Diabetes and Hypertension

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Despite the progress that has been made trying to reduce the occurrence of cardiovascular disease, this pathology continues to be the leading cause of mortality and morbidity worldwide. There are of course many risk factors for cardiovascular disease, including, but not limited to, hypertension, smoking, high cholesterol, diabetes, lack of exercise, being overweight or obese, and a family history of heart disease.

However, among them all, two diseases are probably the most important—hypertension and diabetes. Both conditions significantly contribute to the occurrence of acute coronary syndromes, particularly myocardial infarction, which is a disease first of the coronary artery and second of the heart muscle or the ventricle. Indeed, myocardial infarction itself originates from a thrombus formation in the coronary arteries; the thrombus is often due to a plaque rupture that, in turn, is due to endothelial dysfunction. Possible events that can lead to endothelial dysfunction include lipoprotein retention, inflammatory cell recruitment, release of inflammatory mediators, apoptosis and necrosis, smooth muscle cell proliferation and matrix synthesis, arterial remodeling, etc.

More recently, the concept of the vulnerable plaque has been reconsidered and challenged. Whatever mechanism is involved, thrombus formation in a coronary artery cannot occur if the endothelium is intact, showing that endothelial dysfunction is present in both hypertension and diabetes. This endothelial dysfunction is most likely related to excess apoptosis in the endothelium, where the concomitant regeneration of the endothelium is insufficient, leaving the inside surface of the coronary arteries exposed to thrombus formation.

This new way of looking at the problem also explains the important and often surprising results regarding improved outcomes with angiotensin-converting enzyme inhibitors and statins, both in hypertension and diabetes. In fact, in addition to reducing blood pressure and cholesterol levels, these two classes of drugs also reduce the rate of endothelial apoptosis and improve the rate of endothelial regeneration by molecular...
mechanisms that are complementary to each other. These mechanisms also explain the terrible marriage between these two pathological conditions, both of which have catastrophic effects on the endothelium of the coronary arteries.

This issue of *Dialogues in Cardiovascular Medicine* reviews the most significant advances in understanding and treating hypertension and diabetes. Giuseppe Mancia leads the discussion by providing a global overview of the major adverse clinical impacts that diabetes and hypertension have on cardiovascular and renal diseases. Francesco Cosentino, Francesco Paneni, and Sarah Costantino highlight the fact that both hypertension and diabetes are key risk factors implicated in the development of endothelial dysfunction and atherosclerotic vascular phenotypes. John Chalmers describes diabetes and hypertension as the “bad companions” and reviews the evidence for using double therapy. Nicholas Russell and Richard C. O’Brien round out the discussion by examining whether or not treating hyperglycemia is useful as a means to improve cardiovascular risk in patients with hypertension and diabetes.

We hope that this issue will help in the understanding of these overlapping diseases.
Arnold Martin Katz (born July 30, 1932) died peacefully surrounded by his family in Norwich, VT, USA on January 25, 2016. Arnold was a beloved husband, father, and grandfather as well as a teacher, mentor, physician, professor of cardiology, medical researcher, and author of numerous books and articles. He is survived by his wife Phyllis, his four children, and his eight grandchildren.

Arnold was born in Chicago, IL, USA. His mother, Aline G. Katz, was a gifted pianist and piano teacher and his father, Louis N. Katz, was a world-renowned cardiologist. Arnold earned a Bachelor’s degree at the University of Chicago in 1952 and graduated from Harvard Medical School in 1956. He worked in medical education and research at the University of California, Los Angeles; Columbia University; and the University of Connecticut. In 1969, he became the first Philip J. and Harriet L. Goodhart Professor of Medicine (Cardiology) at the Mount Sinai School of Medicine and, in 1977, he moved to the University of Connecticut’s School of Medicine to become its first Chief of Cardiology. He published over 400 articles and edited or coedited more than 15 books and textbooks. His single-authored text *Physiology of the Heart* is now in its 5th edition, having been translated into numerous foreign languages.

Arnold was a devoted teacher and mentor all his life, winning many teaching awards. Following his retirement in 1998, he served as visiting professor of Medicine and Physiology at Dartmouth Medical School. In 2008, he was also appointed visiting professor of Medicine at Harvard Medical School.

Arnold was honored with various research awards throughout his distinguished career, including the 1975 Humboldt Prize, the Research Achievement Award of the American Heart Association, the Peter Harris Distinguished Scientist Award of the International Society for Heart Research, the Lifetime Achievement Award of the Heart Failure Society of America, and the Medal of Merit of the International Academy of Cardiovascular Sciences. The American Heart Association renamed its young investigator award for basic research the Louis N. and Arnold M. Katz Prize.
Donations can be made in Arnold’s memory to benefit the work done at either the American Heart Association (American Heart Association/American Stroke Association PO Box 417005 Boston, MA, USA 02241-7005) or the Norris Cotton Cancer Center at Dartmouth Hitchcock Medical Center (D-HH/Geisel Office of Development One Medical Center Drive, HB 7070 Lebanon, NH, USA 03756-0001).

TRIBUTE BY ROBERTO FERRARI

I was a PhD student, attending a heart failure meeting in Venice the first time I met Arnold. He gave a fantastic talk, making an analogy between the working myocyte and a Roman rowing ship. My first impression of him was that he was rather unapproachable and very authoritative. I received my PhD and returned to Italy. Years later, I was involved in a series of meetings with Arnold in Sicily. Both of us were giving talks on cardiac metabolism; I gave a lecture on my small research project and Arnold gave the bigger picture. It was on that occasion that I started to know the real Arnold Katz as a person and not only as a scientist. I remember one incredible evening in a small hotel in Agrigento, Sicily where we ate simple food with a view of the temple valley. His enthusiasm was contagious and his wife Phyllis had a huge knowledge of Magna Graecia history. Arnold was not unapproachable at all. He was extremely open and cheerful, and we became great friends. He was no longer Professor Arnold Katz… but Arnold. I also had the pleasure of visiting his wonderful home in Vermont and meeting his children. We visited a school where Phyllis was teaching and we all had breakfast together. It was a particular moment of affection and reminded me of our two different cultures… believe me, an American breakfast is nothing like an Italian one!

As usually happens, as the years went on, Arnold and I also had the same friends, such as Gabriele Stocchi. Believe it or not, Arnold introduced me to Gabriele in Rome where he was staying in a lovely, small hotel that he always visited. Like many great people, 5-star luxury is not always needed, but rather a 5-star spirit. It was in this hotel that he told me that I could call him Arnie, which I did with trepidation. Sadly, I was not able to call him Arnie for long enough.

Ciao Arnie
Your Italian friend Roberto
Hypertension and diabetes have major adverse impacts on cardiovascular and renal disease, and often, these diseases can be found in the same individual. This paper reviews the available data on the high prevalence of the association between hypertension and diabetes. It then shows that this association leads to a marked increase in the risk of many events due to the damage to the microvasculature and macrovasculature that is caused by either high blood pressure or impaired glucose metabolism. Finally, the article focuses on how to treat patients with both diabetes and hypertension. Of note, neither risk factor is irreversible; ie, a reduction in blood pressure or blood glucose has a protective effect on the above-mentioned complications, and, although some differences between different drugs or treatment strategies exist, the benefits appear to be largely related to lowering blood pressure or blood glucose per se regardless of how it is obtained. In both cases, therapeutic success is not easy, as the target systolic blood pressure values recommended by most guidelines are usually reached with a combination of antihypertensive drugs, which should include a renin-angiotensin system blocker to enhance the protective effect of treatment on the kidney.

Keywords: cardiovascular disease; diabetes; hypertension; renin-angiotensin system

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Hypertension and type 2 diabetes, along with dyslipidemia, are the most important risk factors for cardiovascular and renal disease in both developing and industrialized affluent countries. An elevation in systolic or diastolic blood pressure is accompanied by an increased risk of stroke, myocardial infarction, heart failure, peripheral artery disease, dementia, and renal insufficiency at all ages, which increases even more as the blood pressure increase becomes more pronounced. An increase in blood glucose or glycated hemoglobin (HbA1c) also leads to an increased risk in the above-mentioned cardiovascular events with additional major harmful effects on the microvasculature, which makes this condition the main cause of renal failure, dialysis, transplantation, blindness, and lower-limb amputation. Therefore, prevention and treatment of hypertension, diabetes, and their complications are a crucial component of health care strategies to reduce cardiovascular diseases and downgrade their top position among the causes of death worldwide.

Given their high prevalence in the population, hypertension and type 2 diabetes are often found together in an individual. This paper will review the epidemiological, clinical, and therapeutic aspects of this association.

Prevalence of the Association between Hypertension and Diabetes

Hypertension is not particularly frequent in patients with type 1 diabetes, where blood pressure elevation is a late phenomenon believed to start, progress steeply, and become common only when the impaired glucose metabolism leads to nephropathy. Hypertension is more frequent in patients with type 2 diabetes, where blood pressure elevation may occur at the same time or soon after diabetes is detected and involves many patients. In the early 1990’s, the World Health Organization had already alerted the medical community that hypertension could be found in about half of the
patients with type 2 diabetes, its prevalence rising to about two-thirds in those with diabetic nephropathy.\(^4\) The hypertension guidelines issued in the US (Joint National Committee 5) later reported the prevalence of hypertension in type 2 diabetic patients to be even higher, ie, about 90% and 70% in those with and without renal disease, respectively.\(^5\) Other data then concluded that, on average, about 60% of type 2 diabetic patients can be expected to have high blood pressure values. The risk increases with the duration of diabetes and/or the appearance of renal and/or other diabetes-related organ complications.\(^6,7\) Indeed, in patients with long-standing complicated diabetes, finding a normal blood pressure is more the exception than the rule, which justifies the aphorism that “no patient with established diabetes can be called normotensive.”

The frequent association between hypertension and diabetes may be accounted for by the high prevalence of either condition in adults, which is even more pronounced in the elderly population.\(^1,2\) However, evidence shows that this is by no means the only explanation, and that, at a pathogenetic level, the hypertensigenic influence of the factors promoting diabetes and the diabetogenic influence of the factors responsible for blood pressure elevation are also involved. Cross-sectional studies have shown that, compared with the general population, hypertension is two times more frequent in diabetic populations, while diabetes is two to three times more frequent in the hypertensive population.\(^8\) Furthermore, longitudinal studies have reported that, over the years, hypertension develops more commonly in the diabetic population vs the nondiabetic population. Conversely, hypertensive patients develop diabetes more frequently than normotensive patients do. The ARIC community (Atherosclerosis Risk in Communities Study, n=12550) showed that the incidence and risk of developing type 2 diabetes over a 6-year period is almost 2.5 times greater in hypertensive vs normotensive subjects.\(^9\) In hypertension, the risk of developing diabetes does not exhibit an “on-off” pattern, but rather there is a continuous relationship with the blood pressure values. The patients in whom blood pressure is or remains optimal (<120/80 mm Hg) or normal (120-130/80-85 mm Hg) have a lower risk of incident diabetes than those who have or move to higher blood pressure values.\(^10\) More recently, the existence of a quantitative relationship between blood pressure and glucose-related variables has also been cross-sectionally documented in the general population of the PAMELA study (Pressioni Arteriose Monitorate E Loro Associazioni). As shown in Figure 1, serum glucose and the prevalence of diabetes or an impaired fasting glucose condition were found to progressively increase from the lowest to the highest quartile of office blood pressure, which is also the case for both home and mean 24-hour ambulatory blood pressure.\(^11\)

The factors responsible for the quantitative association between development of diabetes and blood pressure are not entirely clear. However, it is well known that insulin increases the following: (i) water and sodium reabsorption from the kidney, (ii) intracellular calcium concentrations, (iii) prorenin formation and perhaps angiotensin II generation via non–angiotensin-converting enzyme (ACE) pathways; (iv) production of growth factors that promote vascular smooth muscle remodeling; and (v) sympathetic nerve activity.\(^12\) All of these changes may lead to an increase in blood pressure also because predisposed subjects have an impairment in the ability of insulin to directly dilate resistance vessels, and thus, to counteract its pressogenic effects. In this context, sympathetic activation (documented in humans by a microneurographic response to insulin infusion) is particularly important because it enhances the influence of a factor involved in the genesis of hypertension and its subsequent progression to more severe states.\(^13,14\) Furthermore, sympathetic nerve activation

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**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ACCORD</td>
<td>Action to Control CardiOvascular Risk in Diabetes [trial]</td>
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<tr>
<td>ADVANCE</td>
<td>Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation</td>
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<tr>
<td>ADVANCE-ON</td>
<td>Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation posttrial ObservatioNal study</td>
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<tr>
<td>ARIC</td>
<td>Atherosclerosis Risk in Communities Study</td>
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<tr>
<td>HOT</td>
<td>Hypertension Optimal Treatment [trial]</td>
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<tr>
<td>INVEST</td>
<td>INternational VErapamil-trandolapril Study</td>
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<tr>
<td>ONTARGET</td>
<td>ONGoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial</td>
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<tr>
<td>PAMELA</td>
<td>Pressioni Arteriose Monitorate E Loro Associazioni [study]</td>
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<tr>
<td>SPRINT</td>
<td>Systolic blood PReSSure INtervention Trial</td>
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<tr>
<td>UKPDS</td>
<td>UK Prospective Diabetes Study</td>
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promotes insulin resistance and hyperinsulinemia via skeletal muscle vasoconstriction and a reduction in capillary density, the latter effect seriously limiting insulin availability by lengthening the path insulin must travel to act on skeletal muscle cells. This “positive feedback” type of insulin-sympathetic nerve interaction is the basis for a vicious circle that may explain why an increased sympathetic activity is associated with increased insulin resistance in a large number of diseases (Table I). This is notoriously the case for essential hypertension, where the ability of insulin resistance to precede and predict the development of diabetes can also account for the frequent association between diabetes and hypertension.

An important “chicken and egg” issue to mention is whether insulin resistance or sympathetic activity is the initial abnormality in patients with diabetes and hypertension. Masuo et al made an interesting observation when they showed that subjects with elevated blood pressure, plasma norepinephrine, and insulin had only been presenting with an increase in plasma norepinephrine 10 years before, which suggests that sympathetic activation might have played an initial role.

Many epidemiological studies have shown that the risk of morbid and fatal cardiovascular events in patients with hypertension and diabetes is greater than that of one or the other condition alone, with either risk factor exerting its adverse effects over and above the other. That is, diabetes is responsible for a further increase in cardiovascular mortality above the progression associated with any blood pressure increase (Figure 2, panel A, page 94). In addition, myocardial infarction, microvascular events, and heart failure all increase progressively with blood pressure in patients with a background diabetes-related risk (Figure 2, panels B-D). Indeed, a large body of evidence provides detailed knowledge of what it means for a patient’s cardiovascular risk to have an association between diabetes and hypertension.
First, in patients with hypertension and diabetes, the increase in cardiovascular risk involves all macrovascular complications, including cerebrovascular events, atrial fibrillation, and coronary event subtypes other than a myocardial infarction, such as angina pectoris, silent ischemia, and sudden death. Second, there is also a greater risk for the appearance and progression of renal damage to end stage renal disease and dialysis in patients with hypertension and diabetes. Third, for both renal and cardiovascular events, the risk progression that accompanies a blood pressure increase is steeper in diabetic patients vs nondiabetic patients. Fourth, as shown in Figure 3, cardiovascular and renal outcomes increase progressively as HbA1c increases throughout a wide range of blood pressure values. Finally, the combined risk of renal deterioration or cardiovascular events is more than additive, i.e., greater than the sum of their single contribution to the risk, except perhaps when the increases in HbA1c and blood pressure are extreme. This places patients with both diabetes and hypertension always in the high cardiovascular risk category, i.e., with a >20% chance of experiencing a macrovascular outcome in 10 years. This can also occur when diabetes and hypertension are mild rather than severe, which is relevant to individuals with an impaired fasting glucose condition who have only a moderate increase in risk if their blood pressure is normal, while they move to a high cardiovascular risk state if they are hypertensive. Of note, the ominous effect of the interaction between diabetes and hypertension can also markedly enhance cardiovascular risk in patients who already have a high level of risk. In the INVEST study (INternational VErapamil-trandolapril Stuudy) on hypertensive patients with coronary disease, diabetes was more important than age and history of stroke in determining the overall risk, with its contribution being only second to heart failure.
Although office blood pressure remains the reference value for the diagnosis and treatment of hypertension, modern management of this condition often uses out-of-office blood pressure, namely the blood pressure obtained by self-measurement at home or automatically over 24 hours. While limited evidence exists on the use of home blood pressure in diabetes, there is a general agreement that, in this condition, ambulatory blood pressure may have important clinical advantages, such as the detection of (i) hypotensive episodes that reflect an incipient diabetes-related dysautonomia that is not evident from blood pressure measurements in the orthostatic position. Furthermore, ambulatory blood pressure may show increased blood pressure variability, namely a blood pressure pattern that, in the general hypertensive population, has been independently associated with increased cardiovascular risk.

Finally, ambulatory blood pressure monitoring allows information to be obtained on the extent to which blood pressure decreases at night, the difference between daytime and nighttime blood pressures that is known to have an inverse relationship with cardiovascular risk, independently of mean 24-hour blood pressure. Evidence has been obtained that “dippers” and “non-dippers,” ie, patients with a nighttime blood pressure reduction greater and less than 10% of the daytime values, have a lower and greater cardiovascular risk, respectively. More recently, it has also been shown that the cardiovascular risk is particularly pronounced in patients with no or even a reversal in the physiological nighttime blood pressure reduction. In diabetic patients, this may occur more frequent-ly than in nondiabetic patients because sleep-related hypotension depends on a centrally induced reduction in “tonic” sympathetic vasoconstrictor and cardiac-stimulating influences, which may be compromised by dysautonomia. Studies on the beat-to-beat relationship between blood pressure and heart rate have now made it clear that dysautonomia is more common and occurs earlier in diabetic patients than previously believed.

The daytime-nighttime blood pressure pattern may also have a special predictive value for diabetic nephropathy. This has been documented in several studies showing that nighttime blood pressure has a close

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**Figure 3.** Relationship between mean arterial or SBP and HbA1c to the decline in GFR, myocardial infarction, and microvascular disease in the UKPDS study.

Abbreviations: HbA1c, glycated hemoglobin; GFR, glomerular filtration rate; SBP, systolic blood pressure; UKPDS, UK Prospective Diabetes Study.


relationship with urinary protein excretion in both diabetic and nondiabetic patients. More importantly, in a longitudinal study on diabetic patients, an abnormal nighttime blood pressure pattern (less nocturnal hypotension) predicted the appearance of microalbuminuria or proteinuria (an accepted marker of nephropathy), whereas this was not the case for office or other blood pressure measurements. This supports the growing use of ambulatory blood pressure monitoring to assess cardiovascular and renal risk in diabetes more accurately.

**ANTIDIABETIC TREATMENT**

Evidence shows that the beneficial effects of antidiabetic agents (metformin, sulfonylurea, glitazons, insulin, etc) can be observed when blood pressure is both within the normal range and when it is elevated. In either normotensive and hypertensive diabetic patients, these effects involve a reduction in microvascular complications; the magnitude of which is more clear and consistent for diabetic nephropathy (delayed appearance or progression to end-stage renal disease) and perhaps retinopathy than for other diabetes-related microvascular outcomes, such as dysautonomia. In contrast, antidiabetic treatment has not previously been associated with a consistent and clear-cut reduction in the macrovascular complications of diabetes. However, recent meta-analyses have shown that antidiabetic treatment results in an overall macrovascular protective effect, although this is limited to myocardial infarction, and more generally, coronary artery disease, with no significant change in stroke and no effect on all-cause mortality.

In addition, a protective effect of antidiabetic treatment on macrovascular events has emerged from a recent trial on type 2 diabetic patients taking a drug from a new class of antidiabetic agents (eg, empagliflozin). Empagliflozin had no effect on stroke, but it reduced heart failure, cardiovascular mortality, and all-cause mortality, which strengthens the possibility that antidiabetic treatments protect diabetic patients from both microvascular and some macrovascular diabetes-related diseases.

There is a general agreement that the protective effects of antidiabetic treatment can be obtained by reducing HbA1c to about 7%, whereas no evidence suggests that further HbA1c reductions translate into additional benefits. In one trial, achieving a 6.5% HbA1c value reduced nonfatal myocardial infarctions, but markedly increased the number of hypoglycemic episodes, had no effect on stroke, and noticeably increased cardiovascular (+35% risk) and all-cause (+22% risk) mortality. In another trial, the same HbA1c target did not have an adverse effect on all-cause mortality, but it showed a beneficial effect only on renal complications, again with an increase in hypoglycemic episodes, which makes the adoption of an aggressive glucose control strategy questionable. This also holds for hypertensive diabetics where a 7% HbA1c value should be the target of treatment, the same as for normotensive patients.

**ANTIHYPERTENSIVE TREATMENT: GENERAL ASPECTS**

Almost 15 years ago Holman et al published the results of the UKPDS trial (UK Prospective Diabetes Study) in which type 2 diabetic hypertensive patients had been randomized to an antihypertensive treatment aiming to achieve lower or higher blood pressure targets, and the treatment was prolonged for about 10 years. The results showed that, at a lower on-treatment blood pressure (144/82 mm Hg), both the microvascular and macrovascular complications of diabetes (myocardial infarction, –21%, cerebrovascular outcomes, –44%) were significantly less common than with the higher on-treatment blood pressure (154/87 mm Hg). This showed that, in hypertensive diabetic patients, the risk component that depends on a blood pressure elevation is reversible, and it can be favorably modified with treatment.

Following UKPDS, other trials have confirmed the protective effect of antihypertensive treatment in hypertensive diabetic patients. However, they also provided two further important pieces of information. First, blood pressure reductions are accompanied by a reduction in virtually all diabetes-related macrovascular outcomes. Results of a recent meta-analysis of trials exclusively focused on or involving a large number of diabetic patients showed that a 10 mm Hg reduction in systolic blood pressure resulted in a 12% reduction in coronary artery disease, a 27% reduction in stroke, and a 14% reduction in heart failure, with an overall 11% and 13% reduction in cardiovascular disease and all-cause mortality, respectively. Second, the protection accompanying a blood pressure reduction can be seen with all major antihypertensive drug classes, ie, ACE inhibitors, angiotensin receptor antagonists, calcium channel blockers, β-blockers, and diuretics. The protective effect of diuretics is shared by thiazides, thiazide-like agents, and indapamide. As exemplified by the data on stroke, which is illustrated in Figure 4, a meta-regression analysis has shown that,
regardless of the drugs used, the treatment-induced blood pressure reduction bears a linear relationship with the magnitude of the protection from macrovascular events. This implies that blood pressure reduction per se is probably the common mechanism behind the protective effect of different antihypertensive treatment strategies in diabetes. This makes blood pressure control the primary goal to be achieved, and, to achieve this goal, all blood pressure–lowering medications to which a patient appears to respond effectively should be used.

**DEBATED ISSUES IN ANTIHYPERTENSIVE TREATMENT**

Other important issues for antihypertensive drug treatment in diabetes have been addressed by trials; however, the results are still being debated.

**Blood pressure thresholds for treatment**

Some guidelines recommend using antihypertensive drugs in diabetic patients with blood pressure in the high portion of the normal range, ie, between 130 to 139 mm Hg for systolic and/or 85 to 89 mm Hg for diastolic blood pressure. However, the trials supporting this more aggressive treatment option have limitations that reduce the scientific strength of this recommendation. For example, in one trial, the overall number of patients studied was very small (~400), which made the few cardiovascular events collected underpowered to give the conclusion statistical reliability. In another larger trial, the blood pressure values dividing normotension from hypertension were not clearly mentioned. Finally, in a third, large-scale trial, a treatment-induced reduction in events was seen in both patients with a baseline systolic blood pressure ≥140 mm Hg and patients with a systolic blood pressure <140 mm Hg, but the difference with the placebo group was significant in the former group only. This has led other guidelines to recommend a blood pressure ≥140/90 mm Hg as the value with the highest evidence-based threshold for antihypertensive drug treatment in diabetic patients, thus with no difference from the recommendation issued for nondiabetic patients. Recently, this was confirmed in a meta-analysis of randomized trials, which has shown that antihypertensive treatment reduces cardiovascular and renal events in diabetic patients with an entry systolic blood pressure ≥140 mm Hg, but not in patients with an entry systolic blood pressure above or below 130 mm Hg, with stroke being the only exception, as discussed below.

**Blood pressure targets for treatment**

Guidelines that recommend starting antihypertensive drug treatment in diabetic patients at blood pressure values <140/90 mm Hg also recommend adopting lower blood pressure targets, ie, <130/80 mm Hg. However, insight into the available evidence does not support this therapeutic goal. In the trials that observed a protective effect of reducing blood pressure in diabetics, the systolic blood pressure achieved in the active treatment group frequently fell below 140 mm Hg, but never below 130 mm Hg with the exception of one very small trial (primarily addressing changes in creatinine clearance rather than cardiovascular events). This is also true for trials addressing the effects of blood pressure reduction on the kidneys, which have not shown greater nephroprotection with intensive vs standard blood pressure targets.
The ACCORD trial (Action to Control CardiOvascular Risk in Diabetes) showed no difference in the risk of overall cardiovascular events in diabetic patients achieving an on-treatment systolic blood pressure of either 133 mm Hg or 119 mm Hg. Several post-hoc analyses of large-scale trials did not observe greater cardiovascular or renal protection by reducing systolic blood pressure below 130 mm Hg or below 140 mm Hg. In the post-hoc analysis of the INVEST trial, type 2 diabetic patients with a systolic blood pressure reduction below 130 mm Hg had a similar or even lower reduction in cardiovascular events than patients remaining at an on-treatment systolic value between 130 and 139 mm Hg; nevertheless, both groups had a clear-cut cardiovascular protection compared with patients remaining above 140 mm Hg. The difference between usual and tight blood pressure control was not significant.

According to the European guidelines, the evidence-based systolic blood pressure target to recommend should be <140 mm Hg for both nondiabetic and diabetic patients. However, the same guidelines also recommend a target diastolic blood pressure <85 mm Hg for diabetic patients (rather than the <90 mm Hg recommended for nondiabetic patients) because, in UKPDS, an on-treatment diastolic blood pressure of 82 mm Hg resulted in fewer cardiovascular events than a diastolic blood pressure of 87 mm Hg. These results are even more stringently supported by the results of the HOT trial (Hypertension Optimal Treatment), where ≈1500 hypertensive diabetic patients showed a significantly smaller number of cardiovascular events when diastolic blood pressure was reduced to 81 mm Hg vs when it remained at 85 mm Hg. At variance from the UKPDS trial, the on-treatment systolic blood pressure values in the HOT trial were similar between the two groups (about 141 to 142 mm Hg). Therefore, the lower diastolic blood pressure values achieved with treatment were presumably responsible for the greater protective effect.

Another unresolved question is where within the 130 to 139 systolic blood pressure range should the target be positioned, ie, closer to the upper or the lower portion of this range. On this issue, however, an important indication is provided by the ADVANCE trial (Action in Diabetes and Vascular disease: PreterAx and Dia-microN MR Controlled Evaluation), in which a large
number of type 2 diabetic patients were randomized to placebo or a fixed-dose combination of perindopril and indapamide. Systolic blood pressure decreased to about 140 mm Hg in the placebo group and to less than 135 mm Hg in the drug-treated group, in whom there was a significant 18% reduction in the combination of macrovascular and microvascular diabetes-related complications and an additional significant 14% reduction in all-cause mortality. Therefore, in diabetes, it might be appropriate for current guideline recommendations to specify that there may be an advantage in pursuing systolic blood pressure values closer to 130 mm Hg rather than remaining just below 140 mm Hg. This goal should be pursued even if diastolic blood pressure falls below 80 mm Hg, because achieving a value lower than the recommended target value did not prevent the treatment-generated benefit in the ADVANCE study (Figure 6).

Finally, a third important question under debate is whether intensive blood pressure reductions may have a differential effect on different hypertension-related outcomes, ie, be protective against cerebrovascular events, but not against other events. With few exceptions, this has been reported to occur in the general hypertensive population where a systolic blood pressure <130 mm Hg has been associated with a reduction in stroke, but less, none, or even some increase in myocardial infarctions. Albeit in a less extensive fashion, similar evidence has been obtained for diabetic patients, where strokes have been reported to decrease with on-treatment systolic blood pressure values <130 mm Hg or even 120 mm Hg, at variance from other events. This may originate from the much higher prevalence among trial patients of those with coronary artery disease rather than cerebrovascular disease, thus with a selective impairment in the mechanisms that preserve cardiac vs cerebral perfusion. However, it may also reflect a truly superior ability of the brain to autoregulate its blood flow when blood pressure decreases. If the latter explanation turns out to be true, future recommendations will have to consider more aggressive blood pressure-lowering strategies in patients in whom the risk of cerebrovascular events exceeds that of coronary events. This is the case in Asian populations or in patients, regardless of ethnicity, with a previous stroke, in whom stroke recurrence is three times more common than a new-onset cardiac event.

A final consideration to make is that an intense antihypertensive treatment is accompanied by a marked increase in the incidence of serious side effects, as shown for diabetes in the ACCORD trial and, more recently, in the nondiabetic patients recruited for the SPRINT trial (Systolic blood Pressure Intervention Trial). In real life, serious side effects are the most common reason to discontinue treatment, a decision that is associated with a clear-cut increase in the risk of cardiovascular death.

![Figure 6. Systolic and diastolic blood pressure reduction over time and incidence of cardiovascular mortality in the type 2 diabetic patients of the ADVANCE trial.](image)

The cumulative incidence of cardiovascular mortality was lower in patients treated with a combination of perindopril and indapamide than in placebo-treated patients, the risk reduction being 18% (95% CI, 12%-32%; P=0.027). Δ refers to the blood pressure difference between the active-treatment group and the placebo-treatment group. The numbers at the end of the blood pressure lines refer to the average values during treatment.

**Abbreviations:** ADVANCE, Action in Diabetes and Vascular disease: PreterAx and DiaMictroN MR Controlled Evaluation.

of disease. This means that any possible benefit of intensive blood pressure reductions may be partly attenuated when implemented in medical practice.

**Different protective effects of antihypertensive drugs**

Past and recent meta-analyses of randomized trials have shown that, when blood pressure is reduced to a similar degree, different antihypertensive drugs reduce the overall cardiovascular risk of diabetic patients similarly, which again, points to the paramount importance of lowering blood pressure per se as a determinant of antihypertensive treatment-related benefits. Meta-analyses, however, also draw attention to the fact that drugs may have different protective effects on some specific cardiovascular events. Similarly to what has been reported for the general hypertensive population, diuretics and angiotensin receptor antagonists appear to offer greater protection against heart failure in diabetic patients than calcium channel blockers and ACE inhibitors, whereas calcium channel blockers appear to protect against stroke more effectively than β-blockers.

However, these data must be interpreted with caution. First, the number of available trials, patients, and events can be markedly different between different drug classes, giving a different solidity to some vs other conclusions. Second, despite the use of statistical adjustments, meta-analyses may only imperfectly take into account blood pressure differences between groups, which can lead to substantial differences in the risk of stroke, even when small. Third, in its incipient phase (the one addressed by antihypertensive treatment trials), diagnosis of heart failure is open to errors, with a possible overestimation with the use of calcium channel blockers (due to ankle edema) and underestimation with the use of diuretics (because diuretics may mask the symptoms and signs of incipient heart failure). Finally, and most importantly, differences in the protective effect of different drugs on specific cardiovascular events should not obscure the fact that the most important effect of treatment is overall event protection, which the latest available meta-analyses show to be superimposable for different drugs in both diabetic patients and the general hypertensive population.

On the other hand, it is clear that renin-angiotensin system blockers protect diabetic patients against renal disease more effectively than any other antihypertensive agent does. ACE inhibitors have been shown to reduce incipient diabetic nephropathy more effectively than other treatments and both ACE inhibitors and angiotensin receptor antagonists have exhibited a more favorable protective influence on the rate of renal deterioration in diabetic patients with established renal disease. Furthermore, in both diabetic and non-diabetic patients, these two drug classes have been long known to have a more marked antiproteinuric effect, which may be a marker of greater renal (as well as cardiovascular) protection.

**Long-term efficacy**

For several reasons (eg, cost, progressive patient dropout, instability of patients and investigators, etc), randomized trials can only have a short duration (ie, a few years). This means that it is uncertain whether the in-trial benefits of major cardiovascular risk-factor corrections are maintained over the patients’ life expectancy and this has remained an unaddressed question. However, in the last decade, important information has been obtained by the prolonged follow-up of patients after the end of the randomized trial phase. Using this approach, the UKPDS study showed that, while the in-trial benefits of antidiabetic treatment were maintained for an additional 10-year period, the benefits associated with antihypertensive treatment showed a progressive attenuation that eventually became nonsignificant. However, few patients were included in UKPDS, and recently, these negative findings were not confirmed in the long-term follow-up of the ADVANCE trial, which involved a larger number of diabetic patients (about 8500, of whom more than 5100 were available for the entire 10-year monitoring period).

The ADVANCE trial showed that the renal benefit characterizing antidiabetic treatment at the end of the randomized trial phase was maintained over the follow-up years. Further, this was also the case for antihypertensive treatment, as the trial showed that the lower incidence of the primary end point—a composite of macrovascular and microvascular events—in patients initially randomized to antihypertensive drug administration remained significant throughout the observational follow-up period (Figure 7). The study performed by Gaede et al showed similar results when they observed a persistence of the early beneficial effects of multifactorial treatment of diabetic patients over almost 14 years. Although the longer life expectancy of most hypertensive diabetic patients makes longer time-based evidence desirable, these data strongly support the conclusion that, in diabetes, the protective effect of both antidiabetic and antihypertensive treatment continues beyond the short trial duration.
Achieving blood pressure control in hypertensive diabetic patients is notoriously more difficult than for nondiabetic patients. This has been shown in medical practice, where the percentage of diabetic patients with a blood pressure <140/90 mm Hg has invariably been lower than in either the general hypertension population or nondiabetic patients. It has also been shown to be the case when treatment is delivered in the context of clinical trials, despite the fact that, in this circumstance, the greater expertise of the physicians and a closer follow-up. Figure 8 (page 102) shows that, in trials on diabetic patients, the initially high systolic blood pressure often remained above 140 mm Hg or went just below this value, which means that almost 50% of the patients or more did not achieve blood pressure control. This is accounted for by the fact that, as shown in ONTARGET and other trials, diabetes is the single most important factor opposing successful antihypertensive treatment, the reasons ranging from a more common concomitance of factors that make effective blood pressure reduction more difficult (eg, overweight, sodium retention, renal damage, etc) to the frequent occurrence of an increase in large artery stiffness, with frequently higher pulse pressure values. Indeed, arterial stiffening is a sort of hallmark of diabetes that may precede other damage and it may already be detected in the early stages.
The above considerations led to the following recommendations for the treatment of hypertension in diabetes. First, physicians should devote great attention to correcting lifestyle characteristics that adversely affect blood pressure and drug treatment efficacy, i.e., reduce body weight and high sodium intake, stop smoking, and modify sedentary lifestyle habits.

Second, drugs should be selected according to their proven blood pressure–lowering efficacy and duration of action to attempt to guarantee therapeutic coverage between dose intervals. Third, unless made necessary by the occurrence of side effects, switching from one monotherapy to another should be avoided and preference should be given to the combination of two or even three drugs either as an addition to the initial single-drug administration or as a two-drug first treatment step. Fourth, drugs should be combined if characterized by different and complementary mechanisms of action because the multifactorial nature of blood pressure regulation makes the multiplicity of the blood pressure–lowering mechanisms much more effective.

Monotherapy

According to the European guidelines, all major drug classes (ACE inhibitors, angiotensin receptor antagonists, calcium channel blockers, β-blockers, and diuretics) are, in principle, suitable for initiation and maintenance of antihypertensive treatment in diabetes because (i) they effectively reduce blood pressure and hypertension-related complications, with no substantial between-drug differences in mortality and composite cardiovascular events; and (ii) patients responding to one drug class are not exactly the same as those responding to another, which means that, with a greater number of drug options, there is a greater chance of finding a successful monotherapy.

However, due to their superior nephroprotective effects, renin-angiotensin system blockers are to be given a preference, because the goal of avoiding new-onset nephropathy or delaying its progression is fundamentally important to prevent cardiovascular disease, which is extremely frequent with advanced renal damage.
Add-on combination therapy

Combination therapy can also make use of many different drugs, however, if no contraindication exists, one of the drugs should always be a renin-angiotensin system blocker, which can be associated with a calcium channel blocker. Although diuretics may somewhat increase insulin resistance (and thus the number and doses of antidiabetic drugs), the relatively small doses employed in combination treatment makes this effect small. Therefore, the combination of a renin-angiotensin system blocker and a diuretic should not be excluded from use. Diuretics are often necessary to counteract the hypervolemia that may accompany diabetes, and they are a recommended component of triple-drug combinations, together with a renin-angiotensin system blocker and a calcium channel blocker.

Other antihypertensive drugs, such as β-blockers, α-blockers, central agents, and mineralocorticoid receptor antagonists could also be considered in a non-marginal number of patients either because the recommended three-drug treatment regimen is not fully effective or because clinical conditions require their use, such as β-blockers in patients with angina or a history of a myocardial infarction. On the other hand, the combination of an ACE inhibitor with an angiotensin receptor antagonist (or of one or the other drug with a renin inhibitor) is strongly discouraged by the guidelines because its use has been associated with serious inconveniences in both diabetic and nondiabetic patients, including hyperkalemia in patients with impaired renal function. When available, antihypertensive drugs can be combined in a single tablet because treatment simplification improves adherence to the prescribed treatment regimen, particularly when, as in diabetes, combined antihypertensive, antidiabetic, and lipid-lowering treatment makes the number of daily pills very high. Whether treatment simplification should consider a single-tablet association of antihypertensive and antidiabetic drugs, the ultimate feasibility and advantages of this association are still under debate.

First-step two-drug combination

Initial use of two antihypertensive agents is a debated treatment strategy. However, European guidelines consider this a possible strategy in patients with a high cardiovascular risk, including diabetes. Starting treatment with two drugs may have disadvantages (eg, unnecessary administration of one drug in the limited number of patients who would respond satisfactorily to monotherapy), however, by achieving rapid blood pressure control, this strategy may offer some additional protection in a clinical circumstance where early events are not uncommon, may shorten the titration phase, thus the number of visits necessary to determine a final effective therapy, and may increase the chance of obtaining long-term blood pressure control and perhaps greater patient protection. This is presumably due to the fact that starting treatment with a drug combination appears to increase long-term treatment adherence, which is an advantage and has significant potential importance because low adherence to prescribed drugs is a devastatingly common phenomenon in hypertension and in other areas of cardiovascular prevention. In the Lombardy population, more than one-third of the patients discontinued antihypertensive, antidiabetic, or lipid-lowering treatment after the first prescription, resulting in a significant increase in the risk of hospitalization for coronary artery disease or cerebrovascular disease compared with more adherent patients.

NEW-ONSET DIABETES

Evidence from several studies has made the medical community aware that antihypertensive drugs appear to influence the risk of developing diabetes differently, namely, that ACE inhibitors and its receptor antagonists decrease it, calcium channel blockers have no effect, and diuretics and β-blockers exert a diabetogenic influence.

Although some disagreement exists as to the prognostic nature, ie, whether drug-induced diabetes is as risky as native diabetes, is not completely clear. This phenomenon has made guidelines cautious about which antihypertensive drugs to recommend in individuals with a higher risk of developing diabetes, such as those with impaired fasting glucose or an insulin-resistant state, such as in obesity or with a metabolic syndrome. Under this circumstance, it is recommended that the antihypertensive treatment make use of a renin-angiotensin system blocker followed by the addition of a calcium channel blocker (if combination treatment is needed) and the use of a diuretic is advised only at small doses, namely when the diabetogenic effect is marginal. Given the high prevalence of these conditions, this treatment strategy may have a rather extended application. It may also become even more common in the future if the growing prevalence of obesity and diabetes worldwide and in particular countries persists.
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Diabetes and Hypertension

*Expert Answers to Three Key Questions*

1. Diabetes and hypertension: are they two diseases of the endothelium?
   
   F. Cosentino, F. Paneni, S. Costantino

2. Diabetes and hypertension: is double therapy useful?
   
   J. Chalmers

3. Diabetes and hypertension: is treating hyperglycemia useful?
   
   N. Russell, R. C. O’Brien
Diabetes and hypertension: are they two diseases of the endothelium?

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Diabetes and hypertension are key risk factors implicated in the development of endothelial dysfunction and atherosclerotic vascular phenotypes. This condition is associated with reduced nitric oxide bioavailability, accumulation of reactive oxygen species, lipid peroxidation, and inflammatory transcriptional programs fostering upregulation of adhesion molecules. The interplay between diabetes and hypertension is characterized by detrimental cross talk between the renin-angiotensin-aldosterone system, redox signaling, and enzymes implicated in the mitochondrial machinery. Understanding these complex networks may reveal novel mechanism-based approaches to counteract the development of atherosclerotic complications in people with diabetes and hypertension. The present article provides a mechanistic overview linking diabetic and hypertensive endothelial dysfunction.

Keywords: cardiovascular disease; endothelial dysfunction; hyperglycemia; hypertension; inflammation; redox signaling

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Figure 1. Estimated prevalence of hypertension among people with type 2 diabetes in Europe. Modified from reference 6: Colosia et al. Diabetes Metab Syndr Obes. 2013;6:327-338. © 2013, Colosia et al.
masked hypertension is not infrequent and monitoring 24-hour ambulatory blood pressure may be a useful approach.

In type 1 diabetes (T1D), hypertension is mainly the result of nephropathy, whereas in T2D, abdominal obesity, reduced physical activity, hyperinsulinemia, sympathetic tone, and activation of the renin-angiotensin-aldosterone system (RAAS) are the main mechanisms involved. Different factors clustering in diabetic patients (ie, renal dysfunction, dyslipidemia, and obesity) significantly contribute to an increase in blood pressure. This aspect explains why an intensive therapeutic regimen that includes a combination of 2 to 3 antihypertensive agents is often required to treat hypertension in diabetic patients. In a large, prospective, cohort study that included 12,550 adults, the development of T2D was almost 2.5 times as likely in patients with hypertension than in their normotensive counterparts. This, in conjunction with the notion that hypertension is highly prevalent in diabetic patients, hints that these two common chronic diseases frequently coexist. This is somewhat unsurprising since each pathophysiological disease entity, although independent in its own natural history, serves to exacerbate the other.

**ENDOTHELIAL DYSFUNCTION IN DIABETES**

The development of micro- and macrovascular disease represents the major cause of morbidity and mortality in patients with diabetes. Endothelial dysfunction plays a critical role in the development of diabetic vasculopathy, which is associated with an overproduction of reactive oxygen species (ROS), reduced nitric oxide (NO) bioavailability, lipid peroxidation, and increased expression of adhesion molecules. A clear proof in this regard was provided several years ago when Johnston et al showed that the forearm vasodilator response to methacholine is impaired in patients with insulin-dependent diabetes (Figure 2). In addition, impaired endothelial function has also been extensively documented in animal models of T1D and T2D. The mechanisms by which hyperglycemia alters endothelial function are complex and include an increased oxidative stress burst, glycation of proteins and lipids, and activation of several enzymes that amplify maladaptive oxidation and inflammatory pathways.

**Hyperglycemia**

In patients with diabetes, elevated blood-glucose levels exert detrimental effects on endothelial homeostasis, thus precipitating the vascular disease phenotypes that are responsible for adverse cardiovascular events and mortality. Chronic hyperglycemia is an independent predictor of micro- and macrovascular diabetic complications. In diabetic individuals, this condition often clusters with concomitant cardiovascular risk factors, such as arterial hypertension, dyslipidemia, and genetic susceptibility, thus amplifying vascular damage. Of note, the detrimental effects of glucose

### SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AngII</td>
<td>angiotensin II</td>
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<tr>
<td>AT1R</td>
<td>angiotensin type 1 receptor</td>
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<tr>
<td>AT2R</td>
<td>angiotensin type 2 receptor</td>
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<td>COX-2</td>
<td>cyclooxygenase 2</td>
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<tr>
<td>eNOS</td>
<td>endothelial nitric oxide synthase</td>
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<td>GLUT4</td>
<td>glucose transporter 4</td>
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<td>ICAM-1</td>
<td>intracellular cell adhesion molecule 1</td>
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<td>IL-1</td>
<td>interleukin 1</td>
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<tr>
<td>JNK</td>
<td>c-Jun N-terminal kinase</td>
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<tr>
<td>MCP-1</td>
<td>monocyte chemoattractant protein 1</td>
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<tr>
<td>NAVIGATOR</td>
<td>Nateglinide And Valsartan Impaired Glucose tolerAnce ouTcomes Research [trial]</td>
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<tr>
<td>NFkB</td>
<td>nuclear factor-kB</td>
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<tr>
<td>NO</td>
<td>nitric oxide</td>
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<tr>
<td>Nox</td>
<td>NADPH oxidase</td>
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<tr>
<td>ONOO⁻</td>
<td>peroxynitrite</td>
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<tr>
<td>PAI-1</td>
<td>plasminogen-activator inhibitor-1</td>
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<tr>
<td>PKC</td>
<td>protein kinase C</td>
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<tr>
<td>PVAT</td>
<td>perivascular adipose tissue</td>
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<tr>
<td>RAAS</td>
<td>renin-angiotensin-aldosterone system</td>
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<tr>
<td>ROS</td>
<td>reactive oxygen species</td>
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<tr>
<td>T1D</td>
<td>type 1 diabetes</td>
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<td>T2D</td>
<td>type 2 diabetes</td>
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<tr>
<td>TNF-α</td>
<td>tumor necrosis factor α</td>
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<tr>
<td>VCAM-1</td>
<td>vascular cell adhesion molecule 1</td>
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<tr>
<td>VSMC</td>
<td>vascular smooth muscle cell</td>
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are already manifest with glycemic levels below the threshold for the diagnosis of diabetes. In fact, a strong inverse relationship between blood-glucose levels and brachial artery flow-mediated dilation has been observed (Figure 3). This may be explained by the concept of a “glycemic continuum” across the spectrum of prediabetes, diabetes, and cardiovascular risk.

Early dysglycemia, a condition commonly observed in subjects with impaired glucose tolerance, plays a key role in triggering the pathological processes responsible for atherosclerotic vascular complications. High glucose levels affect vascular homeostasis mostly by altering the balance between NO bioavailability and accumulation of ROS. Oxidative signals rapidly inactivate NO to form peroxynitrite (ONOO⁻), a powerful oxidant that easily penetrates across phospholipid membranes, thereby suppressing the activity of scavenger enzymes and endothelial NO synthase (eNOS). The importance of redox signaling in the pathophysiology of hyperglycemia-induced endothelial dysfunction is strengthened by the observation that ascorbic acid, a potent ROS scavenger, restores brachial artery flow-mediated dilation in diabetic patients (Figure 4, page 116).

In the diabetic vasculature, oxidative stress triggers an array of cellular pathways including polyol and hexosamine flux, advanced glycation end products, and protein kinase C (PKC) and nuclear factor-κB (NFκB)-mediated vascular inflammation. A recent study showed that PKC is highly activated in endothelial cells isolated from diabetic patients and correlates with oxidative stress, impaired insulin signaling, and, most importantly, endothelial dysfunction as assessed by flow-mediated dilation. Once activated, PKC is...
responsible for different structural and functional changes in the vasculature, including alterations of cellular permeability, inflammation, angiogenesis, cell growth, extracellular matrix expansion, and apoptosis. In the diabetic patient’s endothelium, PKC leads to increased ROS generation via activation of the adaptor protein p66<sup>Shc</sup> and NADPH oxidase signaling (Figure 5). The p66<sup>Shc</sup> adaptor protein functions as a redox enzyme implicated in mitochondrial ROS generation and is responsible for translating oxidative signals into apoptosis. Notably, p66<sup>Shc</sup> gene expression is increased in peripheral blood mononuclear cells obtained from T2D patients and correlates with plasma levels of 8-isoprostane, an in vivo marker of oxidative stress. Moreover, PKC orchestrates many glucose-sensitive pathways responsible for vasoconstriction and thrombosis, such as endothelin-1 and cyclooxygenase 2 (COX-2).

In the vessel wall, PKC-dependent ROS production also participates in the atherosclerotic process by triggering vascular inflammation. ROS production leads to upregulation and nuclear translocation of the NF<sub>K</sub>B subunit p65; hence, transcription of proinflammatory genes encoding for monocyte chemoattractant protein 1 (MCP-1), vascular cell adhesion molecule 1 (VCAM-1), and others. These molecular events precipitate important atherosclerotic features, such as endothelial dysfunction, insulin resistance, and vascular inflammation.

**Figure 4.** Hyperglycemia-induced endothelial dysfunction and oxidative stress are blunted by vitamin C. Flow-mediated dilation, nitrotyrosine levels, and glycemia in type 1 diabetic patients treated with insulin and vitamin C for 24 hours (red), vitamin C for 24 hours + insulin for 12 hours (blue), and vitamin C for 12 hours + insulin for 24 hours (violet). Modified from reference 12: Ceriello et al. Diabetes Care. 2007;30:649-654. © 2007, American Diabetes Association.

**Figure 5.** Molecular mechanisms linking hypertension, diabetes, and endothelial dysfunction.

AngII and hyperglycemia trigger a detrimental cross talk favoring the imbalance between oxidant and antioxidant enzymes. These molecular events precipitate important atherosclerotic features, such as endothelial dysfunction, insulin resistance, and vascular inflammation.

**Abbreviations:** AGE, advanced glycation end product; ALDH2, alcohol dehydrogenase 2; AngII, angiotensin II; HG, hyperglycemia; ICAM-1, intracellular cell adhesion molecule 1; MCP-1, monocyte chemoattractant protein 1; NF<sub>k</sub>B, nuclear factor-kB; NO, nitric oxide; PKC, protein kinase C; ROS, reactive oxygen species; SOD2, superoxide dismutase; VCAM-1, vascular cell adhesion molecule 1.
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Phosphorytatation protein 1 (MCP-1), selectins, vascular cell adhesion molecule 1 (VCAM-1), and intracellular cell adhesion molecule 1 (ICAM-1). This latter event facilitates adhesion of monocytes to the vascular endothelium, rolling, and diapedesis in the subendothelium with subsequent formation of foam cells. Secretion of interleukin (IL)-1 and tumor necrosis factor α (TNF-α) from active macrophages maintains upregulation of adhesion molecules by enhancing NFκB signaling in the endothelium and promotes growth and proliferation of vascular smooth muscle cells (VSMCs). Mitochondrial ROS production also increases intracellular levels of the glucose metabolite methylglyoxal and synthesis of advanced glycation end products, thus fostering ROS-sensitive biochemical pathways, such as the hexosamine flux.

**Endothelial insulin resistance**

Insulin resistance is a major feature of T2D and hypertension, and it develops in multiple organs, including skeletal muscle, liver, adipose tissue, and heart. A recent meta-analysis demonstrated that insulin resistance predicts the incidence of coronary heart disease, stroke, or combined cardiovascular disease. Obesity plays a pivotal role in this phenomenon, providing an important link between T2D and fat accumulation. In subjects with obesity or T2D, the increase in free fatty acids activates toll-like receptor 4, which leads to NFκB nuclear translocation and subsequent upregulation of the inflammatory genes IL-6 and TNF-α. On the other hand, two important kinases, c-Jun N-terminal kinase (JNK) and PKC, phosphorylate the insulin receptor substrate 1 (IRS-1), thus blunting the downstream targets of IRS-1—PI3-kinase and Akt. This results in the downregulation of the glucose transporter GLUT4 and, subsequently, insulin resistance.

Although insulin resistance has been attributed to adipocyte-derived inflammation, recent evidence is overturning the “adipocentric paradigm.” Indeed, inflammation and macrophage activation seem to occur primarily in nonadipose tissue in obesity. This concept is supported by the notion that suppression of inflammation in the vasculature prevents insulin resistance in other organs and prolongs the lifespan of mice. Transgenic mice with endothelium-specific overexpression of the inhibitory NFκB subunit IκBα were protected against the development of insulin resistance. In these mice, obesity-induced macrophage infiltration of adipose tissue and plasma oxidative stress markers were reduced, whereas blood flow, muscle mitochondrial content, and locomotor activity were increased, confirming the pivotal role of the transcription factor NFκB in oxidative stress, vascular dysfunction, and inflammation.

These novel findings strengthen the central role of the endothelium in obesity-induced insulin resistance, suggesting that blockade of vascular inflammation and oxidative stress may be a promising approach to prevent metabolic disorders. Consistently, pharmacological improvement in insulin sensitivity in patients with T2D and metabolic syndrome is associated with restoration of flow-mediated vasodilation.

**Endothelial dysfunction in hypertension**

Impaired flow-mediated dilation is a common feature in hypertensive patients. Endothelium-dependent dilations are reduced in isolated arteries from several animal models of hypertension, including spontaneously hypertensive rats, salt-induced hypertension, and renovascular hypertension. Apart from the impaired dilations, the appearance of endothelium-dependent contractions also contributes to the development of endothelial dysfunction in hypertension. Thus, any pharmacological agent that restores eNOS activity and NO production and/or suppresses oxidative stress are theoretically useful in delaying the onset of endothelial dysfunction associated with hypertension. In this regard, a seminal study has shown that the oxidant scavenger vitamin C rescues hypertension-related endothelial dysfunction in human subjects, thus highlighting the importance of oxidative stress in this phenomenon (Figure 6, page 118).

**Oxidative stress**

The relationship between oxidative stress and increased blood pressure has been demonstrated in many models of experimental hypertension. Increased ROS formation precedes the development of hypertension in spontaneously hypertensive rats, suggesting that ROS participates in the development and maintenance of hypertension. Markers of oxidative stress, such as thiobarbituric acid reactive substances and F2-isoprostanes, tissue concentrations of O₂⁻, H₂O₂, and activation of NADPH oxidase and xanthine oxidase, are increased, whereas levels of NO and antioxidant enzymes are reduced in experimental hypertension. Multiple sources of oxidative stress have been implicated in the pathogenesis of hypertension-related endothelial dysfunction. Investigations over the past years have continued investigating the potential mechanisms regulating two important sources of hypertension-associated oxidative stress: NADPH oxidase and redox-sensitive mitochondrial pathways.
NADPH oxidase

NADPH oxidases of the Nox family are differentially expressed in the cardiovascular system and they may critically contribute to oxidative burden and vascular disease. The Nox family consists of seven members: classic oxidases, Nox1 to Nox5; and dual oxidases, Duox1 and Duox2.27 A significant expression in the cardiovascular system has been reported for Nox1, Nox2, Nox4, and Nox5. As a consequence of the interaction between the different ROS-generating systems, such as the mitochondria and eNOS, NADPH oxidases have been shown to contribute to ROS formation for almost all risk-factor conditions. In rats and mice made hypertensive by angiotensin II (AngII) infusion, expression of NADPH oxidase subunits (Nox1, Nox2, Nox4, and Nox5) as well as oxidase activity, and generation of ROS are increased.27 Moreover, NADPH oxidase activity was shown to be significantly increased in isolated carotid arteries from mice exposed to increasing intraluminal pressure, which was associated with concomitant reductions in endothelium-dependent vasodilation to acetylcholine and increases in vascular superoxide production.28 The relevance of NADPH oxidase signaling in hypertension is supported by the notion that knockout mice for different isoforms of NADPH oxidase, namely p47phox and Nox2, are protected against AngII-induced hypertension, and these animals do not show the same increases in superoxide anion production, vascular hypertrophy, and endothelial dysfunction compared with AngII-infused wild-type mice.29 Additional studies using small interfering RNA and suppressing Rac-1 activity implicate overexpression of integrin-kinase 1 as a key first step in the mechanotransduction of hypertension-induced vascular superoxide production through NADPH oxidase.26

Mitochondria-related pathways

Beside NADPH oxidase, there is increasing evidence that hypertension is associated with an increased mitochondrial-derived production of ROS in various animal models, including AngII-infused mice.30 Mitochondria also contribute to increased vascular ROS production in mesenteric resistance arteries and aortas from DOCA-salt rats.31 There are several mechanisms by which mitochondria may affect vascular function in hypertension. For example, deficiency of mitochondrial aldehyde dehydrogenase, an enzyme that detoxifies aldehydes to carboxylic acids, is known to increase oxidative stress. Interestingly, recent studies suggest that mitochondrial aldehyde dehydrogenase attenuates vascular contractions in AngII-treated hypertensive mice.32 A recent study showed that the mitochondrial adaptor p66Shc seems to play a key role in hypertension.33 Exposure of human aortic endothelial cells to cyclic stretch led to a stretch- and time-dependent p66Shc phosphorylation at Ser36 downstream of integrin α5β1 and JNK. In parallel, NADPH oxidase activation and ROS production were increased, whereas NO bioavailability was reduced. Interestingly enough, silencing p66Shc blunted stretch-increased O2•− production and NADPH oxidase activation, thus restoring NO release. In line with the above, activation of p66Shc increased in isolated aortic endothelial cells of spontaneously hypertensive rats compared with normotensive animals.33 Mitochondrial antioxidant systems also play an important role in pre-
serving organelle function and attenuating vascular oxidative stress. In this regard, manganese superoxide dismutase (SOD2) is a key mitochondrial antioxidant enzyme that is inactivated by reacting with ONOO. Previous studies demonstrated that AngII-induced hypertension is associated with increased tyrosine nitration of SOD2, suggesting that the aforementioned pathway may further exacerbate mitochondrial oxidant stress in the vasculature (Figure 5). NADPH oxidase-derived ROS production was reduced by overexpression of SOD2 and mitochondrial thioredoxin 2 and by treatment with either mitoTEMPO, a mitochondria-targeted SOD mimetic, or 5-hydroxydecanoic acid supplementation, a mitoKATP channel blocker. A recent and interesting observation is that mitochondria seem to regulate both expression and activity of NADPH oxidases (Figure 5). Partial depolarization reduces calcium uptake by the mitochondrial calcium uniporter and increases calcium-dependent activation of phagocytic NADPH oxidase, whereas depletion of SOD2 increases basal and stimulated vascular NADPH oxidase activity. These data show that mitochondrial ROS provides feed-forward regulation of NADPH oxidases, which is likely mediated by activation of the redox sensitive c-Src, a proto-oncogene tyrosine protein kinase, with mitochondrial H₂O₂.

**Inflammation**

Findings from animal studies have also suggested a role for inflammation in the pathophysiology of hypertension. Spontaneously hypertensive rats display higher levels of infiltrating lymphocytes and macrophages and increased activation of NFkB than Wistar Kyoto normotensive control rats. Activation of RAAS plays a key role in the development and pathophysiology of cardiovascular disease by several mechanisms. AngII is one of the final products and the main known mediator of the renin-angiotensin system. AngII induces vascular injury through vasoconstriction, cell growth, oxidative stress production, and inflammation. AngII modulates vascular inflammation by inducing cytokine release and pro-inflammatory transcription factors, such as NFkB. NFkB, in turn, regulates the adhesion molecules VCAM-1/ICAM-1 and cytokine levels in different cell types. These molecules induce and maintain inflammation within the vascular wall, stimulate deposition of extracellular matrix, and promote hypertrophy and/or hyperplasia of VSMCs. AngII also stimulates the production of plasminogen-activator inhibitor-1 (PAI-1), which contributes to the prothrombotic state and atherosclerotic plaque rupture. Moreover, AngII is involved in atherosclerotic lesion progression and plaque instability by stimulating the activation of matrix metalloproteinases, which can digest the fibrous cap, and thereby, trigger plaque rupture.

Over the past decade, researchers and clinicians have increasingly recognized the important role of adipose tissue in regulating metabolism and inflammation through the production of inflammatory and anti-inflammatory adipokines. Inflammation in adipose tissue, apparent in visceral fat deposits, is associated with impaired endothelial function in obese patients. Although most investigations relating adipose inflammation to vascular endothelial function concentrate on insulin resistance and obesity, recent studies have evaluated the effect of perivascular adipose tissue (PVAT) on vascular homeostasis in hypertension. Adipose tissue from hypertensive rats applied to thoracic aorta segments failed to suppress phenyl-ephrine-induced vasoconstriction, which is in contrast with adipose tissue from normotensive animals. Similarly, obese and hypertensive rats with perivascular inflammation show impaired endothelial function relative to control animals. A recent study conducted in obese and hypertensive patients showed that PVAT-derived production of TNF-α and increased vascular expression of endothelin-1 and the endothelin A receptor significantly contributed to the impairment of NO release. Interestingly, TNF-blockade by infliximab blunted NADPH oxidase activity, thus improving the ROS/NO balance. Moreover, removal of PVAT from visceral fat arteries isolated from hypertensive patients was associated with blunted L-N(G)-nitroarginine methyl ester (L-NAME)–induced vasoconstriction. Taken together, these findings show that TNF-α may be regarded as a key player in hypertension-related endothelial dysfunction in obesity (Figure 7). In line with these data, patients with hypertension have high levels of inflammatory mark-

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**Figure 7.** Schematic showing the emerging role of perivascular adipose tissue in the pathogenesis of endothelial dysfunction in obesity and hypertension.
Hypertension, diabetes, and endothelial dysfunction

Cosentino and others

ers, namely C-reactive protein. Most importantly, elevation of such inflammatory molecules is associated with vascular lesions in humans, which is predictive of cardiovascular outcome.

MOLECULAR MECHANISMS LINKING HYPERTENSION AND DIABETES

A growing body of evidence suggests that diabetes and hypertension are highly interconnected and participate in a synergistic manner to the pathophysiology of vascular dysfunction and, more generally, vascular complications. Several examples from clinical and basic studies strengthen the link between hyperglycemia, high blood pressure, and vascular risk. The effectiveness of pharmacological RAAS antagonism in preventing diabetes-related micro- and macrovascular complications indirectly suggests that RAAS dysregulation is heavily involved in triggering organ damage in patients with diabetes. Hyperglycemia directly upregulates intracellular synthesis of AngII in different cell types. AngII, in turn, increases insulin resistance and impairs glucose metabolism, thus enhancing and precipitating diabetes-related damage. This latter concept is supported by the results of the recently published NAVIGATOR trial (Nateglinide And Valsartan Impaired Glucose tolerAnce ouTcOmes Research), which showed that the use of valsartan along with lifestyle modifications for 5 years led to a relative 14% reduction in the incidence of diabetes in patients with impaired glucose tolerance and cardiovascular disease or risk factors. More recently, a large and updated meta-analysis showed that ARBs prevent new onset diabetes significantly more than other active antihypertensive treatments.

Previous seminal work has shown that high glucose levels stimulate angiotensinogen gene expression and cell hypertrophy through activation of the hexosamine biosynthesis pathway. Another mechanism of RAAS upregulation by glucose takes place at the promoter level of the angiotensin gene. Moreover, hyperglycemia leads to an accumulation of succinate, which binds and activates the G protein-coupled receptor GPR91, directly triggering the release of renin. Intracellular levels of renin were found to be markedly increased in cardiomyocytes of diabetic rats, and aliskiren, a direct renin inhibitor, was more efficient than the angiotensin-converting enzyme inhibitor benazepril in blunting intracellular levels of AngII and oxidative stress. These data are indirectly supported by the observed beneficial effects of renin inhibition with aliskiren in patients with diabetes.

Increased tissue AngII concentrations lead to angiotensin type 1 receptor (AT1R) upregulation, which mediates most of the pathologic effects of the hormone. Interestingly, hyperglycemia-induced oxidative stress impairs the activity of angiotensin-converting enzyme 2, a major enzyme generating the proteolytic Ang(1-7). On the other hand, high glucose downregulates the angiotensin type 2 receptor (AT2R) via increased abundance of the transcription factor poly(ADP-ribose) polymerase-1 (PARP), which suppresses AT2R promoter activity. Hyperglycemia-dependent AngII local activation further increases intracellular concentrations of O$_2^-$, thus reducing NO with a subsequent generation of ONOO$^-$ and cellular toxicity. Raised levels of ONOO$^-$ impair the activity of prostacyclin synthase at the expense of increased levels of thromboxane A$_2$, a potent vasoconstrictor.

Reduction in NO availability allows vasoconstrictive substances to increase vascular tone and trigger platelet aggregation, thus precipitating endothelial dysfunction. Moreover, the AngII-dependent rise in O$_2^-$ levels increases the activity of the transcription factor NFkB, which leads to the synthesis of inflammatory cytokines (IL-6, IL-8, TNF-$\alpha$), adhesion molecules (MCP-1, ICAM-1, VCAM-1, and E-selectin), and prothrombotic factors (PAI-1). All of these changes may accelerate the atherosclerotic process in diabetes. RAAS upregulation in the vasculature also leads to contraction and proliferation of VSMCs, leading to pathologic vessel remodeling.

Once hyperglycemia is upregulated by AngII, the increased inflammation and production of ROS induces changes in vascular permeability, recruitment of leukocytes from the circulation, and fibrosis. Indeed, AngII activates a profibrotic cascade, which increases the levels of transforming growth factor $\beta$ and the activity of matrix metalloproteinases. In humans, candesartan and enalapril are able to reduce the media-to-lumen ratio of small arteries, as well as the collagen content. Another study showed that valsartan significantly improved resistance artery remodeling in diabetic hypertensive patients.

THERAPEUTIC PERSPECTIVES

The evidence discussed so far suggests that hypertension and diabetes are capable of triggering common maladaptive pathways, resulting in endothelial dysfunction, atherosclerosis, and vascular events. The most common molecular signal involved in this process is represented by accumulation of ROS. Therefore, targeting hypertension- and diabetes-related...
Hypertension, diabetes, and endothelial dysfunction - accumulation of ONOO–, protein nitrosylation, and cellular dysfunction.

The main problem with tissue-specific treatment is drug delivery. It is clear that a selective rearrangement of maladaptive pathways in the endothelium would be invaluable to restore micro- and macrovascular function. An alternative option may be represented by NO donors or administration of eNOS cofactors to improve tissue capillary recruitment. Unfortunately, this approach has failed many times due to the high oxidative burden in patients with metabolic disease, which rapidly inactivates NO, thus favoring accumulation of ONOO–, protein nitrosylation, and cellular dysfunction. In this respect, an example is provided by a recent clinical trial where oral treatment with the eNOS cofactor tetrahydrobiopterin showed limited effectiveness on endothelial function due to systemic oxidation and poor uptake into the vascular wall. These latter results highlight the need for a more mechanistic understanding and alternative strategies to counteract pathways triggering eNOS dysfunction in patients with diabetes and hypertension. Therefore, further molecular work is warranted to unveil common targets activated in the presence of hypertension and diabetes.

REFERENCES


Hypertension, diabetes, and endothelial dysfunction - Cosentino and others


Diabetes and hypertension are the “bad companions” and each is more common together in the same patient than separately in the general population. Both are risk factors for cardiovascular disease and mortality, and, when both are present, these risks are additive. Fortunately, each is amenable to treatment and double therapy is particularly useful because a more intensive glucose-lowering therapy is especially successful in protecting against microvascular disease, while blood pressure-lowering therapy is highly effective in protecting against major cardiovascular events, such as heart attack and stroke, and in lowering mortality. Furthermore, there is convincing evidence that the two therapies are either additive or at least complementary. Therefore, in answer to the question “is double therapy useful?” we can confidently reply—“Yes, not only useful, but mandatory!”

Diabetes and hypertension are each responsible for extensive morbidity and mortality, much of which results from the vascular system changes that affect large arteries, through the process of atherosclerosis, and smaller blood vessels or the microvascular system. Even worse, diabetes and hypertension often coexist, especially type 2 diabetes, and when they do, the damage is accentuated. Indeed, diabetes and hypertension are often referred to as “the bad companions.” Mogensen attributes this term to Professor Harry Keen, who described high blood glucose, high blood pressure, and albuminuria as “the bad companions” many decades ago. High blood pressure and hypertension on the one hand and raised blood sugar and diabetes on the other both lead to marked increases in morbidity and mortality from coronary heart disease, stroke, and renal failure. When both occur together in the same patient, these effects are exacerbated. Fortunately, effective treatments are available to lower blood pressure and blood glucose effectively, with considerable reductions in organ damage and increases in the benefits to the patient’s health and well-being. It is equally fortunate that some of the benefits of each condition are clearly additive, while others are complementary, so that the answer to the question “is double therapy useful?” must be an emphatic “Yes!”

INCIDENCE AND COINCIDENCE OF DIABETES AND HYPERTENSION

Diabetes and hypertension are both common disorders that have each become more common in recent decades, in both the advanced economies and the developing world. It is estimated that 387 million people had diabetes in 2014 and that this will rise to 592 million by 2035. Furthermore, it is estimated that around 2 billion adults currently have hypertension. One clear factor contributing to and linking the two conditions is the growing proportion of the global population that is overweight or obese, particularly in the “Western World.” At the present time, over 30% of the adult population worldwide suffers from hypertension, which is defined as blood pressure...
over 140/90 mm Hg, while around 10% of the adult population has diabetes, predominantly type 2 diabetes. Furthermore, each is more common together in the same patient than separately in the general population. Thus, hypertension is approximately twice as common in people with diabetes as in those without, and the latest figures indicate that the proportion of diabetics who have hypertension in the USA has grown from 46% to 57% between 1995 and 2009. A recent study from China reported that around one-quarter of patients presenting to hypertension clinics have diabetes, while one study from the UK found that a higher risk of new-onset diabetes (>50%) was associated with a 20 mm Hg higher systolic blood pressure.

Patients with diabetes may have common or garden essential hypertension, but may also suffer from hypertension associated with diabetic nephropathy and from systolic hypertension, which is more common in those with diabetes, due to the greater tendency to have arterial stiffening. They can also have orthostatic hypotension in association with systemic hypertension due to autonomic neuropathy and dysfunction. Furthermore, people with both diabetes and hypertension have more renal disease and more atherogenic risk factors, including dyslipidemia, hyperuricemia, and left ventricular hypertrophy. Hypertension and diabetes each contribute significantly to mortality in the other. Thus, hypertension contributes to the leading causes of mortality in people with diabetes, such as coronary heart disease, stroke, peripheral vascular disease, and end-stage kidney disease. Hypertension also contributes to diabetic retinopathy, a major cause of visual deterioration and blindness worldwide.

For these reasons, it is important for all medical practitioners to be aware of the nexus between these two conditions, to look hard for the second whenever the first appears, and to pursue all possible preventative and therapeutic strategies for each condition as early and actively as possible.

**OBSERVATIONAL STUDIES: ASSOCIATION OF GLYCEMIA AND BLOOD PRESSURE WITH MACROVASCULAR AND MICROVASCULAR DISEASE**

Many observational studies in patients with and without type 2 diabetes have confirmed that there is a progressive linear relationship between both glycemic exposure and systolic blood pressure on the one hand and the risks of vascular complications and death on the other.

**Association of glycemia with vascular complications and death**

While the association between glycemia, as reflected in the levels of glycated hemoglobin (HbA1c), and vascular disease has long been known, the landmark UKPDS study (UK Prospective Diabetes Study) was the first to look systematically at the relationship between glycemic exposure over time and the development of both macrovascular and microvascular complications with-

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**Figure 1. Association of HbA1c and SBP with the incidence of myocardial infarction and microvascular end points.**

Panel A shows the association between HbA1c and both myocardial infarction and microvascular end points. Panel B shows the association between systolic blood pressure and both myocardial infarction and microvascular end points.

**Abbreviations:** HbA1c, glycated hemoglobin; SBP, systolic blood pressure.

in the clinical trial analyzing intensive glucose control. In this study on newly diagnosed patients with type 2 diabetes that was carried out over the last two decades of the twentieth century, every 1% reduction in mean HbA1c was associated with a 14% lower risk of myocardial infarction, 37% lower risk of microvascular complications, and 14% lower risk for all-cause mortality (Figure 1A, page 125). In this study, there was no lower-limit threshold for HbA1c below which further reductions in HbA1c were no longer associated with a risk reduction. In contrast, more recent studies have described nonlinear relationships between glycemia and the risks of cardiovascular disease or death. Furthermore, three large trials of more intensive glucose lowering, which were targeting near-normal glycemia, have individually failed to confirm benefits for major cardiovascular events or mortality, though a pooled meta-analysis of these trials did show a modest 9% reduction in cardiovascular events and a 14% reduction in myocardial infarction.

A more recent observational study based on the ADVANCE trial (Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation) in patients with well-established type 2 diabetes, has also reported on the association of HbA1c with vascular complications and death. This study found that the HbA1c thresholds for microvascular events and macrovascular complications and death were 6.5% and 7%, respectively. Above these thresholds, every 1% increase in HbA1c was associated with a 38% higher risk of a macrovascular event, 40% higher risk of a microvascular event, and 38% higher risk of death (Figure 2). Below these levels, there was no significant relationship between HbA1c levels and risks, indicating that there was no clear evidence of either benefit or harm when reducing HbA1c levels below these thresholds. These observations are consistent with the lack of clear macrovascular and mortality benefits, but the positive benefit for microvascular outcomes observed with more intensive glucose control in the ADVANCE, ACCORD (Action to Control Cardiovascular Risk in Diabetes), and VADT (Veterans Affairs Diabetes Trial) trials.

**Association of systolic blood pressure with vascular complications and deaths**

Individuals with diabetes have a 2- to 3-fold greater risk of suffering a major cardiovascular event than people without diabetes, but epidemiological studies suggest that a higher glycemic load accounts for only part of this increased risk. These increases in risk associated with type 2 diabetes appear to be consistent across different populations.

On average, levels of blood pressure are higher in people with diabetes than in those without, and increased blood pressure or hypertension is more common in those with diabetes than in the general population. Following com-

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**Figure 2. Adjusted hazard ratios for major macrovascular and microvascular events and all-cause mortality, by deciles of mean HbA1c levels during follow-up in the ADVANCE trial showing evidence of glycemic thresholds.**

**Abbreviations:** ADVANCE, Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation; HbA1c, glycated hemoglobin; HR, hazard ratio.

pletion of the UKPDS35 study, (the randomized trial of tighter blood pressure control), the investigators analyzed the association of systolic blood pressure over the course of the trial and the development of macrovascular and microvascular complications.20 They reported a strong and significant association between systolic blood pressure and major clinical complications. Every 10 mm Hg reduction in systolic blood pressure was associated with reductions in myocardial infarction (12%), stroke (19%), microvascular complications (13%), and all-cause mortality (12%) (Figure 1B, page 125).20 Furthermore, no thresholds were found for systolic blood pressure below which the vascular complications of diabetes ceased to decline.

It is uncertain whether blood pressure is a more important determinant of cardiovascular risk among individuals with diabetes. A number of studies have reported similar associations between blood pressure and death or blood pressure and cardiovascular complications in people with and without diabetes.16,19,23 However, the MRFIT trial (Multiple Risk Factor Intervention Trial) reported a higher risk of cardiovascular death associated with hypertension among men with diabetes compared with those without diabetes.24 More recently, this issue has been examined by the Asia Pacific Cohort Studies Collaboration, which involved 350,000 participants in 36 studies across Asia, Australia, and New Zealand.19 This collaboration reported that systolic blood pressure was associated with coronary disease and stroke in a continuous, log-linear manner among individuals with diabetes and those without diabetes. Specifically, the study found that each 10 mm Hg increase in systolic blood pressure was associated with an 18% and 23% higher risk of coronary heart disease in those with and without diabetes, respectively.19 The corresponding figures were 29% and 43% for ischemic stroke and 56% and 74% for hemorrhagic stroke, respectively. However, these differences were not significant. Broadly similar associations were found between people in Asia and those in Australia and New Zealand.19

**LARGE-SCALE RANDOMIZED TRIALS OF TIGHTER BLOOD PRESSURE CONTROL AND MORE INTENSIVE GLUCOSE CONTROL IN PATIENTS WITH TYPE 2 DIABETES**

**Trials of blood pressure control**

The UKPDS study was the first major trial to demonstrate substantial benefits of tighter blood pressure control in hypertensive patients with type 2 diabetes in 1998.25 These benefits included reductions in diabetes-related end points, diabetes-related deaths, stroke, and microvascular end points (mainly retinal), with no separate reductions in all-cause mortality or myocardial infarction. While active treatment achieved a 10/5 mm Hg reduction in blood pressure compared with the control group, the blood pressure remained in the hypertensive range in both groups (144/82 vs 154/87 mm Hg). Approximately half of the study participants were started on an angiotensin-converting enzyme inhibitor (captopril) and half on a β-blocker with similar benefits in these two groups.

The ADVANCE trial was the next trial to report significant benefits from blood pressure lowering and it differed from the UKPDS study in recruiting patients, whether hypertensive or not, and in achieving blood pressures well within the normotensive range during randomized treatment (135 mm Hg systolic in the active treatment group, receiving the fixed-dose combination of perindopril and indapamide). This treatment achieved significant reductions in all-cause mortality (14%), cardiovascular mortality (18%), and all vascular end points (macrovascular and microvascular end points combined; 9%).26 There were also significant reductions in total coronary events (14%) and total renal events (21%), but not for stroke or retinopathy.26 Effects of active treatment on renal events were consistent across subgroups that were defined by baseline systolic blood pressure down to levels below 110 mm Hg.27

Subsequently, the ACCORD trial reported the effects of intensive blood pressure control, targeting a systolic blood pressure below 120 mm Hg, and actually achieving a pressure of 119 mm Hg, compared with the control group that achieved a systolic blood pressure of 134 mm Hg.28 The primary outcome of major cardiovascular events (stroke, myocardial infarction, or cardiovascular death) was reduced by 12%, but this was not significant, which largely reflects the fact that the event rate observed was approximately half that used to calculate study power and sample size. There was no significant reduction in mortality or coronary heart disease, but there was a 41% reduction in stroke. The adverse event rate was low, but it was significantly higher in the active treatment group.28

Another trial that reported significant benefits in patients with diabetes was the HOPE study (Heart Outcomes Prevention Evaluation), which used ramipril to lower blood pressure in 9297 patients at high
### Figure 3. Effects of more vs less intensive glycemic control on major cardiovascular events, stroke, myocardial infarction, and all-cause mortality in major trials of more intensive glucose control.

**Abbreviations:** ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation; HbA1c, glycated hemoglobin; UKPDS, UK Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

cardiovascular risk, 3577 of whom had diabetes, and the results obtained in the latter group were reported in the MICRO-HOPE study in 2000.29 This study reported reductions around one-quarter for total mortality, major macrovascular outcomes, myocardial infarction, and overt nephropathy and reductions around one-third for stroke.

It is clear from these major trials that lowering blood pressure in patients with type 2 diabetes is very effective in reducing the risk of major cardiovascular events, though the magnitude and specifics of the reduced events varied between the trials. Three of the trials used angiotensin-converting enzyme inhibitors to lower blood pressure and it is clear that inhibition of the renin-angiotensin system with these agents is beneficial for patients with diabetes.

Trials of more intensive glucose control

Once again, the UKPDS study led the way with the report from the UKPDS33 study.30 More intensive glucose control, using either sulfonylureas or insulin, decreased the risk of microvascular complications, but not macrovascular disease or mortality. There was, however, a tantalizing trend toward a 16% reduction in myocardial infarction, though the P value of P<0.052 just missed significance. Accordingly, a number of trial groups resolved to address this issue and initiated the ADVANCE, ACCORD, and VADT trials.12-14 All three presented their results in 2008 at the same meeting of the American Diabetes Association and in the same issue of the New England Journal of Medicine, precipitated by early termination of the glucose arm of the ACCORD trial after only 3.5 years of a planned 5-year duration due to an unexpected 22% increase in total mortality.13

The increase in mortality observed in the ACCORD trial was confirmed when the main results were published.13 There was a reduction in the HbA1c to 6.5%, as planned in the intensive control group, compared with 7.5% in the control group, and a substantial increase in both body weight and severe hypoglycemia. However, there was a substantial 24% reduction in nonfatal myocardial infarction, and a trend toward a 10% reduction in the primary composite outcome of stroke, myocardial infarction, and cardiovascular deaths (P=0.16). The VADT study was much smaller, with only 1791 participants, and few significant results. The baseline HbA1c levels were much higher in this study (mean, 9.4%), and, although a differential of 1.5% was achieved, the levels attained during the trial were higher (8.4% and 6.9%, respectively). There were no significant changes in mortality, macrovascular outcomes, or microvascular outcomes.14

The results of the intensive glucose arm of the ADVANCE trial were more positive. This trial, conducted in 11 140 patients with type 2 diabetes, had a baseline HbA1c of 7.5% and it achieved a mean HbA1c of 6.5%, (the same as that in the ACCORD trial), using a gliclazide MR–based regimen, compared with 7.3% in the control group.12 In contrast with the ACCORD trial, there was no tendency for any increase in mortality, but rather toward a decrease in all-cause death (7%) and cardiovascular death (12%). There was an overall significant 10% reduction in the combined primary end point of major macrovascular and microvascular events, which was driven by a 14% reduction in microvascular events that was, in turn, dependent on a 21% reduction in new or worsening nephropathy.12 There were no separate reductions in major macrovascular events. Subsequent analyses confirmed that there was a major 65% reduction in the incidence of end-stage kidney disease in the patients assigned to intensive gliclazide MR–based glucose control, which is the first time that this has been reported.31

These four sets of trialists collaborated to perform a meta-analysis of the effects of more intensive glucose lowering on major macrovascular events, death, and major hypoglycemia.32 This meta-analysis confirmed that more intensive glucose lowering provides a 9% reduction in major cardiovascular events and a 15% reduction in myocardial infarctions (Figure 3). There were no significant changes in mortality (Figure 3), but a clear increase in major hypoglycemia.

COMBINED EFFECTS OF DOUBLE THERAPY WITH BOTH GLUCOSE AND BLOOD PRESSURE CONTROL

Three of the trials described above—UKPDS, ADVANCE, and ACCORD—had a factorial design, permitting analysis of interactions and additive effects between blood pressure–lowering and glucose-lowering therapies.33-35

The UKPDS study reported on the additive effects of glycemia and blood pressure on risk reductions calculated for a 1% decrease in HbA1c and a 10 mm Hg decrease in systolic blood pressure. For “any diabetes-related end point,” there was a 21% and 11% decrease in glycemia and systolic blood pressure, respectively, and a 14% decrease in all-cause mortality. Tests for interactions confirmed that these effects were additive. Furthermore, this study had 887 patients randomized to both the glycemia and the hypertension intervention.
arms. As shown in Figure 4, patients allocated to both intensive glucose and tighter blood pressure control had significantly fewer primary end points (any diabetes-related end point) than those allocated to either intervention alone. Similar trends were seen for diabetes-related deaths and for all-cause mortality. The UKPDS trialists concluded that intensive treatment is required for both glycemia and hypertension to minimize the risk of complications.

The ADVANCE trial also reported on the combined effects of routine blood pressure lowering and intensive glucose control on both macrovascular and microvascular outcomes in 11,140 patients with type 2 diabetes who were randomized into both arms of the study and followed-up for an average of 4.3 years. This report confirmed that the effects of the two interventions were additive on a log scale for both all-cause mortality (Figure 5) and renal outcomes, particularly new or worsening nephropathy and macroalbuminuria, which were reduced by 33% and 54%, respectively (Figure 6).

The ACCORD study group reported on 4.7 years of follow-up in 4,733 patients participating in both the ACCORD blood pressure trial and the ACCORD main trial on more intensive glucose lowering. This study did not report any additive benefit for microvascular outcomes, possibly reflecting the paucity of positive outcomes with both arms of the trial. We are not aware of any reports regarding combined effects for macrovascular outcomes in the ACCORD trial.

There is one other study with very positive results regarding the combined effects of multiple risk factor interventions in 160 patients with type 2 diabetes and microalbuminuria—the Steno-2 study. This randomized trial compared conventional treatment with a multifactorial intensive treatment regimen that included behavioral modification, an angiotensin-converting enzyme inhibitor that targeted the microalbuminuria, more intensive glucose control (usually starting with a glitazide), other antihypertensive agents, as needed, statins, and aspirin. Despite the small number of participants, this intensive treatment regimen produced remarkable benefits after 7.8 years of follow-up, with >50% reductions for the risks of major cardiovascular disease, nephropathy, retinopathy, and neuropathy.

It is very clear that, just as for cardiovascular disease in people without diabetes, the optimal protection against cardiovascular disease—macrovascular and microvascular—in patients with type 2 diabetes requires therapy targeting the major risk factors, among them tighter blood pressure control and more intensive glucose control. It is essential to address both hypertension and diabetes whenever they coexist. It is also imperative to maintain good blood pressure control in all subjects with diabetes and to monitor the glucose levels in all patients with hypertension, given the propensity for each to coexist.

LONG-TERM POSTTRIAL FOLLOW-UP OF GLUCOSE AND BLOOD PRESSURE LOWERING IN TYPE 2 DIABETES

Long-term posttrial follow-up was initiated in studies using more intensive glucose control in patients with type 1 and type 2 diabetes in the hope that beneficial effects for major cardiovascular disease that were not manifest by the end of randomized treatment might emerge over time, as the effects of better
### All-cause mortality

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<td></td>
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<td>15% (-3 to 29)</td>
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- **RRR (95% CI)**
- **0.5**
- **1.0**
- **10**
- **Hazard ratio**

### New onset macroalbuminuria

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- **RRR (95% CI)**
- **0.5**
- **1.0**
- **10**
- **Hazard ratio**

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Figure 5. Combined effects of routine blood pressure–lowering and intensive glucose-control therapy on all–cause mortality in the ADVANCE trial.

**Abbreviations:** ADVANCE, Action in Diabetes and Vascular disease; PreterAx and DiamicroN MR Controlled Evaluation; BP, blood pressure; Ind, indapamide; Per, perindopril; RRR, relative risk reduction.


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Figure 6. Combined effects of routine blood pressure lowering and intensive glucose control on macroalbuminuria in the ADVANCE trial.

**Abbreviations:** ADVANCE, Action in Diabetes and Vascular disease; PreterAx and DiamicroN MR Controlled Evaluation; BP, blood pressure; Ind, indapamide; Per, perindopril; RRR, relative risk reduction.
metabolic control might take longer to develop. This strategy was rewarded by the detection of emerging reductions in major cardiovascular events in both type 1 and type 2 diabetes.\textsuperscript{37,38}

The UKPDS study led the way for type 2 diabetes, with the demonstration that, 10 years after the cessation of randomized glucose-control therapy, there were not only continuing reductions in microvascular events, but also emerging significant reductions in myocardial infarction and all-cause mortality.\textsuperscript{40} In a similar way, a 5-year posttrial follow-up of the VADT trial of more intensive control, reported reductions in major cardiovascular events that were not present during randomized treatment, but no reductions in mortality.\textsuperscript{39}

In contrast, the 5-year posttrial follow-up after the cessation of randomized treatment and convergence of HbA\textsubscript{1c} values between the original randomized groups of the intensive glucose-control arm of the ADVANCE trial did not detect an emergence of benefits for macrovascular disease, but did find a persistence of the major reduction in end-stage kidney disease, which remained significantly reduced by 46\% after 10 years of follow-up. Thus, there were considerable variations in the posttrial benefits reported by these 3 trials: two reported long-term macrovascular benefits, two found continuing microvascular benefits, and one reported long-term reductions in mortality.\textsuperscript{38-40} While the ACCORD trial had reported a so-called long-term follow-up of intensive glucose control, this was limited to following patients to the end of the original 5-year planned follow-up. Not surprisingly, the main findings, which were reported when the study was prematurely terminated, were not significantly altered.\textsuperscript{41}

Posttrial follow-up of the blood pressure arm of the ADVANCE trial (6 years after the cessation of randomized treatment and convergence of blood pressure levels between randomized groups) revealed a clear persistence in the reductions in mortality—both all-cause mortality and cardiovascular death—though both were somewhat attenuated.\textsuperscript{40} However, there were persistent and significant reductions in all-cause mortality (9\%) and cardiovascular mortality (12\%) 6 years after randomized treatment had ceased. While the UKPDS study could not find any persistent reductions in all-cause mortality, it did report a nonsignificant reduction in this major end point (11\%).\textsuperscript{42} The difference between these two reports is probably explained by the difference in patient numbers and study power, as the ADVANCE trial began with 11 140 patients at baseline, while the UKPDS blood pressure trial only had 1148 patients with type 2 diabetes at the start.\textsuperscript{25}

The long-term benefits reported in the posttrial follow-up studies varied considerably, but it is clear that both more intensive glucose control and tighter blood pressure lowering in patients with type 2 diabetes provided some persistent

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure7.png}
\caption{Effects of multifactorial intervention on all-cause mortality and cardiovascular events during the trial and during the posttrial follow-up in the Steno-2 trial.}
\end{figure}

long-term benefits. Possibly the strongest evidence for additivity of long-term effects of glucose control and blood pressure control comes from the Steno-2 study on patients with type 2 diabetes. The Steno-2 study reported that the multifactorial regimen, which included targeting hypertension and glycemic control, caused the emergence of major reductions in all-cause death, cardiovascular death, and major cardiovascular events (>50%) 5 years after the main randomized trial was completed (Figure 7). These benefits are very substantial and greater than those that have been reported with single treatment modalities. It is clearly beneficial to apply optimal therapy for both glucose and blood pressure control in all high-risk patients with hypertension, diabetes, or both.

CONCLUSIONS

Diabetes and hypertension are not only “the bad companions,” they are clearly very constant companions! At the time of first diagnosis, each is more common together in the same patient than separately in the general population, and if not present at that time, it is very likely to develop over time. Furthermore, both hypertension and diabetes are major risk factors for cardiovascular disease and mortality, and when both are present, these risks are additive. Fortunately, each condition is amenable to a treatment that is very effective in reducing the risk of cardiovascular disease. It is in this respect that double therapy is particularly useful, since intensive glucose-lowering therapy is especially successful in protecting against microvascular disease, while blood pressure–lowering therapy is highly effective in protecting against mortality and major cardiovascular events, such as myocardial infarction and stroke.

Furthermore, there is no suggestion for any negative interaction between blood pressure–lowering and glucose-lowering therapies. Rather, there is convincing evidence that the two are additive, or, when not additive, at least complementary! Therefore, in answer to the question “is double therapy useful?” we can confidently reply—“yes, not only useful, but indeed, double therapy is mandatory!”

REFERENCES


Diabetes and hypertension: is treating hyperglycemia useful?

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Diabetes complications are traditionally divided into microvascular and macrovascular categories. Microvascular complications comprise diabetic kidney disease, neuropathy, and retinopathy. Macrovascular complications include atherosclerotic cardiovascular diseases that affect coronary, cerebral, and peripheral vasculature. More recently recognized complications of diabetes, such as dementia and cardiomyopathies that lead to heart failure, do not neatly fit into this dichotomy. Hypertension is an independent risk factor for both microvascular and macrovascular complications.

This is an important consideration because the majority of people with diabetes also have hypertension, and the combination of the two conditions greatly increases the risk of complications. This article will focus on cardiovascular disease as a complication of the combination of diabetes and hypertension, and in particular, whether glycemic control is useful to prevent this disease. Due to the available evidence base, the focus will be on type 2 diabetes. The effects of newer blood glucose–lowering agents on blood pressure will also be discussed. This paper will examine the evidence for treating hyperglycemia.
as a means of improving cardiovascular risk in patients with a combination of hypertension and diabetes or prediabetes. Although type 2 diabetes is defined by hyperglycemia and treatment strategies have been focused on lowering blood glucose, it is important to recognize that hyperglycemia is the clinical result of multiple alterations in metabolism. The mechanism by which glucose is lowered is probably important in the modification of cardiovascular risk. The advent of new classes of medication over the last decade offers additional mechanisms for controlling the metabolic derangements of diabetes. Some of these agents also directly lower blood pressure. There is hope that these medications will also improve cardiovascular outcomes, although evidence for this lags behind the clinical availability of these agents.

Complication rates for people with diabetes are decreasing, although the incidence of complications continues to increase, which is driven by an increasing prevalence of diabetes. Although improvements in care, diabetic patients remain at vastly increased cardiovascular risk, producing all-cause mortality rates approximately twice that of people without diabetes. Although early studies reported that a prior myocardial infarction and diabetes-positive status represented equivalent risks for future myocardial infarction, more recent studies have clarified this relationship, showing that diabetes duration and presence of other risk factors greatly modify the risk. Of these, hypertension is particularly important, which is highlighted by the success of a multifactorial intervention in lowering cardiovascular disease and mortality, whereas trials of intensive glycemic control alone have been generally less successful in this regard.

CARDIOVASCULAR RISK IMPLICATIONS OF THE COMBINATION OF HYPERTENSION AND DIABETES

Epidemiology

Epidemiological studies consistently show that people with diabetes are more likely to be hypertensive. The prevalence of hypertension in populations with diabetes ranges from 40% to 80% and depends on the diabetes type, age, weight, and ethnicity. Excess hypertension occurs in both type 1 and type 2 diabetic populations, although the link for type 1 diabetes is not as strong and is not clearly independent of renal function and body weight. For type 2 diabetes, there are clear epidemiological and pathophysiological links. The presence of abnormal glucose metabolism predicts incident hypertension and people with hypertension are more likely to develop diabetes. This is particularly the case for nocturnal hypertension or a nondipping pattern of hypertension.

Pathophysiology

The pathophysiology of type 2 diabetes and hypertension are interlinked. Both disorders share the common risk factors of excess caloric intake, sedentary lifestyle, and increased visceral adiposity. In susceptible people, these lead to hypertrophy of white adipocytes in visceral depots and chronic low-grade inflammation that results in adipose insulin resistance, enhanced nonesterified fatty acid flux, and ectopic fat accumulation in the liver and muscle, which leads to hepatic and peripheral insulin resistance.

It seems that insulin resistance is the key mediator linking type 2 diabetes and hypertension. Reduced insulin signaling in the vascular endothelium reduces nitric oxide availability and increases vascular stiffness. Insulin-resistant adipose tissue releases angiotensinogen, which upregulates the systemic renin-angiotensin-aldosterone system (RAAS) and leads to hypertension through a number of mechanisms, such as sodium retention, vasoconstriction, and sympathetic nervous system activation. Hyperinsulinemia, in response to insulin-resistant glucose disposal pathways, overstimulates growth-signaling pathways that remain insulin sensitive. This may promote vascular remodeling and hypertension.

Hyperinsulinemia promotes renal tubular sodium reabsorption and activates the RAAS. RAAS activation promotes vascular inflammation, worsens insulin sensitivity, and possibly reduces insulin secretion. Some of these effects appear to be T-cell mediated. Thus, there appears to be a vicious cycle of cardiovascular insulin resistance and RAAS activation that leads to hypertension and further hyperinsulinemia. Clinical trial data supports this concept by demonstrating that RAAS blockade with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers reduces the incidence of diabetes.
Table I. Effect of intensive glucose control on cardiovascular events in the major trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Participants</th>
<th>Proportion with hypertension</th>
<th>Effect of intensive glycemic control on cardiovascular end points</th>
<th>Effect in hypertensive vs normotensive subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT(^{25})</td>
<td>1441</td>
<td>0</td>
<td>Combined cardiovascular end point (RRR, 41%, 95% CI, 10%-68%)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>EDIC(^{28})</td>
<td>1394</td>
<td>70% by end of study</td>
<td>First occurrence of nonfatal myocardial infarction, stroke, or death from cardiovascular disease (RRR, 57%, 95% CI, 12%-97%, (P=0.02))</td>
<td>Data not available</td>
</tr>
<tr>
<td>UKPDS(^{27})</td>
<td></td>
<td></td>
<td>Sulfonylurea or insulin</td>
<td>Data not available</td>
</tr>
<tr>
<td></td>
<td>3867</td>
<td>Not given</td>
<td>Stroke (RR, 1.11; 95% CI, 0.81-1.51)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Myocardial infarction (RR, 0.84; 95% CI, 0.71-1.00)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All-cause mortality (RR, 0.94; 95% CI, 0.80-1.10)</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>753</td>
<td>Not given</td>
<td>Metformin</td>
<td>Data not available</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stroke (RR, 0.59; 95% CI, 0.29-1.18)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Myocardial infarction (RR, 0.61; 95% CI, 0.41-0.89)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All-cause mortality (RR, 0.64; 95% CI, 0.45-0.91)</td>
<td></td>
</tr>
<tr>
<td>UKPDS follow-up(^{27})</td>
<td>3277</td>
<td>Not given</td>
<td>Sulfonylurea or insulin</td>
<td>Data not available</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stroke (RR, 0.91; 95% CI, 0.73-1.13)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Myocardial infarction (RR, 0.85; 95% CI, 0.74-0.97)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All-cause mortality (RR, 0.87; 95% CI, 0.79-0.96)</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
<td></td>
<td>Metformin</td>
<td>Data not available</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stroke (RR, 0.80; 95% CI, 0.50-1.27)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Myocardial infarction (RR, 0.67; 95% CI, 0.51-0.89)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All-cause mortality (RR, 0.73, 95% CI, 0.59-0.89)</td>
<td></td>
</tr>
<tr>
<td>ACCORD(^{28})</td>
<td>10251</td>
<td>Not given</td>
<td>Discontinued early due to higher mortality in intensive treatment group</td>
<td>No significant difference(^{29})</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No significant benefit of intensive treatment on the primary composite cardiovascular end point (HR, 0.90, 95% CI, 0.78-1.04; (P=0.16))</td>
<td></td>
</tr>
<tr>
<td>ADVANCE(^{30})</td>
<td>11140</td>
<td>75%</td>
<td>Composite major macrovascular event end point—death from cardiovascular cause, nonfatal myocardial infarction, nonfatal stroke—(HR, 0.94; 95% CI, 0.84-1.06; (P=0.32))</td>
<td>No significant difference</td>
</tr>
<tr>
<td>VADT(^{31})</td>
<td>1791</td>
<td>72%</td>
<td>No significant benefit to occurrence of a first major cardiovascular event—myocardial infarction, stroke, new or worsening heart failure, amputation, death from cardiovascular cause—was seen with intensive therapy (HR, 0.88, 95% CI, 0.74-1.05; (P=0.14))</td>
<td>Data not available</td>
</tr>
<tr>
<td>VADT follow-up(^{12})</td>
<td>1391</td>
<td>73%</td>
<td>Original VADT primary outcome (HR, 0.83; 95% CI, 0.70-0.99; (P=0.04))</td>
<td>Data not available</td>
</tr>
<tr>
<td>PROactive(^{33})</td>
<td>5238</td>
<td>75%</td>
<td>Main secondary end point—all-cause mortality, nonfatal myocardial infarction, and stroke—(HR, 0.84; 95% CI, 0.72-0.98; (P=0.027))</td>
<td>Data not available</td>
</tr>
</tbody>
</table>

Abbreviations: DBP, diastolic blood pressure; RRR, relative risk reduction; SBP, systolic blood pressure.
Coupled with a progressive decline in β-cell function, insulin resistance leads to hyperglycemia and presents with clinical features of type 2 diabetes. Hyperglycemia activates intrarenal RAAS6 and is associated with upregulation of proximal tubule sodium-glucose cotransporter 2 (SGLT2).20 As a result, renal sodium reabsorption is increased, which potentially contributes to hypertension.16

**HYPERGLYCEMIA AND HYPERTENSION INTERACTION: EFFECT ON CARDIOVASCULAR RISK**

Diabetes and hypertension are strong independent risk factors for cardiovascular disease. Diabetes and even supranormal, but prediabetic, blood-glucose levels are associated with elevated cardiovascular risk.21 Adjusting for age, sex, smoking, body mass index, and systolic blood pressure, people with diabetes are at an approximate 2-fold increased risk of coronary heart disease, ischemic and hemorrhagic stroke, and vascular death.21 However, there appears to be no association with cardiovascular risk for glucose levels within the normal range.21 On the other hand, blood pressure is associated with an elevated risk of ischemic and hemorrhagic stroke and myocardial infarction down to at least 115 mm Hg systolic blood pressure and 75 mm Hg diastolic blood pressure, below which there is insufficient evidence to draw conclusions.22

How combinations of risk factors interact to increase cardiovascular risk is still debated and may depend on how risk factors are ascertained, the severity and duration of exposure, and whether the risk factors have common pathophysiological mechanisms. Diabetes has been shown to double the risk of cardiovascular disease at every level of systolic blood pressure.21 Yet, in a meta-analysis of prospective observational studies, involving 1 000 000 participants and 120 000 observed deaths, diabetes had little modifying impact on the relationship between estimated usual blood pressure and vascular mortality.22 In other very large cohorts, participants with a history of diabetes had age- and sex-adjusted hazard ratios for mortality between 1.6 and 1.9. This relationship was attenuated slightly by adjustment for systolic blood pressure.3

Many other epidemiological and clinical studies suggest that hypertension is a powerful modifier of cardiovascular risk in people with diabetes, for example, cardiovascular risk prediction is most powerful when combinations of risk factors are considered rather than single risk factors in isolation.8,23 Therefore, it is not surprising that the Steno-2 trial showed a reduction in cardiovascular events and mortality with multifactorial interventions in people with type 2 diabetes, albuminuria, and who had a high risk for cardiovascular events.24 This intervention focused on lifestyle (eg, diet, exercise, smoking cessation), lipid lowering, blood pressure lowering with RAAS inhibition, intensive glycemic control, and prophylaxis with aspirin. Over nearly 8 years, patients in the intensive-treatment arm had a significantly lower risk of cardiovascular events (HR, 0.47; 95% CI, 0.24-0.73). This reduced risk persisted after 5.5 years of posttrial observation, at which point the absolute risk reduction for mortality in the intensive-therapy group was 20% (P=0.02).7

Despite such an intensive intervention, Steno-2 did not show a normalization of cardiovascular event rates and mortality, suggesting a residual increased risk of type 2 diabetes, even after intensive control of known risks. This residual risk can be partially explained by accumulated damage prior to the trial, incomplete treatment of identified risk factors, and by nontraditional risk factors in diabetes, such as insulin resistance, low-grade inflammation, and autonomic neuropathy. Unlike Steno-2, trials focusing on intensified glycemic control have been less successful in reducing cardiovascular risk.

**Effect of glycemic control on cardiovascular risk in diabetes**

Studies of the effects of intensive glycemic control on diabetes complications have included hypertensive and normotensive patients. However, the prevalence of hypertension in diabetes is high and, where reported, the effects of lowering glucose have been similar in hypertensive and normotensive individuals (Table I).25-33 Therefore, we will mainly discuss aggregate data, giving the percentage of hypertensive subjects and, where available, the effects of the interaction with hypertension on the overall results.

In type 1 diabetes, observational follow-up of the DCCT participants (Diabetes Control and Complications Trial) demonstrated that 6.5 years of intensive therapy in young patients with type 1 diabetes resulted in a 42% relative risk reduction in cardiovascular events (95% CI, 9% to 63%) after 11 years of posttrial follow-up, despite convergence of glycemic control between participants originally assigned to different treatment arms.25 This occurred even though there was no significant reduction in cardiovascular events during the randomized trial. At trial initiation, participants were...
27±7 years old and were without hypertension. By the end of the 18-year follow-up period, nearly 70% of the participants were hypertensive and their mean body mass index increased from 23 to 28 in both groups.26

In type 2 diabetes, a benefit of the earlier decade of intensified glycemic control (with metformin or sulfonylurea/insulin) became evident on rates of myocardial infarction and mortality.27 Once again this occurred despite convergence of glycemic control between groups at the end of the trial. UKPDS trial participants tended to be hypertensive. At the end of the randomized trial, mean systolic blood pressure was around 138±20 mm Hg and mean diastolic blood pressure was 77±10 mm Hg, with no significant between-group differences.27 The DCCT/EDIC (Epidemiology of Diabetes Interventions and Complications) and UKPDS trials document that a clear, but modest, cardiovascular benefit accrues from intensified glycemic control, but only after a significant lag time. By contrast, shorter-term studies on intensified glycemic control in patients with established diabetes and macrovascular disease have not shown cardiovascular benefits.

In the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes), participants were randomized to intensified glycemic control (HbA1c target <6.0%) using a combination of metformin, insulin secretagogues, thiazolidinediones, exenatide, acarbose, and insulin) or to standard therapy (HbA1c target 7.0% to 7.9%).28 Despite protection against worsening retinopathy, proteinuria, and nonfatal myocardial infarction, patients in the intensive arm experienced a 20% increase in mortality leading to early termination of the trial after a median follow-up of 3.4 years. ACCORD enrolled patients with long-standing type 2 diabetes (median 10 years) who were at a high risk for cardiovascular events. The mean age was 62, mean HbA1c was 8.1%, and 35% had experienced a previous cardiovascular event. The prevalence of hypertension was not directly reported, but would have been high given a mean SBP of 136±17 mm Hg and mean diastolic blood pressure of 75±11 mm Hg.

Post-hoc epidemiological analyses of the ACCORD trial suggest that the risks for mortality from intensive treatment included aspirin use, presence of neuropathy, HbA1c >8.5%, and failure to achieve a HbA1c <7%.29

The ADVANCE trial (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) was similarly disappointing in terms of macrovascular benefit from intensive glycemic control.30 Participants had advanced-stage diabetes and a high risk of cardiovascular events. Mean duration of diabetes was 8 years (HbA1c 7.5%). A total of 32% had a history of macrovascular disease, 27% had microalbuminuria, and 75% were on blood-pressure-lowering medication at study commencement. Participants were randomized to intensive control (target HbA1c ≤6.5%, using gliclazide modified release plus other agents, such as insulin, as needed) or standard control (HbA1c targets based on local guidelines). The achieved mean HbA1c was 6.5% in the intensive group and 7.3% in the standard group. Despite a reduction in nephropathy, the intensive group experienced no improvement in major macrovascular events, death from cardiovascular causes, or overall mortality after a median 5-year follow-up. The subsequent 6-year observational follow-up confirmed a lack of macrovascular or mortality benefit for the period of intensive control.23

The VADT trial (Veterans Affairs Diabetes Trial) confirmed the results of ACCORD and ADVANCE with respect to the lack of cardiovascular benefit after a short duration of intensified glycemic control (achieved HbA1c 6.9% vs 8.4% using rosiglitazone, metformin, or glimepiride, and insulin, as required) in advanced type 2 diabetes.31 A total of 72% of participants had hypertension at baseline and 40% had already suffered a cardiovascular event. Observational follow-up of VADT for an additional 5 years after the median 5.6-year trial did show a significant reduction in cardiovascular events (HR, 0.83; 95% CI, 0.70-0.99) with no cardiovascular mortality or all-cause mortality benefit.32

In the PROactive trial (PROspective pioglitAzone Clinical Trial In macrovascular Events),33 5238 patients with type 2 diabetes and macrovascular disease, 75% of whom had hypertension, were randomized to pioglitazone or placebo added to preexisting glucose-lowering drugs. The study was primarily designed to examine the effects of pioglitazone, rather than intensive glycemic control, on macrovascular events, but HbA1c was reduced in the pioglitazone group (~0.8% vs placebo ~0.3%, P<0.0001). After almost 3 years, the composite end point—all-cause mortality, nonfatal myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle—was not reduced. However, there was a 16% reduction in the main secondary end point—composite of all-cause mortality, nonfatal myocardial infarction, and stroke. Pioglitazone has affects in addition to lowering glucose, such as lowering blood pressure and other metabolic effects that are beneficial to the cardiovascular system, including improving triglyceride lev-
els. Therefore, the relative effect of good glycemic control vs direct metabolic benefit is difficult to quantify.

In acute myocardial infarction, trials of intensive glucose lowering with insulin have been inconclusive with respect to mortality benefit. A 20-year observational follow-up of the DIGAMI I trial (Diabetes mellitus Insulin Glucose infusion in Acute Myocardial Infarction) showed that hyperglycemic patients randomized to intensified insulin-based glycemic control for at least 3 months after an acute myocardial infarction continued to have a survival advantage (2.3 years) compared with those randomized to standard management. Nearly 90% of trial participants were hypertensive at randomization. By the end of the nearly complete 20-year (22±7.3 years) follow-up, 89% and 91% of the patients in the intensive and standard groups, respectively, had died. However, no data on treatment regimen or glycemic control after the first year of follow-up are available, so it is unknown how much of the benefit was due to the in-trial treatment and how much was due to subsequent out-of-trial differences in therapy. The focus in DIGAMI I was on insulin, and it is not possible to determine how much of the mortality benefit was due to lowering glucose and how much can be attributed to insulin itself. The patients in DIGAMI I were also undertreated with statins and angiotensin-converting enzyme inhibitors by current day standards.

Taken together, the results of the major randomized trials of intensive glycemic control show definite cardiovascular benefits of lowering glucose, but they are modest, particularly when compared with results of trials on blood pressure control, lipid control, and a multifactorial intervention. These benefits of intensive glycemic control come with risks in certain populations and they take a long time to become evident. Most of the trials were performed in populations at high cardiovascular risk with a high prevalence of hypertension. Glucose-lowering regimens varied widely. It seems that patients early in the course of diabetes and with longer life expectancies are likely to benefit more from intensifying glycemic control, whereas older people, particularly those with long-standing diabetes, a high burden of other risk factors, and established macrovascular complications, are less likely to benefit. Some have suggested widespread overtreatment in elderly adults; however, care needs to be taken to prevent under treatment in those who stand to benefit.

**BENEFIT OF GLUCOSE CONTROL IN PEOPLE WITH PREDIABETES AND HIGH CARDIOVASCULAR RISK**

In people with nondiabetic HbA1c elevations, there is a wide range of absolute cardiovascular risk determined by the burden of other risk factors. Little evidence is available to show that intensifying glycemic control in very early or prediabetes is beneficial.

Early experimental data in metformin-treated type 2 diabetic patients suggested that there could be a beneficial effect of insulin glargine on endothelial function and raised hopes of a potential cardiovascular benefit. The ORIGIN trial (Outcome Reduction with an Initial Glargine Intervention) investigated the effects of glargine on this patient population. ORIGIN enrolled people aged 50 or older with prediabetes or early type 2 diabetes. Nearly 80% were hypertensive at baseline. Participants were randomized to usual care or to the addition of nocturnal insulin glargine targeting a fasting blood glucose level in the normal range (<5.4 mmol/L). Over 12 000 participants were followed up over a median of 6.2 years, at which point, no significant benefit of the intervention on cardiovascular events was observed.

The NAVIGATOR trial (Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research) examined a similar population with impaired glucose tolerance and high cardiovascular risk. The trial included over 9000 participants, nearly 80% were hypertensive. Participants were randomized to nateglinide or placebo and valsartan or placebo in a 2 by 2 factorial design. After 5 years of follow-up, no significant improvement in cardiovascular outcomes with glucose-lowering therapy was observed. Although fasting plasma glucose levels were lower in the nateglinide group, 2-hour plasma glucose levels after a glucose challenge test were in fact higher in the nateglinide group. This suggests that the study might have been undermined by an insufficient difference in achieved glycemia.

While epidemiological evidence suggests that nondiabetic hyperglycemia is a cardiovascular risk factor, interventions to normalize glycemia have not translated into a beneficial effect on hard cardiovascular end points. This could be because 6 years (as in ORIGIN) is not long enough to see a cardiovascular benefit and because mild, short-duration hyperglycemia is overwhelmed by other risk factors. It is also possibly because hyperglycemia is a marker of a more complex set of adverse metabolic derangements caused by ectopic fat accumulation and insulin resistance, and these
derangements are not addressed by approaches purely focused on normalizing glycemia.

**DOES TREATING DIABETES IMPROVE HYPERTENSION?**

Certain therapies may have benefits beyond lowering glucose. While diabetes is defined solely by glycemia, this measurable clinical feature is the result of an array of metabolic disturbances. Underpinning the pathophysiology of type 2 diabetes is insulin resistance, which also contributes to hypertension and other cardiovascular risk factors. It is important to consider therapy for diabetes beyond the paradigm of glycemic control. Thus, treatment aimed at reducing positive caloric balance, ectopic fat accumulation, and insulin resistance are likely to be beneficial.

Obesity is the most important confounding factor in the relationship between type 2 diabetes and hypertension, as it is causally linked to both conditions. Approaches to manage hyperglycemia through weight reduction are likely to be useful in treating hypertension. For example, caloric restriction reduces ectopic fat accumulation, blood pressure, and glycemia, which reverses some of the hepatic insulin resistance and β-cell dysfunction associated with diabetes. Type 2 diabetes remission can also be achieved by bariatric surgery, particularly if this is performed early, but there is little high-quality evidence showing an effect of bariatric surgery on pressure or cardiovascular risk. Currently, studies are limited by a short duration of follow-up after surgery.

The effect of insulin on blood pressure is complex. Insulin activates the sympathetic nervous system, exerts an antinatriuretic effect in the renal tubule, and contributes to vascular remodeling via growth factor–signaling pathways. However, evidence shows that hyperinsulinemia does not cause hypertension, as these effects are balanced by insulin-induced vasodilatation. Interestingly, patients with insulinoma did not have elevated blood pressure, and resection of their tumors was not associated with any reduction in blood pressure. However, the situation in insulin-resistant individuals with diabetes may be different.

**Blood pressure effects of hypoglycemic agents**

The thiazolidinediones as well as two new pharmacologic categories of hypoglycemic medication have receptor-mediated and pleotropic effects that contribute to lowering blood pressure.

**Thiazolidinediones**

In the PROactive trial, pioglitazone significantly lowered blood pressure by –3/–2 mm Hg compared with the control (0/–1 mm Hg), although this study was not designed to assess blood pressure. Blood pressure lowering has also been consistently shown with rosiglitazone, suggesting a class effect with thiazolidinediones. The mechanism for blood pressure lowering is likely due to a range of cardiovascular effects mediated by enhanced insulin sensitivity, and the result of agonism of the peroxisome proliferator–activator receptor γ (PPAR-γ). Despite a suggested reduction in cardiovascular events in the PROactive study, concerns about increases in myocardial infarction with rosiglitazone and bladder cancer with pioglitazone (neither of which has been confirmed), weight gain, and increased heart failure events and fractures has limited widespread use of these agents.

**Incretin-based drugs**

Incretin-based therapy for diabetes comprises two drug classes: dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists. These classes have overlapping mechanisms of action resulting in increased signaling via the GLP-1 receptor, which leads to inhibition of gastric emptying, enhanced glucose-stimulated insulin secretion, inhibited glucagon secretion, and increased satiety. DPP-4 inhibitors block the endogenous enzyme that degrades human gut-derived GLP-1. GLP-1 receptor agonists are analogues of human GLP-1 that are resistant to proteolytic degradation by DPP-4.

A meta-analysis of the LEAD randomized trials (Liraglutide Effect and Action in Diabetes) demonstrated a small reduction in blood pressure with this GLP-1 receptor agonist. Similar observations were made in a meta-analysis of trials of both liraglutide and exenatide. However, there are difficulties in drawing blood pressure conclusions from these trials because they were designed primarily to measure glycemia. Prospective trials aimed to assess blood pressure reduction with GLP-1 receptor agonists (eg, BOLT, Liratime) have not yet been reported. The magnitude of this blood pressure lowering with GLP-1 receptor agonists appears to be about 2 to 6 mm Hg for systolic blood pressure with lower reductions in diastolic blood pressure (Table II).

This effect appears to be independent of lowering glucose and occurs before any weight loss induced by GLP-1 receptor agonists.

GLP-1 receptor agonists exert cardiovascular effects independent of the GLP-1 receptor. GLP-1 receptor agonists seem to lower total periph-
Diabetes and hypertension: is treating hyperglycemia useful? - Russell and O'Brien

...promote natriuresis. DPP-4 is suggesting that DPP-4 inhibitors such as B-type natriuretic peptide, degrades a variety of other peptides, DPP-4 inhibitors. Of note, DPP-4 increment has been reported with assessing blood pressure. No heart rate trials have not been designed to small reduction. Once again, these neutral effect and some observing a lowering with some observing a tent with respect to blood pressure DPP-4 inhibitor studies are inconsis-
tent with respect to blood pressure lowering with some observing a neutral effect and some observing a small reduction. Once again, these trials have not been designed to assess blood pressure. No heart rate increment has been reported with DPP-4 inhibitors. Of note, DPP-4 degrades a variety of other peptides, such as B-type natriuretic peptide, suggesting that DPP-4 inhibitors may promote natriuresis. DPP-4 is expressed in CD4+ and CD8+ T cells and there is evidence that, via these receptors, DPP-4 inhibitors may improve the chronic inflammation that contributes to insulin resistance.

Some data from cardiovascular safety trials for some DPP-4 inhibitors have been reported. The SAVOR-TIMI, EXAMINE, and TECOS trials were designed to demonstrate the cardiovascular safety of saxagliptin, alogliptin, and sitagliptin, respectively, for regulatory authorities. While confirming safety, these trials did not show cardiovascular benefit, albeit with a short-term follow-up. Notably, heart failure admissions unexpectedly increased with saxagliptin in the SAVOR-TIMI trial, which is disappointing because preclinical data suggested that DPP-4 inhibitors might be cardio-protective.

Sodium-glucose cotransporter 2 inhibitors

The vast majority of filtered glucose is reabsorbed in the proximal tubule. This is mediated by two tubular apical cell membrane transporters: SGLT1 and SGLT2. Both are sodium-glucose cotransporters. SGLT1 reabsorbs glucose and sodium molecules in a 1:2 ratio and SGLT2 re-absorbs glucose and sodium molecules in a 1:1 ratio. In diabetes, there is a paradoxical increase in SGLT2 expression, and therefore, glucose reabsorption capacity. SGLT2 inhibition lowers the plasma glucose threshold for glucose to spill into the urine by about 2 mmol/L, thus acting as an insulin-independent mechanism for lowering plasma glucose and eliminating calories. As they are dependent on functioning nephrons to excrete glucose, SGLT2 inhibitors are ineffective in chronic kidney disease stages 3-5.

Evidence suggests that enhanced sodium reabsorption via SGLT2 is important in the development of hypertension. This effect is enhanced by both insulin and angiotensin II, suggesting that it might be particularly important in the development of hypertension in the context of obesity and insulin resistance. Although SGLT2 inhibitors block proximal sodium reabsorption, they have a minimal net natriuretic effect due to upregulation of compensatory sodium resorptive pathways, including SGLT1. Nevertheless, SGLT2 inhibitors do lower blood pressure, probably due to their osmotic diuretic effect.

The magnitude of this effect was a 3 mm Hg decrease in DBP.

Table II. Effect of newer glucose-lowering agents on blood pressure and cardiovascular events.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Reported effects on blood pressure</th>
<th>Effect on cardiovascular events</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 receptor agonist</td>
<td>2-6 mm Hg decrease in SBP</td>
<td>Outcome studies yet to report</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>0-2 mm Hg decrease in SBP</td>
<td>Cardiovascular safety, but no benefit seen in short-term cardiovascular safety trials of sitagliptin and alogliptin. Saxagliptin may increase heart failure admissions.</td>
</tr>
<tr>
<td>SGLT2 inhibitor</td>
<td>3 mm Hg decrease in SBP</td>
<td>Composite cardiovascular event primary end point of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke (HR, 0.86; 95% CI, 0.74-0.99, P=0.04).</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>3 mm Hg decrease in SBP and 2 mm Hg decrease in DBP</td>
<td>Main secondary composite outcome of all-cause mortality, nonfatal myocardial infarction, and stroke with pioglitazone (HR, 0.84; 95% CI, 0.72-0.98, P=0.027).</td>
</tr>
</tbody>
</table>

Abbreviations: DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter 2.
decrease in systolic blood pressure after 1 year of treatment with dapagliflozin.51

Long-term cardiovascular safety trials of SGLT2 inhibitors are being conducted, but few data have been reported. The EMPA-REG OUTCOME trial (EMPAgliflozin Cardiovascular OUTCOME Event Trial in Type 2 Diabetes Mellitus Patients) is the first trial to report their findings.52 This industry-funded study enrolled 7020 patients with type 2 diabetes and a previous cardiovascular event. HbA1c levels were between 7% and 10% and participants with chronic kidney disease stages 4 or 5 were excluded. A total of 39% of participants were hypertensive at the time of randomization, 95% were on antihypertensive therapy, and approximately 75% were taking metformin at baseline. Glycemic targets were in agreement with local guidelines and other therapies were added as required. Median follow-up was 3 years. The primary composite end point was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The empagliflozin group had a hazard ratio of 0.86 for this outcome compared with placebo (95% CI, 0.74-0.99; \( P = 0.04 \) for superiority) (Figure 1). Hospitalization for heart failure was also lower (HR, 0.65; 95% CI, 0.50-0.85; \( P = 0.02 \)). Outcome curves for the primary end point diverged within a few months and occurred despite only a minor improvement in glycemic control (0.25%-0.5% difference in HbA1c) in the empagliflozin group. The use of insulin and sulfonylureas was higher in the placebo group than in the empagliflozin group, although there was no excess hypoglycemia in this group to explain any difference in mortality. The study was not designed to assess the mechanisms for this reported cardiovascular benefit.

CONCLUSION

The majority of major randomized trials of intensive glycemic control contain high proportions of hypertensive patients. These trials show modest cardiovascular benefits of lowering glucose that become apparent only after prolonged follow-up and that the proportional benefits are similar in hypertensive and normotensive individuals. People with diabetes and hypertension, who are early in the course of diabetes and have a longer life expectancy, are likely to benefit more from an intensified glycemic control. Conversely, older people with a high burden of other risk factors and established macrovascular complications are less likely to benefit. Newer agents for the control of blood glucose, such as DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors have small beneficial effects on blood pressure that are secondary to a number of complex mechanisms. The SGLT2 inhibitor class looks particularly promising, with a recent, large, randomized study showing a significant cardiovascular risk reduction. Further cardiovascular endpoint studies with these classes and the other new drug classes, which are due to report their results over the next few years, will provide clinicians with important therapeutic guidance.
REFERENCES


Many effective therapeutic agents were initially discovered by physicians who also had strong scientific skills. The classic European example is William Withering who practiced medicine in the country town of Stafford (Staffordshire), UK. Withering created a large herbarium at his home, collecting plants from all over England, which he subsequently described in his book *A Botanical Arrangement of All the Vegetables Naturally Growing in Great Britain*.¹ This was first published in 1776 and it ran until 1796 with a total of four editions.

A patient told Withering about a novel treatment for dropsy (heart failure) that was made from herbs. Withering studied this carefully over 10 years, which culminated in the publication titled *An Account of Foxglove and Some of Its Medical Uses: With Practical Remarks on Dropsy and Other Diseases* (Figure 1).² His isolation of digitalis and its evaluation remains a classic example of careful clinical research,³ and it is a characteristic example of the discovery and medical application of a natural product.

Historically, natural products have had widespread use in medical treatment in many countries and cultures, especially in China and other Asian countries. This essay will focus on Chinese herbalism and the discovery of the effective antimalarial drug artemisinin, which was isolated by Professor Tu Youyou (Figure 2, page 148) from *Artemisia annua*, the annual wormwood herb (Figure 3, page 148). The herbalist tradition in China has a long history, as exemplified by the book titled *The Handbook of Prescriptions for Emergency Treatments* written in 340 AD by Ge Hong.

An even more ancient herbal handbook is the Egyptian *Ebers Papyrus*, a book that is >3000 years old, and in which garlic extract was recommended for cardiovascular diseases. In China, a handbook of herbal remedies (*Pun-tsao*) was published in the sixteenth century.

The Greek philosopher Hippocrates recommended herbal treatments for diseases. He was also the founder of the Vitalist philosophy that claimed there was an intrinsic “force” in living organisms, which he called physis. He believed that a physician (named after physis) should focus on the patient’s nutritional status and devise ways of increasing the excretion of materials.⁴ This theory influenced several physicians, even in the twentieth century; for example, Dr Edward Bach, who was practicing in London in 1920, subsequently changed his approach to therapy by developing flower essences designed to treat the cause rather than the symptoms of diseases.⁵ His practice was markedly influenced by his predecessor Samuel Hahnemann, a German physician and the father of homeopa-
thy in the early nineteenth century. Thus, it is clear that the herbalist tradition of treatment emerged independently in several different national cultures.

One such example is the remarkable work of Tu Youyou. Tu Youyou qualified in medicine in Peking University, but subsequently trained in traditional Chinese medicine. Seemingly, by chance, she was requested by the then Chinese Premier Zhou Enlai to try to identify a new drug to treat malaria. The rationale for this high-level request was primarily a political one, because, in 1967, the leader of North Vietnam, Ho Chi Minh, was increasingly concerned that his troops, who were fighting the US–South Vietnamese war, were dying from chloroquine-resistant malaria, which is caused by the parasite Plasmodium sp. (Figure 4).

Ho Chi Minh sought help from Zhou Enlai to find an antimalarial agent to replace chloroquine. Zhou Enlai created a research priority that was termed project 253, which was designed to identify a better antimalarial agent. He asked Tu Youyou to lead the project because she was trained in both pharmaceutical sciences and traditional Chinese medicine.

Tu Youyou initially screened Chinese herbs based on consultations with expert Chinese herbalists. Her scientific notebook listed 640 potential herbal sources of antimalarial agents, which was based on the examination of 2000 traditional Chinese herbal recipes. Her group subsequently tested 350 herbal extracts in mice infected experimentally with Plasmodium berghei.

Positive results were observed with the modified extracts from the Chinese herb Artemisia annua and its close analogues A apacea and A lancea. As often happens with exploratory herbal extracts, the extraction process can markedly influence the evaluation of its efficacy. In the case of the plant Qing Hao (wormwood), which had been used in ancient times to treat non-specific fevers, the eminent Chinese physician Ge Hong recommended soaking fresh plants in cold water, wringing the plants out by hand, and drinking the extracted juice. Comparative studies subsequently showed that only the extract from A annua had antimalarial properties. Furthermore, the method of extraction influenced the efficacy; for example, the aqueous extraction of the whole plant was shown to be more effective than either
drying the herb or making an herbal tea. The use of appropriate extraction techniques is of great practical importance because it is possible to grow the *Artemisia* plant in countries with low health incomes (ie, in countries where people either do not have access to medical care or cannot afford effective drugs) and a high incidence of malaria. Juice obtained by pounding the herb (ie, grinding the herb using a mortar and pestle) was the most effective against malaria.9,10 By 1971, Tu Youyou identified the most potent plant extract using an aqueous solution (pH 7.0).

Over the next 5 years, the active principle artemisinin (Figures 5 and 6) was eventually identified based on the initial synthesis of the analogue dihydroartemisinin, which had been synthesized by Tu Youyou and subsequently shown to have antimalarial properties.11

Subsequently, Tu Youyou evaluated the efficacy of artemisinin in malaria-infected mice and she evaluated its tolerability on herself. Thereafter, the Chinese pharmaceutical companies Kimming and Guiling brought out artemisinin analogues to the Chinese as novel antimalarial drugs. The utility of artemisinin was kept quiet in China until December 1979 when an English language report was published,12 which was followed by the publication of a comparative trial in the *Lancet* in 1982.13 The achievements of Tu Youyou were finally acknowledged when she was awarded the Lasker Prize for Clinical Medical Research in 2011 and the Nobel Prize in October 2015 for Physiology and Medicine. Although it took many years of hard work and study, the World Health Organization recommends artemisinin as a first-choice antimalarial treatment provided that other antimalarial agents are coadministered in order to reduce the possibility of drug resistance arising from monotherapy (ie, artemisinin-combination therapies).14

Tu Youyou’s extraordinary achievements were made possible by ancient knowledge hidden in scrolls and passed down through word of mouth, by perseverance, and by serendipity. Not only has the combination of Chinese herbal and pharmacological sciences contributed to advancements in malaria treatment, but this combination also has a strong role and influence in cardiovascular research in China, which has recently been reinforced in a review article by Gao et al in 2015.15

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Cardiovascular research is thriving in China. 
Diabetes and Hypertension

Summaries of Ten Seminal Papers

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Milan - ITALY (e-mail: guido.grassi@unimib.it)


1. Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial
   J. Stamler and others. Diabetes Care. 1993

2. Suppression of insulin-induced sympathetic activation and vasodilation by dexamethasone in humans
   U. Scherrer and others. Circulation. 1993

3. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38
   UK Prospective Diabetes Study Group. BMJ. 1998

4. Systolic and diastolic blood pressure control in antihypertensive drug trials

5. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis
   J. P. Casas and others. Lancet. 2005

6. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis
   W. J. Elliot and P. M. Meyer. Lancet. 2007

7. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial)
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8. Effects of intensive blood pressure control in type 2 diabetes mellitus

9. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes

10. Usual blood pressure and risk of new-onset diabetes: evidence from 4.1 million adults and a meta-analysis of prospective studies
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Selection of seminal papers by Guido Grassi, MD
Clinica Medica - Ospedale San Gerardo dei Tintori - Monza - University of Milano-Bicocca - Milan - Italy

Highlights of the years by Sherri Smith, PhD
Publications office
Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial

J. Stamler, O. Vaccaro, J. D. Neaton, D. Wentworth

*Diabetes Care.* 1993;16:434-444

The Multiple Risk Factor Intervention Trial, a randomized primary prevention study, investigated the effects of a multifactorial intervention program on mortality from coronary artery disease in a large number of high-risk patients. In addition, the possible predictors of cardiovascular disease mortality were assessed in both the general population and a consistent group of patients treated for diabetes mellitus. The trial was conducted in more than 5000 diabetic patients who were monitored over a long follow-up period (on average 12 years), and the data were compared with data from a group of about 340,000 nondiabetic subjects. The results provide strong evidence on the very high cardiovascular risk profile displayed by diabetic patients who showed a 3- to 4-times higher incidence of fatal cardiovascular events than did age-matched nondiabetic subjects. However, in this paper by Stamler et al, many other findings need to be briefly discussed, including the evidence that the detection of other cardiovascular risk factors in diabetic patients, such as cigarette smoking, elevated serum cholesterol levels, and augmented systolic blood pressure values, exponentially increase the overall risk profile of the patient.

A number of new findings since the publication of this paper have been discovered in relation to the association between hypertension and diabetes. From an epidemiological point of view, many recent studies, such as UKPDS (UK Prospective Diabetes Study) and DECODE (Diabetes Epidemiology COllaborative analysis of Diagnostic criteria in Europe), have shown that, when blood pressure values are elevated in diabetic patients, there is a linear relationship between the risk of macrovascular disease (coronary heart disease, stroke, and peripheral artery disease) and systolic blood pressure values. The evidence collected over the years suggests that the increased risk of macrovascular complications is likely due to not only general hemodynamic overload, but also, more specifically, to elevated shear stress alterations induced by the increased blood pressure values, resulting in increased arterial stiffness. Further information on the epidemiological characteristics between cardiovascular risk and diabetes mellitus was obtained after analyzing the data collected in the PAMELA study (Pressioni Arteriose Monitorate E Loro Associazioni), which was initially performed about 23 years ago in a general population in northern Italy. For the first time, the results of the study clearly documented that the prevalence of diabetes, impaired fasting blood glucose, and hypercholesterolemia is not only related to clinic blood pressure values, but also to home and ambulatory blood pressure values throughout a 24-hour period. Furthermore, absolute blood pressure load and blood pressure oscillations through a single day or between days appear to be increased in diabetic hypertensive patients, presumably because the blood pressure regulation by arterial baroreceptors is markedly compromised in these patients. The increased blood pressure variability detectable in these patients may represent a further factor adversely affecting cardiovascular prognosis.

Czechoslovakia separates into the Czech Republic and Slovakia in the so-called Velvet Divorce; the first Life Ball, a large public charity event for HIV/AIDS in Europe, takes place in Vienna, Austria; and electrochemist Faiza Al-Kharafi is appointed the first female president of Kuwait University.
Suppression of insulin-induced sympathetic activation and vasodilation by dexamethasone in humans

U. Scherrer, P. Vollenweider, D. Randin, E. Jéquier, P. Nicod, L. Tappy

* Circulation. 1993;88:388-394

Scherrer et al provide one of the first pieces of evidence in humans concerning the sympathoexcitatory effects of insulin. The impact of euglycemic hyperinsulinemia (obtained via the euglycemic clamp technique) on directly recorded muscle sympathetic nerve traffic (evaluated via microneurography) in healthy lean subjects was examined. An additional study objective was to assess the mechanisms responsible for the adrenergic effects of insulin, particularly on the role of glucocorticoids and the corticotropin-releasing hormone secreted by the hypothalamus.

The study can be summarized by two main findings. First, acute hyperinsulinemia triggers a marked sympathoexcitation, which is coupled with a remarkable vasodilation effect due to the direct effects of the hormone on vascular tone. This vasodilation explains why systemic blood pressure values were almost completely unaffected by the intervention, despite the marked increase in peripheral sympathetic vasoconstrictor tone. Second, acute oral administration of dexamethasone (1.0 mg/os at midnight) suppressed both the sympathoexcitation and the concomitant insulin-induced vasodilation, suggesting a participation of corticotropin-releasing hormone and other peptides (e.g., neuropeptide Y), which are secreted by the hypothalamus (and blocked by dexamethasone), on the neural and vascular effects of insulin.

The pioneering study by Scherrer et al was followed by a number of other investigations exploring whether and to what extent the acute effects of insulin and the hypothalamus-hypophysis axis blockade are a laboratory finding or relevant in clinical conditions characterized by chronic sympathetic overactivity, such as obesity and hypertension. The results of such studies provided evidence that the marked adrenergic overdrive characterizing human obesity is attenuated by treatment with dexamethasone, thereby indicating the participation of the hypothalamic-hypophysis axis in the "chronic" activation of the sympathetic nervous system that has been described for obesity. In addition, evidence shows that the effects of insulin on the sympathetic and vascular targets are attenuated, if not abolished, in obese individuals. Despite the intriguing information provided in the study by Scherrer et al, several aspects related to the relationship between insulin and the sympathetic nervous system remain undefined. The most important one is the so-called chicken and egg question, namely whether the sympathetic overdrive could be regarded as the cause or rather as the effect of hyperinsulinemia. The question has important clinical and therapeutic implications, considering that the exact definition of the sequence of events may allow for properly targeting the therapeutic intervention toward the original pathophysiological factor responsible for the phenomenon. Unfortunately, we still do not have the definitive answer to this question. However, indirect evidence taken from longitudinal studies has shown that sympathetic activation may indeed precede the occurrence of insulin resistance by several years, and, as a result, this activation may predict the development of insulin resistance. If confirmed in large-scale population studies, this finding may imply that therapeutic modulation of sympathetic neural drive may help guarantee a eumetabolic state, thus preventing the development of insulin resistance. This development may have obvious favorable consequences, considering that both hyperinsulinemia and the related insulin resistance have detrimental effects on the cardiovascular risk profile.

1993

Two-hundred people die when a floating pagoda sinks during the Bocaue River Festival in Bocaue, Bulacan; Bence Biczó, a Hungarian swimmer and Youth Olympic Games gold medalist, is born; and Rudolf Khametovich Nureyev, a Soviet ballet dancer, dies at age 54 from cardiac complications
Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38

UK Prospective Diabetes Study Group

BMJ. 1998;317:703-713

The UKPDS 38 study (UK Prospective Diabetes Study) assessed the effects of a strict blood pressure reduction on fatal and nonfatal cardiovascular events, retinal alterations, and microalbuminuria. Of the 1148 hypertensive patients with diabetes mellitus recruited by 20 UK clinical centers, 758 were allocated to the group with a strict blood pressure reduction (144/82 mm Hg), while 390 were allocated to the group with a less strict reduction (154/87 mm Hg). Pharmacological treatment included the angiotensin-converting enzyme (ACE) inhibitor captopril plus a β-blocker (atenolol). Follow-up was prolonged for an average of 8.4 years.

Strictly controlling blood pressure results in a reduction in stroke (–44%, \( P=0.013 \)), myocardial infarction (–21%, ns), any diabetes-related end point (–24%, \( P=0.0046 \)), and diabetes-related death (–32%, \( P=0.019 \)). In addition, the group of patients assigned to strict blood pressure control showed a 37% reduction in the risk of microvascular disease compared with the less strict group (\( P=0.0092 \)). The difference between groups was also significant for microalbuminuria (–29%, \( P=0.009 \)), but not for overt proteinuria. The UKPDS study documents that progression to renal events and fatal or nonfatal cardiovascular outcomes in diabetic hypertensive patients can be favorably affected by antihypertensive drug treatment capable of achieving a tight reduction in blood pressure values.

Therefore, no doubt exists that an effective and strict blood pressure control should benefit diabetic hypertensive patients. In recent years, however, a debate started regarding the question of how low blood pressure should be in order to maximize the renal and cardiovascular protective effects of the blood pressure–lowering intervention under this critical circumstance. The main debate is centered on whether the target should be similar to that set for the general hypertensive population (ie, 140/90 mm Hg) or even lower. Recent intervention trials and meta-analyses show that an aggressive blood pressure reduction slows the progression of renal dysfunction in diabetic nephropathic patients. The slowest progression rate for renal dysfunction occurs in patients who achieve systolic values lower than 120 mm Hg with antihypertensive treatment. However, other studies have failed to show additional benefits of lowering blood pressure well below 140/90 mm Hg, which is also supported by the results of an intensive blood pressure–control study that will be discussed in a later summary (page 159).

In addition, guidelines do not have univocal positions. Guidelines on prevention, detection, evaluation, and treatment of high blood pressure recommend that blood pressure be reduced to 130/80 mm Hg in patients with diabetic or nondiabetic nephropathy and is the recommendation of the Joint National Committee, the American Diabetic Association, and the European Association for the Study of Diabetes. The new American hypertension guidelines, which are no longer supported by the Joint National Committee, do not consider that the target blood pressure for these patients should be lower than 140/90 mm Hg, ie, similar to the one recommended for all hypertensive patients up to 60 years of age. The same target has been adopted by the hypertension guidelines of the European Society of Hypertension and the European Society of Cardiology, which also provide an intermediate recommendation for patients with pronounced proteinuria where the possibility of lowering blood pressure below 130/80 mm Hg is not excluded, if patients are closely monitored and renal function frequently tested.

The first computer-assisted bone segment navigation is performed at the University of Regensburg, Germany; the first euro coins are minted in Pessac, France; and Hugo Chávez, politician and former member of the Venezuelan military, is elected President of Venezuela.
Grassi and Grassi comprehensively examined the main features of blood pressure control in 10 major intervention trials that investigated the effects of different drug treatments (and treatment combinations) on cardiovascular morbidity and mortality. The results provided evidence that while diastolic blood pressure values are almost invariably reduced below 90 mm Hg in all examined trials, no more than 20% to 25% of the systolic blood pressure values are controlled below 140 mm Hg. The situation is even worse in high-risk diabetic patients where a target systolic blood pressure value below 130 mm Hg is obtained in very few patients.

The data examined in the paper, which have been more recently expanded and confirmed by taking into account the results of the most recently published clinical trials in the field of antihypertensive treatment, confirm the difficulty of achieving full blood pressure control in the treatment of hypertension. They also emphasized that this difficulty particularly refers to systolic blood pressure, which is a hemodynamic variable that is much more relevant than diastolic blood pressure in terms of cardiovascular risk.

Although recent epidemiological surveys tell us that blood pressure control in treated hypertensive patients has been remarkably improved in the past few years, the situation is still unsatisfactory in several European countries as well as a few outside of Europe. Data collected by Italian investigators analyzing all antihypertensive drug prescriptions made by doctors within 4 years in northern Italy (Lombardy) provided evidence that the lack of blood pressure control frequently depends on poor patient and doctor compliance with the prescribed drugs. In current clinical practice, doctors do not follow-up a first antihypertensive drug prescription with a second prescription in 40% of cases. In addition, drug treatment is changed frequently and quickly by either doctors or patients without waiting for a proper amount of time to achieve the full effects of the antihypertensive drugs. The data related to poor blood pressure control detected in clinical practice emphasizes the importance of combination drug treatment as the first therapeutic approach to hypertension. However, in the above-mentioned survey, the evidence shows that combination drug treatment is still not frequently used in clinical practice, particularly in the case of newly diagnosed hypertensive patients. In other words, combination drug treatment is rarely used as a first-step approach, despite the recommendations included in recent European and American guidelines on hypertension diagnosis and treatment.

Improvement in blood pressure control (particularly systolic blood pressure) can only be achieved by more frequently using combination drug treatment. This conclusion is supported by several interventional trials and clinical studies showing that better patient adherence with the therapeutic intervention increases when using combination treatment. One advantage of combination drug treatment is the use of low doses of the drugs; therefore, since side effects are directly related to the daily dosage of the drug(s) administered, the use of combination treatment at low dosages represents one of the recommended approaches to improve patient compliance.

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Astrid Anna Emilia Lindgren, a Swedish writer of children’s fiction, picture books, and screenplays, dies at age 94; NASA’s 2001 Mars Odyssey space probe begins to map the surface of Mars using its thermal emission imaging system; and a Legionnaires’ disease outbreak in Barrow-in-Furness becomes the worst in UK history and fifth worst worldwide.
Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis

J. P. Casas, W. Chua, S. Loukogeorgakis, P. Vallance, L. Smeth, A. D. Hingorani, R. J. MacAllister

Lancet. 2005;366:2026-2033

Casas et al’s meta-analysis addresses the clinically relevant issue of whether and to what extent angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers have more favorable effects vs other drug treatments on renal disease progression in patients with or without diabetes mellitus. The results of the meta-analysis, which included 13 interventional studies, provide evidence that ACE inhibitors and angiotensin II receptor blockers are more effective in reducing the incidence of both end-stage renal disease and doubling creatinine values. However, the results also suggest that the nephroprotective effects of the drugs acting on the renin-angiotensin system are closely dependent on the blood pressure reduction per se, thus implying that the difference between drug classes virtually disappears once the blood pressure is controlled.

As is true for all meta-analyses, the investigation by Casas et al has its strong and weak points. The strong point is represented by the confirmation, which is based on large clinical datasets, that pharmacological blockade of the renin-angiotensin system is superior to other therapeutic approaches regarding nephroprotective effects. This has been recognized by the most recent guidelines, which strongly recommend ACE inhibitors and angiotensin II receptor blockers as an initial regimen of choice to protect the kidney. A large meta-analysis by Jafar et al (Ann Intern Med. 2003;139:244-252) confirmed these findings in non-diabetic patients and showed that ACE inhibition was associated with an overall 30% to 40% risk reduction for doubling of serum creatinine or end-stage renal disease, with the greater benefits being detectable in patients with higher proteinuria. This result has been confirmed by findings reported in other studies, which suggest that the greater nephroprotective effects of drugs acting on the renin-angiotensin system are mediated by blood pressure-independent mechanisms. How can this conclusion be reconciled with the results of Casas et al’s meta-analysis, which only attributes the blood pressure-lowering effects of ACE inhibitors and angiotensin II receptor antagonists to greater nephroprotection?

Casas et al’s meta-analysis has been repeatedly criticized because it aggregated results of heterogeneous studies, particularly the data collected in the ALLHAT study (Antihypertensive Lipid Lowering intervention to prevent Heart Attack Trial), which did not define renal protection as a primary end point or provide data on proteinuria. However, a large amount of experimental and clinical data shows that drugs acting on the renin-angiotensin system protect the kidney not only through their blood pressure-lowering effects, but also, and to a consistent degree, via their so-called ancillary properties, which include direct antiproteinuric effects, action on the glomerular cell wall and fibrosis, vascular protective effects, which are mediated by a favorable action on endothelial function, antioxidant properties, and sympathomodulatory and antiatherogenic effects. Altogether, these different ancillary properties concur with the blood pressure-lowering effects of the drugs acting on the renin-angiotensin system to determine their nephroprotective action.

YouTube, the most popular video sharing website, is founded; Pierre Daninos, a French writer and humorist, dies at age 91; and Jorge E. Hirsch publishes his proposal for an h index to quantify a scientist’s publication productivity.
Hypertension is frequently associated with alterations in blood glucose and the lipid profile. In addition, the prevalence of pre-diabetes, diabetes, dyslipidemias, and metabolic syndrome is much greater in subjects with high blood pressure than in those with normal blood pressure. The picture is even more complex when the effects of antihypertensive drugs on glycemic profile and diabetogenic risk are taken into account. This large meta-analysis by Elliott and Meyer examines the effects of different antihypertensive drugs on diabetogenic risk in hypertensive patients. The meta-analysis included more than 140,000 patients treated with antihypertensive drugs from 22 clinical trials. The results show that the diabetogenic risk is greater for diuretics and β-blockers. This risk is minimal for angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers, and these drugs may even exert antidiabetogenic properties.

The effect of antihypertensive drugs on the incidence of new-onset diabetes could have a predominant hemodynamic basis. That is, the diabetogenic effect of diuretics and β-blockers could occur because these drugs reduce blood flow to the skeletal muscle tissue via a reduction in blood volume and cardiac output or β2-adrenergic receptor inactivation, respectively. These diabetogenic effects increase the distance that insulin has to travel to favor glucose entering the cell. Conversely, the lack of a diabetogenic effect (or possibly a real antidiabetogenic effect) by ACE inhibitors and angiotensin II receptor antagonists could originate from the fact that these drugs cause vasodilatation and may increase skeletal muscle blood flow. This is supported by studies using the glucose-clamp technique, which have shown a remarkable correspondence between increases in insulin sensitivity and antihypertensive drugs that increase skeletal muscle blood flow. There is no question that a reduction in insulin sensitivity is relevant to the development of diabetes, because diabetes occurs more frequently in insulin-resistant states, such as obesity, hypertension, heart failure, and metabolic syndrome. Drugs interfering with the renin-angiotensin system may exert favorable effects directly on insulin sensitivity, which is in line with the evidence that important alterations in insulin sensitivity can occur at the membrane and intracellular level. These may be multi-fold effects that range from the removal of the oxidative influence of angiotensin II on cell membranes to the stimulation of insulin secretion from pancreatic islets via potassium retention, to a peroxisome proliferator-activated receptor γ agonist action that can make angiotensin II antagonists similar to insulin sensitizers, such as glitazones, or to an effect on adipocytes that can lead to a different mobilization of fatty acids.

It is likely, although not conclusively proven, that the above-described phenomenon may have important clinical implications, which is supported by clinical evidence. First, results from an Italian study where the group of hypertensive patients receiving treatment was followed for up to 16 years (average 6 years) show that new-onset diabetes and previously diagnosed diabetes had significantly higher incidences of cardiovascular events than patients who remained free of diabetes. Unfortunately, the conclusions of the study are weakened by the fact that they were derived from only 43 cases of new-onset diabetes in which only cardiovascular events occurred. The low statistical power of the study may also explain the unusual finding that the rate of cardiovascular events appears to increase at approximately the same time or earlier in new-onset and established diabetes (<3 years).

The TGV, a French high-speed passenger train, breaks the record for the world’s fastest conventional train with a top speed of 574.8 km/hour; Thomas Stoltz Harvey, the pathologist who conducted Albert Einstein’s autopsy, dies at age 94; and the space probe New Horizons makes a gravitational slingshot around Jupiter to change its trajectory toward Pluto.
Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomized controlled trial


Lancet. 2007;370:829-840

The ADVANCE study (Action in Diabetes and Vascular disease: PreterAx and DiamicroN-MR Controlled Evaluation) investigated the effects of glucose (intensive gliclazide MR-based treatment regimen) and blood pressure (perindopril/indapamide fixed combination vs placebo) control in 11,140 patients with type 2 diabetes. This study extended previous knowledge, and, due to its factorial design, allowed the two therapeutic interventions to be administered either alone or in combination.

One of the most appreciable results of the ADVANCE study is that the relative risk of all-cause and cardiovascular mortality were both substantially reduced after a mean follow-up of 4.3 years in the group of patients receiving the fixed combination of perindopril/indapamide vs placebo, superimposed over current treatment. Furthermore, this drug combination reduced coronary outcomes by an average of 14%. These data are particularly noteworthy in light of the high incidence of all-cause mortality, cardiovascular mortality, and coronary events associated with diabetes mellitus. The data are also important because previous studies performed in diabetic patients failed to show clear-cut benefits from antihypertensive treatment.

The results from ADVANCE also suggest that treatment with the fixed combination of perindopril/indapamide has significant renal benefits. Renal outcomes improved with active treatment, which was associated with a clear-cut reduction in the risk of developing microalbuminuria, suffering from a renal event, or experiencing worsening nephropathy. Interestingly, when new-onset microalbuminuria was analyzed by patient subgroups, the effect of the perindopril/indapamide treatment remained significant regardless of age, baseline blood pressure values, baseline glycated hemoglobin (HbA1c) levels, and background treatment.

In ADVANCE, treatment with the fixed combination of perindopril/indapamide had no appreciable effect on other microvascular complications of diabetes, ie, neuropathy and retinopathy. The negative findings on neuropathy are in line with the results of previous studies, whereas those on retinopathy add to the controversy as to whether and to what extent this potentially devastating complication of diabetes can be avoided by treatment. This is because available data range from a clear-cut beneficial effect of blood pressure reduction to only a partial benefit (prediction of new-onset retinopathy in hypertensive patients with diabetes, with no effect in normotensive patients with diabetes, and no regression in the existing damage), and finally to negative findings, such as those obtained in ADVANCE.

In general, although not univocally, guidelines recommend lower blood pressure targets in patients with diabetes. They also recommend initiating antihypertensive treatment in diabetic patients when blood pressure is at the high end of the normal range, ie, a systolic value between 130 and 139 mm Hg. Both recommendations receive crucial support from the data collected in the ADVANCE trial, where the beneficial effect of the fixed combination of perindopril/indapamide was similar in the groups with and without hypertension. Although, as in virtually all other trials, the average on-treatment blood pressure remained above the recommended goal of 130 mm Hg for systolic blood pressure (with diastolic blood pressure well below 80 mm Hg), the value achieved in the active treatment group was well below 140 mm Hg (135 mm Hg vs 140 mm Hg in the placebo group). This result suggests that there is a need for lower blood pressure targets than those traditionally and currently recommended for high-risk patients.

Wolf Hilbertz, a German-born futurist architect, inventor, and marine scientist, dies at age 69; the Greek ship Server breaks in half off the Norwegian coast, releasing over 200 tons of crude oil; and Atle Selberg, a Norwegian mathematician who won the Fields medal in 1950, dies at age 90.
Effects of intensive blood pressure control in type 2 diabetes mellitus


As mentioned in the commentary regarding the UKPDS 38 study (UK Prospective Diabetes Study), the issue related to the effects of very aggressive blood pressure–lowering interventions in diabetic patients has been tested in a number of randomized clinical studies. These include the AASK (African American Study of Kidney disease and hypertension), REIN-2 (Ramipril Efficacy In Nephropathy), and ACCORD (Action to Control Cardiovascular Risk in Diabetes) studies. Specifically, the ACCORD study investigated the effects of more aggressive vs less aggressive blood pressure reductions (135 to 140 mm Hg vs ≤120 mm Hg for systolic blood pressure) in a large population sample of patients with diabetes mellitus, with an average follow-up of 4.7 years.

The ACCORD study results show that reducing systolic blood pressure below 120 mm Hg in diabetic hypertensive patients resulted in a significantly lower common risk of new-onset proteinuria than in patients with a systolic blood pressure remaining above 130 mm Hg. However, the occurrence of end-stage renal disease was superimposable in the two groups, and the final estimated glomerular filtration rate was lower in patients with the lower blood pressure target (5.8 mL/min/1.73 m²) and a more common deterioration of renal function (estimated glomerular filtration rate <30 mL/min/1.73 m²). In addition, and more importantly, the occurrence of the primary composite outcome (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) did not significantly differ between the two groups. Thus, it appears that, in patients with diabetes mellitus at high cardiovascular risk, a more aggressive blood pressure reduction does not produce greater benefits.

Similar conclusions have been reached in the other above-mentioned studies. The AASK trial showed no outcome differences between the lower and higher on-treatment blood pressure groups (128/78 and 141/85 mm Hg) during the randomized phase of the trial. The REIN-2 trial, which included 338 patients with diabetic nephropathy (glomerular filtration rate, ~35 mL/min/1.73 m²; proteinuria, ~3 g/day) and end-stage renal disease, also showed no differences in patients achieving a mean blood pressure value of 130/80 mm Hg vs those remaining around 134/82 mm Hg.

In the ACCORD trial, the only significant difference in the outcome to favor the more intensive blood pressure reduction was represented by the occurrence of stroke. However, the absolute number was so small (41 in total) that it was not adequate to establish between-group differences or similarities between different blood pressure target strategies. Finally, it should be highlighted that, in the ACCORD trial, the lack of benefits related to an intensive blood pressure reduction was associated with a significantly higher incidence of serious adverse events attributed to antihypertensive treatment (3.3% in the intensive treatment group and 1.3% in the less intensive treatment group; P<0.001). These adverse events—hypotension, syncope, and renal failure—emphasize the overall unfavorable effects of a marked blood pressure reduction in diabetic hypertensive patients.

The Kasubi Tombs, Uganda’s only cultural World Heritage Site, are destroyed in a fire; the President of Poland, Lech Kaczyński, is killed in a plane crash while on his way to commemorate the Soviet Katyn massacre; and Solar Impulse completes the first 24-hour solar-powered flight.
In 2007, the ADVANCE study (Action in Diabetes and Vascular disease: PreterAx and DiamicroN-MR Controlled Evaluation) investigated the effects of combining the blood pressure–lowering intervention (based on the perindopril/indapamide combination) with an intensive blood glucose–lowering strategy (based on gliclazide MR) vs a standard blood glucose–lowering treatment. The results showed no differences in terms of mortality rates when reducing the glycated hemoglobin (HbA1c) levels to an average of 6.5% vs the group where the HbA1c remained at 7.3%. However, the intervention was associated with a reduction in the combined incidence of macrovascular and microvascular events (the primary end point of the study), although the benefit largely depended on the favorable effects of the treatment strategy on the kidney.

In the present paper, Zoungas et al reported the results of the extended follow-up (on average 6 years) of the ADVANCE trial—ADVANCE-ON. While the favorable effects of the blood pressure–lowering intervention on reducing fatal and nonfatal cardiovascular events and total mortality were still detectable in the long term, these benefits were not seen for the intensive blood glucose–lowering treatment. Indeed, this latter result confirms and strengthens the previous findings obtained in a shorter follow-up of ADVANCE.

Two further findings of ADVANCE-ON deserve to be briefly mentioned. First, even though some markers of renal function evaluated in ADVANCE showed some benefits of strictly controlling blood glucose, such as microalbuminuria and proteinuria, these benefits were not confirmed in the long-term follow-up. Second, there was a lack of favorable interactions between blood pressure and blood glucose control on primary and secondary end points.

How can the results of ADVANCE-ON be reconciled with the findings of other studies? Indeed, the DCCT trial (Diabetes Control and Complications Trial) and the UKPDS 38 study (UK Prospective Diabetes Study) have shown that the reduced risk of macrovascular and microvascular events reported with an intensive blood glucose–lowering treatment was maintained in the long-term follow-up. Patients in the ADVANCE-ON trial were much older than those recruited in the other two studies and they displayed lower baseline levels of HbA1c. These differences may suggest that benefits associated with an intensive blood glucose–lowering treatment may be more easily detectable in younger patients with a more compromised dysmetabolic state.

Despite the negative results of the metabolic intervention, ADVANCE-ON confirms the usefulness of an intensive blood glucose–lowering treatment even over the long term, a finding that is based on the perindopril/indapamide drug combination. This latter observation once again supports the long-term benefits of such a therapeutic approach in high-risk patients.

Follow-up of blood-pressure lowering and glucose control in type 2 diabetes

S. Zoungas, J. Chalmers, B. Neal, L. Billot, Q. Li, Y. Hirakawa, H. Arima, H. Monaghan, R. Joshi, S. Colagiuri; ADVANCE-ON Collaborative Group

Usual blood pressure and risk of new-onset diabetes: evidence from 4.1 million adults and a meta-analysis of prospective studies


*J Am Coll Cardiol.* 2015;66:1552-1562

Emdin et al attempted to determine whether and to what extent the risk of diabetes mellitus relates to blood pressure values, and specifically, whether elevated blood pressure is associated with an increased diabetogenic risk. Prospective data from more than 4 million subjects were analyzed by evaluating records from the UK clinical practice data link and the results of a meta-analysis that included 30 prospective observational studies. Results show that individuals with elevated blood pressure values display a greater incidence of new-onset diabetes during the follow-up. The association was stronger for patients with a mild blood pressure elevation. Overall, a 20 mm Hg higher systolic blood pressure and a 10 mm Hg higher diastolic blood pressure were accompanied by a significant 58% and 52% increase, respectively, in the diabetogenic risk. The relationship between the two variables was still found even after excluding patients who were on antihypertensive or statin therapy at baseline or during the follow-up. Of note, the association between blood pressure elevation and diabetogenic risk declined with the presence of a body mass index greater than 30 kg/m² or in older individuals.

In analyzing the main study findings, an obvious question was raised, namely, what are the factors potentially involved in determining the above-mentioned association? At least three major classes of pathophysiological variables should be taken into account. First, animal studies have highlighted the relevance of mediators of chronic inflammation, which characterizes some conditions that predispose patients to diabetes mellitus, such as hypertension or being overweight. In particular, it has been shown that adipose tissue accumulation, especially visceral and ectopic (e.g., intramuscular and hepatic), induces a spectrum of metabolic and hormonal changes, which may progressively lead to an impairment in insulin signaling. These changes manifest as increased insulin resistance in the adipose tissue, liver, skeletal muscle, and vascular endothelium. Additionally, obesity alters adipokine production, which increases tumor necrosis factor α and decreases adiponectin secretion, thus potentiating the inflammatory load.

Two further pathophysiological factors are important. (i) Endothelial dysfunction, a common finding of both hypertension and diabetes, that potentially favors the development and progression of the metabolic alterations; and (ii) the sympathetic nervous system and the renin-angiotensin system, two key systems involved in maintaining blood pressure homeostasis, are functionally altered in essential hypertension and may directly or indirectly exert prodiabetogenic effects.

What are the therapeutic implications of these findings? Taking into account the above-mentioned pathophysiological background and considering that pharmacological blockade of the renin-angiotensin system has been shown to reduce the incidence of new-onset diabetes in randomized clinical trials, the indication is to use angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers more frequently in the treatment of hypertension to prevent or delay the development and progression of diabetes.

Iranian chemists from the Ferdowsi University of Mashhad created biodiesel fuel from soya oil; the first comprehensive analysis of the mammoth genome is completed; and a titanium 3D-printed prosthetic jaw is successfully implanted in a male patient by surgeons in Melbourne, Australia.
Diabetes and Hypertension

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selected by Giuseppe Mancia, MD
University of Milano-Bicocca - Milan - ITALY
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