Do effects on blood pressure contribute to improved clinical outcomes with metformin?

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SUMMARY
Hyperinsulinaemia and hypertension commonly coexist, and a large body of evidence points to a common pathogenesis based on the presence of underlying insulin resistance (the “insulin hypothesis” of hypertension). Metformin improves insulin sensitivity in liver and muscle as its primary anti-hyperglycaemic mechanism of action, and intensive glycaemic management with metformin significantly reduced the risk of macrovascular diabetic complications in the UK Prospective Diabetes Study. The clinical outcome benefits in the metformin group included a significant reduction in the risk of stroke (−41% vs +14% with sulphonylurea or insulin treatment, p = 0.032), which is well known to be highly sensitive to changes in blood pressure. Furthermore, a placebo-controlled study has shown that metformin significantly improved endothelial function, a key regulator of vascular tone and blood pressure, in type 2 diabetic patients. However, clinical studies have shown that metformin treatment is not associated with clinically relevant reductions in blood pressure in man. These apparently conflicting observations are difficult to reconcile. Either the beneficial vascular actions of metformin involve physiological systems not involved in the control of blood pressure, or counter-regulatory mechanisms prevent beneficial effects of metformin on the vasculature being translated into a clinically meaningful antihypertensive effect. Further research will be required to resolve this paradox.

Key-words: Metformin · Blood pressure · Type 2 diabetes.
High blood pressure significantly contributes to the increased risk of cardiovascular events and nephropathy in patients with type 2 diabetes [1, 2]. Metformin has been shown to significantly improve clinical outcomes in these patients, including significant reductions in the risk of all-cause mortality, and diabetes-related death, in the landmark UK Prospective Diabetes Study (UKPDS) [3]. The principal mode of action of metformin is a reduction in insulin resistance (discussed elsewhere in this supplement by S. Del Prato), and a substantial body of evidence supports a role for insulin resistance in the pathogenesis of hypertension. It is therefore possible that positive effects on blood pressure may contribute to the improved clinical outcomes with metformin. This paper will review the available data on the effects of metformin on blood pressure.

Diabetes and hypertension

The clinical perspective

The importance of blood pressure as a risk factor for coronary artery disease and stroke has long been recognised, and recent meta-analyses have confirmed and refined this association [4-6]. Cardiovascular disease is the main cause of death in type 2 diabetic patients and the risk of death from coronary artery disease in a type 2 diabetic patient without a previous myocardial infarction is comparable to the risk of a non-diabetic patient with a prior myocardial infarction [7]. High blood pressure is extremely common in type 2 diabetic patients and contributes significantly to the already increased risk of mortality and morbidity associated with the disease [8-10]. The importance of high blood pressure as a risk factor for adverse outcomes in patients with type 2 diabetes has been recognised by the World Health Organisation (WHO) and the International Society of Hypertension (ISH), whose joint recommendations stratify type 2 diabetic patients with only mild hypertension into a high-risk group with a 20-30% probability of suffering a cardiovascular event within the next 10 years [11].

Large-scale placebo-controlled mortality and morbidity intervention trials evaluating antihypertensive drug therapy have included subgroup analyses in patients with type 2 diabetes [12, 13]. These, and other subgroup analyses from non-placebo controlled trials, have clearly demonstrated that effective lowering of blood pressure leads to a reduction in cardiovascular morbidity and mortality in hypertensive type 2 diabetic patients [12-15]. Indeed, the benefits of antihypertensive drug treatment for most endpoints were more pronounced in diabetic compared to non-diabetic patients in these studies, indicating the importance of blood pressure control for improving prognosis in type 2 diabetes (Fig 1).

This was confirmed impressively by the Hypertension Optimal Treatment (HOT) study [15]. A total of 18,790 patients with a mean diastolic blood pressure of 105 mmHg at baseline were prospectively randomised into one of three groups, where they received antihypertensive treatment applied with the intention of achieving a diastolic blood pressure of ≤ 90 mmHg, ≤ 85 mmHg, or ≤ 80 mmHg. The actual mean final diastolic blood pressures at study end in the three groups were 85.2 mmHg, 83.2 mmHg, and 81.1 mmHg, respectively. There was no difference in total mortality or cardiovascular mortality between the three groups in the overall study population. However, a subgroup of 1,501 type 2 diabetic patients randomised to the diastolic blood pressure ≤ 80 mmHg target group benefited from lower total mortality (p = 0.068), with a significant reduction in cardiovascular mortality (p = 0.016), compared with less tight blood pressure control (Fig 2). Indeed, total and cardiovascular mortality at study end on the most intensive blood pressure control group were similar to that seen in non-diabetic patients! The HOT study also laid to rest concerns that over-aggressive lowering of blood pressure may be harmful for the diabetic patient.

In line with these subgroup analyses, the UKPDS demonstrated marked reductions in diabetes-related endpoints (24%) and in diabetes-related deaths (32%) in type 2 diabetic patients subjected to tight blood pressure control (mean blood pressure 144/82 mmHg) relative to patients who had been treated less intensively (mean blood pressure 154/87 mmHg). Tight blood pressure control not only reduced morbidity and mortality from macrovascular disease, particularly stroke (44%), but also from microvascular complications (37%) [16]. The benefits from tight versus less tight con-

![Figure 1](image_url)

Increased rates of mortality and fatal or non-fatal strokes or cardiac events in hypertensive patients with type 2 diabetes, compared with hypertensive non-diabetic subjects, from the placebo group of the Syst-Eur trial [13].
control of blood pressure [16] were generally more pronounced than the benefits from intensive blood-glucose control with a sulphonylurea or insulin, versus a conventional management policy based on treatment with diet [17]. This was true for all three primary aggregate endpoints (any diabetes-related endpoint, diabetes-related death, and all-cause mortality).

These findings emphasise the need not only for excellent metabolic control, but also for excellent blood pressure control in the type 2 diabetic patient. Indeed, there is now a general agreement that blood pressure should be more tightly controlled in the hypertensive patient with diabetes than in the non-diabetic hypertensive population, with target blood pressures well below the conventional goal of < 140/90 mmHg.

For example, current WHO/ISH guidelines for the management of blood pressure [11] recommend a target blood pressure of < 130/85 mmHg for the hypertensive diabetic patient without nephropathy, and an even lower target level for the diabetic patient with nephropathy (see reference 2 for a review of this topic). Similarly, the most recent guidelines from the US Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommend a target blood pressure of < 130/80 mmHg for diabetic patients [18].

Epidemiological evidence clearly suggests that even small reductions in blood pressure translate into clinically significant reductions in mortality and morbidity from cardiovascular disease and, particularly, from stroke [4-6]. For example, in trials of antihypertensive drug therapy, a 5-6 mmHg reduction in diastolic blood pressure maintained for 5 years resulted in 42% fewer strokes and 14% fewer cases of ischaemic heart disease [4]. The importance of even small reductions in blood pressure for improving clinical outcomes has recently been confirmed by the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [19, 20]. In ALLHAT, the diuretic, chlorthalidone, lowered systolic blood pressure by approximately 2 mmHg more than the alpha1-adrenoceptor blocker, doxazosin [19] and the angiotensin converting enzyme inhibitor, lisinopril [20]. The relatively minor additional reductions in blood pressure with chlorthalidone, compared with doxazosin and lisinopril, were associated with additional reductions in the risk of stroke of 19% and 15%, respectively. Hence even small reductions in blood pressure by metformin could account for a substantial proportion of its clinical benefits.

The pathophysiological perspective

Diabetes and hypertension are important cardiovascular risk factors in determining the prognosis of the patient with type 2 diabetes, and both share a common pathogenetic background in insulin resistance. Indeed, insulin resistance and hyperinsulinaemia are frequent findings in many hypertensive patients, even in the absence of hyperglycaemia and obesity. Accordingly, it has been suggested that insulin resistance plays a key role in the pathogenesis of hypertension and its cardiovascular complications [21, 22] (see the accompanying paper by E. Eschwège for more detail).

Hyperinsulinaemia may increase blood pressure by several pathophysiological mechanisms, including insulin-mediated increases in renal sodium reabsorption [23], activation of the central sympathetic nervous system [24, 25], and proliferation of vascular smooth muscle cells [26]. On the other hand, insulin has direct vasodilator properties which may potentially counteract its pressor actions [27], although clinical studies indicate that the vasodilator effects of insulin are impaired in hypertensive or obese subjects [28]. The vasodilator effects of insulin are related to its glucoregulatory effects, with vasodilator capacity decreasing with increasing degrees of insulin resistance [29]. In summary, there is convincing pathophysiological evidence in support of the “insulin hypothesis” [27] of hypertension.
Does metformin affect blood pressure?

Mode of action of metformin and its effects on clinical outcomes

A large body of both experimental and clinical data convincingly demonstrates that a reduction in insulin resistance, mainly in liver and muscle, is the key antihyperglycaemic mechanism of action of metformin. Therefore, metformin addresses key pathophysiological disturbances underlying both type 2 diabetes and hypertension. Further, it appears reasonable to suggest that the mode of action of metformin may be responsible for its therapeutic effects beyond glucose lowering, and may underlie the improved prognosis of type 2 diabetic patients observed in the UKPDS.

In the overweight, newly-diagnosed type 2 diabetic patients randomised to receive intensive glycaemic management with metformin in the UKPDS, any diabetes-related endpoint was reduced by 32%, and all-cause mortality by 36%, relative to patients treated with a conventional diet-based policy (Fig 3). Moreover, metformin was significantly more effective in reducing the risk of any diabetes-related endpoint, all-cause mortality and stroke, compared with intensive glycaemic management with a sulphonylurea or insulin (Fig 3) [3].

The finding that metformin was significantly more effective than sulphonylureas and insulin in reducing strokes (Fig 3) is particularly intriguing, because of the strong association between blood pressure and stroke and the particular effectiveness of antihypertensive therapy in stroke reduction (described above). Moreover, there was an increase in both systolic and diastolic blood pressure in patients assigned to the sulphonylurea, chlorpropamide, in the UKPDS (143/82 mmHg vs 138/80 mmHg in patients assigned to conventional therapy) and the prevalence of hypertension was significantly higher in patients treated with chlorpropamide (43% vs 34% on conventional therapy) [17]. Since metformin lowered fasting plasma insulin in the UKPDS, and this parameter increased slightly in patients treated with chlorpropramide compared with patients assigned to conventional therapy [3, 17], this observation provides additional, albeit very circumstantial, evidence in support of the insulin hypothesis of hypertension. On the other hand, increases in blood pressure were not observed with either glibenclamide or insulin treatment.

The suggestion that the beneficial effects of metformin on mortality and morbidity in patients with type 2 diabetes may at least in part be mediated by a reduction in blood pressure therefore appears pathophysiologically plausible and warrants closer examination. In addition, the observation that the biguanide, phenformin, increased both blood pressure and heart rate in the University Group Diabetes Program [30, 31] adds a further reason to undertake such an investigation.

Metformin and blood pressure: methodological aspects

Due to its placebo-controlled design and to the large number of persons enrolled in this trial (1,082 in the placebo and 1,073 in the metformin group) the Diabetes Prevention
Program (DPP) [32] would have the power to detect even small changes in blood pressure induced by metformin in non-diabetic persons at high risk of developing diabetes. Similarly, the UKPDS, which investigated the effects of intensive blood glucose control with metformin on the risk of diabetic complications in newly-diagnosed type 2 diabetic patients [3] might have been expected to quantify the contribution of blood pressure changes, if any, on the improved prognosis of type 2 diabetic patients treated with metformin. However, blood pressure was not among the main outcome variables in either study, although blood pressures at baseline were reported for both trials [3, 33], and preliminary data on blood pressure changes from the Diabetes Prevention Program are described below [34].

Other than these landmark trials, this analysis must rely on a relatively small number of, mostly, relatively small studies. Moreover, many of these studies employed an uncontrolled design, and we should remember that few reliable conclusions can be drawn from such “before treatment vs at the end of treatment” comparisons. There is no doubt that blood pressure is subject to a marked placebo effect. For example, in 1,706 patients in the placebo group of the Australian therapeutic trial in mild hypertension, there was an average fall in diastolic blood pressure from baseline of 6.6 mmHg [35].

Studies comparing metformin with diet in non-diabetic patients

The suggestion that metformin has blood pressure-lowering effects in non-diabetic patients originates from two uncontrolled studies [36, 37]. The impact of metformin on blood lipids was investigated in a group of 254 hyperlipidaemic patients, many of them hypertensive, with a mean baseline blood pressure of 156/95 mmHg. After 6 months of therapy, mean blood pressure was reduced to 138/82 mmHg [36]. Even more pronounced reductions in systolic and diastolic blood pressures of 40 mmHg and 24 mmHg, respectively, after only 6 weeks of treatment with metformin were observed in a study of nine non-obese, non-diabetic men with untreated hypertension [37]. These changes in blood pressure were associated with improved glucose disposal in an euglycaemic clamp test, seemingly supporting the hypothesis of a causal link between an improvement in insulin resistance and the fall in blood pressure. Due to their uncontrolled study design, however, these studies cannot establish an unambiguous cause-effect relationship between the treatment with metformin and the observed effects on blood pressure.

A number of subsequent placebo-controlled studies in non-diabetic hypertensive patients have built on this earlier experience to analyse the effects of metformin on blood pressure, and their relationship with changes in insulin resistance. In one of these trials, in 12 obese, non-diabetic hypertensive women undergoing an euglycaemic clamp, metformin lowered blood pressure and increased glucose disposal rate in parallel [38]. In contrast, no reductions in blood pressure were observed in two studies in insulin-resistant, obese [39] and lean [40] hypertensive patients, despite an improvement in insulin-mediated glucose disposal [40].

In a further study, metformin did not significantly affect insulin sensitivity, or the two most reliable indices of sympathetic nervous system activity available in man in vivo: resting sympathetic nerve activity (measured by direct microneurography), and resting total and renal noradrenaline spillover [39]. Similarly, metformin administered for 6 weeks to 18 non-obese men did not change either blood pressure or insulin sensitivity [41]. The interpretation of these data is, however, limited by the fact that patients recruited for the study on the basis of a medical history of hypertension had normal blood pressure during the study period after withdrawal of their antihypertensive medication. Finally, metformin did not affect 24-hour ambulatory blood pressure in a placebo-controlled trial [42]. A decline in diastolic office blood pressure occurred in this trial during metformin treatment, which was not significantly different from blood pressure reductions observed in the placebo group. This example highlights the absolute need for placebo-controlled trials in evaluating drug effects on blood pressure.

Overall, these studies in non-diabetic, mostly hypertensive, patients do not support the concept that improvements in insulin sensitivity during metformin therapy translate into clinically relevant reductions in blood pressure.

Studies comparing metformin with diet in type 2 diabetic patients

No effect of metformin on blood pressure has been observed in four placebo-controlled clinical trials conducted in type 2 diabetic patients with hyperglycaemia despite diet treatment. The largest of these studies, by DeFronzo et al., randomised 143 obese patients to receive metformin (plus diet) and 146 patients to diet alone (plus placebo) [43]. For inclusion in the study, diastolic blood pressure had to be below 100 mmHg, and diuretics were permitted as antihypertensive therapy. Supine blood pressure was measured at baseline and at each of six subsequent follow-up visits. Mean blood pressure was normal at baseline and did not change with therapy in either group. Similarly, there was no difference between groups in changes in body weight, with modest weight loss observed in patients treated with placebo or metformin. Given the large sample size, the reasonably long duration of treatment (29 weeks), and the number of repeat blood pressure measurements made, it would be expected that this study would have adequate power to detect even minor differences in blood pressure between the metformin and placebo groups, although sufficient data are not provided in the publication to enable a formal power calculation.

Three smaller, placebo-controlled studies similarly found no effect of metformin on blood pressure relative to placebo [44-46]. One of these studies included 24-hour ambulatory blood pressure measurements, in addition to the conventional office blood pressure readings and, once again, no significant

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effects on 24-hour blood pressure profiles were observed [46]. Essentially similarly results were obtained in another comparative clinical investigation that compared the effects of diet alone with a diet plus metformin combination, but without a proper placebo control in the diet alone group. After 2 years of treatment the reduction in blood pressure in the diet only group was similar to that in the metformin group [47]. Changes in body weight, a major potential confounding factor affecting blood pressure, were similar in the metformin and placebo groups in all of these studies.

A number of additional observational studies are available, which provide little reliable information due to a lack of adequate control groups in their study designs. Briefly, blood pressure did not change in a study in 14 patients treated with metformin for a total of 6 months [48]. A further study in 1,823 type 2 diabetic patients inadequately controlled by diet and a sulphonylurea showed that the addition of metformin for 12 weeks resulted in small reductions of both systolic (– 4 mmHg) and diastolic (– 2 mmHg) blood pressure [49]. However, a weight loss of 1.9 kg may have accounted for the change in blood pressure in this study.

Studies comparing metformin with a sulphonylurea in type 2 diabetic patients

In a large clinical trial by DeFronzo [43] blood pressure did not change significantly during treatment with either metformin (n = 210), glibenclamide (n = 209) or a combination of metformin with glibenclamide (n = 213). No differences in blood pressure between treatment groups were noted, despite a more favourable change in weight in patients treated with metformin (– 3.8 kg) relative to patients treated with glibenclamide (– 0.3 kg) or with the two agents in combination (+ 0.4 kg).

Twenty-four hour ambulatory blood pressure profiles did not differ following treatment with metformin or glibenclamide in 14 patients in a double-blind, randomised, 4-week crossover study [50]. In addition, the responses in forearm blood flow or forearm vascular resistance to a number of endothelium-dependent and independent vasodilators (acetylcholine, diazoxide, sodium nitroprusside) and to noradrenaline did not differ between metformin and glibenclamide treatment. However, the rise in systolic blood pressure in response to intravenous infusions of pressor agents (noradrenaline or angiotensin II) was significantly blunted following treatment with metformin, compared with glibenclamide. Similarly, the systolic blood pressure response to a cold pressor test, a strong sympathoexcitatory stimulus, was attenuated with metformin therapy, to an extent which almost achieved statistical significance (p = 0.052). A further placebo-controlled study in type 2 diabetic patients also supports a positive effect of metformin on the vascular endothelium in type 2 diabetic patients (see Discussion). Finally, in a cross-over study involving non-invasive haemodynamic monitoring, systemic vascular resistance increased slightly with glibenclamide and decreased slightly with metformin (p < 0.05) [51]. In addition, the observed reduction in standing diastolic blood pressure was more pronounced with metformin (p < 0.05), though no changes were observed in systolic blood pressure or blood pressures measured in the supine position, or following exercise.

Taken together, the results of these studies do not provide evidence for a blood pressure-lowering effect of metformin in type 2 diabetic patients.

Subjects at high risk of developing diabetes

As explained above, the DPP enrolled 3,234 non-diabetic individuals with IGT, and hence a high risk of developing diabetes, and should have sufficient statistical power to detect even small changes in blood pressure due to metformin treatment [32]. Preliminary data from the DPP indicate that mean reductions in systolic and diastolic blood pressures in subjects randomised to standard lifestyle advice plus placebo (– 0.6 mmHg and – 1.9 mmHg, respectively) or metformin (– 0.3 mmHg and – 1.6 mmHg, respectively) were small and similar [34]. In addition, similar proportions of subjects receiving metformin or placebo required antihypertensive therapy at baseline (17% in each case) and at study end (32% and 31%, respectively). In contrast, larger reductions in blood pressures were observed in the intensive lifestyle intervention group (– 3.3 to 3.8 mmHg, p < 0.05-0.001 vs metformin and placebo), and fewer patients (23%) required antihypertensive therapy at the end of the study (p < 0.001 vs the other interventions), confirming the ability of the DPP to detect effects on blood pressure. These results add further evidence to suggest that metformin does not decrease blood pressure significantly in man.

Discussion

Available data from normotensive or hypertensive non-diabetic patients and from patients with type 2 diabetes do not support a clinically relevant effect of metformin on blood pressure. Hence, it appears unlikely that any effects on blood pressure per se contribute to the improved clinical outcomes in diabetic patients observed after treatment with metformin. These findings are surprising, given the strong evidence in support of a pathophysiological link between insulin resistance, hyperinsulinaemia and hypertension. As metformin counters insulin resistance as its principal antihyperglycaemic mechanism of action, its lack of effect on blood pressure does not appear to fit well with the insulin hypothesis of hypertension.

This conclusion is all the more surprising, since metformin has been shown both in animals [52] and in man [53] to improve endothelial function and, especially, endothelium-dependent vasodilatation. The role of impaired endothelial function in the genesis of the macrovascular complications of...
type 2 diabetes are outside the scope of this paper, and are reviewed elsewhere in this supplement by E. Eschwège (impact of insulin resistance on the endothelium with regard to mechanisms of atherogenesis) and by P. Grant (effects of metformin on the production of endothelial proteins that influence fibrinolysis and coagulation). However, the role of the endothelium in regulating blood pressure is highly relevant to the haemodynamic profile of metformin, and is discussed below.

The endothelium is the key regulator of vascular tone, and produces, or responds to, a number of potent vasoconstrictors, such as endothelin-1 and angiotensin II, and vasodilators, such as prostacyclin and nitric oxide. Normally, in the normotensive individual, vasoconstrictor and vasodilator activity within the endothelium is in balance. Damage to the endothelium may lead to a predominance of vasoconstriction, loss of endothelium-mediated vasodilation, and hypertension. Conversely, improved endothelial function may lead to increased production of nitric oxide, restored endothelium-dependent vasodilatation, and a decrease in blood pressure. A placebo-controlled study in 44 diet-failed type 2 diabetic patients showed that 12 weeks of treatment with metformin at a dose of 1,000 mg/day significantly improved endothelium-dependent blood flow in the forearm, while measures of endothelium-independent blood flow were unchanged (Fig 4) [53]. This study, together with the study, described earlier in this paper, in which the haemodynamic responses to vasoconstrictor agents were blunted in subjects treated with metformin, compared with gliclazide [50] strongly suggests that treatment with metformin exerts a potentially beneficial effect on the endothelium.

We can only speculate why such effects do not appear to translate into a clear lowering of blood pressure. One possibility is that counter-regulatory mechanisms offset the beneficial effects of metformin on the endothelium that might have been expected to result in vasodilatation, for example, an increase in the activity of vasoconstrictor systems such as the sympathetic nervous system, the renin-angiotensin system or the endothelin system. However, we have few data to test such a hypothesis, and further study of this important question is required. One small study included a detailed evaluation of the effects of metformin on the activity of the sympathetic nervous system in insulin-resistant hypertensive men, and did not reveal any significant effect of metformin on sympathetic nerve activity [39], while another study demonstrated a slight decrease in plasma catecholamines after metformin treatment [38].

Methodological issues may render such studies difficult to interpret. In particular, the easily-accessible regional vascular beds in which improvements in endothelial function have often been demonstrated in man (most usually in the forearm) may not be truly representative of the resistance vasculature which is the dominant regulator of peripheral vascular resistance and blood pressure. Nevertheless, endothelial dysfunction is prognostically important. A study of 147 patients with coronary artery disease showed that the

![Figure 4](image-url)

**Figure 4** Improvement of endothelial function by metformin in type 2 diabetic patients inadequately controlled by diet treatment [53].
prognostic value of coronary endothelial dysfunction, as assessed by endothelium-dependent vasoreactivity of the coronary arteries was independent of conventional cardiovascular risk factors [54].

Conclusions

The UK Prospective Diabetes Study proved beyond doubt that treatment with metformin significantly reduces the risk of morbid cardiovascular events, compared with conventional treatment based on diet. In addition, well-designed clinical studies have demonstrated beneficial effects of metformin on the vascular endothelium that would normally be associated with reductions in blood pressure. Paradoxically, clinical studies have not revealed a clinically relevant antihypertensive effect of metformin in man. The vasoprotective effects of metformin in man therefore appear to exist independently of changes in blood pressure.

References