemia, ischaemic preconditioning may become clinically important. Myocardial ischaemia can also develop during emergency or elective angioplasty and during coronary bypass surgery. Therefore discontinuation of sulfonylurea treatment should be considered in these circumstances.

sulfonylurea agents individually, as they differ with respect to their selectivity for SUR receptor subtypes. Tolbutamide—the oldest member of the sulfonylurea family—has a high affinity for B cell SUR 1 receptors, but only a very low affinity for SUR 2A receptors expressed on cardiomyocytes<sup>10–12</sup> (table 1). In contrast, glibenclamide inhibits cardiac SUR 2A as well as pancreatic SUR 1 with high affinity.<sup>11</sup> Gliclazide, a second generation sulfonylurea, is characterised by a higher selectivity for pancreatic  $K_{ATP}$  channels.<sup>13</sup> As with glibenclamide, glimepiride—the most novel sulfonylurea—does not differentiate between B cells, cardiac muscle, or smooth muscle  $K_{ATP}$  channels.<sup>14</sup> The benzoic acid derivatives meglitinide and repaglinide also target SUR 1 and SUR 2A receptors potently,<sup>11 15</sup> whereas nateglinide shows a higher selectivity for SUR 1 receptors<sup>16</sup> (table 1).

## EXPERIMENTAL EVIDENCE FOR IMPAIRMENT OF ISCHAEMIC PRECONDITIONING BY SULFONYLUREAS

### Insights from animal models

Evidence produced from various animal studies supports the hypothesis that ischaemic preconditioning is impaired by sulfonylureas. Gross and Auchampach studied the effects of glibenclamide in dogs.<sup>3</sup> The animals were subjected to a 60 minute occlusion of the left circumflex coronary artery, followed by five hours of reperfusion. Ischaemic preconditioning (that is, repetitive, short lasting occlusions of the coronary artery before a prolonged occlusion) led to a significant reduction in myocardial necrosis; however, this effect was completely abolished by glibenclamide.<sup>3</sup> In agreement with this, Toombs *et al* found that co-administration of glibenclamide reversed the cardioprotective effect of ischaemic preconditioning in rabbits.<sup>4</sup> Using perfused rat hearts, Mocanu *et al* showed that glibenclamide, but not glimepiride, abolished ischaemic preconditioning.<sup>17</sup>

### Controlled myocardial ischaemia in humans

As studies involving the induction of repeated ischaemic episodes in humans are simply not feasible, evidence can only be derived indirectly. Cleveland *et al* studied ischaemic preconditioning in isolated human atrial muscle trabeculae

Owing to their potent antidiabetic properties, sulfonylureas have become the leading oral antihyperglycaemic agents over the past half century.<sup>1</sup> The ongoing discussion about potentially detrimental side effects produced by sulfonylureas started in the 1970s with the publication of the university group diabetes program (UGDP) study. This study showed an increase in cardiovascular mortality in type 2 diabetic patients taking tolbutamide, a first generation sulfonylurea.<sup>2</sup> For a long time, no mechanism was proposed to explain the detrimental effects of tolbutamide. The discovery of sulfonylurea receptors (SUR) on vascular cells (SUR 2B) and on cardiomyocytes (SUR 2A) triggered the discussion about impairment of ischaemic preconditioning as the most probable mechanism underlying the increased mortality observed.<sup>3–6</sup> Today, sulfonylureas are still the most frequently prescribed drugs for the treatment of type 2 diabetes mellitus.<sup>7</sup> However, opinions on their potentially detrimental effects continue to diverge.<sup>8 9</sup>

## TISSUE SPECIFIC SUR AFFINITIES OF SULFONYLUREAS AND RELATED SUBSTANCES

When evaluating studies on the effects of sulfonylureas in relation to ischaemic preconditioning, it is important to assess the various

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**Abbreviations:** DIGAMI, diabetes mellitus, insulin glucose infusion in acute myocardial infarction; SUR, sulfonylurea receptor; UGDP, university group diabetes program; UKPDS, UK prospective diabetes study

**Table 1** Different affinities of sulfonylurea and benzoic acid derivatives for SUR subtypes

Generic name	SUR 1 (pancreatic B cells) K <sub>i</sub> *[unit]	SUR 2A (cardiomyocytes) K <sub>i</sub> *[unit]	Relative affinity SUR 1/SUR 2A	Reference
Tolbutamide	5.4 (3.4) μmol/l	1.7 (0.2) mmol/l	314.8	11, 12
Glibenclamide	4.2 nmol/l	27 (2) nmol/l	6.4	11
Gliclazide	50 (7) nmol/l	0.8 (0.1) mmol/l	16 000	13
Glimepiride	5.4 (0.1) nmol/l	7.3 (0.23) nmol/l	1.35	14
Meglitinide	0.26 (0.06) μmol/l	0.53 (0.11) μmol/l	2.0	11
Repaglinide	7.4 (1.2) nmol/l	8.7 (1.5) nmol/l	1.2	15
Nateglinide	7.4 (0.2) μmol/l	2.3 (1.2) mmol/l	311	16

Values are mean (SD).

\*Concentration of half maximal inhibition.

SUR, sulfonylurea receptor.

obtained from type 2 diabetic patients treated with or without sulfonylureas before coronary artery surgery.<sup>18</sup> The trabeculae were subjected to 45 minutes of ischaemia followed by 120 minutes of reperfusion. Ischaemic preconditioning was simulated by prior induction of ischaemia for five minutes. The muscular contractile force, a marker of myocardial integrity, was increased by ischaemic preconditioning; however, this protective effect was absent in the patients receiving sulfonylureas.<sup>18</sup>

Changes in left ventricular ejection fraction and end diastolic volume—indicators of ischaemic myocardial dysfunction—were recently assessed by echocardiography during dipyridamole administration in a study by Scognamiglio *et al.*<sup>19</sup> These investigators found a significant reduction in both variables during glibenclamide administration but not during insulin treatment, indicating a reduction in ischaemic preconditioning by the sulfonylurea drug.

Tomai and colleagues recorded ST segment shifts on an intracoronary ECG and applied them as an index of myocardial alterations during two subsequent episodes of intracoronary balloon inflation in 20 patients pretreated with either glibenclamide or placebo.<sup>5</sup> The investigators found that the ST shifts were reduced during the second balloon inflation in the placebo treated patients, whereas the ST segment remained unchanged during the first and second inflation in patients pretreated with glibenclamide.<sup>5</sup> Similarly, Lee *et al* found that glibenclamide increased the ST segment deviations after the administration of the K<sup>+</sup> channel opener nicorandil.<sup>20</sup> Klepzig *et al* compared the effects of glibenclamide, glimepiride, and placebo administration on ST segment shifts.<sup>21</sup> Glibenclamide prevented ischaemic preconditioning, while it was largely maintained after glimepiride administration. These data are strongly supported by a recent study by Lee and Chou, which showed that shifts of the ST segment were increased by pretreatment with glibenclamide in patients with and without type 2

diabetes.<sup>22</sup> In contrast, pretreatment with glimepiride only marginally affected cardioprotection arising from ischaemic preconditioning.<sup>22</sup>

A word of caution is necessary regarding the interpretation of studies using ST segment deviations as an indicator of myocardial ischaemia, as a large part of the ST segment change is mediated by sarcolemmal K<sub>ATP</sub> channels.<sup>23</sup> It is possible that sulfonylureas block these channels as well, thereby perturbing ST segment changes recorded on the ECG. This may limit the interpretation of studies using ST segment changes as a surrogate for the cardiac effects of compounds with a modulating activity at K<sub>ATP</sub> channels, such as the sulfonylureas.

The different effects of glimepiride and glibenclamide on ischaemic preconditioning<sup>17, 21, 22</sup> are surprising, as the relative affinity to cardiac SUR 2A receptors compared with pancreatic SUR 1 receptors has been shown to be comparable for both compounds when studied in excised patches.<sup>14</sup> However, in isolated ventricular myocytes, the half maximal inhibitory concentration of glimepiride has been reported to be 31.6 nM, compared with 6.8 nM for glibenclamide<sup>24</sup>. Thus it appears possible that the selectivity of glimepiride for the different types of sulfonylurea receptors in isolated cell patches differs from the *in vivo* situation. The reasons for these discrepancies, however, remain to be clarified.

As an induction of ischaemic precondition may also underlie the so called “warm up phenomenon”, Ovunc investigated the effects of glibenclamide on this phenomenon in type 2 diabetic patients with chronic stable angina pectoris during two consecutive exercise stress tests.<sup>25</sup> Under these conditions, glibenclamide abolished the improvement of the heart rate–pressure product during the second exercise test.<sup>25</sup>

However, clinical data are conflicting. Bogaty *et al* reported no effect of antidiabetic treatment with glibenclamide on the electrocardiographic shifts of the ST segment during repeated exercise tests in patients with type 2 diabetes,<sup>26</sup> while Correa

**Table 2** Acute mortality after myocardial infarction in patients with type 2 diabetes mellitus treated with oral antidiabetic drugs including sulfonylureas and in normal subjects

Author	Non-diabetic		Type 2 diabetic patients with sulfonylureas*		Type 2 diabetic patients without sulfonylureas			Deceased (%)	p Value
	No.	Deceased (%)	No.	Deceased (%)	No.	Diet/other OAD†	Insulin		
Soler <i>et al</i> <sup>24</sup>	–	–	129	59 (45.7)	156	31	125	54 (34.6)	0.068
Rytter <i>et al</i> <sup>30</sup>	751	152 (20.2)	54	27 (50.0)	19	8	11	5 (26.3)	0.023
Garratt <i>et al</i> <sup>41</sup>	–	–	67	7 (11.0)	118	48	70	28 (24.0)	0.032
Klamann <i>et al</i> <sup>38</sup>	357	72 (20.2)	76	25 (32.9)	89	42	37	29 (32.6)	1.0
Halkin <i>et al</i> <sup>36</sup>	–	–	121	19 (15.7)	124	96	28	22 (17.7)	0.73

p Value:  $\chi^2$  test.

\*Including chlorpropamide, tolbutamide, and glibenclamide.

†Including metformin and acarbose.

OAD, oral antidiabetic agents.

**Table 3** Clinical situations where sulfonylurea treatment may be harmful and should therefore be avoided or discontinued

Clinical situation	Explanation	Reference
(1) Acute myocardial infarction		
(a) with acute angioplasty	Balloon inflation causes a second period of ischaemia following acute myocardial infarction	41
(b) without emergency coronary intervention	Angioplasty can be necessary at any time	No studies available
(2) Unstable angina pectoris	Repeated or prolonged episodes of myocardial ischaemia	5
(3) Elective angioplasty	Artificial induction of repeated or prolonged intracoronary occlusion	42

and Schaefer found that exercise induced ST depression was not affected by glibenclamide pretreatment.<sup>27</sup>

All aspects considered, the available data indicate that the cardioprotective effect of ischaemic preconditioning can be abolished *in vivo*—in animals as well as in humans—by giving sulfonylurea compounds, particularly glibenclamide, in standard therapeutic doses.

### ENDPOINT TRIALS AND REGISTRIES

To date, only two prospective and randomised studies have targeted the association between sulfonylurea treatment and cardiovascular mortality: the UGDP study and the UKPDS (UK prospective diabetes study).<sup>2,28</sup> In the UGDP study, tolbutamide, a first generation sulfonylurea drug, was tested.<sup>2</sup> The trial revealed an increased cardiovascular mortality in the sulfonylurea group.<sup>2</sup> Glibenclamide, a second generation sulfonylurea with proved pharmacological affinity for SUR 2A receptors and sufficient potential to interfere with ischaemic preconditioning<sup>11</sup> (table 1), was investigated in the UKPDS. No significant effect was found on either mortality or the incidence of cardiovascular events.<sup>28</sup> Recently, an assessment of the Saskatchewan health databases over a follow up period of 5.1 years showed a significantly lower mortality in patients treated with metformin (13.8%) compared with sulfonylurea monotherapy (24.7%).<sup>29</sup> However, while that result may have resulted from detrimental effects of sulfonylureas, it could also reflect a cardioprotective effect of metformin. The latter explanation is supported by a low mortality (13.6%) in patients receiving metformin and sulfonylureas in combination.<sup>29</sup> Also, the treatments were not randomised.

Because of the lack of clear evidence from prospective randomised trials, various smaller studies have targeted the interactions between sulfonylureas and ischaemic preconditioning. However, data are conflicting. Rytter and colleagues studied the acute mortality in 73 patients with type 2 diabetes who had developed acute myocardial infarction.<sup>30</sup> They found that mortality was significantly higher in patients treated with oral antidiabetic agents (50.0%) than in those treated with insulin (9.1%) or diet alone (25%). However, as tablet treatment was not further specified and included patients on treatment with tolbutamide, glibenclamide, metformin, or a combination of these agents, any detrimental effects such as increased mortality cannot be attributed to sulfonylureas alone with certainty. In addition, it is unclear whether the differences observed reflect detrimental effects of oral hypoglycaemic agents or beneficial effects of insulin treatment in the postinfarction period. The benefit arising from insulin treatment in patients with acute myocardial infarction has been demonstrated impressively in the DIGAMI

(diabetes mellitus, insulin glucose infusion in acute myocardial infarction) study. In that study, 620 patients with type 2 diabetes who were admitted with a diagnosis acute myocardial infarction were randomised to either treatment with an insulin–glucose infusion followed by intensive subcutaneous insulin treatment in the postinfarction period, or to standard treatment.<sup>31,32</sup> The investigators found a 28% relative risk reduction for mortality during a 3.4 years follow up in the treatment group.<sup>31</sup> However, these data might also be interpreted to show that withdrawal of sulfonylureas in the treatment group had contributed to a better outcome.<sup>33</sup>

Other follow up studies could not confirm an increased mortality after acute myocardial infarction in patients treated with sulfonylureas.<sup>34–36</sup> In line with earlier data from Paasikivi,<sup>37</sup> in our German cohort we did not find an association of sulfonylurea treatment before an acute myocardial infarct with either increased hospital mortality or infarct size.<sup>38</sup> Long term follow up for more than 3.5 years showed no detrimental effects of sulfonylureas either.<sup>39</sup> Using the Health Care Financing Administration cooperative cardiovascular project database, 64 171 patients with diabetes mellitus who had suffered a myocardial infarct were included in a recent analysis; it was shown that patients treated with sulfonylureas developed *fewer* complications and had lower in-hospital mortality than those treated with insulin.<sup>40</sup> Again, treatment was not assigned by randomisation.

In conclusion, from the currently available clinical study data, there is no evidence that sulfonylureas increase the rate of cardiovascular events or mortality in patients with spontaneous coronary stenosis or occlusion.

### USE OF SULFONYLUREAS DURING REPEATED INTRACORONARY BALLOON INFLATION

Although there is no evidence for detrimental effects of sulfonylureas in patients with type 2 diabetes under normal conditions, their use may worsen the prognosis of patients with type 2 diabetes mellitus in certain clinical situations. Such conditions arise if a period of myocardial hypoxia is followed by a second episode—that is, if ischaemic preconditioning is induced. A second ischaemic episode can be artificially produced by repetitive inflation of an intracoronary balloon catheter,<sup>3</sup> but it can also occur spontaneously. In case of emergency angioplasty after acute myocardial infarction, balloon inflation in the coronary artery irritates the myocardium a second time. Accordingly, Garratt *et al* reported an increased in-hospital mortality in type 2 diabetic patients taking sulfonylureas following immediate balloon angioplasty for acute myocardial infarction.<sup>41</sup> Moreover, O’Keffe *et al* analysed the long term survival after elective coronary angioplasty and coronary bypass surgery in 1938 patients with type 2 diabetes mellitus. They found that the use of sulfonylureas was associated with a worse outcome after angioplasty, but not after coronary bypass surgery.<sup>42</sup>

### SUMMARY AND CONCLUSIONS

Despite the fact that clear evidence for an impairment of ischaemic preconditioning by sulfonylureas can be obtained from various animal studies and from indirect experimental studies in humans, there is still no evidence for a detrimental effect on cardiovascular mortality in patients with type 2 diabetes mellitus. Our discussion of any potentially detrimental effects of the sulfonylureas is based on the increased cardiovascular mortality observed in the UGDP study.<sup>2</sup> However, as the affinity of tolbutamide, the sulfonylurea used in the UGDP study, for cardiac SUR 2A receptors is relatively low,<sup>11</sup> an interference with ischaemic preconditioning seems an unlikely explanation for the results found in that study (table 1). In contrast, glibenclamide—a



sulfonylurea with a high affinity for cardiac SUR2A receptors<sup>11</sup> and with well documented effects on ischaemic preconditioning under experimental conditions<sup>18</sup>—failed to alter cardiovascular mortality in the UKPDS.<sup>28</sup> Thus the UGDP results are more likely to reflect methodological deficiencies of the study design than any direct detrimental effects exerted by sulfonylureas per se.<sup>43</sup>

Taking smaller follow up studies into consideration, the use of sulfonylureas does not appear to worsen the prognosis of patients with type 2 diabetes after acute myocardial infarction in general terms (table 2). In contrast, sulfonylurea treatment may increase mortality in patients with type 2 diabetes when subjected to elective or emergency balloon angioplasty.<sup>41–42</sup> Although experimental data highlight compound specific differences between the various sulfonylureas<sup>17</sup> (table 1), this has not yet been evaluated in clinical trials. Further clinical trials will be necessary.

In conclusion, from the present data it seems worth reconsidering the use of sulfonylureas in cases of elective or emergency angioplasty (table 3). As the DIGAMI study provided striking evidence for the benefit of tight glucose control with an intensive insulin treatment regimen during the peri-infarction period,<sup>31</sup> this method of treatment appears to be a suitable alternative.

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