

Sulfonylureas and cardiovascular effects: from experimental data to clinical use. Available data in humans and clinical applications

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SUMMARY

Objectives: 33 years after the UGDP study, the question of deleterious effects of the sulfonylurea (SU) is still raised. We have made a systematic review of the literature from experimental studies to clinical and epidemiological studies.

Results: The main molecule studied is glibenclamide (GB). *In vitro* and in animal studies, GB is both deleterious for ischemic preconditioning (IPC) and protective for arrhythmia during acute ischemia. Glimépiride (GM) and gliclazide (GCZ) do not seem to have effect on IPC. These effects have been few studied in diabetic animals. In human, according to the investigations used, the GB seems nil or suppressing for IPC, it seems elsewhere decreases ventricular arrhythmias during periods of acute ischemia. It is possible that these two actions account for the non-appearance of concordant deleterious effects between short and long-term studies. With regards to other drugs, only the GM has been specifically studied in human and appears to be nil on IPC. The only prospective clinical study available, although not having for objective to answer to this question, is the UKPDS study. This trial demonstrates the absence of deleterious cardiac effects of GB compared to chlorpropamide and particularly compared to insulin.

Conclusion: In conclusion, in experimental studies the cardiac effects of SU differ: both deleterious and protective for GB, nil for GM and GCZ on IPC. In all cases the clinical consequences seems to be nil.

Key-words: Cardiac Effect · Diabetes · Sulfonylurea Drug.

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RÉSUMÉ

Sulfonylurées et effets cardiovasculaires : des données expérimentales à l'usage clinique. Données disponibles chez l'homme et applications cliniques

Objectif : Trente-trois ans après l'UGDP, la question des effets délétères cardiaques des sulfonylurées (SU) reste posée. Nous avons réalisé une revue systématique de la littérature, des études expérimentales aux études cliniques et épidémiologiques.

Résultats : La principale molécule étudiée est le glibenclamide (GB). *In vitro* et chez l'animal le GB présente des effets à la fois délétères sur le pré-conditionnement ischémique (PCI) et protecteurs sur les troubles du rythme en situation d'ischémie aiguë. Le glimépiride (GM) et le gliclazide (GCZ) paraissent dénués d'effet sur le PCI. Ces effets ont été peu étudiés chez l'animal diabétique. Chez l'homme, selon les tests utilisés, le GB apparaît sans effet ou inhibiteur sur le PCI, il semble par ailleurs diminuer les arythmies ventriculaires en périodes d'ischémie aiguë. Il est possible que cette dualité d'action rende compte de l'absence d'effet délétère concordant entre les études à court ou long terme. Parmi les autres SU, seul le GM a été spécifiquement étudié chez l'homme et semble dénué d'effet sur le PCI. La seule étude clinique prospective disponible, encore que n'ayant pas pour objectif de répondre à cette question, est l'UKPDS. Cette étude démontre l'absence d'effet délétère cardiaque du GB comparativement au chlorpropamide et surtout à l'insuline.

Conclusion : En conclusion, dans les études expérimentales, les effets cardiaques des SU diffèrent : à la fois délétère et favorable pour le GB, nul sur le PCI pour le GM et le GCZ.

Dans tous les cas, la résultante clinique paraît nulle.

Mots-clés : Cardio-vasculaire · Diabète · Sulfamides hypoglycémiant.

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After 8 years of a prospective randomized study, the UGDP announced in 1970 that the cardiovascular mortality of type 2 diabetic patients treated with tolbutamide was significantly ($p = 0.005$) higher (14.7%) in comparison with patients given a placebo (10.2%), insulin at fixed dose (9.5%), or insulin at variable doses (8.8%) [1]. The trial was therefore interrupted for the group of patients on tolbutamide and the FDA published a warning regarding increased cardiovascular risk related to tolbutamide. The UGDP results aroused lively controversy at the time and were brought into question because of methodology open to criticism, with randomization errors in particular, the inclusion of non-diabetics and poor compliance [2, 3]. Shortly afterwards, some clinical trials were published showing results of the same type: less survivors after myocardial infarction in diabetics treated with oral anti-diabetics in comparison with diet only [4, 5] or treated with insulin [6]. In contrast, other studies failed to reveal any link between the type of anti-diabetic treatment and long-term survival [7] or after myocardial infarction [8] or showed a very significant advantage in terms of overall mortality for patients treated with sulfonylureas (SU) in comparison with those treated by diet or insulin [9]. However these were retrospective studies, involving very different groups of patients evaluated without statistical adjustment of all main confusing factors. The Malmo prospective and controlled trial [10], with prolonged follow-up for up to 12 years, showed that tolbutamide prevented the deterioration of glucose intolerance to diabetes, and that cardiovascular mortality was less in patients not progressing to diabetes. The Bedford survey showed, in 248 moderately hyperglycemic patients monitored for 5 years, a significant reduction in cardiovascular events in tolbutamide-treated patients in comparison with those who had only a placebo dose [11]. Nevertheless this protective effect was not confirmed after 10 years of follow-up [12]. The matter appeared to be closed with the publication of the results of the UKPDS [13] showing after about 10 years of treatment the absence of any perceptible difference regarding morbidity and mortality between groups of patients treated with insulin, glibenclamide (Gb) or chlorpropamide. Discovery of the heterogeneity of SU receptors, with SUR2 A and SUR2 B receptors present in the heart, as well as heterogeneity of interaction of the various SU with these

receptors and their effects in animal models, relaunched the discussion concerning the potential cardiac danger of SU or of some of them. Several reviews or editorials have recently reconsidered this topic, with different conclusions: some propose banning SU in diabetics with coronary artery disease [14, 15], while others do not express an opinion considering that there are not enough data in order to be able to draft guidelines [16-18], while others finally consider that there are not currently sufficient data to withdraw SU from diabetics with coronary artery disease [3, 19] or feel that new generations of insulin secretagogues such as glimepiride and meglitinides seem very safe [20]. This discussion, not devoid of commercial considerations for the industrial companies which market these drugs, nevertheless raises a question of major importance: are SUs a therapeutic class, or just some of them, dangerous or not for diabetics? In order to shed light on the debate, if not to provide an answer to it, we have attempted to review currently available data, and in particular clinical findings in diabetics.

Mode of action of sulfonylureas (SU)

The target of SU is now known: it is an ATP-dependent potassium channel located in many tissues, including β cells, but also the heart, skeletal muscle, smooth muscle, the pituitary, the central nervous system and the kidney. This channel is a heterodimer formed from the association of two distinct proteins, SUR (1 or 2), for "sulfonylurea receptor", and Kir6.2. The structure of this receptor differs according to its site: SUR1/Kir6.2 in beta cells and SUR2/Kir6.2 in the myocardium. The SUR sub-unit is the main target of SU. The latter bind to the pancreatic channel (SUR1/Kir6.2) with high affinity resulting in closure of the KATP channel, stimulating insulin secretion. This interaction depends upon the chemical nature of the SU: for example, tolbutamide has less affinity for its receptors than Gb (EC50: 1 mM *vs.* 1 μ M) [21]. The affinity of SU for SUR2 is less than for SUR1 but varies according to the structure of the molecule. For example, the affinity of tolbutamide is 500 times less for SUR2 than for SUR1 while Gb has an affinity only ten times less for SUR2 in comparison with SUR1 [22].

The cardiac KATP channel during myocardial ischemia: experimental findings

Many authors have studied the role of the KATP channel in cardiac adaptation during ischemia. Because of the high concentration of ATP in the cardiac myocyte, the KATP channel is closed under baseline conditions. It opens in various situations: drop in concentration of ATP, accumulation of lactates and protons, activation of adenosine A1 receptor. During acute ischemia, such metabolic changes can occur leading to opening of the potassium channel and emergence

Abbreviations

SU :	sulfonylureas
IPC :	ischemic preconditioning
GB :	glibenclamide
GCZ :	gliclazide
GM :	glimepiride
FBF :	forearm blood flow
VPC :	ventricular premature complexes
BP :	blood pressure
OR :	odd ratio
LVEF :	left ventricular ejection fraction
BMI :	body mass index

of potassium from the cell. This is followed by membrane repolarization and shortening of action potential which leads to reduced inflow of intracellular calcium. Resultant reduced myocardial contractility protects the myocardium by limiting its oxygen consumption.

Furthermore, opening of the KATP channel present in arterial wall during ischemia decreases vascular resistance leading to increased coronary flow. These events are mediated by adenosine among others, resulting from breakdown of ATP leading to opening of the KATP channel.

The KATP channel also plays a role in another self-protection activity of the myocardium during ischemia: ischemic preconditioning (IPC). Brief episodes of repeated ischemia render the heart more resistant to later ischemic events with a marked reduction in the size of infarction and myocardial contractile malfunction. IPC occurs in all species including humans. For example, in the rabbit, an episode of preconditioning may decrease the surface area of the zone of infarcted myocardium during subsequent ischemia from 40 to 8% [23]. Activation of the KATP channel activates IPC [24]. Absence of IPC in mice knock-out for Kir6.2 strengthens the hypothesis of a central role of the KATP channel in this event [25].

Gb is by far the SU the myocardial action of which has been most extensively studied. Since the 1990s, more than 200 studies have evaluated its effects on the heart in animals. Its affinity for the myocardial SUR2/Kir6.2 KATP channel is greater than that of other commonly used SU [26]. It is considered to be the reference inhibitor of the myocardial KATP channel although reversibility of its binding is much faster with SUR2 than with SUR1.

Three types of effects are seen:

- an effect on vascular tone;
- an effect on the myocardium;
- an anti-arrhythmic effect.

Effects of glibenclamide on vascular tone and myocardial blood flow

Intracoronary injection of Gb increases vascular resistance and decreases the blood flow in coronary arteries in the dog with an open thorax [27, 28]. This vasoconstrictor effect is dose-dependent and is accompanied by increased lactate formation. Simultaneous infusion of pinacidil, which opens the myocardial KATP channel, protects the myocardium against glibenclamide. In contrast, pinacidil-induced vasodilation is abolished by the administration of high doses of Gb. Similar results have been reported using perfused isolated heart preparations [27, 29, 30]. These results are surprising since intracellular ATP levels in vascular smooth muscle are sufficient to keep the KATP channel closed. Hence no further effect of Gb is expected. Gb has nevertheless proven its ability to inhibit ischemia-induced vasodilation [31, 32] and to lessen adenosine-induced vasodilation [33]. High doses of Gb induce oscillations in the diameter of

coronary arteries and in blood flow [27, 34]. This dose-dependent event occurs at supra-therapeutic doses [35] can be blocked by adenosine receptor inhibitors [27] and is believed to be independent of myocardial ischemia [34].

Effect of glibenclamide on myocardial tissue in a situation of ischemia

Direct effect of glibenclamide on the myocardium

Do SU increase the extent of myocardial cell lesions during myocardial infarction by neutralizing the cardioprotective mechanisms which come into play during ischemia? Numerous *in vitro* studies, using isolated or *in vivo* hearts, with open thorax animals exposed to acute ischemia then to reperfusion, have shown that Gb increased the size of infarctions and contractile dysfunction [36-43]. It has also been shown that SU abolish the protective effects of substances which open the KATP channel [37, 43-49]. These studies led to the conclusion that an SU such as Gb worsened myocardial lesions during ischemia by blocking the protective effects of endogenous or exogenous substances which open the KATP channel. Without returning to the effects of modulations of the KATP channel on vascular tone, other authors have failed to find these effects of Gb on myocardial infarction size or on myocardial functional recovery after a phase of ischemia and during reperfusion [20, 40, 47, 49-53]. These discrepancies would be explained by methodological differences.

Different doses of Gb were used in these studies. Most often high doses (3 mg/kg) increased the size of an infarction while low doses (0.3 mg/kg), i.e. the same as therapeutic doses in humans, had no effects [40]. There are other confusing factors since some authors reported increased size of an MI on 0.15 mg/kg of Gb [39] while others found no effect with high concentrations (100 μ mol/l) [59]. Ischemic preconditioning of the myocardium is unavoidable when the heart is isolated. It is therefore possible that the apparent effect of Gb could be linked more to inhibition of protective preconditioning than to a direct toxic effect of the drug.

Effect of glibenclamide on IPC

Many animal studies have shown that Gb inhibited IPC via closure of the myocardial KATP channel. One of the first is that of Toombs [40] who exposed rabbits to myocardial ischemia for 30 minutes followed by reperfusion for 120 minutes. Animals with a substantial IPC in a prior ischemia phase lasting 5 minutes followed by reperfusion for 10 minutes had an infarction zone reduced by 63% in comparison with controls. Rabbits who were also given Gb had an infarction zone similar in size to controls. Hence the reduction in infarction size related to IPC is abolished by Gb in the rabbit. Abolition of the beneficial effect of IPC on the size of the infarcted zone and on post-ischemic recovery of myocardial function by Gb has been confirmed in other species: in the dog [24] and piglet [50]. In contrast, inhibition of IPC by blockage of the KATP channel by Gb is not always seen in

the rat [51, 54]. In the rabbit, the inhibitory effect of Gb on IPC depends upon the anesthetic agent used: it is present with ketamine-xylazine but not with pentobarbital [55]. These findings emphasize the complexity of these ischemic preconditioning events.

Extrapolation of these acute studies to situations involving chronic treatment with an SU is by no means evident. It is also not evident that these substances influence IPC during the complex situation of a myocardial infarction. Only one study has evaluated cardiac response to acute ischemia during prolonged treatment with an SU administered to rats rendered diabetic by streptozotocins. Baseline and post-ischemic myocardial function was paradoxically improved [56].

Effect of Gb on arrhythmia during myocardial ischemia

Ventricular arrhythmia is common during periods of myocardial ischemia and during reperfusion phases. It is a major cause of death associated with myocardial infarction. Mechanisms of this occurrence appeared to be related to emergence of potassium from the intracellular medium through open KATP channels. This leads to shortening of the length of the action potential making the heart more sensitive to reentry mechanisms. Events which protect the heart against ischemia appear to increase the risk of arrhythmia. This situation is particularly complex regarding the consequences of myocardial ischemia. Many authors have shown that substances which open the KATP channel increase the incidence of ventricular arrhythmia [48, 57-59] while others paradoxically have found an anti-arrhythmic effect of the substances [60]. This suggests that the pathophysiology of arrhythmia during myocardial ischemia is complex and involves various mechanisms.

SU, and Gb in particular, have anti-arrhythmic properties in a situation of acute ischemia in most animal models studied [30, 41, 59-61]. Most of these studies showed a decreased incidence of ventricular tachycardia and fibrillation. Two studies failed to show any such decrease but there was shortening of the duration of these arrhythmias [30, 62]. One author confirmed the decrease under the influence of Gb in ventricular arrhythmias during ischemia in rabbits but also showed that this effect did not involve shortening of the action potential [63]. Others did not find this effect and in particular in the rat [64] and sheep [65]. These authors even found a pro-arrhythmic effect of Gb.

Furthermore, IPC, in addition to its favorable effects on the size of myocardial infarctions and myocardial malfunction, reduces the onset of serious ventricular arrhythmias during ischemia and reperfusion [66]. It is of interest to note that Gb does not abolish the anti-arrhythmic effect of IPC [66]. The mechanisms which reduce the seriousness of arrhythmias and those which decrease the size of myocardial infarction hence seem to be distinct.

Cardiac actions of other SU

There are relatively few available data concerning the cardiac effects of other SU. It has been well established that these effects involve binding of the substance with the myocardial Kir6.2/SUR2A receptor. The affinity of each SU for SUR2A is individually specific. Their effects on the myocardium should be dependent upon this affinity.

Effect of gliclazide

This substance has been used therapeutically for many years. Its affinity for pancreatic and myocardial SU receptors has been studied recently. Evidence has been found of powerful binding of this substance to the pancreatic SUR1/Kir6.2 receptor and its very low affinity to myocardial SUR2A/Kir6.2 and smooth muscle SUR2B/Kir6.2 receptors [67]. These data have emerged from studies using Xenopus oocytes, with coexpression of Kir6.2 and various isoforms of SUR 1, 2A, 2B. In this model, the effect of nicorandil (100 $\mu\text{mol/l}$), a substance which specifically activates the myocardial KATP channel, is decreased by Gb and glimepiride, and little or not by gliclazide [68]. In this *in vitro* model, gliclazide does not bind to the cardiac sulfonylureas receptor. The rare studies which have evaluated the cardiac effect of gliclazide have found evidence of pro-arrhythmic properties in the rat [69] with an increased incidence of ventricular fibrillation during myocardial ischemia. Another study found decreased coronary blood flow and increased vascular resistance in the dog with an open thorax following the intracoronary administration of gliclazide [70]. Hence gliclazide appears to be free of any effect on IPC but in contrast could have a pro-arrhythmic effect in animals.

Effect of glimepiride

Glimepiride has powerful affinity for both the pancreatic SUR1/Kir6.2 and myocardial SUR2A/Kir6.2 receptors (IC₅₀ 3.0 mM and 5.4 mM respectively) [71]. This affinity is similar to that of Gb (4 mM and 5.4 mM respectively). However, the effects of this substance on the myocardium in animals, as compared with Gb, seem to be far more modest: a decrease in coronary blood flow analogous to that of Gb has been found *in vitro* [35, 70] using perfused rat hearts. In contrast, reduced loss of post-ischemic myocardial function has been found with glimepiride but not with Gb [35]. Several *in vitro* [72, 73] or *in vivo* [74] studies have failed to find any effect of glimepiride on IPC. Hence, despite probable binding to the myocardial receptor, glimepiride does not seem to have any cardiac effect in the animal and during an ischemic period.

Effect of tolbutamide

This substance was that used in the UGDP study. It therefore raised the question of the alleged myocardial toxicity of SU. However the affinity of tolbutamide for myocar-

dial SUR2/Kir6.2 receptors is very slight [26]]. Tolbutamide consists of a sulfonylurea group without a benzamide group. The specific binding site of the sulfonylurea group is absent from the myocardial SUR2 sub-unit. This could explain why this substance is capable of blocking the pancreatic KATP channel (on SUR1) with high affinity but appears to have no effect on the myocardial (SUR2) KATP channel [26, 27]. There are few data in the literature concerning the cardiac effects of tolbutamide in animals. Several studies have reported only transitory inhibition of potassium flow in cardiac myocytes of rats on doses of tolbutamide far greater than those required to inhibit the pancreatic KATP channel (1 mM *vs.* 1 μ M) [75, 76]. It is therefore unlikely that this substance has any direct cardiac action. Anti-arrhythmic effects have nevertheless been reported in the rabbit, *in vitro* [77] and *in vivo* [78] but at markedly supra-therapeutic doses.

In all, *in vitro* or in animals, the cardiac effects of glibenclamide may be at one and the same time harmful and protective. In myocardial ischemia, this SU can increase myocardial vascular resistance and inhibit the protective event of IPC. However it has also been shown that the substance has anti-arrhythmic properties in a situation of acute ischemia. There have been few studies of these effects in diabetic animals. Data concerning the cardiovascular effects of other SU in animals are rare. Compared to glibenclamide, glimepiride appears to be free of any effect on IPC. What is the situation in humans?

SU and myocardial ischemia: experimental studies in humans

Glibenclamide (Gb)

Most clinical studies have been done using this medicine. Parameters include exercise ECG, echocardiogram, angioplasty or 24-hour cardiac Holter. Some have studied the blood supply of forearm by plethysmography or ultrasound technique.

Exercise ECG

There are four available studies involving small series of patients (10 to 26) with coronary artery disease documented by coronary angiogram including several > 70% stenoses or by myocardial isotope scan (with reversible significant hypoperfusion). All of these patients did two consecutive exercise tests, separated by a 15-minute interval. The first test was supposed to induce the "warm-up phenomenon" equivalent to IPC. The second test enabled measurement of the effect. Two series of tests were done, one without and the other with pretreatment with 10 mg of Gb as a single dose [79-81] or as chronic treatment (\geq 10 mg Gb/day) [82]. Methodology varied from one study to another (*Tab I*). All of these four studies showed a significant increase in peak rate-pressure product (RPP) (+ 7 to + 19%) and RPP when the exercise test became positive (+ 17 to + 18%), indicating an

increase in ischemic threshold during the second test in the placebo groups (*Tab I*). Exercise tolerance also increased with the increase of time to ST segment depression and test becoming positive (+ 26 to + 40%) or increase of time to angina pain onset (+ 28 to + 31%). Pretreatment with Gb completely suppressed the increase in RPP in only two studies out of four [79, 81] as well as the lengthening of time to positive the test or the time to pain onset (*Tab I*). Maximum ST Depression (Max STD) remained unchanged. Authors reached various conclusions: Gb prevents IPC [79, 81] or seems to have no effect, in particular in diabetics on chronic treatment with Gb [82]. In this latter study, there was no perceptible difference between subgroups with low (< 0.24 μ mol/l) or high (> 0.60 μ mol/l) plasma Gb levels.

Echocardiogram

There is one available study of left ventricular (LV) function by echocardiogram, with much more clear-cut conclusions [83]: 19 type 2 diabetics aged 61 with coronary artery disease including two or three more than 70% stenoses by angiogram, were treated for two 12-week periods after randomization and cross-over, with either Gb 5 to 15 mg/day or insulin (two to three injections per day). A two-dimensional echocardiogram was done at rest then after infusion of dipyridamole (DPD), at the end of these two periods. This investigation showed that during treatment with Gb, LV ejection fraction (LVEF) decreased by 12% and LV dyskinesia evaluated by the wall motion score index (WMSI) increased significantly. In contrast, during treatment with insulin, neither of these two indices were significantly modified. Consequences on LV function of induced myocardial ischemia hence seem to be less severe when diabetics with coronary artery disease are treated with insulin rather than Gb.

Angioplasty

Coronary angioplasty is a model of ischemic preconditioning in man. There have been three studies in non-diabetic patients with coronary artery disease including > 70% coronary artery stenoses requiring angioplasty. The balloon was inflated twice for 120 seconds, at an interval of at least 5 minutes, in patients who had taken either Gb (10 mg per os 90 minutes before the test or 2.5 mg IV started 3 minutes before the test), or a placebo. In placebo patients, the first coronary occlusion induced typical IPC, characterized during the second occlusion with a significant decrease in ST segment depression in the intracoronary ECG (of - 35 to - 63%). The severity of anginal pain evaluated by visual analogic scale (VAS) was less during the second occlusion (- 60%) [84, 85] or its onset was delayed [86]. These results were seen consistently in all three studies, in middle-aged adults (age < 65). In contrast, no IPC was seen in the subgroup of patients aged over 65 [85], it was only obtained by longer occlusion (180 sec). Prior administration of Gb completely suppressed the protective effects of the first occlusion regarding ST depression and chest pain in all three studies.

Table I

Effects of Gb on rate-pressure product (RPP), ST depression (STD) and time to angina in patients with coronary artery disease, during repetitive exercise tests. All patients underwent two consecutive tests (ET1 and ET2) separated by 15 minutes interval, either with pre-treatment by 10 mb Gb or not.

	Patients	Method		Peak RPP		Time to STD (s)		Maximum STD		Time to Angina (s)		RPP at 1.5 mm STD	
				No Gb	Gb	No Gb	Gb	No Gb	GB	No Gb	Gb	No Gb	GB
Tomai [79] 1994	n = 26 no diabetes 60 y old	Parallel group single blind placebo or 10 mg Gb	ET1	201	196	331	323	2.4	2.2	337	324	186	187
				+ 18%	+ 1%	+ 33%	+ 26%	- 12%	- 9%	+ 28%	+ 18%	+ 18%	+ 2%
		90 min prior ET	ET2	237	198	439	407	2.1	2.0	431	383%	220	191
			p	< 0.01	NS	< 0.01	< 0.01	NS	NS	< 0.01	< 0.05	< 0.01	NS
Correa [80] 1997	n = 10 no diabetes 61 ± 10.3 y old	Double blind, cross over, placebo or 10 mg	ET1	223	230	no difference between 2 groups		2.40	2.11				
				+ 7%	+ 4%			- 41%	- 43%				
		Gb 180 min prior ET	ET2	238	239			1.42	1.20				
			p	0.04	0.07								
Ovung [81] 2000	n = 18 type 2 diabetes. All medications discontinued 2 days before study	no randomisation tests were done without Gb the first day (control), and with	ET1	200	194	334	326	2.3	2.2	330	328	184	185
				+ 19%	+ 1%	+ 26%	+ 4%	- 13%	- 4%	+ 29%	+ 2%	+ 17%	+ 4%
		10 mg Gb 90 min prior the tests, the day after	ET2	235	197	422	338	2.0	2.1	425	336	216	192
			p	< 0.05	NS	< 0.05	NS	NS	NS	< 0.05	NS	< 0.05	NS
Bogaty [82] 1998	n = 12, no diabetes (control) 57 y old n = 10 diabetes type 2, 65 y old	No randomisation Patients without diabetes received no Gb. Diabetes patients received > 10 mg/d as usual treatment	ET1	221	233	498	480	2.2	2.3	564	414		
				+ 7%	+ 12%	+ 40%	+ 16%	- 41%	- 39%	+ 31%	+ 30%	+ 18%	+ 16%
			ET2	237	262	696	558	1.3	1.4	738	540		
			p	0.046	0.006	< 0.001	0.048	0.005	0.006	< 0.001	0.04	0.001	0.02

In contrast, there was no effect of Gb in the subgroup of elderly patients. Gb appears to act only by suppressing a protective effect when it is present without any additional worsening events.

Interaction with nicorandil

Nicorandil is a KATP channel agonist widely used in the treatment of angina pectoris. Its effect appears to be antagonized in the dog by Gb [87]. Results of human experimental studies are contradictory, but in very different experimental situations: during angioplasties [85], acute IV administration of nicorandil to non-diabetics significantly decreased angina pain and ST depression starting from the first episode of ischemia induced by coronary occlusion, in comparison with untreated individuals. Nicorandil also restored IPC in elderly patients during the second ischemic episode induced by the second angioplasty balloon inflation. In this situation, pretreatment with Gb completely suppressed the effects of nicorandil. In contrast, in diabetics with coronary artery disease ($n = 22$), chronic treatment with nicorandil (15 mg/day for 8 weeks) significantly decreased the number of angina attacks per week and improved exercise tolerance in the same way, whether patients were on chronic treatment with Gb or not [86]. Gb given as a single IV dose in non-diabetics also appears to antagonize the myocardial protective effect of nicorandil during acute ischemia, such antagonism not being found during chronic oral treatment of diabetics [88].

Coronary blood flow

Intracoronary injection of high doses (50 $\mu\text{g}/\text{kg}/\text{min}$) of Gb reduced coronary blood flow in the dog by 50% [89]. It blocked hypoxia-induced coronary vasodilation in the guinea pig heart [90]. The question therefore arises of a direct effect of Gb on coronary blood flow in humans. Coronary blood flow was measured by intracoronary Doppler in 12 patients with a tight (>90%) single vessel stenosis of the left anterior descending (LAD) or circumflex coronary artery and requiring angioplasty, prior to the procedure. This measurement was made before and after IV infusion of 50 $\mu\text{m}/\text{kg}$ of Gb [91]. Post-stenotic coronary flow or flow in an angiographically normal coronary were in no way decreased by Gb under baseline conditions nor after adenosine- and/or papaverine-induced vasodilation. Hence, Gb seems to have no effect on coronary blood flow in humans.

Peripheral arterial flow

SUR and KATP channels are present in peripheral arteries as they are in coronary arteries. Study of brachial blood flow by plethysmography or brachial artery flow by high resolution ultrasonography was hence suggested as a model of arterial reaction to ischemia more accessible than the coronary arteries. It was shown that forearm ischemia was accompanied by post-ischemic vasodilation and an increase in arterial blood flow proportional to the duration of ischemia created. IV diasoxide, an opener of arterial KATP channels, induced the same regional vasodilation which was dose-

dependent. Gb was given to healthy volunteers by brachial intra-arterial injection at doses enabling the creation of a regional plasma level of Gb not exceeding 200 ng/ml, the usual plasma concentration seen at the time of peak absorption after oral administration. This revealed a trend ($p < 0.07$) to a decrease in forearm blood flow (FBF) [92]. In contrast, FBF was decreased more significantly by Gb when administered after diasoxide [92]. When Gb was administered orally as chronic treatment in diabetics, no decrease in brachial vascular reserves was seen fasting, at sometime after the drug was taken [93]. When these measurements are made just after the drug is taken, results are controversial: moderate but significant decrease in brachial vascular reserves during the hours after taking 5 mg of Gb [93] or no change in regional hemodynamic parameters measured by plethysmography [94] or high resolution Doppler ultrasonogram scan. In total, the closure of the KATP channels of arterial smooth muscle cells in the forearm by Gb seems to have slight but measurable effects when it is administered acutely in non-diabetics. This effect becomes more minimal and more difficult to show when the drug is taken orally as chronic treatment by diabetics.

Anti-arrhythmic effect

Opening of KATP channels during an episode of myocardial ischemia induces leakage of intracellular potassium which results in shortening of action potential and heterogeneity of refractory periods between ischemic and normal myocardial cells. This leads to a risk of reentry ventricular arrhythmias, a major cause of death after myocardial infarction. Hence the closure of these channels would have beneficial anti-arrhythmic effects, as a counterpoint to the potentially harmful effects on myocardial function described earlier. This has been shown consistently with Gb in *in vitro* or animal experiments (see above). There is only one human study involving a small group of diabetics with coronary artery disease ($n = 19$) selected because they had episodes of ventricular arrhythmia during transitory myocardial ischemia recorded by a 24-hour Holter ECG [95]. These patients were studied prospectively, by 24-hour cardiac Holter before then after two periods of 2 weeks of treatment with metformin (500 mg b.i.d.) or Gb (5 mg b.i.d.) after randomization and cross-over. The frequency of solitary ventricular premature complexes (VPC) and of non-sustained ventricular tachycardia during non-ischemic periods was the same before and during treatment with metformin or Gb. Total mean duration of episodes of transitory ischemia was also the same (11 min/24 hours) regardless of anti-diabetic treatment. In contrast the frequency of solitary VPC/minute of ischemia decreased very significantly on Gb in comparison with baseline conditions without treatment or on metformin ($p < 0.001$) and the mean percentage of ventricular premature complexes per number of ischemic beats decreased by $28 \pm 8\%$ baseline and $28 \pm 7\%$ on metformin to $2.6 \pm 2\%$ when patients were treated with Gb ($p < 0.001$). Hence, glib-

enclamide does not appear to have any actual anti-arrhythmic effect but decreases ventricular arrhythmias only during periods of ischemia, probably via its action of closure of myocardial KATP channels.

Glimepiride (Gm)

Glimepiride, the most recent sulfonylurea used widely in the treatment of type 2 diabetes is alleged to have only slight or nil interaction with cardiovascular SUR2 receptors, and in any event far less than that of Gb. It would therefore be expected that effects seen in human experiments with Gb, and which brought into question the safety of use of this medicine in diabetics with coronary artery disease, would not be found with Gm. This is indeed what has been seen up till now in the few currently published clinical studies.

Peripheral vascular effect

Gm by brachial intra-arterial infusion at doses providing plasma levels markedly greater than those used therapeutically (815 ng/ml) caused no perceptible change in regional vasodilator responses to ischemia. Following intra-arterial infusion of diasoxide (an opener of vascular KATP channels) in 12 healthy volunteers, the dose-vasodilator response curve expressed by the FPF ratio of diasoxide was unchanged whether diasoxide was infused with Gm or with a placebo [92]. The vasodilator response to forearm ischemia was studied by plethysmography in two groups of 12 type 2 diabetics treated for 8 weeks, in the first group with 6 mg of Gm or 15 mg of Gb cross-over, or in the second group with 15 mg of Gb or 1500 mg/day of metformin cross-over. Metformin, with no known vascular effect, was used here as a placebo [96]. There was no difference between responses seen on Gm, Gb and metformin. Regional vasodilator response curves obtained on Gm and Gb or on Gb and metformin, expressed as max FPF or flow debt repayment after increasingly long periods of anti-brachial ischemia (2, 5 and 13 minutes) were similar. No change in the vasodilator response curve to intra-arterial infusion of diasoxide, acetylcholine or dipyridamole was seen between patients treated with Gm, Gb or metformin. In another study [97] vasodilator response after 4.5 minutes of forearm ischemia, evaluated by variation in the diameter of the brachial artery and its blood flow, was measured by high resolution ultrasound in 12 type 2 diabetics. They had been treated cross-over for three 8-week periods with either Gm, Gb or diet only. At the end of these three periods there was no difference in post-ischemia vasodilator response, regardless of the treatments chosen. Hence, Gm appeared to have no effect on peripheral vascular motility in response to ischemia, including following the intra-arterial administration of pharmacological doses.

Coronary arteries

The effect of Gm on IPC in humans has been studied during angioplasty and compared with the effects of Gb or placebo: three groups of 15 non-diabetic patients with stable

ischemic heart disease, including more than 70% stenosis of at least one coronary artery, were selected after a first dilation inducing > 0.3 mV ST depression in the intra-coronary ECG [86]. They then underwent a second dilation used as a reference and for ischemic preconditioning, followed by a third dilation after IV injection of either Gm, Gb or placebo. Doses used resulted in maximum plasma levels as seen during the oral administration of 4 mg of Gm or 10 mg of Gb (on average 485 and 475 ng/ml at the 12th minute). Clear evidence was found of IPC in the placebo group with a lesser variation of 34% and 40% in mean and maximum ST depression, and 30% prolongation of the mean latent period before the onset of angina pain. Gb totally abolished IPC. The Gm group showed the same significant improvements as in the placebo group: improved ischemia tolerance during the 3rd dilation with a lesser decrease of 34% and 33% in mean and maximum ST depression, as well as significant 13% prolongation of the latent time to the onset of angina pain, indicative of the good preservation of IPC on Gm (*Tab II*).

Other sulfonylureas

We have not found any published clinical experimental studies in humans evaluating any possible effect of gliclazide (Gcz) or glipizide (Gpz) nor tolbutamide on the heart. However the effect of tolbutamide and of Gcz has been studied on the vascular response of the arm to ischemia, using venous occlusion plethysmography. In 12 healthy volunteers [98], diasoxide (opener of KATP channels) caused a dose-dependent increase up to a maximum of 691% in FBF. During a 2nd infusion, tolbutamide did not significantly modify this vasodilation (+ 542%). Gliclazide was studied in 15 type 2 diabetics [93] and compared after cross-over with Gb treatment, following acute or 4-week administration of treatment (Gb: 5 mg b.i.d.; Gcz: 80 mg b.i.d.). Under baseline conditions, before the morning dose, there was no change in vascular reserves of the forearm, measured after 5 minutes of ischemia. Immediately after the morning dose of the medicine, patients treated with gliclazide showed no change in their hemodynamic parameters. However when they were treated with Gb, there was a modest (– 17%) but significant ($p = 0.004$) reduction in their vascular reserves. It is therefore difficult to reach conclusions concerning these drugs, for which there is no available clinical study in humans, whether invasive or not, with regard to their cardiac effects. At the very most, it could be hoped that these would be modest or nil on the basis on what is known about their weak or nil affinity for SUR2 receptors, in addition to the absence of any effect seen on brachial arterial vascular activity.

In total, there is certainly an interaction between SU and the heart, via cardiac SUR. Gb, the SU most widely used clinically throughout the world, is one of the reference substances used in the laboratory to study the closure of KATP channels. However extrapolation of experimental results

seen with SU *in vitro* or in animals, then in non-diabetic humans by acute treatment, as well as in diabetics chronically treated with these medicines, is hazardous. There are several reasons for this: the pharmacological doses used are very often far above plasma levels seen in chronically treated diabetics. In addition, SU are strongly bound to proteins (> 98%) which further limits the active unbound fraction. Most studies have been done with Gb, which appears to have a powerful interaction with cardiac SUR. Other substances such as Gm or Gcz appear to have weaker interactions. The resultant cardiac effect could be harmful or favorable. Hence a substance without an effect on IPC could have an indirect pro-arrhythmic effect. The great majority of studies involve the acute administration of SU, a situation far different from the clinical context applying to chronic impregnation with the drug. There could be pharmacological tolerance after prolonged use. Most experimental studies have used non-diabetic models. It is possible that the heart of a diabetic might respond differently to SU. This hypothesis appear to be contradicted by direct study of the human myocardium [99]: three biopsies of right atrial myocardium were obtained during coronary artery surgery in 16 patients, 11 of whom were diabetics: four treated with insulin and seven with SU (six Gb, one Gpz). The last dose had been taken on average

17 hours before the *in vitro* study of these muscle strips. This confirmed abolition of IPC in patients who had taken SU, while it was preserved and in every way comparable with non-diabetic controls in diabetics on insulin.

In practice, are these cardiac effects of SU associated with any sort of risk and in particular, do patients treated with them have more coronary events and are these events more serious as compared with patients on other treatments? Or is the cardiac impact of SU of no clinical importance, at least in that the presumed harmful effects on IPC are compensated for by an anti-arrhythmic effect? In essence, only retrospective studies or a few prospective surveys are available to try to answer these questions. There is also the UKPDS.

Short-term prognosis after myocardial infarction

There are four retrospective studies [100-103] and one prospective epidemiologic study [104] in type 2 diabetics hospitalized for a myocardial infarction, in whom factors "independently" linked to death were sought by multivariate analysis. Parameters taken into account are usually those which in univariate analysis were linked to early death ($p < 0.10$), such as age, gender, BP, initial cardiologic sever-

Table II

Pain and the ST shift in the intra coronary ECG following first and second coronary occlusion by inflated balloon, with or without Glibenclamide (GB) or Glimepiride (GM) in middle aged or elderly patients. Pain is measured with Visual Analogic Scale in mm.

Patients	ST shift (mV)			Pain (mm)				
	Placebo	GB	GM	Placebo	GB	GM		
Tomai [84] 1994	n = 10 × 2 54/57 y old	Inflation 1	1.10 ± 0.6	0.80 ± 0.6	42 ± 19	43 ± 13		
			- 63%	+ 50%	- 60%	+ 28%		
	p	< 0.001	ns	< 0.01	< 0.05			
Lee [85] 2002	n = 13 45 ± 5 y old	Inflation 1	1.10 ± 0.31	1.12 ± 0.20	60 ± 8	62 ± 8		
			- 61%	- 2%	- 62%	0		
	p	< 0.05	ns	< 0.05	ns			
	n = 13 71 ± 3 y old	Inflation 1	1.04 ± 0.13	1.05 ± 0.21	61 ± 7	70 ± 9		
			- 3%	- 3%	- 3%	- 3%		
	p	ns	ns	ns	ns			
Kliepzig [86] 1999	n = 45	Inflation 1	0.23	0.24	0.35	37	30	
			- 35%	0	- 34%	+ 30%	0	+ 13%
		p	0.049	ns	0.01	0.16	ns	0.023

ity and sometimes smoking or lipids, but only one study [104] has been adjusted for initial blood glucose whereas intensity of initial glycemic abnormalities seems to be an important prognostic factor at the initial myocardial infarction phase [105], another one for HbA_{1c}, and none for duration of diabetes (*Tab III*). The percentage death rate during the period of hospitalization or the 4 weeks following myocardial infarction varied between 10.2 and 25%. In one study only [101], SU were found to be harmfully associated with early death in patients treated with direct coronary angioplasty at the acute stage of myocardial infarction, with OR = 2.5. However patients treated with SU were notably and significantly older (68.4 *versus* 63.2 years old) with less good myocardial function (LVEF: 47.3 ± 14.7 *vs.* 55.3 ± 14, *p* = 0.019). Two studies found no significant independent link [100, 103] and the last two reported a favorable effect of SU: slight effect with OR = 0.95 [102] in comparison with patients without treatment, but obtained from the enormous American Medicare database consisting of 64,171 diabetics over 65 years of age. A much greater protective effect of SU with an OR of 0.45 in comparison with patients not treated with SU was seen in the USIC 2000 prospective epidemiological survey [104]. This concerned 83% cardiology intensive care units in France and included all patients admitted with a myocardial infarction less than 48 hours old to these units for a period of 1 month. In contrast, insulin was found once to have a harmful influence on prognosis [103] with an OR = 4.5 (*p* < 0.05) in comparison with patients on diet only. This latter result is in contradiction with the DIGAMI prospective study [106] in which type 2 diabetics given insulin immediately after a myocardial infarction then for 1 year were found to have mortality reduced by a third in comparison to those who continued their treatment with oral anti-diabetics (OAD). It is not known whether this result is linked to the direct beneficial effect of insulin on the myocardium, or to an improvement in blood glucose during the critical period following an MI, or even, according to some, to the stoppage of SU which some patients were taking before.

Ventricular arrhythmias following myocardial infarction have been evaluated specifically in these studies. They do not appear to be more frequent in patients on an SU [101-103]. Under glibenclamide, ventricular fibrillation seems to be less frequent than with insulin (OR = 2.8, *p* < 0.05) or gliclazide (OR = 1.9 (0.8-4.4, *p* = 0.07) [109] or with all other treatments considered together (2.3% *vs.* 5.9%, *p* = 0.052) [104]. In the Lomusio study [107], there was no difference regarding the frequency of post-infarction deaths between diabetics treated with Gb (11%) and non-diabetics (8.8%) while the figure was 25.5% in patients treated with other SU or diet only. In contrast, atrial fibrillation (AF) appeared to be significantly less frequent on Gb (1.9%) in comparison with patients treated with other hypoglycemic agents (7.9%, *p* < 0.05) or in non-diabetics (9.9%, *p* < 0.01).

Long-term prognosis

There are six retrospective studies available which have attempted to evaluate the possible influence of SU on cardiac events or deaths in the long term, involving a mean follow-up of 2.5 to 7.5 years, and after statistical adjustment of possibly confusing available parameters (*Tab IV*). Four studies have involved diabetics with a high coronary risk, since at the time of inclusion in the studies they have proven ischemic heart disease [108] or a history of myocardial infarction [101, 109, 110]. In two of these studies [101, 109], no harmful effect of SU was seen in comparison with patients on other treatments, including insulin. In another [108], patients treated with Gb had a slightly greater risk of death in the long term (HR = 1.21) than patients treated with diet only. In contrast, in the final study [110] involving very elderly patients (age 80 ± 9), patients on an SU had a lesser risk of recurrence of coronary events than patients not taking these drugs (RR = 1.35). Two other retrospective analyses concern diabetics at the time when they were given oral anti-diabetic treatment for the first time: these studies involved use of the Swedish primary health care centers (910 patients followed-up for 6.1 years) [111] or the Canadian province of Saskatchewan (8866 patients followed-up for 5.1 years) [112] databases. In the Swedish study, patients on SU had significantly lower mortality than those on SU + metformin (OR = 1.63) (1.27-2.09). On the contrary, in the Canadian study, mortality was lower in patients treated with metformin or metformin + SU, as compared with patients on an SU only (RR = 0.78 (0.65-0.92) and 0.63 (0.66-1.07) respectively). The reason for these discrepancies is no doubt related to the actual methodology of these studies: in the absence of randomization of treatments, local therapeutic habits tend to select quite different groups of patients, with in particular clinical notable differences in mean age: 3.2 years [111], 5.1 years [112] and 5.2 years [101], but also concerning BMI, smoking, duration of diabetes, gender ratio, blood glucose or lipid control, cardiac past history or LVEF, etc. In order to attempt to compensate for these differences, statistical adjustment has been applied to many of these parameters but the doubt exists as to whether all of the parameters potentially intervening in such different groups could have been taken into account [113]. This explains why the level of evidence in this type of study is low (level 3 or 4) [114] and allows only for hypotheses needing to be confirmed by randomized double-blind prospective trials. In this area, if the UGDP is left to one side, only the UKPDS is currently available [13]. The primary objective of the latter was certainly not to evaluate the cardiovascular effects of SU and some consider that it is of no value whatsoever in reaching a conclusion as to this controversy [115]. However, this study does provide reliable data. It concerned patients with recent onset type 2 diabetes, with a mean age of 54 and randomized double-blind to either so-called "conventional" treatment or to so-called "intensified" treatment with three groups taking

Table III

Short term mortality and ventricular arrhythmia after acute myocardial infarction (AMI) in diabetic patients, following previous treatment by Sulfonylurea (SU) or not.

	Data base	Inclusion criteria	Number of Patients	% death In-hospital or < 1 month	OR for death In-hospital or < 1 month	Adjusted for	Ventricular arrhythmia OR or %	Age
Davis [100] 1998	Monica	AMI	745		NS	Age, sex ratio, shock, peak CPK, AMI site, smoking thrombolysis	Gb: 1 Gpz: 1.9(0.8-4.4) Insulin: 2.8(1.2-6.3)	NS
Garrat [101] 1999	Mayo clinic	AMI angioplasty	SU: 67	24	2.53 (1.13-5.67)	A1c, LVEF, CHF, sex ratio, prior CABG, HT, HC, emergency procedure, age, F.CHD, multivessel disease, prior MI	27%	68.4 ± 10.5
			No SU: 118	11	1		NS	p = 0.003
Jollis [102] 1999	Medicare	AMI < 65 y old	SU: 25 035	14.7	0.95	Age, sex, race, SBP, pulse, respiratory rate, creatinin, Killip class, prior MI, CHF, prior CABG, smoking, HT, cerebral or peripheral VD	NS	75.5
			Insulin: 18 935	16.1	1.02			74.5
			Neither: 17 801	17.7	1			76.1
Halkin [103] 2001	ARGAMI 2	AMI	SU: 121	10.7	1.4 (0.5-4.6)	Age, previous MI, HT, killip class, MI site, thrombolysis	NS	63 ± 1.1
			Met ± Ac: 17	23.5	3.7 (0.7-17.7)			62 ± 10
			Insulin: 28	21.4	4.5 (1.17-18.3)*			61 ± 13
			Diet: 79	8.9	1			61 ± 12
Danchin [104] 2003	Prospective national survey	AMI < 48 h	SU: 215	10.2	0.43 (0.20-0.94)	Age, Killip class, FBG, Heart rate, DBP, renal insufficiency	2.3%	71 ± 10
			No SU: 272	16.9	p = 0.034		P = 0.052	p = 0.027
Lomuscio [107] 1994		1° AMI	Gb: 106	11			1.9	66 ± 15
			Other/diet: 126	25			P < 0.05	63 ± 18

Met: metformin. Ac: acarbose. Gb: glibenclamide. LVEF: left ventricular ejection fraction. CHF: congestive heart failure. CABG: coronary artery bypass grafting. HT: hypertension. HC: hercholesterolemia. F.CHD: familial history of coronary heart disease. SBP and DBP: systolic and diastolic blood pressure. * p < 0.05.

either Gb, chlorpropamide or insulin. These three latter groups are those of interest to us. At the end of about 10 years, 90 patients among those treated with 615 patients under Gb (14,6%) and among the 619 having taken chlorpropamide 100 patients (16,2%) had had a myocardial infarction, i.e. 190 infarctions in 1234 patients (15.4%) having taken a SU. Among the 911 patients on insulin, 149 (16.4%) had had a myocardial infarction during this same period. There was

hence no significant difference ($p = 0.66$) nor even any "trend" to the disadvantage of SU, while insulin is alleged to reduce by one-third deaths after myocardial infarction in diabetics as compared with patients not on insulin [106]. In order that appear a significant difference between SU and insulin treatment, it would be necessary to have 243 myocardial infarctions among the 1234 patients treated with SU rather than 190, this means 27% of additional events which is

Table IV

Late mortality (or new coronary events), in patients with type 2 diabetes: comparison following treatment by SU or others.

	Inclusion Criteria	Follow up (years)	Nb Patients	HR, RR or OR for all cause death	Adjusted for	Features
Brady [109] 1998	MI Population study 1/88-10/96	2.7 ± 2.3	SU: 46 Insulin: 56	NS	No difference at entry for LVEF, previous MI, CAD, PA, smoking, CT	
Garratt [101] 1998	MI, angioplasty Mayo clinic data base 1/85-12/94	3.8 ± 2.3 3.6 ± 2.3	SU: 51 No SU: 105	NS (new MI: NS)	?	Differences for age and LVEF in defavor of SU group New angioplasty less frequent in SU group (18v47%, $p = 0.05$)
Olsson [111] 2000	New OAD users Primary care centers data base 1/84-12/96	6.1 (0.1-13)	SU: 741 SU + M: 169	OR 1 1.63 (1.27-2.09)	Age, gender, duration of diabetes, study area, year of inclusion, FBG	Groupe SU + M: 3.6y younger, + 3.2 y longer duration, HbA _{1c} : + 1.0%, compared to Groupe SU alone
Fisman [108] 2001	45-74 y Proven CAD Bezifibrate Infarction prevention Study	7.7 ± 1.5	Diet: 990 Gb: 953 M: 79 Gb + M: 253	HR 1 1.21 (1.02-1.44) 1.19 (0.76-1.84) 1.53 (1.20-1.95)	Gender, weight, BMI, glucose, triglycerides	Differences for BMI, sex ratio, FBG, TG, in favor of diet group and in defavor of Gb + M group
Johnson [112] 2002	New OAD users Saskatchewan Health data base 1/91-12/96	5.1 ± 2.2	SU: 3033 M: 1150 SU + M: 4683	RR 1 0.78 (0.65-0.92) 0.63 (0.66-1.07)	Age, sex, nitrate use, comorbidity	Age, sex ratio and nitrate use, different in defavor of SU group
Aronow [110] 2001	MI Long term health care facility	2.5 ± 1.7	SU: 278 No SU: 358	RR 1 1.35 (1.13-1.63)	Age, smoking, hypertension, LDLc, HDLc	80 ± 9 y old at entry

MI: myocardial infarction. OAD: oral agent. CAD: coronary arterial disease. SU: sulfonylurea. M: metformin. Hr: hazard ratio. RR: risk ratio. OR: odd ratio.

an important difference. In the same way, deaths of all causes involved 124 cases on Gb and 136 on chlorpropamide, i.e. 257 out of 1234 patients treated with SU (20.8%), and 184 out of 911 patients treated with insulin (20.2%). Once again, there was no difference ($p = 0.62$) nor even any trend to the disadvantage of SU. In order that appear a significant difference ($p = 0.046$) between SU and insulin it would have been necessary to see 294 rather than 257 deaths in the SU groups this means 10% of additional events. All of these aspects are of a sufficiently high evidence level (level 1 A) to justify the following "evidence based message": "patients with type 2 diabetes who receive SU as part of an intensive policy of glycaemic control are not at increased risk of death, myocardial infarction, or other cardiovascular event, compared to patients treated conventionally" [116].

Conclusion

The cardiovascular effects of Gb, demonstrated in animal models or in humans after acute administration, are a decrease in ischemic preconditioning, impairment of myocardial contractile function and an anti-arrhythmic effect during the ischemic period. At present, there is no evidence that these effects have clinical consequences, during chronic treatment. In contrast, the anti-diabetic effect is powerful: mean gain on HbA_{1c} is usually 1 to 2% [117] and the UK-PDS has shown a 21% decrease in diabetic complications for each drop of 1% in HbA_{1c} [118]. With regard to other drugs in this therapeutic group, such as glimepiride or gliclazide, their interaction with SUR2 is less than that of Gb. Their acute effect on the heart has been studied in humans only with glimepiride and appears to be nil and we have found no study concerning chronic treatment. There is nevertheless no reason to think that these substances could have any harmful clinical effect, as there is no clinical evidence of a deleterious effect with Gb. In 2007, the ADVANCE study which is just starting, will provide information regarding the impact of gliclazide on morbidity and mortality, but the study design does not plan to compare this medication with other SU or other oral anti-diabetic classes in the same conditions, in particular regarding the glycaemic target [119]. The DIGAMI 2 study, currently underway, may provide additional information though its primary objective is to measure the benefits of insulin during the acute phase then during the year following any myocardial infarction [120]. The final answer could be given only by prospective studies in diabetics with a high coronary risk, using the primary objective of evaluating the cardiac effects of SU [121]. Such studies have not been planned at present, and SU, in particular those of the new generation free of any experimentally perceptible clinical coronary or myocardial effect, fully retain their place in the addition strategy used for the treatment of type 2 diabetes.

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