

RENIN ANGIOTENSIN SYSTEM IN CARDIOVASCULAR MEDICINE

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Cover photo: Moderate hypertension. Interior view of hypertensive patient's heart seen from the apex. Courtesy Lennart Nilsson.

ONTARGET ante portas!

“Hannibal ante portas!” – You will certainly remember this outcry from good old Rome. Now it is the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) knocking on the door. By the end of March, we will know what has been revealed in the largest trial in cardiovascular risk patients ever performed.

Are these patients really at high risk or is the ONTARGET trial just another hypertension study?

Yes, these patients are definitely at high risk. Although 68% of the patients have hypertension, they also have ample cardiovascular disease and events: 49% with myocardial infarction, 35% with stable angina, 21% with stroke or transient ischaemic attack, 12% with claudication, 37% with diabetes mellitus and, not forgetting, 13% are current smokers.

What can we expect in terms of therapy? Well, let's be realistic: we cannot expect a so-called *restitutio in integrum*, i.e. we will never be able to cure at this advanced stage of disease. However, we may be able to prolong life, cut down on events during the time of the trial, and substantially improve quality of life. The ONTARGET trial does not allow for a comparison with “placebo”-treated patients at similar risk as the study is designed to compare the angiotensin II receptor blocker (ARB), telmisartan, with the angiotensin converting enzyme (ACE) inhibitor, ramipril, and their combination. A comparison with “placebo”-treated patients will come out somewhat later this year with the results of the TRANSCEND (Telmisartan Randomized Assessment Study in aCE-iNtolerant subjects with cardiovascular Disease), which, in parallel to the ONTARGET trial, compares telmisartan with background “placebo” treatment in patients intolerant of ACE inhibitors.

What do I mean by background “placebo” treatment? Well, we have to acknowledge that today, for ethical reasons, a trial of this

format can no longer be performed comparing a drug or verum treatment arm against a true placebo arm, i.e. in patients receiving no active drug. Thus, the “placebo” arm has to include active ingredients representing the respective state-of-the-art drug therapy. After the success of the HOPE trial (Heart Outcomes Prevention Evaluation) in a similar group of high-risk patients, it even became impossible not to include ACE inhibition in this “placebo” arm unless patients were intolerant of ACE inhibitors, as in the TRANSCEND study.

Thus the patients in ONTARGET and TRANSCEND are on substantial background medication, and the drugs tested, i.e. telmisartan and ramipril, are given on top of this therapy.

For instance, in the ONTARGET trial, of the 25,620 patients included, 58% had a history of ACE inhibition and 9% of ARB treatment. During the trial, they remained on beta-blockers (57% at baseline), diuretics (28%), calcium-channel antagonists (34%), antiplatelet drugs (87%), oral anticoagulants (8%), statins (61%), and antidiabetic drugs (35%).

If this background treatment is compared against that in the HOPE trial, it becomes apparent that medical treatment has improved in the last 10 years: for instance, a much larger proportion of patients are now on statins compared with the days of the HOPE trial. This, of course, has implications for the outcome of the ONTARGET trial: it has become more difficult to show the same benefit for any treatment added because the background has improved.

Despite all this, I am confident that the ONTARGET trial, with all its substudies and facets, will substantially contribute to a better treatment of high-risk patients and, furthermore, to our understanding of cardiovascular disease.



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Early-morning surge in blood pressure (BP) corresponds with an increase in clinical events, particularly stroke.¹ People with hypertension who experience a larger-than-average morning surge in BP are at increased risk by two mechanisms.² The first is the acute risk of an event associated with the BP surge. The second is the acceleration of disease processes – such as left-ventricular hypertrophy (LVH), increased intima–media thickness, and remodelling of resistance arteries – that are associated with this BP hyperreactivity.^{3,4} The morning surge in BP has also been associated with a pro-inflammatory response associated with increased carotid plaque instability.^{5,6} In a minority of hypertensive patients, there is no nocturnal fall in BP. Although this pattern is at least as pernicious and deserves the same attention for tight BP control,⁷ morning surges, which may be missed by office-based BP monitoring, are a particular mechanism of risk when 24-hour BP control is not achieved.

Targeting morning hypertension for perfect 24-hour blood pressure control

2

Diurnal BP variation

In normotensive people, a decrease in BP during sleep is followed by a morning surge, which raises BP for the remainder of the day. The increase in BP is accompanied by an increase in heart rate and is mediated by increased plasma renin and increased secretion of catecholamines. Catecholamines, such as norepinephrine, and renin are vasoconstrictors and their release in normotensive people is a physiological and expected pattern in the circadian rhythm.

In hypertensive people, there are two variations in this pattern. The most common is an exaggeration of

the surge observed in normotensive people, producing a relatively rapid BP rise to levels that place the patient at increased risk of vascular events.^{8,9} The second is a non-dipper pattern. Substantially less common, it is characterized by the absence of diurnal variation in which there is no nocturnal reduction in BP.

These abnormalities in diurnal BP patterns appear to be driven by different pathophysiological mechanisms. Although it is important to

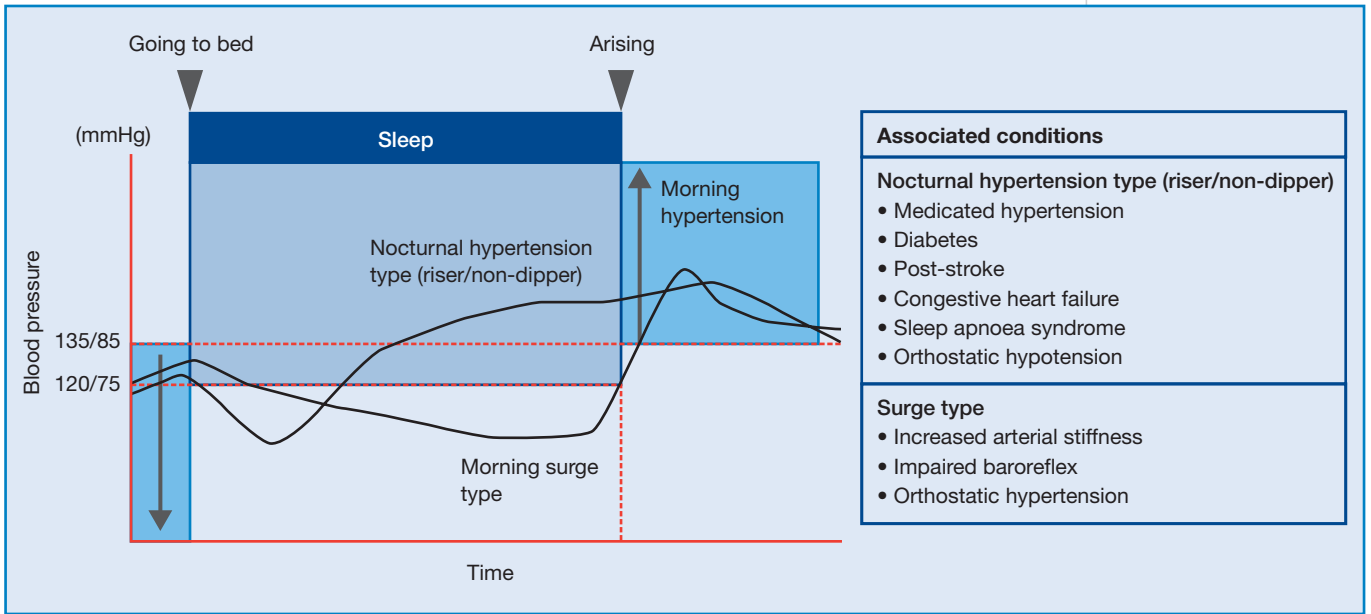
emphasize that the most important predictor of cardiovascular events is the average ambulatory BP throughout the 24-hour period,¹⁰ each of these patterns appears to define specific risk groups (Figure 1).

The morning surge in hypertension poses clinical risks by two mechanisms. Acutely, the surge can precipitate events, such as plaque rupture, in a vulnerable population.^{11,12} Additionally, morning surges increase cardiac afterload and arterial stiffness, contributing to disease progression. Specifically, while the former is a mechanism for the increased LVH associated with BP hyperreactivity, the latter is likely to be a trigger of hypertrophy in the vessels.

Both contribute to a progressive pathophysiology that increases the risk of clinical events. For example, the LVH associated with BP hyperreactivity appears to contribute to heart failure,^{3,4} whereas vessel changes may explain why the exaggerated morning BP surge is specifically associated with an increased risk of ischaemic and haemorrhagic stroke.^{9,13,14} BP hyperreactivity is associated with other pathophysiological processes that

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also contribute to target-organ damage, such as endothelial dysfunction and prothrombotic effects.¹⁵⁻¹⁷

Non-dipper hypertension, which is characterized by an absence of the nocturnal reduction in BP, is the product of blunted autonomic nervous function.¹⁸ Some patients with non-dipper hypertension have higher nocturnal BP than daytime BP, which may explain the association of this pattern of hypertension with poor sleep quality.¹⁹ Relative to hypertensive patients who experience an exaggerated morning surge, non-dipper hypertensive patients are at a higher risk of developing congestive heart failure and chronic kidney disease.²⁰

Mechanism of cardiovascular risk in the morning hours

While tight 24-hour BP control would be expected to reduce the clinical risks associated with both patterns of hypertension, the morning surge poses its own specific risk of inadequate BP control. Whether antihypertensive agents are dosed once in the morning or twice daily, the trough drug level occurs in the morning hours just prior to the next dose. If trough levels do not provide adequate antihypertensive activity, the loss of BP control occurs during a period of exceptional vulnerability for both acute events and activities that drive chronic disease progression.

Progress in understanding the mechanisms of the morning BP surge in hypertensive patients and its risks are a basis for advocating more attention to treatment strategies that will ensure antihypertensive efficacy during this period of vulnerability. Many mechanisms are interrelated, producing the potential for a

vicious cycle of increased hyperreactivity and increased disease progression. However, the central mediator is an activated sympathetic nervous system, including upregulation of the renin-angiotensin system (RAS), which drives vasoconstriction and increases BP.^{21,22}

This results in increased mechanical stresses on the vascular wall, endothelial dysfunction, and oxidative stress, setting the stage for downstream pathophysiology that includes release of pro-inflammatory factors, such as C-reactive protein, release of prothrombotic factors, such as plasminogen-activator inhibitor 1, and proliferative factors that contribute to cardiac and vascular remodelling (Figure 2).

Ultimately, these events create an environment that promotes not only growth of atherosclerosis but also the potential for plaque rupture leading to myocardial infarction and stroke.²³

However, effective control of early-morning BP may be important even at the earliest stages of increased BP when the risk of events remains low. Again, the morning surge contributes to the pathophysiology that drives the cardiovascular continuum of disease progression. As small-artery remodelling is initiated both from the earliest stage of pathogenesis of hypertension and by the pathological processes associated with the morning BP surge,^{24,25} even otherwise normotensive patients who experience an exaggerated morning surge would be expected to be at risk for the pathogenic processes that drive disease progression (Figure 3).⁷

This risk may be best illustrated in the

Figure 1. Morning hypertension and diurnal blood pressure variation.

Relative to hypertensive patients who experience an exaggerated morning surge, non-dipper hypertensive patients are at a higher risk of developing congestive heart failure and chronic kidney disease

cerebrovascular system, which appears to be particularly vulnerable to the diurnal pattern of BP hyperreactivity. Several studies suggest that the risk posed to cerebrovascular disease may be at least partially related to small-vessel remodelling in the cerebral circulation.^{6,26} During the morning BP surge, the forces of oxidative stress that increases arterial stiffness impair the ability of small vessels to protect themselves from the conspiracy of factors that promote hypertrophy.

In turn, oxidative stress stimulates the ubiquitin–proteasome system to induce pro-inflammatory activities through the activation of nuclear transcription factors such as kappa B.⁵ The ensuing pathogenic state becomes self-sustaining as the surge in BP drives the factors that promote chronic hypertension.

Limitations of current clinical BP-based antihypertensive therapy

In hypertensive patients, the early-morning BP surge should be considered an essential goal to control and modify disease progression. Current evidence suggests that the majority of patients are not achieving adequate control

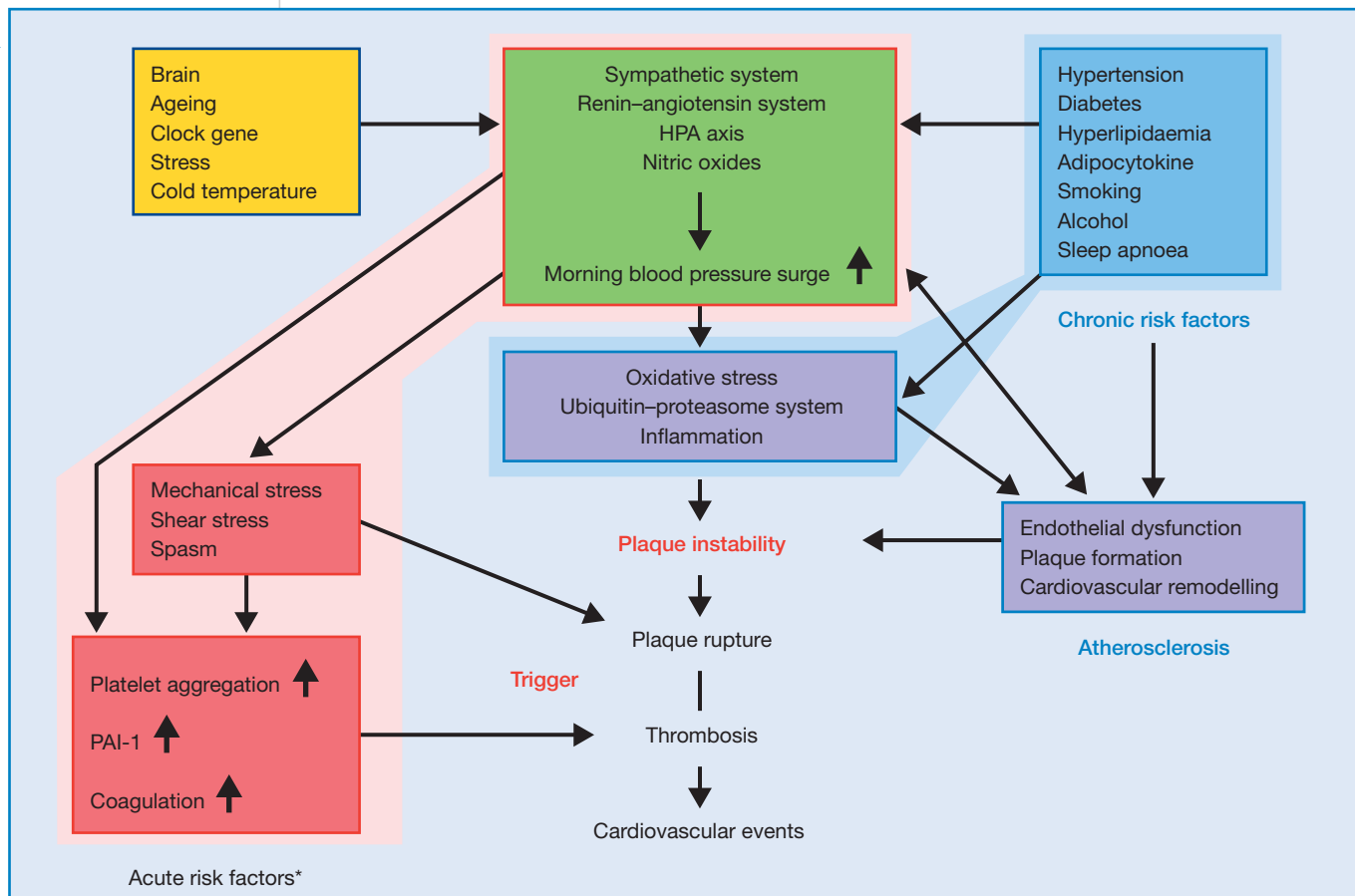
during this vulnerable period.²⁷ In the SURGE study (Study of a hypertensive population Under treatment in Real clinical conditions with the Goal of controlling Early morning blood pressure rise), an observational study that evaluated morning BP in a large cohort of patients on antihypertensive therapy, 60% were not at the goal established by European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines.²⁸

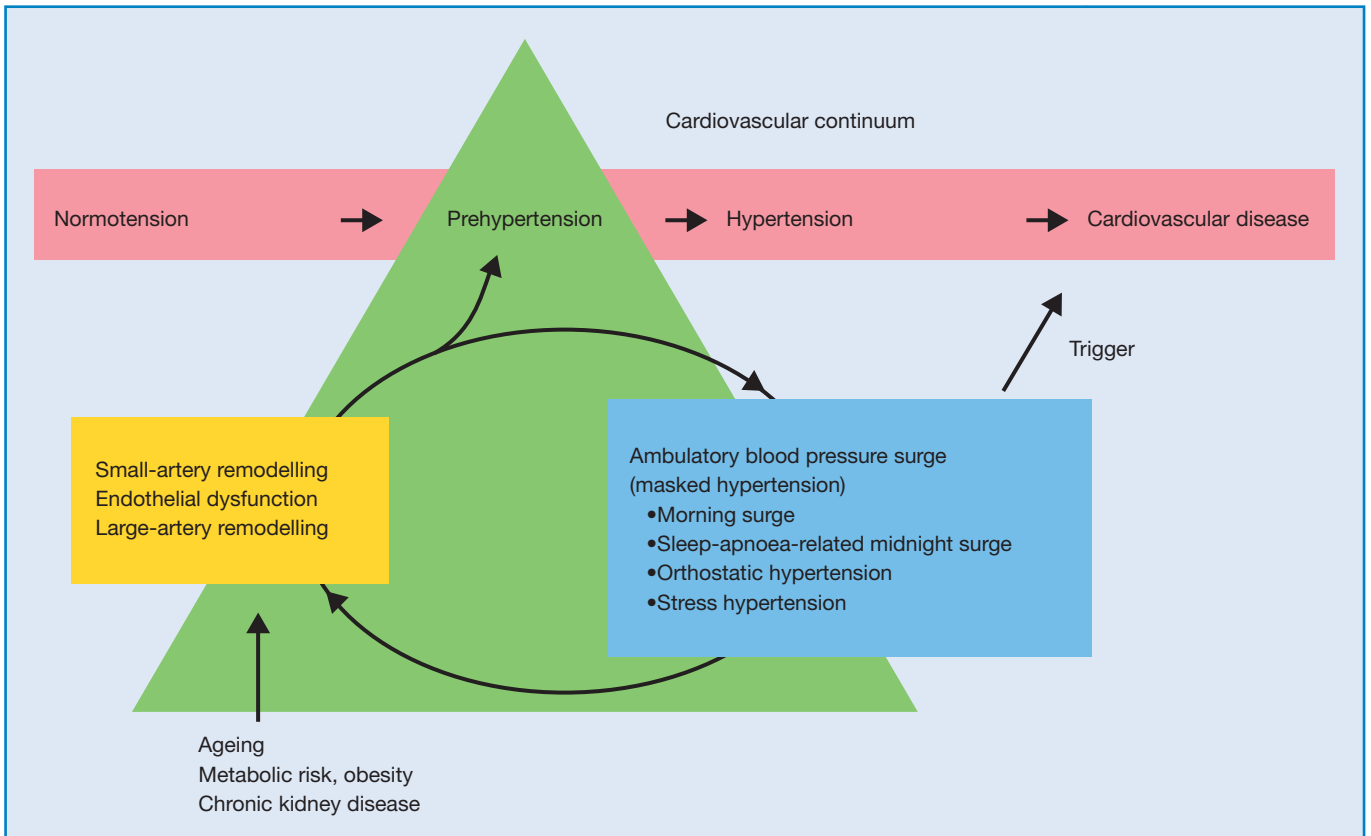
The major obstacle to 24-hour BP control is considered to be the duration of antihypertensive activity of currently available therapies. While many antihypertensive drugs are indicated for once-daily therapy, few have half-lives exceeding 12–15 hours. The value of longer half-lives in maintaining 24-hour BP control is illustrated in several studies with the angiotensin II receptor blocker (ARB) telmisartan, including SURGE-2.²⁹

In SURGE-2, an 8-week, open-label prospective, practice-based study in more than 26,000 patients, telmisartan doubled the proportion of patients at treatment goals compared with alternative strategies. The tight control over a full dosing period is attributed to the 24-hour half-life of telmisartan, which is considerably longer than other ARBs. Irbesartan has the next longest half-life of available ARBs at 15 hours,

The value of longer half-lives in maintaining 24-hour BP control is illustrated in several studies with the angiotensin II receptor blocker (ARB) telmisartan, including SURGE-2

Figure 2. Morning blood pressure surge – related cardiovascular risk. HPA = hypothalamic–pituitary–adrenal; PAI-1 = plasminogen-activator inhibitor 1. *With diurnal variation.





but most have half-lives ranging from 6 to 9 hours. In another study of telmisartan, MICCAT-2 (the second MICardis Community Ambulatory monitoring Trial), 1,842 patients were evaluated for 24-hour BP control on telmisartan with or without the addition of hydrochlorothiazide.³⁰ Efficacy was evaluated with remote ambulatory BP monitoring to which study investigators were blinded.

About 60% of patients were previously untreated and 40% had previous treatment. At the end of 10 weeks, 70% of patients achieved 24-hour BP < 130/85 mmHg. The early-morning BP control was improved over baseline in those who had been on previous antihypertensive therapy and those who had not. To achieve this control, nearly 60% were on telmisartan 40 mg or 80 mg alone.

In PRISMA I and II studies (first and second Prospective Randomized Investigation of the Safety and efficacy of Micardis versus ramipril using Ambulatory blood pressure monitoring),³¹ telmisartan 80 mg was compared with ramipril 10 mg for the last 6 hours of the dosing interval (early morning hours).

While telmisartan produced significantly greater reductions in BP than did ramipril 10 mg overall (mean systolic BP reduction of 14.1 mmHg compared with 11.0 mmHg, $p < 0.0001$; and mean diastolic BP reduction of 9.6 mmHg compared with 7.2 mmHg, $p < 0.0001$, respectively), the magnitude of the systolic early-morning BP surge was reduced

by 4.9 mmHg more with telmisartan 80 mg than with ramipril 10 mg in the group of patients with the highest early-morning BP surge (mean systolic BP reduction of 12.7 mmHg compared with 7.8 mmHg, $p = 0.0004$, respectively).

Expectation for ONTARGET

Early-morning antihypertensive activity may be particularly relevant to RAS inhibitors such as telmisartan and ramipril because of the role of angiotensin II and other neurohormones in driving the morning BP surge. However, RAS inhibitors have been associated with a number of BP-independent benefits, such as protection against cardiovascular and cerebrovascular events in a number of large controlled trials.

These independent benefits are credited to the suppression of the effects of angiotensin II on target organs even in the absence of hypertension. This premise will be further tested in the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) programme, which is comparing telmisartan, ramipril, and their combination in the largest study of its kind.³²

More than 30,000 patients participated in this programme. In addition, a substudy will evaluate 24-hour BP readings and risk of events, yielding another opportunity to evaluate the influence of

Figure 3. Exaggerated morning blood pressure surge as a measure of prehypertension (hypothesis).

Early-morning antihypertensive activity may be particularly relevant to RAS inhibitors such as telmisartan and ramipril because of the role of angiotensin II and other neurohormones in driving the morning BP surge

this variable on risk reduction. The ONTARGET study arm in which patients will receive both telmisartan and ramipril will also provide critical new information about the importance of dual RAS inhibition. While a meta-analysis has indicated that dual therapy provides greater reductions in BP compared with an ARB or an angiotensin-converting enzyme (ACE) inhibitor alone,³³ the more important question will be whether this combination reduces the risk

of target-organ damage as revealed by LVH, proteinuria, or other organ-specific changes. A variety of other substudies in the ONTARGET programme are also designed to address these questions. Again, even in the absence of hypertension, the ability of dual inhibition to better modify early-morning neurohormonal activation may be relevant to risk reduction. It is possible that pathophysiological processes such as small-artery remodelling in the cerebrovascular circulation may be prevented in patients at high risk even without pressure-mediated damage. Thus, complete inhibition of the RAS by combined ARB and ACE inhibitor treatment that covers the vulnerable morning period when RAS activation is greatest would be promising.

Conclusion

The correlation between the early-morning BP surge and the increased risk of cardiovascular events has previously provided a rationale for providing effective BP control during this period. However, the greater detail with which this relationship is understood has made early-morning BP control a more urgent target. Due to dosing schedules, antihypertensive therapies are most likely to offer inadequate control during the early morning, when patients are vulnerable to acute events as well as to disease progression. Strategies to better address BP control during the early morning hours favour drugs that control the RAS, a major driver of early-morning BP surge, as well as therapies with a half-life of sufficient duration that antihypertensive activity remains adequate. ◀

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In comparative trials, antihypertensive therapies have differed in their relative protection against stroke at similar levels of blood pressure (BP) control. The reasons for these differences may provide insight into the pathophysiology of stroke and generate new opportunities to control the current stroke epidemic. Two trials nearing completion are expected to substantially increase current information about relative stroke protection using different pharmacological strategies. In the ONTARGET trial (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), the angiotensin II receptor blocker (ARB) telmisartan, the angiotensin-converting enzyme (ACE) inhibitor ramipril, and the combination of both agents are being compared for protection against major cardiovascular events, including primary stroke prevention. In the PRoFESS study (Prevention Regimen For Effectively avoiding Second Strokes), a secondary stroke prevention study with a factorial design, telmisartan will be compared with placebo in addition to standard antiplatelet stroke prevention therapy. Both studies offer an opportunity to consider mechanisms of action in the context of relative efficacy.



Björn Dahlöf

Mechanisms of blood pressure control and prevention of stroke

Risk factors for stroke

The steep worldwide increase in the incidence of stroke over the past decade parallels similarly steep increases in the incidence of hypertension. Stroke incidence in a country reflects level of BP control. In the year 2000, the estimated global prevalence of hypertension, a major risk factor for stroke, had reached 25% of the world's adult population or nearly one billion individuals.¹

Some estimates place the worldwide prevalence of hypertension by the year 2025 at almost 30%. The increasing prevalence of hypertension is expected to drive a rising prevalence of stroke with substantial public-health implications, unless major interventions take place. Stroke is the second most common cause of death (5 million individuals die per year) worldwide after cardiac events.² Of those who survive, about two-thirds have some

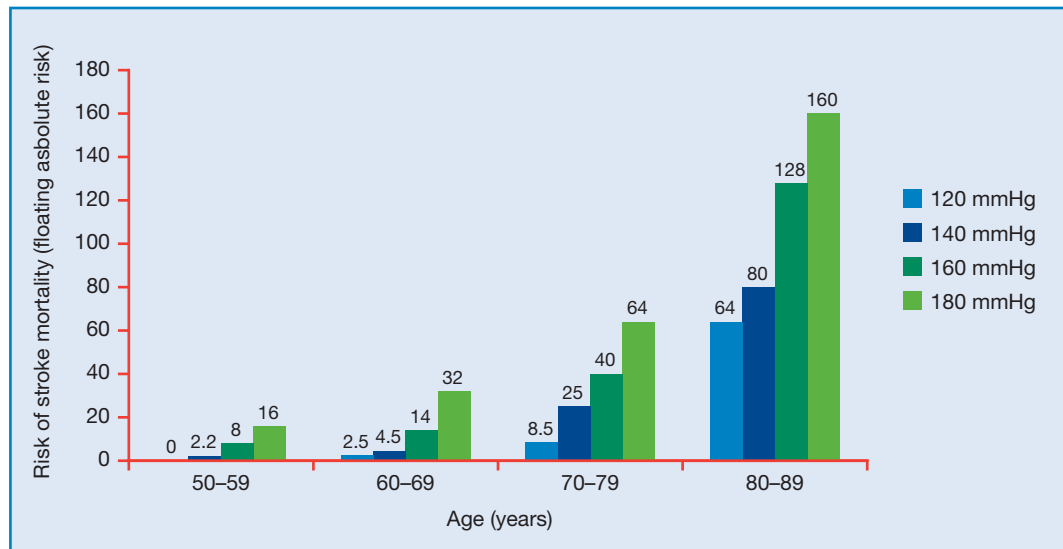
degree of disability.³ This disability, stemming from both physical and mental impairments, is sufficiently severe to require institutional care in approximately 20% of patients.⁴

The two most important risk factors for stroke are advancing age and hypertension.⁵ These are independent risks. Although there is an age-related increase in the prevalence of hypertension, the risk of a fatal stroke correlates with rising systolic or diastolic BP at any age.⁶ In addition to age, the non-modifiable risk factors include family history and male sex. The modifiable risk factors other than hypertension include diabetes mellitus, atrial fibrillation, hyperlipidaemia, cigarette smoking, and obesity.^{7,8}

Recognizing and treating modifiable risk factors to prevent a first stroke should be considered a critical clinical goal. Due the narrow window of time in which ischaemia causes irreversible

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Figure. Stroke mortality rises with blood pressure and age. (Data from Lewington S, et al.⁶)



damage, the opportunity for acute treatments remains limited. Preventing a first stroke is particularly important because of the high risk of recurrence. The risk of a second stroke after a primary stroke exceeds 10% at 2 years and 25% at 5 years.⁹

Stroke refers to a heterogeneous group of pathophysiological causes of impaired blood supply to the brain, including thrombosis, embolism, and haemorrhage. More than 80% of strokes are due to a thrombotic event.¹⁰ There are numerous causes of thrombosis, including debris from the vessel wall or emboli (e.g. from the heart) travelling from the cardiovascular system, and rupture of atherosclerotic plaque in cerebrovascular arteries and carotids.

Hypertension appears to play an important pathophysiological role regardless of stroke cause. One basis for this assertion is the highly significant correlation between the circadian pattern of the morning BP surge and increased risk of stroke.¹¹ Many cerebrovascular events

occur between 06:00 and noon, when BP rise is observed even in individuals whose hypertension is otherwise well controlled. This pattern of risk has been observed for both haemorrhagic strokes and ischaemic strokes.

Diastolic BP, pulse pressure, and mean arterial pressure are all significant predictors of stroke risk, but the consistency of the predictive value of systolic BP is not exceeded or improved by considering these

alternative measures independently of systolic BP.¹² Stroke mortality increases progressively and linearly from BP levels as low as 115 mmHg systolic and 75 mmHg diastolic.¹³ The correlation between increasing degrees of hypertension and increasing rates of stroke is

linear and independent of other risk factors.¹⁴ It is estimated that up to 44% of strokes can be prevented with hypertension control only.¹⁵ In one meta-analysis using data from primary-prevention studies, each 10 mmHg decrease in systolic BP was associated with a 33% reduction in stroke in people between the ages of 60 and 79 years.¹⁶

Prevention of stroke

In guidelines for primary prevention, BP treatment goals for stroke are typically the same as those for prevention of other vascular diseases. In Europe and the USA, the target for systolic and diastolic BP is < 140/90 mmHg.¹³ However, a meta-analysis of prospective studies with data on one million patients suggests optimal BP levels are < 120/80 mmHg.⁶ For patient groups at high risk of stroke and cardiovascular events, such as those with diabetes or prior myocardial infarction, most guidelines identify the target BP as < 130/80 mmHg.^{12,13,17}

All antihypertensive agents, including beta-blockers, diuretics, calcium-channel antagonists, ACE inhibitors, and ARBs, have been associated with a reduction in the risk of stroke.^{14,18-21} Some studies, such as PROGRESS (Perindopril pROtection aGainst REcurrent Stroke Study) and HOPE (Heart Outcomes Prevention Evaluation),^{22,23} suggest, however, that stroke risk reductions can even be achieved in normotensive people and with small differences in BP. Remarkably, antihypertensive agents do not appear to be interchangeable for stroke risk reduction when titrated to provide the same BP control.

This was first suggested by results of the ALLHAT trial (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial),²⁴ but has been demonstrated even more compellingly

In the year 2000, the estimated global prevalence of hypertension, a major risk factor for stroke, had reached 25% of the world's adult population

by results of the LIFE (Losartan Intervention For Endpoint reduction in hypertension) and ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm) studies.^{25,26} In LIFE, a therapy based on the ARB losartan was associated with a 25% reduction ($p < 0.001$) in fatal and non-fatal stroke relative to a therapy based on the beta-blocker atenolol for the same BP control. In the ASCOT-BP, the calcium-channel antagonist amlodipine with or without perindopril was associated with a 23% reduction ($p = 0.0003$) in stroke relative to treatment with atenolol with or without a diuretic and with marginal BP difference.

Secondary stroke prevention trials also suggest BP-independent differences in risk reduction with antihypertensive agents. In MOSES (MOrbidity and mortality after Stroke, Eprosartan compared with nitrendipine for Secondary prevention), the ARB eprosartan was associated with a 21% reduction ($p = 0.014$) in all-cause mortality plus all cerebrovascular and cardiovascular events relative to the calcium-channel antagonist nitrendipine, with the same BP control over 24 hours.²⁷

In the SCOPE study (Study on COgnition and Prognosis in the Elderly), the ARB candesartan, in a subgroup analysis, was associated with a 23% reduction ($p = 0.056$) in stroke relative to placebo.²⁸ Although results were confounded by a lower BP in the candesartan group, there was a 42% reduction in stroke associated with candesartan in a substudy limited to those who had isolated systolic hypertension at baseline and achieved similar BP control (a non-significant 2/1 mmHg greater reduction in the candesartan arm) during the trial.²⁹

Stroke protection from RAS inhibitors: conflicting data

Of the potential differences between antihypertensive agents for stroke prevention, the disparate results observed with ARBs and ACE inhibitors is one of the most intriguing.

Although both drug classes block the actions of an upregulated renin-angiotensin system (RAS), pooled data have associated ARBs with a 24% ($p = 0.0002$) reduction but ACE inhibitors with a 10% ($p = 0.03$) increase in risk of stroke relative to older antihypertensive agents, such as diuretics and beta-blockers.³⁰

This difference may be related to the way in which the RAS is inhibited. While ACE inhibitors reduce systemic production of angiotensin II, other converting enzymes, such as chymase, may be an important source of angiotensin in target tissues.³¹ In contrast, experimental studies suggest that the ability of ARBs to block angiotensin at the angiotensin II type 1 (AT1) receptor, which is the final common pathway for vasoconstriction, may be particularly important to the cerebrovascular system. In animal models, ischaemia enhances the AT1-receptor-mediated contractile responses to angiotensin II, suggesting that direct AT1 receptor blockade may be more important than systemic angiotensin II inhibition.³²

In addition, by blocking the AT1 receptor, ARBs increase the amount of circulating angiotensin II available for stimulation of the AT2 receptor,³³ which, in another set of studies in animal models, has been associated with protection against cerebral ischaemia and improved survival.³⁴

In a recent meta-analysis of 200,000 patients treated for hypertension, it was strongly indicated that antihypertensive drugs that could potentially stimulate the AT2 receptor in the brain through more endogenous angiotensin II (ARBs, calcium-channel antagonists, and diuretics) were more stroke protective than other antihypertensive drugs.³⁵ Confirmation of differences between ACE inhibitors and ARBs for prevention of stroke may be generated by the ONTARGET study, which randomized 25,620 high-risk hypertensive patients to the ARB telmisartan, the ACE inhibitor ramipril, or

Although there is an age-related increase in the prevalence of hypertension, the risk of a fatal stroke correlates with rising systolic or diastolic blood pressure at any age

Table. Angiotensin II receptor blockers (ARBs): relative characteristics in the stroke context.

| Characteristic | ARB | | | | | | |
|---|----------|-------------|-----------|------------|-------------|------------------------------|-------------|
| | Losartan | Oltmesartan | Valsartan | Irbesartan | Candesartan | Telmisartan | Eprosartan |
| Half-life (hours) | 6–9 | 13 | 6 | 11–15 | 9 | 24 | 5–9 |
| Crosses blood–brain barrier | No | No | No | No | Yes | Yes | No |
| Evaluated in trial with stroke as primary end-point | No | No | No | No | Yes (SCOPE) | Ongoing (PROFESS + ONTARGET) | Yes (MOSES) |

a combination of the two.³⁶ The primary end-point of ONTARGET is a composite of events that includes cardiovascular mortality, non-fatal stroke, non-fatal myocardial infarction, and hospitalization for heart failure.

The study provides the opportunity not only to evaluate whether ARBs and ACE inhibitors differ in relative protection against vascular events such as stroke but also whether their effects are additive. In the placebo-controlled HOPE trial, ramipril was associated with a 22% ($p < 0.001$) reduction in the risk of a comparable primary end-point in a similar population.³⁷

Telmisartan has several features that would make it particularly suitable for demonstrating differences with an ACE inhibitor, particularly in stroke. This includes a longer half-life (24 hours) than other available ARBs, including irbesartan (15 hours), valsartan (6 hours), and candesartan

(9 hours).³⁸ This may be important for reducing high BP in the risky morning hours when the prevalence of stroke is high. In animal models, telmisartan has also been found to penetrate the blood-brain barrier, a potential advantage in providing protection from angiotensin-mediated vasoconstriction in the central circulation.³⁹ The same characteristics make telmisartan appropriate for study in secondary stroke prevention. In PROFESS, in which more than 20,000 stroke survivors were randomized in a 2 x 2 trial design to aspirin plus dipyridamole or clopidogrel and to telmisartan or placebo (to existing antihypertensive therapy),⁴⁰ each study arm is designed to explore the possibility of reducing the risk of stroke by mechanisms independent of BP reductions. Both ONTARGET and PROFESS will generate important new information about current strategies for stroke prevention, moving the focus from BP control alone to BP-independent benefits.

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Conclusion

In patients at risk of stroke, control of elevated BP is essential, but the increasing evidence of BP-independent benefits may provide new opportunities for stroke prevention. Several large trials have provided evidence that ARBs may be particularly protective against stroke, a finding that is consistent with experimental evidence of the importance of AT1 receptor blockade and AT2 receptor stimulation for homeostasis in the cerebrovascular circulation. The ONTARGET trial will provide an opportunity to evaluate the potential differences between telmisartan, an ARB with a long half-life, and ramipril, an ACE inhibitor previously associated with benefits in a high-risk population, as well as the combination of both agents. The size of the study will yield robust data. For secondary prevention, the PROFESS study will also evaluate BP-independent benefits in a study including telmisartan. Each will not only generate new insights about stroke prevention but will also provide evidence-based guidance for stroke prevention strategies. ◀

Professor Koon K. Teo (Department of Medicine [Cardiology], McMaster University, Hamilton, Ontario, Canada) is a senior member of the investigating team conducting the ONTARGET/TRANSCEND (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial / Telmisartan Randomized Assessment Study in aCE-iNtolerant subjects with cardiovascular Disease) trial programme.¹ Professor Teo, who has a research interest in clinical trial design, also helped plan and conduct the HOPE trial (Heart Outcomes Prevention Evaluation)², which established the benefit of the angiotensin-converting enzyme (ACE) inhibitor ramipril in a population similar to that recruited for ONTARGET/TRANSCEND. Professor Teo has held similar senior positions in the design and execution of the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation)³, which compared percutaneous revascularization to medical therapy in patients with chronic coronary disease, the ASTRONOMER trial (Aortic STenosis pROgression Observation: Measuring Effects of Rosuvastatin)⁴, which is now evaluating aggressive lipid-lowering in patients with aortic stenosis, and the WATCH trial (Warfarin and Antiplatelet Therapy in Chronic Heart failure)⁵, which evaluated antithrombotic therapy in heart failure. Professor Teo is well represented in the medical literature as an author or co-author of publications that address diverse subjects such as results of clinical trials on cardiovascular diseases, meta-analyses of trial data, and management of atrial fibrillation.



Koon Teo

ONTARGET/TRANSCEND trial programme: the making of a landmark study

The largest clinical trial programme ever conducted with an angiotensin II receptor blocker (ARB) is nearing completion. It consists of 2 trials evaluating strategies for cardiovascular risk reduction in high-risk patients aged ≥ 55 years. High risk is indicated by coronary artery disease, peripheral artery disease, previous stroke, transient ischaemic attack, or diabetes mellitus with organ damage. The ONTARGET trial compares the ARB telmisartan alone, the ACE inhibitor ramipril alone, and the two drugs in combination for

protection against major events, such as myocardial infarction (MI) and stroke. The TRANSCEND trial compares telmisartan to placebo in patients who are ACE-inhibitor-intolerant for the same set of major events. The ONTARGET/TRANSCEND trial programme¹ is expected to clarify several important clinical issues, particularly whether it is possible to build on the previously established benefits of the ACE inhibitor ramipril in a high-risk population by substituting or adding the ARB telmisartan. The ONTARGET trial will be presented at the

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annual meeting of the American College of Cardiology in March 2008. The TRANSCEND trial will be reported later in 2008.

ONTARGET/TRANSCEND programme

The ONTARGET/TRANSCEND trial programme¹ poses an important practical question regarding drug selection for preventing events in high-risk patients: can the protection previously associated with the ACE inhibitor ramipril as shown in the HOPE trial² be equalled or improved upon by the substitution or the addition of the ARB telmisartan?

The trial programme, in which more than 30,000 high-risk patients are randomized, is generating a large pool of data with which to address this and a number of other questions about the role of the modulation of the renin-angiotensin system (RAS) in preventing progressive pathological processes that culminate in cardiovascular events.

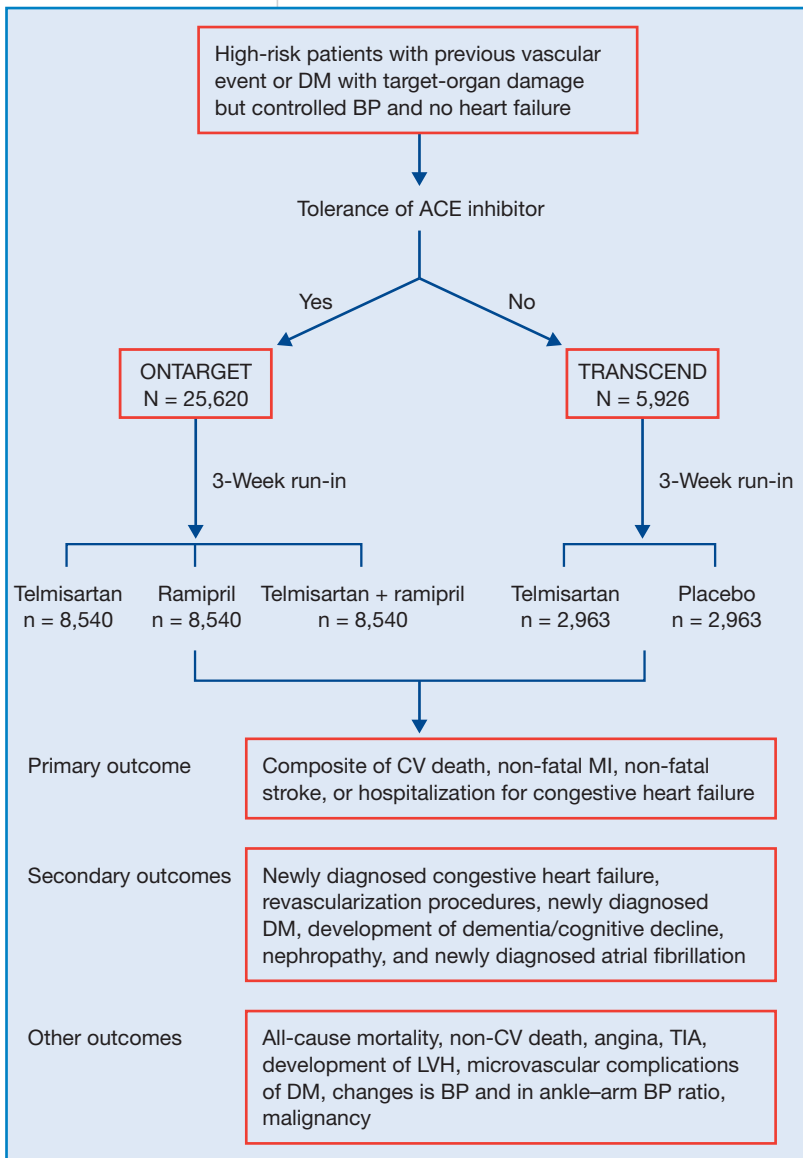
Appropriately characterized as a mega-trial, the ONTARGET/TRANSCEND programme has the potential to be a landmark in defining optimal therapy for the patient population being evaluated. The study is comparing strategies in the treatment of high-risk individuals commonly encountered in daily practice for their effect on the hard life-threatening end-points of greatest concern to patients and physicians, including MI and stroke.

For entry into the ONTARGET/TRANSCEND programme, patients were required to be aged ≥ 55 years, and at high risk of cardiovascular events due to the presence of vascular disease (coronary, peripheral, or cerebrovascular) or diabetes with end-organ damage. Patients with a history of hypertension were required to have controlled blood pressure. Patients with heart failure were excluded. Of the 31,546 patients recruited at 730 participating centres in 40 countries, 25,620 were entered into the ONTARGET trial.

The remaining 5,926 patients entered the TRANSCEND trial. All of the patients in the latter group had a history of ACE inhibitor intolerance (Figure). The entry criteria for ONTARGET and TRANSCEND were essentially identical, although patients with baseline proteinuria were excluded from TRANSCEND because this trial included a placebo arm. The chairman of the Steering Committee of the ONTARGET/TRANSCEND trial programme, which is being sponsored by Boehringer Ingelheim Inc., is Salim Yusuf (McMaster University, Hamilton, Canada). Peter Sleight (John Radcliffe Hospital, Oxford, UK) and Craig Anderson (University of Sydney, Sydney, Australia) are serving as co-chairmen.

Within 2 weeks of randomization, the active drugs in each treatment arm of both trials were titrated to full dose. For telmisartan alone, the dose was 80 mg once daily. For ramipril alone, the dose was 10 mg once daily. For the combination treatment, the doses were also telmisartan 80 mg and ramipril 10 mg taken once daily. All medications were administered in a double-blind fashion. Follow-up visits were conducted at 6 weeks, 6 months, and then every 6 months for the duration of the study. Recruitment for ONTARGET, with more than 8,000 patients in each of the 3 treatment arms, was completed in July 2003. Recruitment for TRANSCEND was completed in May 2004. When results are presented, the minimum follow-up for ONTARGET will be more than 4.5 years and the average follow-up will be approximately 5.5 years.

Figure. Study design and outcomes.
 ACE = angiotensin-converting enzyme;
 BP = blood pressure;
 CV = cardiovascular;
 DM = diabetes mellitus;
 LVH = left-ventricular hypertrophy;
 MI = myocardial infarction;
 TIA = transient ischaemic attack.



One of the most important features of the ONTARGET/TRANSCEND programme is that it was specifically designed to recruit a typical high-risk population. The participating institutions are distributed across both industrialized and developing nations, with representation from every inhabited continent in the world. Results of the trial are therefore expected to redefine medical practice. As the study tests new strategies against established practice, the results have the potential to reaffirm the current strategy or confirm a new standard of care.

Objectives of the ONTARGET trial

The primary objectives of the ONTARGET trial are to determine whether telmisartan plus ramipril is superior to ramipril alone, and whether telmisartan is at least as effective as ramipril (not inferior) at reducing the composite end-point of cardiovascular death, MI, stroke, or hospitalization for heart failure over the course of the trial.

In the TRANSCEND trial, telmisartan is being compared with placebo for the same primary outcomes. The secondary outcomes for

both studies are relative protection against newly diagnosed congestive heart failure, revascularization procedures, newly diagnosed diabetes, decline in cognitive function, nephropathy, and newly diagnosed atrial fibrillation. Other outcomes include rate of microvascular complications of diabetes and development of left-ventricular hypertrophy. In total, 7 substudies are embedded in the trial programme to evaluate further functional and morphological effects of angiotensin II type 1 (AT1) receptor blockade by telmisartan, ACE inhibition by ramipril, and the combination of both. The objectives of the substudies are mentioned in the Table. The TRANSCEND parallel trial programme permits relative benefits of RAS inhibition to be studied in ACE-inhibitor-intolerant patients, provides a placebo control arm for demonstrating the activity of telmisartan, and increases the power of the data for substudy outcomes looking at the role of RAS inhibition on related pathophysiological processes mediated by upregulation of the RAS, such as impaired glucose metabolism, renal dysfunction, and changes in cognitive function.

**The ONTARGET/
TRANSCEND trial
programme is
expected to clarify
whether it is
possible to build
on the previously
established benefits
of an ACE inhibitor
in a high-risk
population**

| Title of substudy | Objectives | Number of patients |
|---|--|--------------------|
| Biological samples collection for central laboratory analysis | Collection and storage of blood samples at baseline for analysis of novel risk factors and markers for cardiovascular disease | 12,000 |
| Oral glucose tolerance test (OGTT) | OGTT carried out in all TRANSCEND patients who are not known to have diabetes mellitus at baseline; 2-year follow-up and close-out; in a subsample, insulin sensitivity will be determined | 4,000 |
| Health economics | To determine resources used and direct medical costs associated with clinical events; to evaluate the impact of treatment programme on patient preference | 7,000 |
| Ambulatory blood pressure monitoring | To determine prognostic value of ambulatory blood pressure monitoring; to determine the effects of study medications | 1,000 |
| Cardiac MRI | To examine effects of treatment on cardiac structure and function | 350 |
| Arterial stiffness | To determine efficacy of telmisartan on arterial stiffness, estimated by pulse-wave velocity | 264 |
| Erectile dysfunction | To examine the effects of treatment on erectile dysfunction | 1,500 |

MRI = magnetic resonance imaging.

Table. Summary of substudies.

The primary objectives of ONTARGET are to determine whether telmisartan plus ramipril is superior to ramipril alone and whether telmisartan is at least as effective as ramipril

The 24-hour half-life of telmisartan may be relevant to many cardiovascular events associated with an early-morning surge in risk, such as stroke

The baseline characteristics of the patients recruited for the ONTARGET/TRANSCEND programme are representative of a high-risk population and are largely comparable to the patient population recruited for the HOPE trial. The average age in both the ONTARGET/TRANSCEND studies and in the HOPE trial was approximately 66 years. While 73% of those recruited for the ONTARGET and HOPE trials were male, 43% of those in the TRANSCEND study were male. In the HOPE trial, 53% of participants had a previous MI, while the percentages for ONTARGET and TRANSCEND are 49% and 46%, respectively. Slightly more than 35% of patients in all 3 studies were diabetic at baseline, but a previous diagnosis of hypertension was more common in the ONTARGET (68%) and TRANSCEND trials (76%) than in the HOPE (47%) trial. Although about 80% of patients in the HOPE trial had angina (about two-thirds of whom had stable angina), the proportion was half or less in the ONTARGET and TRANSCEND trials.

In contrast, about 20% of patients in the ONTARGET or TRANSCEND trial had previous stroke versus only 10% of patients in the HOPE trial. One particular difference between these studies is that only 11% of HOPE patients were taking an ACE inhibitor and no patients were taking an ARB at baseline. In the ONTARGET trial, 65% of patients were on one of these medications at baseline, and the proportion was close to 90% in the TRANSCEND trial.¹

The average baseline blood pressures in the HOPE (139/79 mmHg), ONTARGET (143/82 mmHg), or TRANSCEND trial (142/82 mmHg) were similar. In all three studies, the patients included did not have hypertension or were treated for this condition, as the goal was to investigate the effect of RAS blockade independent of change in blood pressure. In the HOPE trial, this strategy proved to be highly effective as the cardiovascular benefits demonstrated went beyond blood pressure lowering: the ACE inhibitor ramipril was associated with a 22% reduction ($p < 0.001$) in the composite end-point of MI, stroke, or death from cardiovascular causes relative to placebo, with only a modest change in blood pressure.

A subsequent trial with the ACE inhibitor perindopril, EUROPA (EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease), generated similar results in patients soon after MI.⁶ However, the relative benefits of an ARB in this population have not been well studied. Such relative benefits are important to explore for several reasons. One reason is that ARBs are

better tolerated than ACE inhibitors. Another is that these two classes of RAS inhibitor have different mechanisms of action, which may yield relative advantages or disadvantages for the composite primary outcome or for one or more of the secondary outcomes, such as protection from stroke, new-onset diabetes, or atrial fibrillation.

ACE inhibitors lower circulating levels of angiotensin II by blocking one of the enzymes involved in its synthesis.⁷ They also increase levels of bradykinin, a potent vasodilator. ARBs block angiotensin II at the AT1 receptor, the common final pathway of its effects. ARBs do not affect bradykinin levels but they do increase stimulation of the AT2 receptor, which has been associated with antiproliferative effects.⁸

The differences in these actions are the basis for suggesting that the two classes of drug may not be interchangeable for relative protection against an upregulated RAS. There has been frequent debate about the relative protection of ARBs and ACE inhibitors for numerous end-points, including stroke, MI, and nephropathy, but comparative data remain limited. The ONTARGET study will address these effects prospectively. In addition, the ONTARGET study will demonstrate whether dual blockade (ARB plus ACE inhibitor) provides additional benefits in terms of cardiovascular protection.

Although the ONTARGET trial has sometimes been characterized as an ACE-inhibitor-versus-ARB comparison, this is not entirely accurate. One reason is that dual RAS inhibition may prove to be the most potent strategy for reducing clinical events. There are already preliminary data supporting this hypothesis from a study in patients with left-ventricular dysfunction. In the RESOLVD trial (Randomized Evaluation of Strategies for Left Ventricular Dysfunction), which randomized patients with heart failure to an ARB, an ACE inhibitor, or their combination, dual therapy was associated with improved control of blood pressure, a reduction in activation of neurohormones, such as brain natriuretic peptide, and an improvement in left-ventricular function.⁹ The potential benefits of dual RAS inhibition may emanate from more complete blockade of angiotensin II, benefits mediated by their independent activities, or both.

The characterization as an ACE-inhibitor-versus-ARB comparison may also be inappropriate because the agents selected for study are not necessarily representative of their respective drug classes. Ramipril was an ACE inhibitor of interest because its benefits in a population such as that recruited for the ONTARGET/

TRANSCEND programme were already established in the HOPE trial. As a comparator, telmisartan has the longest duration of action of currently available ARBs.

The 24-hour half-life may be relevant to many cardiovascular events associated with an early-morning surge in risk, such as stroke. In addition, telmisartan has been associated with activities on nuclear receptors linked to favourable changes in glucose and lipid metabolism. Moreover, even differences in relative pharmacokinetics between telmisartan and other ARBs, such as the levels of tissue penetration or the rate of dissociation from the receptor, may be meaningful when administered chronically to explain differences in the prevention of disease processes. As a result, translation of ONTARGET/TRANSCEND results to other agents must be undertaken cautiously. If clear and convincing differences are observed between treatment strategies, the results of the ONTARGET/TRANSCEND programme have the potential to influence treatment guidelines. The study addresses a pertinent and pressing question in clinical management about the impact of the method and extent of RAS inhibition on cardiovascular event reductions. In addition, the relative benefits of the strategies evaluated in this study may provide new insight into the role of RAS in mediating vascular pathophysiology.

Conclusion

The HOPE trial established cardiovascular benefits of ACE inhibition with ramipril beyond blood pressure lowering. After the HOPE trial, some questions remained open regarding the cardiovascular benefits of other ways to block the RAS.

The results of the ONTARGET/TRANSCEND trial programme are expected to clarify whether the ARB telmisartan offers protection comparable to that of the ACE inhibitor ramipril and whether their combination is better than either RAS inhibitor alone. If significant differences are observed, they should redefine optimal clinical management in patients with established vascular disease as well as providing insight into the mechanisms by which RAS inhibition yields clinical risk reductions. ◀

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Akihiro Tojo

How to optimize the treatment of a hypertensive patient with multiple cardiovascular risk factors

Summary

Hypertensive patients often present with the metabolic syndrome, which includes central obesity, impaired glucose metabolism, and hyperlipidaemia, and they consequently have a high risk of cardiovascular diseases.

We treated a patient with a typical case of hypertension and metabolic syndrome with telmisartan. It reduced not only blood pressure but also fasting plasma glucose and glycosylated haemoglobin (HbA_{1c}). The angiotensin II type 1 (AT1) receptor blocker telmisartan also has peroxisome-proliferator-activated receptor gamma (PPAR-γ)-agonistic activity. Both working mechanisms may have influenced the beneficial effects of telmisartan in our patient.

Case report

A 62-year-old male was admitted to our hospital with renal dysfunction. He had an 18-year history of hypertension and was treated with amlodipine 5 mg and spironolactone 12.5 mg; he had been diabetic for 4 years and was treated with glimepiride 1 mg and was maintaining HbA_{1c} at 7.0%. His height was 166 cm, body weight was 83 kg, body mass index was 30.1 kg/m², and waist circumference was 92 cm (Japanese guidelines defining the metabolic syndrome specify a waist circumference > 85 cm in men). His blood pressure was 154/110 mmHg, fasting plasma glucose was 146 mg/dL, HbA_{1c} was 7.0%;

however, triglycerides and high-density lipoprotein (HDL) cholesterol were normal with simvastatin treatment.

He was diagnosed with the metabolic syndrome and multiple risk factors. His renal function was decreased with a serum creatinine level of 1.79 mg/dL and estimated glomerular filtration rate (eGFR) of 29 mL/min after treatment of lumbago with non-steroidal anti-inflammatory drugs (NSAIDs) for 1 month. After admission, NSAIDs were withdrawn and his serum creatinine decreased to 1.10 mg/dL and his eGFR increased to 50 mL/min, indicating that his renal function was at stage 3 of chronic kidney disease. Ultrasonography showed normal renal size and the carotid artery had hyper-echoic cholesterol plaque with a thickness of 1.5 mm even after the use of simvastatin and antiplatelet drugs for 3 years.

We changed his amlodipine treatment to telmisartan and we prescribed a diet with NaCl 6 g, protein 40 g, 1,600 kcal/day, and exercise on discharge. Sixteen weeks after discharge, not only blood pressure but also fasting plasma glucose, HbA_{1c}, and urinary protein were significantly ameliorated – associated with a 5 kg body weight reduction as shown in the Table.

Comment

In patients with the metabolic syndrome, we first manage their condition with diet, exercise, and changes in lifestyle. In cases of blood

Table. Effect of treatment with telmisartan on blood pressure, proteinuria, and HbA_{1c}.

| | Before | 4 weeks | 8 weeks | 16 weeks |
|-----------------------|---------|---------|---------|----------|
| Telmisartan (mg) | 0 | 20 | 40 | 40 |
| Spironolactone (mg) | 12.5 | 12.5 | 12.5 | 12.5 |
| Amlodipine (mg) | 5 | 2.5 | 0 | 0 |
| BP (mmHg) | 154/110 | 124/88 | 122/86 | 110/70 |
| UP (mg/g Cr) | 714 | 482 | 638 | 196 |
| FPG (mg/dL) | 146 | | | 112 |
| HbA _{1c} (%) | 7.0 | | | 6.1 |
| Triglycerides (mg/dL) | 103 | | | 101 |
| Body weight (kg) | 83 | | | 78 |

BP = blood pressure; Cr = creatinine; FPG = fasting plasma glucose; HbA_{1c} = glycosylated haemoglobin; UP = urinary protein.

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pressure ranging 130–139/80–89 mmHg, we observe the patients with lifestyle changes for a few months; however, patients with metabolic syndrome with blood pressure > 140/90 mmHg are started on treatment with a long-acting calcium-channel antagonist, angiotensin-converting enzyme (ACE) inhibitor, or AT1 receptor blocker (ARB) soon after we rule out the possibility of secondary hypertension by evaluating renal function, urinalysis, renin, aldosterone, cortisol, catecholamine, and renal ultrasonography as well as screening for hypertensive end-organ complications.

When possible, the patient receives in-hospital diet with 22–25 kcal/kg body weight, NaCl 6 g/day, and low cholesterol for 1 week. This effectively decreases blood pressure, especially in salt-sensitive hypertensive patients. When a patient shows a non-dipper hypertension profile by 24-hour blood pressure monitoring, we check the possibility of secondary hypertension as well as sleep apnoea syndrome. We check HOMA-IR (homeostasis model assessment of insulin resistance) to evaluate insulin resistance, and we also evaluate 24-hour creatinine clearance, urinalysis including microalbuminuria, funduscopy, electrocardiogram, and ultrasonography of the kidney, heart, and carotid arteries to evaluate micro- and macrovascular complications.

Previously, low-density lipoprotein (LDL) cholesterol levels, smoking, age, male gender, diabetes, hypertension, and obesity were considered independent additive risk factors

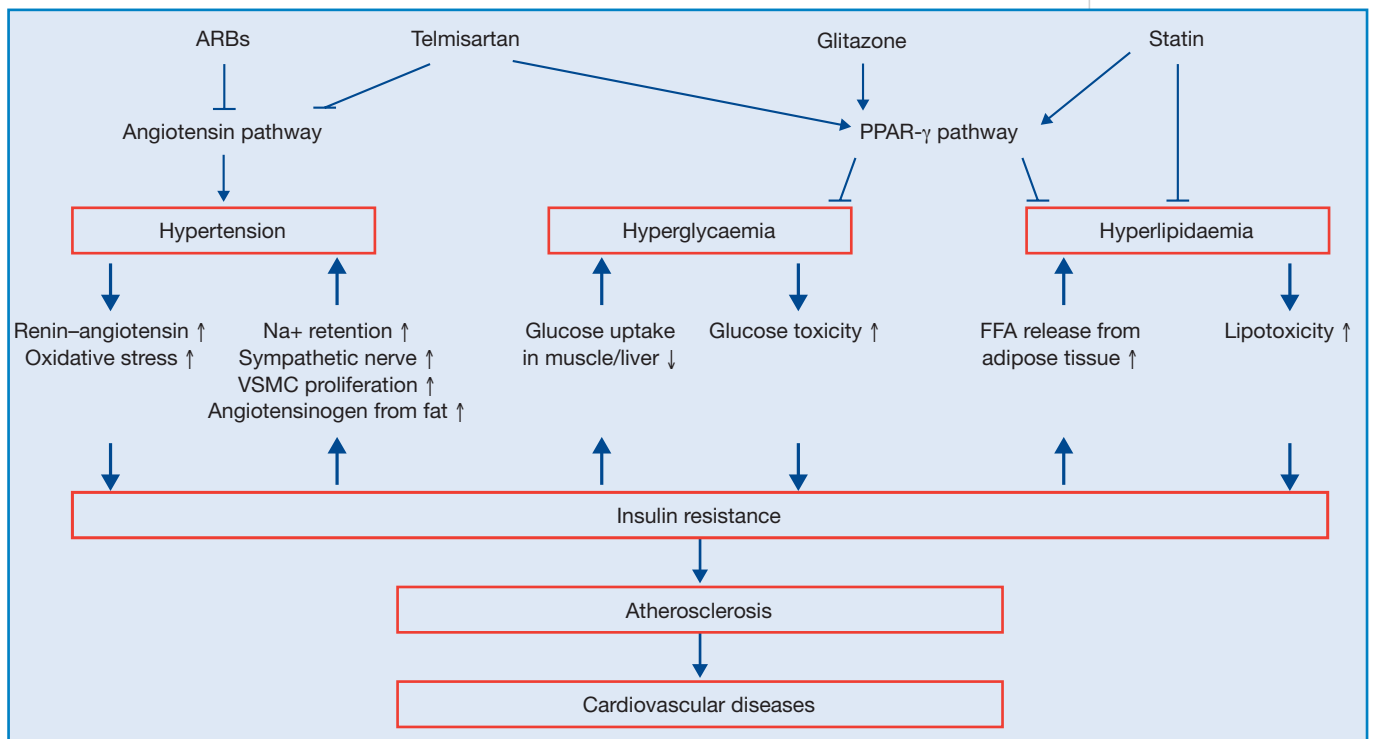
for the development of cardiovascular diseases, and of these, hypertension was considered the most important factor to be controlled. Recently, the number of obese patients has increased, and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria defined the metabolic syndrome as having 3 or more of the following: 1) central obesity (waist circumference > 102 cm in men or > 88 cm in women), 2) raised triglycerides (≥ 150 mg/dL), 3) reduced HDL cholesterol (< 40 mg/dL in men or < 50 mg/dL in women), 4) raised blood pressure (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg), 5) fasting glucose ≥ 110 mg/dL (including those with diabetes).¹

These are often coincident in the same patient. The risk of cardiovascular diseases increases 2–3 times in metabolic syndrome patients compared with non-metabolic syndrome patients.² In the metabolic syndrome, hyperinsulinaemia induces hypertension by several mechanisms, such as increased circulating volume consequent to increased sodium reabsorption, sympathetic nerve activation, vascular smooth-muscle cell proliferation, and angiotensinogen production from adipose tissue. In addition, hypertension itself stimulates the metabolic syndrome via an upregulated renin–angiotensin system (RAS) that increases oxidative stress and induces insulin resistance.³ Blood pressure should be kept below 130/80 mmHg and below 125/75 mmHg if proteinuria of more than 1 g/day is present.

Figure. Mechanism of cardiovascular disease in the metabolic syndrome, and the effect of telmisartan on the metabolic syndrome via angiotensin II receptor blockade and activation of PPAR- γ .

ARBs = angiotensin II receptor blockers; FFA = free fatty acid; PPAR- γ = peroxisome-proliferator-activated receptor gamma; VSMC = vascular smooth-muscle cell.

↑ = stimulation; ↓ = inhibition. Statin activates the PPAR- γ pathway and inhibits hyperlipidaemia. The angiotensin pathway accelerates hypertension; however, ARBs including telmisartan inhibit the angiotensin pathway.



It is important to control dyslipidaemia in patients with metabolic syndrome to prevent cardiovascular diseases. Insulin resistance stimulates triglyceride degradation and increases release of free fatty acid (FFA) from adipose tissue, which will increase triglyceride synthesis in the liver. Increased FFA induces insulin resistance in the muscle cells. The relationships between hypertension, hyperglycaemia, hyperlipidaemia, and insulin resistance are summarized in the Figure, and these factors promote atherosclerosis and result in cardiovascular diseases.

Hypertensive patients often present with the metabolic syndrome, including central obesity, impaired glucose metabolism, and hyperlipidaemia, increasing their risk for cardiovascular diseases

Our case illustrates how lifestyle changes, including exercise, weight management, and changing eating habits, are important in the metabolic syndrome and a reduction of 5 kg in body weight strikingly ameliorates metabolic disorders. If the patient remains hypertensive after a few months of lifestyle changes, we use ACE inhibitor or ARB treatment. Angiotensin II is known to activate nicotinamide adenine dinucleotide 3-phosphate (NADPH) oxidase and to increase oxidative stress, and the

blockade of the renin-angiotensin-aldosterone system (RAAS) decreases oxidative stress and ameliorates insulin resistance.⁴

Thiazide diuretics and beta-blockers are not first indicated because they can exacerbate metabolic disorders. ACE inhibitors and ARBs have been shown to reduce the incidence of new-onset type 2 diabetes.³ Among the ARBs, telmisartan and, to a lesser extent, irbesartan have PPAR- γ -agonist action and have been shown to ameliorate insulin resistance and triglycerides in rats fed a high-fat/high-

carbohydrate diet.^{5,6} Treatment with telmisartan even at a low dose improved insulin sensitivity in hypertensive patients with the metabolic syndrome.⁷

In addition, Miura et al.⁸ showed that treatment with telmisartan decreased fasting plasma insulin and serum triglycerides and improved total HDL cholesterol in hypertensive patients with type 2 diabetes. These results suggest that telmisartan has a beneficial effect in hypertensive patients with metabolic syndrome by suppression of the RAS, but it is reasonable to hypothesize that these specific actions of telmisartan are the result of telmisartan's PPAR- γ activity.

The beneficial cardiovascular effects of PPAR- γ activation were recently demonstrated by the PROactive trial (PROspective pioglitazone Clinical Trial In macroVascular Events), showing that a glitazone significantly reduced secondary cardiovascular events in 16% of patients with type 2 diabetes.⁹

Recently, we also demonstrated that telmisartan reduced plasma asymmetric dimethylarginine (ADMA), one of the new risk factors for cardiovascular diseases, by regulation of protein arginine N-methyltransferase 1 (PRMT-1) and dimethylarginine dimethylaminohydrolase (DDAH)-1 and DDAH-2 expression in the diabetic kidney.¹⁰

In the case reported here, the patient also had stage 3 chronic kidney disease, an important risk factor for cardiovascular diseases, and proteinuria was reduced by telmisartan treatment. Recently, the beneficial renal effects of telmisartan have been shown by the INNOVATION study (Incipient to Overt: Angiotensin II Receptor Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy), where telmisartan reduced the transition from incipient to overt nephropathy and induced remission of albuminuria in Japanese patients with type 2 diabetes.¹¹

Telmisartan has been shown to have beneficial effects on various parameters of the metabolic syndrome. These beneficial effects could be the result not only of its well-known potent AT1-receptor-antagonistic effect but also of its PPAR- γ -agonistic activity. However, specific actions of telmisartan need to be convincingly demonstrated in clinical trials in the metabolic syndrome. ◀

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Diabetic nephropathy represents the main cause of end-stage renal disease in western countries, and its incidence has grown dramatically over the last decades. Control of hypertension with agents that target the renin–angiotensin system has been shown to be renoprotective in both type 1 and 2 diabetic nephropathy. To maximize their effect, these therapies should be introduced in the early phases of the disease, before the development of microalbuminuria.



Giuseppe Remuzzi

What is the impact of RAS blockade on the progression of diabetic nephropathy?

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in western countries, and carries a 20- to 40-fold increased risk of cardiovascular mortality. In the past 2 decades, there has been a progressive increase in the incidence of ESRD in patients with diabetes, predominantly those with type 2 diabetes. The incidence of type 2 diabetes is greater than that of type 1 diabetes, and it has increased dramatically in the past few years. This is expected to translate into a growing number of patients who reach ESRD.^{1,2}

The natural history of diabetic nephropathy begins with an increase in renal perfusion, glomerular filtration rate (GFR), and probably also in intraglomerular capillary pressure. This is accompanied by a modification of the glomerular components (largely the basement membrane), particularly those resulting from non-enzymatic glycation and the accumulation of advanced-glycation end-products. These combined mechanisms result in pathological changes in the glomerular structure. In the initial phases of the disease, albumin appears selectively in the urine; subsequently, other proteins appear non-selectively, followed by loss of filtrate, and finally renal failure.³

Factors identified as determinants of the progression of diabetic nephropathy

Many factors have been identified as determinants of the progression of diabetic nephropathy, the most important of which

are hypertension and proteinuria.^{4,5} In diabetic patients, there is a clear relationship between mean arterial pressure and the annual percentage increase in urinary albumin excretion. Indeed, the diabetic kidney is very sensitive to increased blood pressure, as its regulation of intraglomerular pressure is impaired, so that small increases in blood pressure directly translate into increased urinary protein excretion.³ Thus, the ideal treatment for this population of patients should be based on drugs able to reduce both systemic and glomerular blood pressure, such as inhibitors of the renin–angiotensin system (RAS). The anti-proteinuric and nephroprotective effects of such drugs were originally thought to be attributable purely to haemodynamic effects, relieving the glomerulus by opening the efferent arterioles, thereby reducing glomerular capillary pressure.⁶ However, it has become apparent that angiotensin-converting enzyme (ACE) inhibitors also affect glomerular function by their effects on glomerular size and permeability, and by increasing the negative electrical charge of the glomerular membrane.⁷

A meta-analysis of 12 trials in 698 patients with type 1 diabetes followed up for at least 1 year showed that therapy with ACE inhibitors reduced the risk of progression to macroalbuminuria by 62% compared with that of the placebo group.⁸ Moreover, data are available showing that the beneficial effect of not only ACE inhibitors but also angiotensin II receptor blockers (ARBs) on

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Diabetic nephropathy is the leading cause of end-stage renal disease in western countries and carries a 20- to 40-fold increased risk of cardiovascular mortality

preventing progression from microalbuminuria to overt nephropathy is long-lasting (8 years), and is associated with preservation of normal GFR.⁹ Interestingly, the growing use of ACE inhibitors in the USA has been paralleled by a decrease in the incidence of ESRD due to type 1 diabetic nephropathy.¹⁰

A similar figure can be found when we consider patients with type 2 diabetes. The IRMA-2 trial (Irbesartan in patients with type 2 diabetes and MicroAlbuminuria) examined the effect of blockade of the RAS with ARBs in 590 hypertensive patients with type 2 diabetes and microalbuminuria.¹¹ The primary outcome was the time to onset of diabetic nephropathy, defined as persistent albuminuria. Ten (5.2%) of the 194 patients receiving 300 mg/day of irbesartan, 19 (9.7%)

of those on 150 mg/day, and 30 (14.9%) of the 201 patients in the placebo group reached the primary end-point (hazard ratios 0.30 and 0.61 for the two irbesartan groups, respectively). A more recent trial compared the effect of telmisartan over placebo in the prevention of transition from incipient to overt nephropathy in patients with type 2 diabetes.¹² After 1.3 ± 0.5 years of follow-up, transition rates to overt nephropathy were 16.7%, 22.6%, and 49.9% in the telmisartan 80 mg, telmisartan 40 mg, and placebo groups, respectively ($p < 0.0001$ for both doses of telmisartan vs placebo).

Two large trials examined the role of ARBs on the progression of renal disease in patients with type 2 diabetes and macroalbuminuria.^{13,14} The RENAAL study (Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan) showed that, compared with conventional

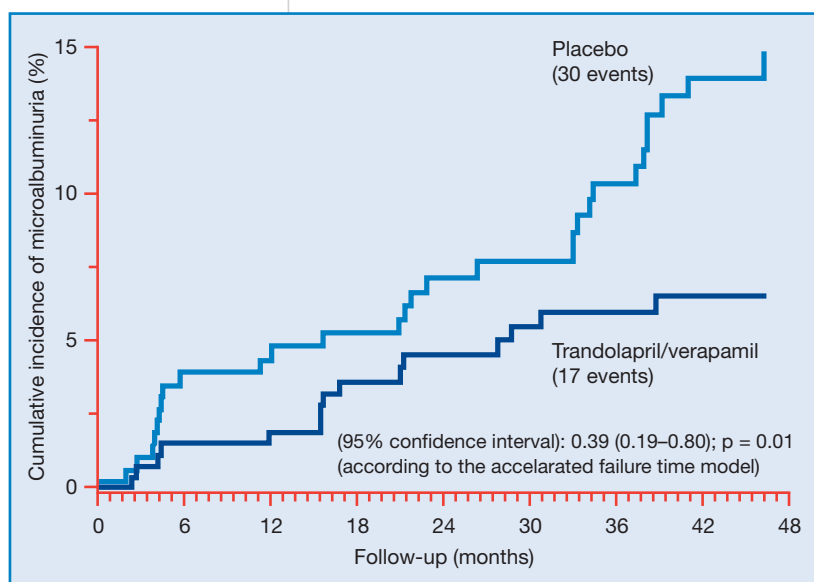
treatment alone (i.e. treatment without ACE inhibitors or ARBs), losartan combined with conventional treatment decreased the level of urinary protein excretion by 35% and reduced the risk of the composite end-point of doubling serum creatinine, ESRD, or death, by 22%.¹³ This beneficial effect was achieved at similar blood pressure control in the two treatment arms. In the IDNT (Irbesartan in Diabetic Nephropathy Trial), the risk of the combined end-point of a doubling of the baseline serum creatinine level, the onset of ESRD, or death from any cause was 20% lower in patients who were treated with irbesartan than in those treated with conventional therapy, and 23% lower than in those treated with amlodipine.¹⁴

Preventing the onset of microalbuminuria

However, the majority of patients with type 2 diabetes and renal involvement invariably progress towards ESRD or die prematurely of cardiovascular events. Thus, efforts should be aimed at preventing the onset of microalbuminuria, taken as an early marker of renal disease and/or cardiovascular risk. Using ACE inhibitors to control blood pressure in hypertensive diabetic patients with normoalbuminuria might prevent the future development of microalbuminuria. Moreover, as non-dihydropyridine calcium-channel blockers (nDCCB) seemed to possess nephroprotective effects as well as antihypertensive activity, a combined therapy with ACE inhibitors and nDCCB was speculated to be even more effective in preventing the onset of microalbuminuria than either drug alone.¹⁵

On this basis, we designed the BENEDICT (BErgamo NEphrologic DIabetes Complications Trial), which was a prospective, randomized, double-blind, parallel-group study aimed at assessing the efficacy of the ACE inhibitor trandolapril, the nDCCB verapamil, and the trandolapril plus verapamil combination compared with placebo in the prevention of microalbuminuria in hypertensive patients with type 2 diabetes and normal urinary albumin excretion rate.¹⁶ The primary end-point was the onset of microalbuminuria, which developed in 18 (6.0%) of 301 patients in the trandolapril group, 36 (11.9%) of the 303 patients receiving verapamil, 17 (5.7%) of those receiving combined therapy, and 30 (10%) of patients in the placebo group (Figure). Hence, compared with placebo, trandolapril delayed the onset of microalbuminuria by a factor of 2.1 ($p = 0.01$), and decreased the risk of microalbuminuria by 53% ($p = 0.01$), whereas verapamil had no significant effects.

Figure. Kaplan-Meier curves for patients with microalbuminuria during treatment with trandolapril plus verapamil versus placebo in the BENEDICT (BErgamo NEphrologic DIabetes Complications Trial).¹⁶



These data show that, in hypertensive patients with type 2 diabetes and normal renal function, an ACE inhibitor is effective in controlling blood pressure and at the same time preventing the onset of proteinuria. Moreover, 3 patients in the placebo group, 1 in the trandolapril group, and 1 in the verapamil group had a fatal cardiovascular event. No fatal cardiovascular events were reported in patients who received the combined treatment. These data confirm that, provided intensified metabolic and blood pressure control is pursued, patients with diabetes and normal urinary albumin excretion do not have a substantial excess cardiovascular risk compared with patients without diabetes. Thus, the BENEDICT study showed that diabetic nephropathy can be prevented by early intervention.

Renoprotection through combined RAS inhibition

Another example of renoprotection through RAS inhibition at the very early stage was given by Schmieder et al.,¹⁷ in the TRENDY trial (Telmisartan versus Ramipril in renal ENdothelium DYsfunction). This trial studied the effect of ramipril versus telmisartan on renal endothelial function (endothelial dysfunction is one of the earliest signs of vascular change provoking albuminuria and predicting cardiovascular outcomes) in hypertensive patients with type 2 diabetes without albuminuria. Both telmisartan and ramipril improved renal endothelial function, supporting the preservation of renal function.

Whether ACE inhibitors and ARBs exert the same anti-proteinuric and nephroprotective effects is still poorly defined. Results of the DETAIL trail (Diabetics Exposed to Telmisartan And enalapril) showed that, in patients with type 2 diabetes and early nephropathy, telmisartan was not inferior to enalapril in providing long-term renoprotection.¹⁸ Trials directly comparing the nephroprotective effects of ARBs and ACE inhibitors in later stages of diabetic nephropathy are lacking. Interest is now growing around the possibility that combined RAS inhibitor therapy might be more anti-proteinuric and nephroprotective compared with single RAS blockade therapy.

Recently, a sequential study compared the effect of single-drug therapy with telmisartan or lisinopril to combined telmisartan plus lisinopril therapy in type 2 diabetic patients with hypertension and microalbuminuria.¹⁹ Results showed a significant reduction in blood pressure and microalbuminuria using combined therapy compared with either

single-drug therapy. These promising data may prompt the design of larger randomized prospective trials comparing the effects of dual versus single RAS blockade at similar blood pressure levels in patients with type 2 diabetic nephropathy. Indeed, combined therapy might induce remission/regression of urinary protein excretion also at later stages of the disease. Moreover, at the stage of normal renal function, intervention with dual RAS blockade might prevent microalbuminuria more effectively compared with single-drug RAS inhibition.

Ongoing trails comparing ARBs to ACE inhibitors

A long-term landmark trial answering questions regarding the effects of ARBs compared with ACE inhibitors and the combination of both classes on diabetic nephropathy is the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial).²⁰ In the ONTARGET programme, more than 25,000 patients with elevated cardiovascular risk are being randomized to telmisartan 80 mg, ramipril 10 mg, or their combination. A parallel study in the ONTARGET programme called TRANSCEND (Telmisartan Randomized Assessment Study in aCE-iNtolerant subjects with cardiovascular Disease) is comparing telmisartan 80 mg with placebo in patients intolerant to ACE inhibitor. While the primary end-point of both studies is a composite end-point of cardiovascular events, secondary end-points will include protection against ESRD. Data from this trial programme will be available in the first half of 2008.

Conclusion

Before these data are available, nephrologists, diabetologists, and general practitioners should continue to cooperate closely to optimize metabolic and blood pressure control by using a RAS inhibitor (whenever it is not contraindicated), and to intensify patient monitoring (in particular of serum potassium levels) to increase compliance and minimize the risks of treatment. ◀

[References available from the publisher.](#)

A large body of evidence demonstrated a beneficial effect of both ACE inhibitors and ARBs in preventing diabetic nephropathy and slowing its progression

Improved insulin sensitivity and lipid profile with telmisartan in hypertension

Telmisartan was superior to enalapril in controlling 24-hour blood pressure in a study of patients with hypertension, glucose intolerance, hypercholesterolaemia, and obesity. Telmisartan, but not enalapril, was also shown to improve insulin sensitivity and lipid profile.

In a prospective, open-label, parallel-group trial, 80 patients with mild-to-moderate hypertension were randomized to treatment with telmisartan 40–80 mg/day (n = 40) or enalapril 10–20 mg/day (n = 40) for 8 weeks. After 8 weeks, 24-hour mean diastolic blood pressure was < 85 mmHg in 72% of telmisartan-treated patients but in only 48% of enalapril-treated patients (p < 0.05). Systolic and diastolic blood pressures were reduced more with telmisartan than with enalapril during the last 8 hours of the dosing interval (p < 0.05).

Telmisartan, but not enalapril, reduced fasting plasma glucose by 7%, fasting plasma insulin by 8%, HOMA-IR (homeostasis model assessment of insulin resistance) by 21% and glycosylated haemoglobin (HbA_{1c}) by 8% (all p < 0.05). Telmisartan, but not enalapril, also improved lipid profile, with a 17% reduction in plasma total cholesterol (p < 0.01), 13% reduction in low-density lipoprotein cholesterol (p < 0.01), and a 25% reduction in triglycerides (p < 0.05).

Demin A, Schuljatjeva O, Bondar I. New opportunities of PPAR(gamma)-activating angiotensin type-1 receptor blocker telmisartan in treatment of arterial hypertension with metabolic disturbances. *Eur Heart J.* 2007;28(Abstract Suppl):867 [P4842].

Telmisartan more effective than carvedilol in preventing atrial fibrillation

One of the goals of antihypertensive therapy is a lower incidence of atrial fibrillation (AF). In a study of 144 patients with mild hypertension and previous episodes of AF, telmisartan was more effective than was carvedilol in preventing new AF episodes.

The study recruited out-patients with mild hypertension who had experienced 1–4 electrocardiogram-documented episodes of AF in the previous 6 months, and it was completed by 124 patients (telmisartan, n = 66; carvedilol, n = 58). Following a 1-week placebo period, patients were randomized to treatment with telmisartan 80 mg/day or carvedilol 25 mg/day. After 12 months, blood pressure was significantly reduced in both groups (both p < 0.001) with no significant difference between groups.

An AF episode (symptomatic or asymptomatic) was reported in 13.6% of patients in the telmisartan group and 36.2% in the carvedilol group (p < 0.007, χ^2 -test). Left-atrial diameter was also smaller in the telmisartan group, but the difference was not significant (3.4 cm versus 3.6 cm, respectively). The results from this study suggest that telmisartan could favourably affect electrical and structural atrial remodelling in hypertensive patients.

Galzerano D, Caselli S, Breglio R, et al. Comparison of telmisartan with carvedilol in preventing atrial fibrillation recurrence in hypertensive patients: a multicentre study. *Eur Heart J.* 2007;28(Abstract Suppl):243 [P1488].

Telmisartan modulates lymphocyte activation through PPAR- γ

CD4-positive (CD4⁺) lymphocyte migration into the vessel wall is an important step in early atherogenesis. CD4⁺ lymphocytes express both angiotensin II type 1 (AT1) receptors and peroxisome-proliferator-activated receptor gamma (PPAR- γ). Telmisartan was shown to inhibit CD4⁺ cell migration stimulated with stromal-cell-derived factor 1 (SDF-1), and this effect was independent of angiotensin II receptor blockade but acted through PPAR- γ . SDF-1 stimulation of CD4⁺ lymphocytes induced a 4.5-fold increase in cell migration and this was dose-dependently inhibited by telmisartan pre-treatment. Telmisartan also inhibited RANTES-induced cell migration, suggesting an effect independent of the chemotactic stimulus used. The PPAR- γ activators rosiglitazone, pioglitazone, and GW1929 had similar effects, whereas eprosartan, an AT1 receptor blocker without PPAR- γ -activating activity, did not.

The use of phosphoinositide 3 (PI-3)-kinase activity assays showed that telmisartan's effect on CD4⁺ lymphocyte migration was induced through early chemokine-induced PI-3-kinase activity. Telmisartan also inhibited F-actin formation and intracellular adhesion molecule 3 (ICAM-3) translocation. Transfection of CD4⁺ lymphocytes with PPAR- γ small interfering RNA abolished telmisartan's effect, suggesting that telmisartan acts via PPAR- γ .

Marx N, Hess K, Heinz P, et al. Telmisartan inhibits CD4-positive lymphocyte migration via PPARgamma. *Eur Heart J.* 2007;28(Abstract Suppl):618 [P3637].



Telmisartan reverses loss of PPAR- γ signalling in ageing endothelial cells

Ageing of endothelial cells is associated with a reduction in synthesis of the vasodilator nitric oxide (NO). This study showed that ageing of endothelial cells in culture was associated with reduced expression of peroxisome-proliferator-activated receptor gamma (PPAR- γ), and this effect was reversed by telmisartan.

Endothelial cells were cultured until the 12th passage. Some cells were incubated with telmisartan, some with angiotensin II, and some with GW9662 (a PPAR- γ antagonist), with replacement every 48 hours, starting at the 4th passage. During endothelial ageing, PPAR- γ protein expression decreased significantly, whereas protein expression of angiotensin II type 1 receptor (AT1) increased. Telmisartan reversed these effects and dose-dependently decreased reactive oxygen species and 8-iso-prostaglandin F_{2 α} formation.

This was associated with upregulation of dimethylarginine dimethylaminohydrolase (DDAH), a decrease in asymmetric dimethylarginine (ADMA), increased NO metabolite, and delayed senescence. Activation of AT1 receptor with angiotensin II or blockade of PPAR- γ signalling with GW9662 prevented the effect of telmisartan on the ADMA-DDAH-NO system. The results suggest that telmisartan upregulates DDAH expression via decreased oxidative stress, causing ADMA to diminish and NO synthesis to increase.

Bode-Boeger SM, Martens Lobenhoffer J, Taeger M, et al. Influence of telmisartan on NO-asymmetric dimethylarginine (ADMA) system – role of AT1R and PPAR- γ signaling during the process of endothelial aging. *Eur Heart J.* 2007;28(Abtract Suppl):482 [P2861].

Visceral fat area reduced with telmisartan

Telmisartan treatment was shown to reduce the visceral fat area in patients with the metabolic syndrome. This randomized, prospective, open-label study enrolled 53 patients with the metabolic syndrome. Patients were randomized to treatment with either telmisartan (n = 27) or amlodipine (n = 26) for 24 weeks.

Telmisartan and amlodipine both reduced systolic and diastolic blood pressure to similar levels. Insulin and glucose levels during an oral 75 g glucose loading test, however, were decreased only in the telmisartan group. Visceral fat area as measured by an abdominal computerized tomography scan was reduced by telmisartan at 24 weeks but not by amlodipine. Adiponectin, a hormone produced from adipose

tissue that modulates glucose regulation and fatty acid catabolism and is inversely correlated with body fat percentage, was increased and plasma C-reactive protein was decreased with telmisartan treatment. These results suggest that telmisartan could treat both the haemodynamic and metabolic aberrations of the metabolic syndrome, with improvement of insulin resistance and adipocytokine profiles at least partly through visceral fat remodelling.

Shimabukoro M, Tanaka H, Shimabukoro T. Effects of telmisartan on fat distribution and adipocytokine profiles in subjects with the metabolic syndrome. *Eur Heart J.* 2007;28(Abtract Suppl):348 [P2096].

VCAM-1 expression and oxidative damage modulated by telmisartan

Telmisartan modulated the expression of vascular cell adhesion molecule 1 (VCAM-1), which promotes the adhesion of inflammatory cells to the endothelium, and reduced oxidative damage in cultured cells. These effects were found to be independent of angiotensin II receptor blockade and peroxisome-proliferator-activated receptor gamma (PPAR- γ) agonism.

Cultured human umbilical-vein endothelial cells (HUVEC) were stimulated by tumour necrosis factor alpha, an inflammatory cytokine that acts independently of angiotensin II receptor stimulation, to produce VCAM-1, which was measured by enzyme-linked immunosorbent assay (ELISA). Telmisartan was found to dose-dependently reduce the stimulation of VCAM-1, whereas losartan, another angiotensin II receptor blocker, and dexamethasone were ineffective.

Ciglitazone and rosiglitazone, PPAR- γ agonists, did not reduce VCAM-1 stimulation, and two PPAR- γ antagonists did not reverse telmisartan inhibition of VCAM-1 expression. Telmisartan, but not losartan, also reduced the damage to DNA caused by H₂O₂.

The modulation of VCAM-1 expression and protection against oxidative damage by telmisartan may contribute to its clinical effects.

Del Fiorentino A, Cianchetti S, Colognato R, et al. Telmisartan modulates endothelial inflammation and oxidative damage independent of angiotensin II antagonism and PPAR-gamma agonism in human umbilical vein endothelial cells. *Eur Heart J.* 2007;28(Abtract Suppl):477-8 [P2844].

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European Society of Cardiology (ESC) Congress 2007; 1–5 September; Vienna, Austria.

Hypertension control outside the clinic

Banegas JR, Segura J, Sobrino J, et al. Effectiveness of blood pressure control outside the medical setting. Hypertension. 2007;49:62-8.

Adequate control of hypertension is low in population and medical settings. However, physicians frequently mis-classify patient blood pressure (BP) status at the office compared with ambulatory BP monitoring (ABPM). In particular, BP readings are higher in standard clinical practice than in ambulatory readings. Nevertheless, the magnitude of the difference in control between office and ambulatory BP has not been noted in large-scale studies addressing daily practice. We have studied, for the first time, the effectiveness of BP control outside the clinic, by using ABPM in a large number of hypertensive patients treated in primary-care centres across Spain.

We used the Spanish Society of Hypertension (SEH) ABPM Registry, based on a large-scale network of Spanish physicians trained in ABPM – a network of approximately 1,100 clinical researchers using the same methodology to perform ABPM on more than 36,000 out-patients. The present study consisted of 12,897 consecutively recruited, treated hypertensive patients who had indications for ABPM. Office-based BP was calculated as the average of two readings. 24-Hour ABPM was then performed using a SpaceLabs 90207 monitor under standardized conditions. ABPM was regarded as valid only if at least 80% of systolic (SBP) and diastolic (DBP) blood pressures during the 24-hour period were satisfactory.

The mean age of the patients was 61.9 ± 12.3 years (52.4% males), SBP/DBP at the office was 149.4 ± 19.3 / 86.8 ± 11.6 mmHg, and

daytime ambulatory BP was 133.1 ± 14.7 / 78.7 ± 10.5 mmHg. A total of 3,047 (23.6%) patients had their office BP controlled, 6,657 (51.6%) were controlled according to daytime ABPM, and 2,351 (18.2%) were controlled by both methods (Table). The proportion of office resistance or underestimation of patient BP control by physicians in the office (office BP ≥ 140/90 mmHg, and average daytime ambulatory BP < 135/85 mmHg) was 33.4%, and the proportion of isolated office control or overestimation of control (office BP < 140/90 mmHg, and average daytime ambulatory BP ≥ 135/85 mmHg) was 5.4%. Some factors partially explained the disparity between ABPM and office BP control in the present study. BP control was more commonly underestimated in patients who were older, female, obese, or with morning BP determination, than in their counterparts. BP control was more commonly overestimated in those who were younger, male, non-obese, smokers, or with evening BP determination.

In conclusion, this study shows ABPM-based hypertension control at about 52% – a much better value than that for office-based hypertension control (24%). In particular, the gap between office and ambulatory control was most marked among women (33%), older patients (32%), and those presenting with obesity (32%) (data not shown). This conveys a reassuring message to practising physicians, inasmuch as they are doing better in BP control than is believed on the basis of office- or population-based surveys, especially in Europe. However, the burden of under- and overestimation of BP control at the office is still remarkable. Physicians should be aware that the likelihood of mis-estimating BP control is higher in some hypertensive patients.

| Office BP (SBP/DBP) | Daytime ambulatory BP (SBP/DBP) | | Total |
|---------------------------------------|---|---|-----------------------------|
| | Controlled (< 135/< 85 mmHg) | Uncontrolled (≥ 135 and/or ≥ 85 mmHg) | |
| Controlled (< 140/< 90 mmHg) | Concordant control 2,351 18.2% (17.5–18.9%) | Isolated office control 696 5.4% (5.0–5.8%) | 3,047 23.6% (22.9–24.3%) |
| Uncontrolled (≥ 140 and/or ≥ 90 mmHg) | Office resistance 4,306 33.4% (32.6–34.2%) | Concordant lack of control 5,544 43.0% (42.1–43.8%) | 9,850 76.4% (75.7–77.1%) |
| Total | 6,657 51.6% (50.7–52.5%) | 6,240 48.4% (47.5–49.3%) | 12,897 100% |

Data presented are number and percentage (95% confidence interval) of patients.
BP = blood pressure; DBP = diastolic BP; SBP = systolic BP.

Table. Control of blood pressure among treated hypertensives, according to office and ambulatory blood pressure criteria.

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14.05 – 17.05.2008 New Orleans (USA)

23rd Annual Meeting of the American Society of Hypertension (ASH)

Information: The American Society of Hypertension, 148 Madison Avenue, 5th Floor, New York, NY 10016, USA, tel: +1 2126969099, fax: +1 2126960711, internet: www.ash-us.org/

18.05 – 21.05.2008 Buenos Aires (Argentina)

16th World Congress of Cardiology



Information: ICS, C.C. (PO Box) 73, C1084ZAA, Buenos Aires, Argentina, tel: +54 1148123444, fax: +54 1148130073, email: wcc2008@congresosint.com.ar, internet: www.worldcardiocongress.org/

14.06 – 19.06.2008 Berlin (Germany)

18th Scientific Meeting of the European Society of Hypertension and the 22nd Scientific Meeting of the International Society of Hypertension (ESH-ISH)

Information: Hypertension 2008 Conference Secretariat, c/o K.I.T. GmbH Association & Conference Management Group & Co. KG, Ms. Vanessa King, Kurfürstendamm 71, 10709 Berlin, Germany, tel: +49 30246030, fax: +49 3024603200, email: vking@kit-group.org, internet: www.hypertension2008.com/

30.08 – 03.09.2008 Munich (Germany)

European Society of Cardiology Congress 2007 (ESC)

Information: European Society of Cardiology, The European Heart House, 2035 Route des Colles, B.P. 179 – Les Templiers, 06903 Sophia Antipolis, France, tel: +33 492947600, fax: +33 492947601, email: webmaster@escardio.org, internet: www.escardio.org

25.09 – 27.09.2008 Los Angeles (USA)

6th Annual World Congress on Insulin Resistance Syndrome (WCIRS)

Information: Metabolic Endocrine Education Foundation, 18372 Clark Street, Suite 212, Tarzana, CA 91356, USA, tel: +1 8183421889, fax: +1 8183421538, email: insulinresistance@pacbell.net, internet: www.insulinresistance.us/

29.10 – 02.11.2008 Barcelona (Spain)

2nd Congress on Controversies to Consensus in Obesity, Diabetes and Hypertension (CODHy)

Information: Comtecmed Medical Congresses, Headquarters and Administration, 53 Rothschild Blvd, PO Box 68, Tel Aviv 61000, Israel, tel: +972 35666166, fax: +972 35666177, email: info@comtecmed.com, or: codhy@codhy.com, internet: www.codhy.com/

2009

01-04 – 04.04.2009 Nice (France)

3rd International Congress on Prediabetes and the Metabolic Syndrome

Information: Kenes International, Global Congress Organizers and Association Management Services, 17 Rue du Cendrier, PO Box 1726, 1211 Geneva 1, Switzerland, tel: +41 229080488, fax: +41 227322850, email: prediabetes2009@kenes.com; internet: www.kenes.com/prediabetes/



05.05 – 08.05.2009 San Francisco (USA)

24th Annual Meeting of the American Society of Hypertension (ASH)

Information: The American Society of Hypertension, 148 Madison Avenue, 5th Floor, New York, NY 10016, USA, tel: +1 2126969099, fax: +1 2126960711, internet: www.ash-us.org/

29.08 – 02.09.2009 Barcelona (Spain)

2009 Congress of the European Society of Cardiology (ESC)

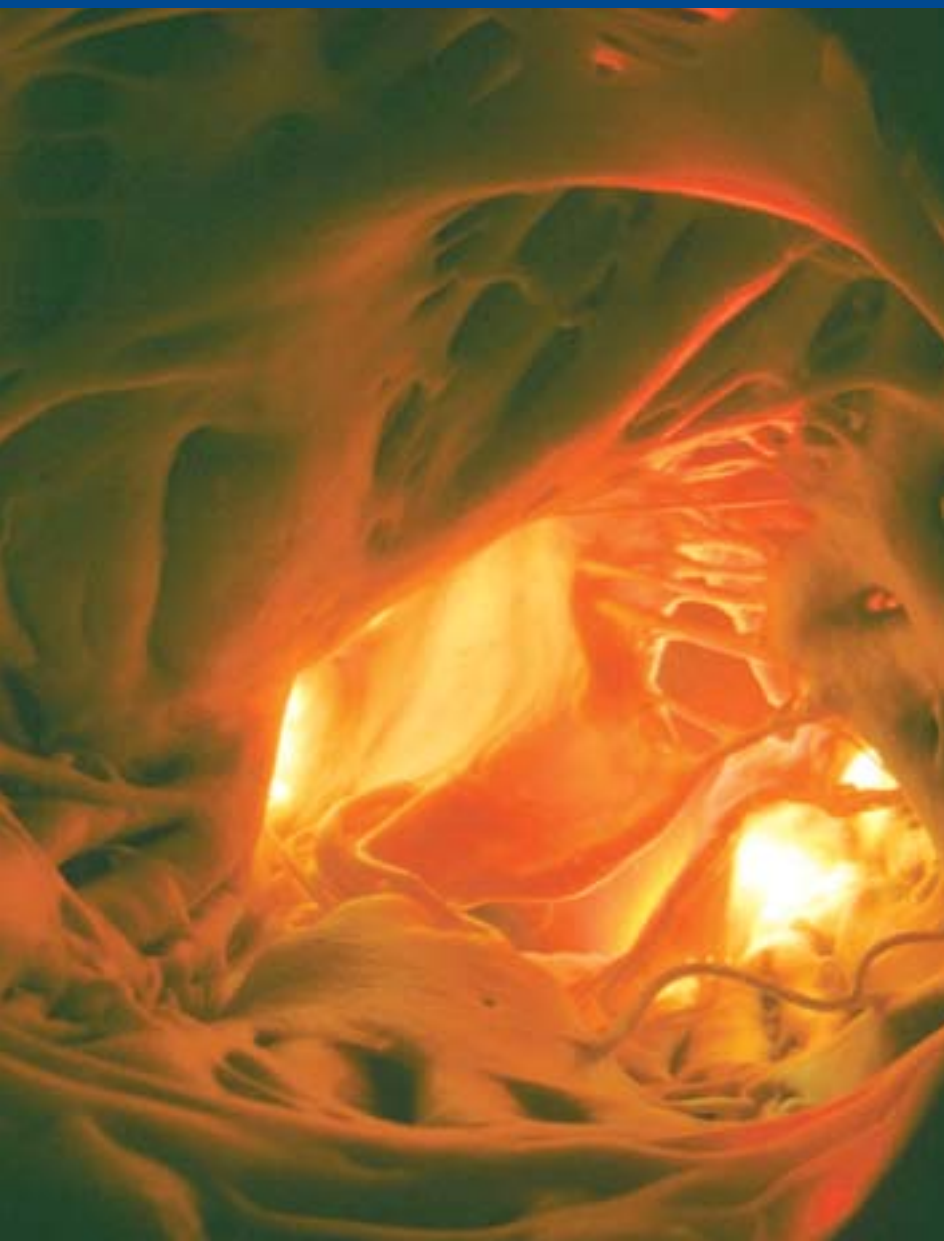
Information: European Society of Cardiology, The European Heart House, 2035 Route des Colles, B.P. 179 – Les Templiers, 06903 Sophia Antipolis, France, tel: +33 492947600, fax: +33 492947601, internet: www.escardio.org/

26.09 – 01.10.2009 Vienna (Austria)

45th Annual Meeting of the European Association for the Study of Diabetes (EASD)

Information: EASD Secretariat, Rheindorfer Weg 3, 40591 Düsseldorf, Germany, tel: +49 2117584690, fax: +49 21175846929, email: secretariat@easd.org, internet: www.easd.org/





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