

RENIN ANGIOTENSIN SYSTEM IN CARDIOVASCULAR MEDICINE

EDITORIAL

How can we identify patients at risk, and how do we prevent cardiovascular events?

CLINICAL ARTICLE

Renoprotection by blockade of the RAAS: a matter of blood pressure or more?

PHYSIOLOGICAL ARTICLE

Emerging risk biomarkers of cardiovascular disease and the metabolic syndrome

CASE REPORT

Microalbuminuria: an intermediate end-point when treating hypertension

CLINICAL QUERY

How to best manage high morning blood pressure in patients with diabetic nephropathy?

INTERVIEW

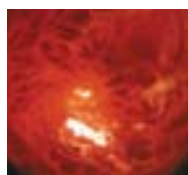
Prospects for better prevention of stroke: the RAS system

NEWS ITEMS

EXTENDED ABSTRACTS

CONGRESS CALENDAR





E D I T O R I A L

- 1** **How can we identify patients at risk, and how do we prevent cardiovascular events?**
Ulrich Kintscher, and Thomas Unger

C L I N I C A L A R T I C L E

- 2** **Renoprotection by blockade of the RAAS: a matter of blood pressure or more?**
Adrienne A.M. Zandbergen, Liffert Vogt

P H Y S I O L O G I C A L A R T I C L E

- 5** **Emerging risk biomarkers of cardiovascular disease and the metabolic syndrome**
Ulrich Kintscher

C A S E R E P O R T

- 9** **Microalbuminuria: an intermediate end-point when treating hypertension**
Josep Redon

C L I N I C A L Q U E R Y

- 12** **How to best manage high morning blood pressure in patients with diabetic nephropathy?**
Philippe Gosse

I N T E R V I E W

- 14** **Prospects for better prevention of stroke: the RAS system**
with Hans-Christoph Diener – By Ted Bosworth

N E W S I T E M S

18

E X T E N D E D A B S T R A C T S

20

C O N G R E S S C A L E N D A R

25



EDITORIAL BOARD

Editor-in-Chief

Thomas Unger
Director, Center for Cardiovascular Research (CCR)
Institut für Pharmakologie und Toxikologie
Campus Charité Mitte
Charité – Universitätsmedizin Berlin
Berlin, Germany

Adviser

Kazuomi Kario
Jichi Medical School
Yakushiji, Minamikawachi-cho
Kawachi, Tochigi, Japan

Board Members

Toshiro Fujita
Dept. of Nephrology and Endocrinology
The University of Tokyo, Tokyo, Japan

Giuseppe Mancia
Dept. of Clinical Medicine, University of
Milano-Bicocca, San Gerardo Hospital
Monza-Milan, Italy

Eberhard Ritz
Dept. of Internal Medicine, Ruperto Carola
University, Heidelberg, Germany

Luis M. Ruilope
Hypertension Unit, Hospital 12 de Octubre
Madrid, Spain

Michael A. Weber
Professor of Medicine and Associate Dean
for Clinical Research, SUNY Downstate
College of Medicine, Brooklyn, NY, USA

© 2007 Elsevier BV

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior written permission of the copyright owner. No responsibility is assumed by the Publisher for any injury and/or damage to persons or property as a matter of products liability, through negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein. Because of rapid advances in the medical sciences, the Publisher recommends that independent verification of diagnoses and drug dosages should be made. Opinions expressed in this publication are those of the original authors and

do not necessarily reflect those of the Publisher, the sponsor, or the editors. Elsevier assumes no liability for any material published herein.

ISSN 1574-2466

Supported by an educational grant from Boehringer Ingelheim

Produced by Excerpta Medica
Radarweg 29, 1043 NX Amsterdam
Netherlands

Telephone +31 20 485 3909
Fax +31 20 485 3199

Editorial Executive: Emmy Vermeulen
Email: E.Vermeulen@elsevier.com

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

How can we identify patients at risk, and how do we prevent cardiovascular events?

In the present issue of *RAS in Cardiovascular Medicine* the role of microalbuminuria as a cardiovascular risk marker and the potential function of adipose secretion products as biomarkers for cardiometabolic risk are discussed. Josep Redon emphasizes the importance of the analysis of urinary albumin excretion (UAE) for cardiovascular risk assessment, and points out that microalbuminuria might even be an intermediate end-point itself. Along these lines, Ulrich Kintscher discusses the role of adipocytokines as important mediators of the pathogenesis of cardiovascular disease in patients with metabolic risk (e.g. patients with the metabolic syndrome), and their future capabilities as new biomarkers for such diseases. Despite the availability of valid risk markers such as UAE, the adequate detection of individuals from the general population who are at risk of developing cardiovascular disease or disease-mediating risk factors still remains a matter of debate.

In January 2007 the European Society of Cardiology together with the European Association for the Study of Diabetes published new guidelines on diabetes, pre-diabetes, and cardiovascular disease,¹ in which this problem with respect to diabetes/pre-diabetes is discussed. The guidelines state that 3 general approaches for early detection do exist: 1) measuring biochemical parameters (in this case blood glucose) to determine prevalent impaired glucose homeostasis; 2) using demographic and clinical characteristics and previous laboratory tests to determine the likelihood of future diabetes; and 3) collecting questionnaire-based information on factors that provide information about the presence and extent of a number of aetiological factors for disease (such as type 2 diabetes). After discussing the different conditions under which the distinct strategies are most suitable, the authors come to a recommendation that primary screening for the potential of disease (type 2 diabetes) can be done most efficiently using a non-invasive risk score, subsequently combined with a diagnostic laboratory analysis (oral glucose tolerance test) to test people with high scores.

Based on extensive experience in risk stratification for diabetes in Finland, the guidelines recommend the use of a very simple risk assessment form developed by the Finnish Diabetes Association.² This form comprises

a number of simple questions, which can be answered directly by patients while they wait for their doctor's appointment. Completed by the anthropometric measurement of body mass index and waist circumference, any practising doctor could have a valid risk score on hand when the patient enters their office. Depending on the resulting score, the decision for subsequent laboratory tests such as UAE, blood glucose, glucose tolerance test, etc., could be made. The implementation of such questionnaires in additional areas of cardiovascular risk management that go beyond glucose homeostasis may be a promising and cost-effective tool for the identification of people at risk.

The next question in cardiovascular risk management we have to answer is: What might be the best strategy to prevent cardiovascular events and to lower risk? With a focus on primary prevention, it has now been established and widely accepted that lifestyle interventions are very efficient in reducing not only the incidence of disease-mediating risk factors but also end-organ damage. However, these interventions are labour intensive, and results achieved in research settings are often difficult to replicate even in well-funded healthcare systems. Therefore, considerable interest has focused on prevention with drugs. In this issue, Zandbergen and Vogt, Gosse, and Diener discuss different topics in cardiovascular prevention including renoprotection and stroke prevention with inhibitors of RAS. With regard to this, the pharmacological characteristics of preventive drugs need to be analysed. The following prerequisites should be fulfilled: 1) clinical efficacy; 2) high tolerability for long-term treatment; and 3) cost-effectiveness. Based on multiple randomized clinical trials, blockers of the RAS seem to be optimal substances for prevention, particularly ARBs. It is well documented that ARBs effectively prevent risk factor occurrence such as new-onset diabetes, as well as end-organ damage such as renal failure or stroke, as discussed in articles in this issue.

References

1. Ryden L, Standl E, Bartnik M, et al. *Eur Heart J*. 2007;28:88-136.
2. Finnish Diabetes Association. Type 2 diabetes risk assessment form. Available from: www.diabetes.fi/tiedoston_katsominen.php?dok_id=567.



Thomas Unger



Ulrich Kintscher

**Thomas Unger and
Ulrich Kintscher**
Center for Cardiovascular
Research (CCR)
Institut für Pharmakologie
und Toxikologie
Campus Charité Mitte
Charité – Universitäts-
medizin Berlin
Berlin, Germany

Clinical studies have shown that lowering blood pressure (BP) reduces the rate of renal function loss in patients with chronic renal disease. There is evidence that intervention with the renin–angiotensin–aldosterone system (RAAS) has additive renoprotective effects next to BP reduction. Proteinuria is an accepted risk factor for renal function loss. In intervention studies it has been shown that the more proteinuria is reduced, the better the kidney appears to be protected. The main evidence for a specific renoprotective action of RAAS inhibitors is provided by their consistent antiproteinuric action that cannot completely be attributed to the BP-lowering effects of these drugs.

Renoprotection by blockade of the RAAS: a matter of blood pressure or more?

2

Blocking the RAAS has additive renoprotective effects next to BP reduction

Adrienne A.M. Zandbergen¹, Liffert Vogt^{2*}

¹Department of Internal Medicine, Erasmus Medical Centre, Rotterdam; ²Division of Nephrology, Dept of Internal Medicine, Westfries Gasthuis Hospital, Hoorn; Netherlands
*Corresponding author.

It is widely recognized that renoprotective therapy starts with antihypertensive treatment. Numerous recent large clinical trials indicate that, in patients suffering from diabetic or non-diabetic nephropathy, antihypertensive treatment intervening with the RAAS in particular appears to be effective in retarding the decline of renal function.¹

Other clinical trials suggest that BP reduction itself may be more important than the treatment used in reducing the incidence of diabetic complications, such as nephropathy.²

Here we focus on the question whether some classes of antihypertensive drug have additive renoprotective effects next to BP reduction in diabetic and non-diabetic renal disease patients.

Reduction of BP affords renoprotection

Elevated BP is considered the most important risk factor for renal function loss. Reduction of an elevated BP lowers the incidence of renal deterioration in high-risk patients.^{2,3}

In the Modification of Diet in Renal Disease (MDRD) study, patients with chronic renal disease of diverse cause were randomly assigned to either a usual or a low BP goal (i.e. mean arterial pressure [MAP] 98 vs 92 mmHg).³ In this study, a higher mean MAP was associated with a faster decline in glomerular filtration

rate, particularly in patients with higher baseline proteinuria (≥ 1 g/day). Also, a review of long-term clinical trials in both diabetic and non-diabetic hypertensive patients showed a positive relationship between the achieved BP and the rate of renal functional decline.⁴ Data from this review indicate that the BP goal should be $< 130/80$ mmHg to optimally preserve renal functioning in patients with diabetic and non-diabetic nephropathy.

In line with the latter, current guidelines for antihypertensive treatment, such as the 2004 guidelines of the Kidney Disease Outcomes Quality Initiative (K/DOQI), therefore advise to pursue a strict BP control of 130/80 mmHg or even lower in diabetic patients and proteinuric non-diabetic patients.⁵

Specific renoprotective effect depends on class of antihypertensive drug

Notwithstanding the improvement of renal outcome by lowering BP, interesting differences in renoprotective effects have been observed between different classes of antihypertensive drug. In patients with chronic renal disease of diverse causes, RAAS inhibitors have shown renoprotective effects that cannot be completely attributed to the BP-lowering effect of the drugs.¹

A recent study by Zandbergen et al.⁶ in diabetic patients showed that the antiproteinuric effect

- Correction of volume excess
 - restriction of dietary sodium intake to 50–100 mmol/day and/or
 - combined therapy with diuretic
- Dose titration with ACE inhibitor or ARB to reduce proteinuria further than needed for adequate blood pressure control
- Combined treatment with both an ACE inhibitor and an ARB
- Combined treatment with a statin
- Combined treatment with an NSAID

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; NSAID = non-steroidal anti-inflammatory drug; RAAS = renin-angiotensin-aldosterone system.

Table. Strategies for optimizing the antiproteinuric response of a RAAS-blockade-based regimen in patients with proteinuria ≥ 1 g/day.

of the angiotensin II receptor blocker (ARB) losartan was independent of the associated reduction in BP. In line with this study, the IRbesartan MicroAlbuminuria in type 2 diabetes mellitus (IRMA-2) study demonstrated that this ARB dose-dependently reduced the risk of progression to overt diabetic nephropathy, without additional BP effects.⁷ Another study⁸ in non-diabetic patients showed that a shift to a higher dose of a RAAS inhibitor did not improve BP reduction, whereas proteinuria was additionally reduced. Similar results were found in hypertensive diabetic patients. When the ARB telmisartan was combined with amlodipine, up-titration of telmisartan, despite similar BP reduction, resulted in better proteinuria reduction. Up-titration with amlodipine with stable telmisartan did not have additional renoprotective effects.⁹

In addition, the second Ramipril Efficacy in Nephropathy (REIN-2) trial with hard renal end-points showed that intensified BP control by adding a calcium-channel antagonist to an angiotensin-converting enzyme (ACE)-inhibitor-based regimen provided added BP reduction, but proteinuria remained equal in the two treatment arms throughout the study.¹⁰ Thus, these studies show that RAAS inhibitors, but not conventional antihypertensive drugs, have additive effects on proteinuria that are independent of changes in BP. In these studies, the relationship between proteinuria and renal function decline was shown to be threefold. Firstly, baseline proteinuria is an important determinant of the renoprotective benefit in the follow-up after reduction of BP, as demonstrated by the MDRD and REIN-2 studies.^{1,3} Secondly, the extent to which proteinuria is reduced during antihypertensive treatment is also of prognostic value.¹ Thirdly, the residual proteinuria during treatment was correlated with the subsequent progression of renal function loss.¹

This observation that residual proteinuria is a main prognostic factor has implications for

therapy, as monitoring residual proteinuria during therapy can serve as a short-term indicator of renoprotective efficacy in the long term. Given that both ACE inhibitors and ARBs exert BP-lowering and antiproteinuric effects, it can be conceived that both classes of drug have renoprotective effects in common, although a direct comparison between the different RAAS inhibitors has not yet been made. This question is currently being addressed by the VIVALDI and AMADEO trials comparing the effects of telmisartan and valsartan, and telmisartan and losartan, respectively, on proteinuria as well as mediators of endothelium-mediated vascular function and inflammation.

Proteinuria as treatment target

For the purpose of optimal management of renal risk, it has been advocated to reduce proteinuria to the lowest possible level. The K/DOQI guidelines state that RAAS inhibitors are the preferred antihypertensive drugs in patients with diabetic or non-diabetic proteinuric nephropathy, because these drugs exert renoprotective effects exceeding the reduction in BP.⁵

According to the guidelines, additional measures to a RAAS-based regimen should be undertaken when proteinuria exceeds 1 g/day. For optimizing proteinuria reduction, different measures are available, as outlined in the Table. Among them is more complete blockade of the RAAS by using both ACE inhibitors and ARBs, i.e. dual RAAS blockade with drugs interfering with the RAAS on different levels.

Currently, a large ongoing clinical trial in more than 31,000 high-risk patients, the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in aCE-

The current guidelines for antihypertensive treatment advise to pursue a strict blood pressure control of 130/80 mmHg or even lower

The available evidence emphasizes the need for reduction of proteinuria to levels as low as possible

intolerant subjects with cardiovascular Disease (ONTARGET/TRANSCEND),¹¹ is investigating whether dual RAAS blockade may more effectively prevent cardiovascular events and reduce the incidence of nephropathy compared with single RAAS blockade. It would be of

particular interest whether this study confirms the expected benefits of dual RAAS blockade to be related to a dissociation of drug-specific characteristics and BP effects, on renal as well as hard cardiovascular end-points.

In conclusion, specific renoprotective effects of RAAS blockade are related to proteinuria reduction. Therefore, the available evidence emphasizes the need for reduction of proteinuria to levels as low as possible, in addition to optimal BP control. ◀

References

1. Vogt L, Navis G, de Zeeuw D. *J Am Soc Nephrol.* 2002;13 Suppl 3:S202-7.
2. UK Prospective Diabetes Study Group. *BMJ.* 1998;317:713-20.
3. Peterson JC, Adler S, Burkart JM, et al. *Ann Intern Med.* 1995;123:754-62.
4. Bakris GL, Williams M, Dworkin L, et al. *Am J Kidney Dis.* 2000;36:646-61.
5. Kidney Disease Outcomes Quality Initiative (K/DOQI). *Am J Kidney Dis.* 2004; 43(5 Suppl 1):S1-S290.
6. Zandbergen AA, Baggen MG, Lamberts SW, et al. *Ann Intern Med.* 2003;139:90-6.
7. Parving HH, Lehnert H, Brochner-Mortensen J, et al. *N Engl J Med.* 2001;345:870-8.
8. Gansevoort RT, de Zeeuw D, de Jong PE. *Kidney Int.* 1994;45:861-7.
9. Fogari R. *J Clin Hypertens.* 2006;8 Suppl:361A.
10. Ruggenenti P, Perna A, Loriga G, et al. *Lancet.* 2005;365:939-46.
11. Teo K, Yusuf S, Sleight P, et al. *Am Heart J.* 2004;148:52-61.

Visceral obesity as part of the metabolic syndrome is an important mediator of cardiovascular risk implicating adipose tissue and its secretion products as central pathophysiological contributors. Therefore, diagnostic monitoring and therapeutic regulation of adipose tissue products such as adipocytokines seem to be revealing biomarkers and future tools for metabolic-syndrome and cardiovascular risk management, whereby adiponectin holds a unique position.

Modulation of adiponectin by renin–angiotensin system (RAS) inhibitors may provide a new therapeutic strategy for people with the metabolic syndrome. More importantly, the therapeutic application of multimodal drugs such as peroxisome-proliferator-activated receptor gamma (PPAR- γ)-activating angiotensin II type 1 (AT1) receptor blockers (ARBs), which effectively target adiponectin, might even be more effective for cardiovascular risk reduction in patients with the metabolic syndrome.



Ulrich Kintscher

Emerging risk biomarkers of cardiovascular disease and the metabolic syndrome

Obesity, the metabolic syndrome, and cardiovascular risk

The prevalence of overweight and obesity continues to increase at dramatic, epidemic rates. The International Obesity Task Force estimates that at present at least 1.1 billion adults worldwide are overweight including 312 million who are obese.¹

Obesity is strongly associated with an increased risk of type 2 diabetes, hypertension, dyslipidaemia, and subsequent cardiovascular disease.¹ Therefore, obesity, and in particular visceral obesity, has been defined as the major component of a risk factor cluster for the atherosclerotic cardiovascular disease known as the metabolic syndrome.²

Currently, the International Diabetes Federation defines the metabolic syndrome as central obesity (defined as waist circumference \geq 94 cm for European men, and \geq 80 cm for European women, with ethnicity-specific values for other groups) plus 2 of the following 4 factors: 1) raised triglyceride level (\geq 150 mg/dL), or specific treatment for this lipid abnormality;

2) reduced high-density lipoprotein cholesterol ($<$ 40 mg/dL in males, and $<$ 50 mg/dL in females), or specific treatment for this lipid abnormality; 3) raised blood pressure (systolic blood pressure \geq 130 mmHg or diastolic blood pressure \geq 85 mmHg), or treatment of previously diagnosed hypertension; and 4) raised fasting plasma glucose (\geq 100 mg/dL), or previously diagnosed type 2 diabetes.²

Each component of the metabolic syndrome is an established cardiovascular risk factor; however, it has now become increasingly clear that the presence of multiple components of the metabolic syndrome confers greater risk than the sum of the risks associated with each individual factor.³

The Kuopio Ischaemic Heart Disease Risk Factor study showed that cardiovascular disease and cardiovascular mortality increased in men with the metabolic syndrome. There was a relative risk of almost 4.0 for coronary heart disease, and 3.5 for cardiovascular mortality in patients with the metabolic syndrome.⁴

Ulrich Kintscher
Center for Cardiovascular Research (CCR)
Institut für Pharmakologie und Toxikologie
Campus Charité Mitte
Charité – Universitätsmedizin Berlin
Berlin, Germany

Adiponectin as a new biomarker and therapeutic target

Given the dramatic increase in the prevalence of obesity and the metabolic syndrome, prevention of the long-term complications and comorbidities becomes increasingly important. The key to a successful prevention programme depends on the early identification, treatment, and monitoring of people with the metabolic syndrome who are at high risk of cardiovascular events.

To improve the accuracy of risk identification, the use of additional biomarkers has been proposed. Given the major role of adipose tissue in the pathophysiology of the metabolic syndrome and associated cardiovascular disease, bioactive proteins secreted by adipocytes – known as adipocytokines (adiponectin, leptin, tumour necrosis factor- α [TNF- α], interleukin-6, etc.) – may act as such biomarkers. Adiponectin is a peptide with 247 amino acids, predominantly secreted by fat cells, and a promising candidate for future risk evaluation.⁵ Adiponectin has been identified as an important insulin-sensitizing hormone.⁵

Accumulating experimental evidence indicates that adiponectin possesses potent anti-inflammatory and antiatherogenic actions.⁶ More importantly, clinical studies have demonstrated that low plasma concentrations of adiponectin are closely associated with coronary artery disease and cardiovascular events, whereas high plasma concentrations are associated with a lower risk of myocardial infarction (Table).^{7,8}

In addition, adiponectin has been well characterized as a potential predictor of type 2 diabetes. Low concentrations of plasma adiponectin correlated strongly with reduced insulin sensitivity, and individuals with high concentrations of adiponectin were less likely to develop type 2 diabetes than those with low concentrations.⁹ Therefore, adiponectin may not only serve as a future biomarker for cardiovascular risk and diabetes development, but may also provide a promising target for drug therapy to lower the risk of cardiometabolic disease.

TNF- α and cardiometabolic disease

In addition to “classic” adipocytokines such as adiponectin, adipose tissue produces numerous other cytokines among which TNF- α is an important player during the development of the metabolic syndrome and associated cardiovascular disease. TNF- α is secreted by adipocytes and markedly contributes to the initiation and progression of obesity-related insulin resistance.

Increased TNF- α plasma levels are observed in patients with the metabolic syndrome, and TNF- α induces vascular dysfunction as assessed by endothelium-dependent vasodilation.^{10,11} Experimental and clinical studies have identified TNF- α as a potential pathophysiological arbitrator between metabolic disorders and cardiovascular end-organ damage – depicting this adipocytokine as a potential biomarker of the metabolic syndrome and related cardiovascular disease.

Table. Estimated RR of MI during 6 years of follow-up according to the quintile of baseline adiponectin levels (n = 798). (Reproduced with permission from Pischon T, et al.⁸)

	Quintile*					p value for trend†
	1	2	3	4	5	
Plasma adiponectin level, mg/dL, median (range)*	7.9 (2.4–10.5)	12.6 (10.6–14.5)	16.5 (14.6–18.5)	21.1 (18.6–24.8)	29.2 (24.9–56.1)	
Model, RR (95% CI)						
Adjusted for matched variables‡	1.00	0.70 (0.45–1.08)	0.63 (0.40–0.99)	0.61 (0.39–0.96)	0.39 (0.23–0.64)	< 0.001
Multivariable§	1.00	0.72 (0.46–1.14)	0.69 (0.43–1.09)	0.70 (0.44–1.13)	0.41 (0.24–0.70)	< 0.001

After adjustment for matched variables, participants in the highest compared with the lowest quintile of adiponectin levels had a significantly decreased risk of MI (RR, 0.39; 95% CI, 0.23–0.64; p < 0.001 for trend on a log scale). Further adjustment for body mass index, family history of MI, history of diabetes and hypertension, alcohol consumption, and physical activity at baseline did not substantively affect this relationship (RR, 0.41; 95% CI, 0.24–0.70; p < 0.001 for log trend).

*Quintiles, medians, and ranges of adiponectin levels are based on controls only.

†p value for trend based on log-transformed adiponectin levels.

‡Adjusted for matched variables (age, smoking status, and month of blood draw).

§Adjusted for matched variables, body mass index, family history of MI before age 60 years, history of diabetes, history of hypertension, alcohol intake, and physical activity.

CI = confidence interval; MI = myocardial infarction; RR = relative risk.

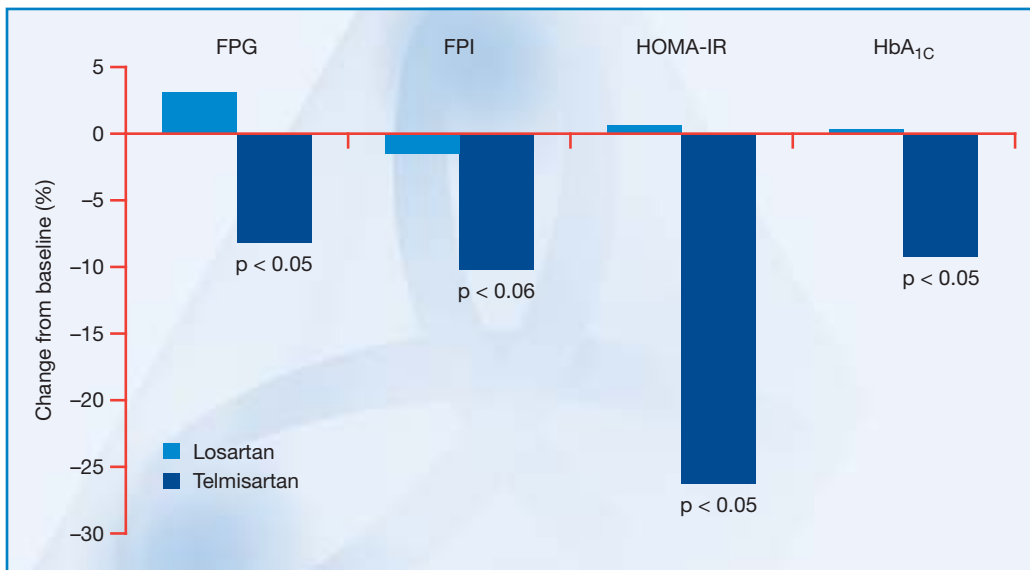


Figure. Effect of telmisartan and losartan on measures of glycaemia and insulin resistance in 40 patients with the metabolic syndrome. *p* values indicate telmisartan vs losartan comparison. Compared with losartan, telmisartan reduced FPG by 8% ($p < 0.05$), FPI by 10% ($p < 0.06$), HOMA-IR by 26% ($p < 0.05$), and HbA_{1c} by 9% ($p < 0.05$). FPG = fasting plasma glucose; FPI = fasting plasma insulin; HbA_{1c} = glycosylated haemoglobin; HOMA-IR = homeostasis model assessment – insulin resistance. (Reproduced with permission from Vitale C, et al.¹⁹)

Assuming that bioactive adipocytokines play a major role in the development of the metabolic syndrome and cardiovascular disease, pharmacological modulation of adipocytokine expression or plasma levels would be a promising preventive tool for such cardiometabolic risk management.

Adiponectin – a target of the RAS

The RAS is a major peptide hormone system involved in the regulation of blood pressure and fluid homeostasis. Recently, blockade of the RAS by either angiotensin-converting enzyme (ACE) inhibitors or selective ARBs has been shown to exert potent antidiabetic actions.¹²

Interestingly, adiponectin has been identified as one of the potential mechanistic mediators of the antidiabetic actions of RAS inhibitors. In experimental studies, Clasen et al. used murine 3T3-L1 adipocytes, and found that angiotensin II via AT2 receptor stimulation increased adiponectin protein expression.¹³

In addition, treatment of cells with ARBs also led to a significant increase in adiponectin protein. However, ARB-mediated adiponectin upregulation started beyond the concentrations needed for AT1 receptor blockade, implicating additional AT1-receptor-independent mechanisms of adiponectin regulation.

The clinical significance of this effect was demonstrated by a study of 12 insulin-resistant and 18 non-insulin-resistant hypertensive patients, 16 of whom were given either temocapril 4 mg or candesartan 16 mg for 2 weeks.¹⁴ Both treatments significantly increased adiponectin levels, although the magnitude of the effect in the candesartan group (increase of 30%) was double that in

the temocapril group (15%). In summary, these data indicate that the RAS and RAS-interfering compounds are important regulators of adiponectin.

ARBs induce adiponectin independently of AT1 receptor blockade

The fact that ARB concentrations for adiponectin stimulation are far higher than concentrations needed for AT1 receptor blockade implies potential “pleiotropic” compound actions responsible for these effects. A subgroup of ARBs has been identified as partial agonists at the nuclear hormone receptor PPAR- γ , independently of their AT1-blocking actions.^{15,16} Among the PPAR- γ -activating ARBs, telmisartan seems to be the most potent activator of PPAR- γ , reaching sufficiently high concentrations during usual antihypertensive dosing.

In addition to its role in adipocyte differentiation, PPAR- γ has been described as a central modulator of insulin and glucose metabolism.¹⁷ An important insulin-sensitizing mechanism of PPAR- γ ligands is a marked upregulation of adiponectin plasma levels.¹⁸ In accordance with these results, PPAR- γ -activating ARBs have been demonstrated to induce adiponectin protein expression in adipocytes, whereas non-PPAR- γ -activating ARBs lack this effect.¹³

Furthermore, the results of studies showing adiponectin regulation by PPAR- γ -activating ARBs are in line with the metabolic actions observed in clinical trials. Telmisartan has been shown to improve parameters of insulin resistance and glucose intolerance in patients with the metabolic syndrome or type 2 diabetes, whereas ARBs with less PPAR- γ -activating potency failed to exert these actions. In addition, a clinical study in diabetic patients



demonstrated that telmisartan significantly induced adiponectin levels, whereas treatment with an ACE inhibitor failed to show this effect (Figure).¹⁹

In summary, visceral obesity as part of the metabolic syndrome is an important mediator of cardiovascular risk implicating adipose tissue and its secretion products as central pathophysiological contributors. Therefore, diagnostic monitoring and therapeutic regulation of adipose tissue products such as adipocytokines seem to be future tools for metabolic-syndrome and cardiovascular risk management, whereby adiponectin holds a unique position.

Modulation of adiponectin by RAS inhibitors may provide a new therapeutic strategy for individuals with the metabolic syndrome. More importantly, the therapeutic application of multimodal drugs such as PPAR- γ -activating ARBs, which effectively target adiponectin, might even be more effective for cardiovascular risk reduction in patients with the metabolic syndrome. ◀

References

1. Haslam DW, James WP. *Lancet*. 2005;366:1197-209.
2. Alberti KG, Zimmet P, Shaw J. *Lancet*. 2005;366:1059-62.
3. Isomaa B, Almgren P, Tuomi T, et al. *Diabetes Care*. 2001;24:683-9.
4. Lakka HM, Laaksonen DE, Lakka TA, et al. *JAMA*. 2002;288:2709-16.
5. Kadowaki T, Yamauchi T, Kubota N, et al. *J Clin Invest*. 2006;116:1784-92.
6. Nakamura T, Funayama H, Kubo N, et al. *Circ J*. 2006;70:1557-62.
7. Kumada M, Kihara S, Sumitsuji S, et al. *Arterioscler Thromb Vasc Biol*. 2003;23:85-9.
8. Pischon T, Girman CJ, Hotamisligil GS, et al. *JAMA*. 2004;291:1730-7.
9. Lindsay RS, Funahashi T, Hanson RL, et al. *Lancet*. 2002;360:57-8.
10. Matsushita K, Yatsuya H, Tamakoshi K, et al. *Arterioscler Thromb Vasc Biol*. 2006;26:871-6.
11. Rask-Madsen C, Dominguez H, Ihlemann N, et al. *Circulation*. 2003;108:1815-21.
12. Scheen AJ. *Drugs*. 2004;64:2537-65.
13. Clasen R, Schupp M, Foryst-Ludwig A, et al. *Hypertension*. 2005;46:137-43.
14. Furuhashi M, Ura N, Higashiura K, et al. *Hypertension*. 2003;42:76-81.
15. Benson SC, Pershadsingh HA, Ho CI, et al. *Hypertension*. 2004;43:993-1002.
16. Schupp M, Janke J, Clasen R, et al. *Circulation*. 2004;109:2054-7.
17. Picard F, Auwerx J. *Annu Rev Nutr*. 2002;22:167-97.
18. Maeda N, Takahashi M, Funahashi T, et al. *Diabetes*. 2001;50:2094-9.
19. Vitale C, Mercurio G, Castiglioni C, et al. *Cardiovasc Diabetol*. 2005;4:6.

Microalbuminuria: an intermediate end-point when treating hypertension

Summary

A stage II hypertensive patient with well-controlled type 2 diabetes who met the criteria for the metabolic syndrome showed an increased urinary albumin excretion (UAE), the only marker of target-organ damage. After treatment with telmisartan, blood pressure was reduced, UAE was normalized, and the metabolic parameters improved. The possible explanation for these findings is discussed here.

Case report

A 54-year-old man attended the hypertension clinic because of the recent onset of frequent headaches. Four years ago, at a routine visit, his blood pressure was 150/100 mmHg. Salt restriction and antihypertensive medication were prescribed, but the patient only took the medication for 2 months. One year ago, type 2 diabetes was discovered, and a tailored diet and metformin treatment were introduced. The patient lost weight, and fasting glycaemia and glycosylated haemoglobin (HbA_{1c}) values decreased below the goal thresholds.

On physical examination, the patient's weight was 81 kg with a body mass index of 28 kg/m², and his waist measured 103 cm. The patient's blood pressure was 162/98 mmHg, and his pulse was 76 beats per minute; other vital signs were normal. Extraocular movements and visual fields were intact. Funduscopy demonstrated Keith-Wagener grade II hypertensive retinopathy. Thyroid size was normal, with no palpable nodules. There was no increase in supraclavicular or dorsal adipose tissue. The abdomen was not tender, and murmurs or masses were absent. Proximal muscle strength and reflexes were normal. There was no peripheral oedema, and symmetric pulses were present in the four extremities.

Haematological laboratory values were normal. No sign of left-ventricular hypertrophy (Cornell criteria) was present in the electrocardiogram. Blood chemical and enzyme levels were normal except for fasting glucose (112 mg/dL), serum creatinine (1.4 mg/dL) (estimated glomerular filtration rate: 53 mL/min/1.73 m²), high-density lipoprotein (HDL) cholesterol (35 mg/dL), triglycerides (198 mg/dL), and uric acid (7.8 mg/dL). HbA_{1c} was 5.9%. UAE was 102 mg/24 hours.

Albumin:creatinine ratio in a spot urine sample was 14 mg/mmoL Cr.

In summary, the patient had stage II hypertension, type 2 diabetes, clear signs of the metabolic syndrome according to the Adult Treatment Panel III criteria¹ (5 criteria of the metabolic syndrome: blood pressure, waist, fasting glucose, triglycerides, and HDL) and a clear increase in UAE. Despite the fact that the patient was clearly overweight, his diabetes was under control.

According to guidelines from the European Society of Hypertension and the European Society of Cardiology,² the patient was at high risk of cardiovascular events (20–30% absolute risk, Framingham score) and mortality. Likewise, according to the UK Prospective Diabetes Study, microalbuminuric diabetes patients have a 3 times greater risk of cardiovascular events than those with normal UAE.³

Microalbuminuria is a sign of nephropathy and indicates a higher risk of cardiovascular and cerebrovascular disease, and progression of renal damage. In line with the guidelines, the patient was treated with inhibitors of the renin-angiotensin-aldosterone system: telmisartan 80 mg once daily was prescribed.

Twelve weeks later, the patient's blood pressure remained at about 145/85 mmHg, and his fasting blood glucose level ranged between 105 and 110 mg/dL. HbA_{1c} and triglyceride values decreased to 5.7% and 135 mg/dL, respectively. Albumin:creatinine ratio in a morning spot urine was reduced to 6 mg/mmoL Cr. Treatment with hydrochlorothiazide 12.5 mg once daily was added, with further improvement of blood pressure values (135/80 mmHg), and normalization of microalbuminuria (2 mg/mmoL Cr) in the absence of significant changes in the metabolic parameters (fasting glycaemia 110 mg/dL, HbA_{1c} 5.7%, and triglycerides 145 mg/dL).

Comments

In this patient, microalbuminuria is not only a marker of cardiovascular risk and progression of renal damage but it is also an intermediate end-point to be targeted during antihypertensive treatment. As a measure of this intermediate



Josep Redon

Microalbuminuria is not only a sign of nephropathy and a marker of cardiovascular risk, but it is also an intermediate end-point to be targeted during antihypertensive treatment

Josep Redon
Hypertension Clinic,
Internal Medicine,
University of Valencia,
Valencia, Spain

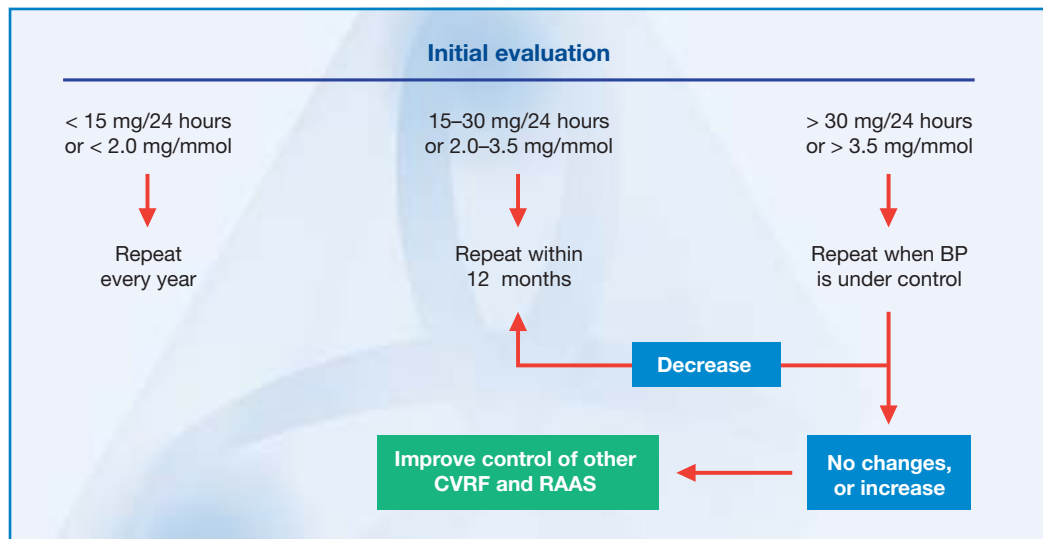


Figure. Microalbuminuria during antihypertensive treatment in type 2 diabetes. BP = blood pressure; CVRF = cardiovascular risk factors; RAAS = renin-angiotensin-aldosterone system.

end-point, UAE is cheap and easy to use, and it can be repeated when necessary. Furthermore, changes induced by therapy are rapidly observed.

Microalbuminuria has become a prognostic marker for cardiovascular risk and/or progression of renal damage in diabetic and non-diabetic patients.⁴ Consequently, microalbuminuria assessment is now recommended in a risk stratification strategy not only in diabetic patients, but also in hypertension management because assessment of subtle increases in UAE is a powerful way to identify those with multiple cardiovascular risk factors. Changes in UAE seem to run in parallel with cardiovascular risk, and prompt intervention to avoid the progressive increase in UAE may result in better protection against hypertension-induced morbidity and mortality.

Prevalence of microalbuminuria in the general population is less than 10%, but in hypertensive and diabetic patients the prevalence rises to about 20% and 30%, respectively. The

definition of microalbuminuria comes from studies that have established its value as a marker of risk of progression of renal damage in diabetic patients. When the potential prognostic value of microalbuminuria with respect to cardiovascular disease was being assessed in both diabetic and non-diabetic populations, the threshold pointing to an increased risk was largely below the UAE value of 30 mg/24 hours regardless of the population studied. Consequently, the use of the term microalbuminuria as defined by values according to conventional thresholds (UAE 30–300 mg/24 hours) may be misleading, and the use of UAE per se, avoiding categorization

with a given threshold, should be encouraged. How to assess UAE is an important issue. Collecting and measuring albumin in urine samples over 24 hours (mg/24 hours) or timed-overnight ($\mu\text{g}/\text{minute}$) is frequently used in specialized settings. In contrast, for primary-care and epidemiological studies, a correction is performed by simultaneously assessing creatinine excretion (mg/mg Cr or mg/mmol Cr) in spot samples, collected from the first voided urine or at the time of the clinic visit. The Figure shows an algorithm giving recommendations for assessing UAE in patients with type 2 diabetes. Correspondence between the different UAE values at the level of the classic threshold to define microalbuminuria (> 30 mg/24 hours) and the lowest UAE that points to an increased cardiovascular risk ($5 \mu\text{g}/\text{minute}$ at night) has been published.⁵ Measuring the albumin:creatinine ratio in a spot urine is a reliable method not only for screening but also for monitoring the success of treatment.

Both antidiabetic and antihypertensive treatments affect UAE: blood pressure reduction and improved glucose metabolism decrease UAE. The main factors during antihypertensive treatment that reduce UAE are both blood pressure reduction itself and adequate 24-hour blood pressure control. In addition, blocking the renin-angiotensin system exerts an additional UAE reduction beyond the blood-pressure-lowering effect.⁶

In the patient discussed in this case report, UAE was high despite the diabetes being under control. Administration of telmisartan reduced UAE almost 50%, achieving a successful reduction when blood pressure was totally under control after adding the thiazide diuretic. Effective 24-hour blood pressure control with telmisartan has been shown in many

As a measure of the intermediate end-point of microalbuminuria, UAE is cheap and easy to use, it can be repeated when necessary, and changes induced by therapy are rapidly observed

studies.^{7,8} A significant UAE-reducing effect with telmisartan, beyond the blood-pressure-lowering effect, has been described by Vogt et al.⁹ In the patient discussed here, the following factor seems to be important in the UAE reduction seen after treatment with telmisartan: reducing the angiotensin-II-mediated impact on the endothelium and glomerulus by blocking the angiotensin II type 1 (AT1) receptor. ◀

References

1. Available from: www.nhlbi.nih.gov/guidelines/cholesterol/index.htm.
2. European Society of Hypertension-European Society of Cardiology Guidelines Committee. *J Hypertens*. 2003;21:1011-53.
3. UK Prospective Diabetes Study Group. *BMJ*. 1998;317:713-20.
4. Redon J. *Nephrol Dial Transplant*. 2006;21:573-6.
5. Klausen KP, Scharling H, Jensen G, et al. *Hypertension*. 2005;46:33-7.
6. Parving HH, Andersen S, Jacobsen P, et al. *Semin Nephrol*. 2004;24:147-57.
7. Battershill AJ, Scott LJ. *Drugs*. 2006;66:51-83.
8. Neutel J, Smith DH. *J Clin Hypertens (Greenwich)*. 2003;5:58-63.
9. Vogt L, Navis G, Koster J, et al. *J Hypertens*. 2005;23:2055-61.



Philippe Gosse

Patients with diabetic nephropathy have a very high risk of cardiovascular events. They require optimal blood pressure (BP) control both during the day and night and especially during the early morning hours. High morning BP, which can now be assessed with ambulatory blood pressure monitoring (ABPM) or home measurements, has been shown to be associated with an increased incidence of cardiovascular events, and usually coincides with the trough period of most antihypertensive drugs. The use of a long-acting drug blocking the renin–angiotensin–aldosterone system (RAAS) is certainly the first step in BP control for such patients.

How to best manage high morning blood pressure in patients with diabetic nephropathy?

What is optimal BP control?

When cardiovascular risk is high, which is especially true in patients with diabetic nephropathy, optimal BP control is mandatory to reduce the risk of renal failure and cerebral or cardiac complications. However, there is increasing evidence that not only high BP, but also an increase in BP variability is an important risk factor for cardiovascular and cerebrovascular disease. Precise assessment of BP variability requires sophisticated methods and 24-hour ABPM, for which the invasive (but not yet any more advisable) intra-arterial method could be used.

However, there are upcoming data stating that simply measuring BP on rising in the morning gives a rough but reliable indication of both BP level and variability.

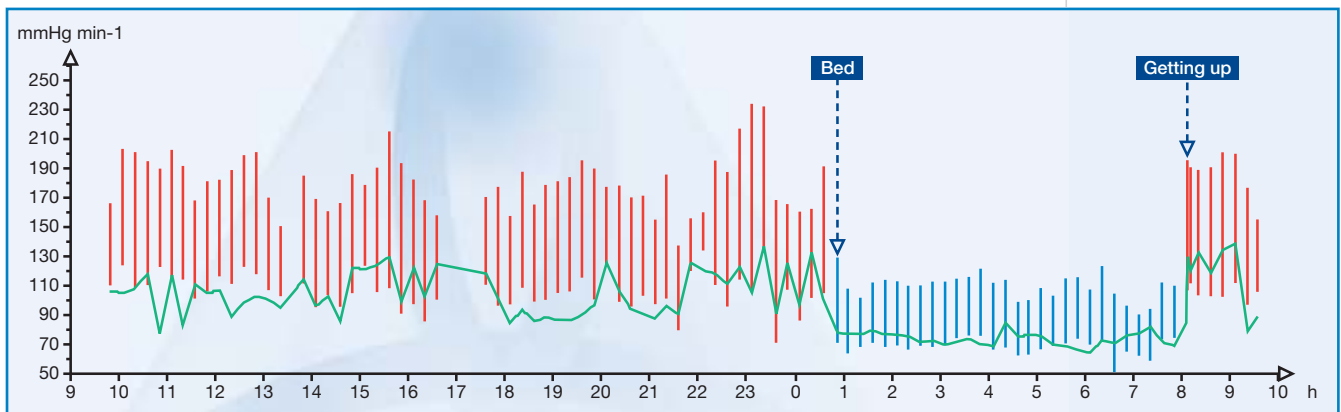
High morning BP is dangerous

The increase in BP when getting up in the morning is known to be related to target-organ damage (left-ventricular hypertrophy, increased carotid media thickness) and to future cardiovascular events (stroke and coronary heart diseases). It is also a strong indicator of decline in renal function in non-diabetic¹ and diabetic patients.²

Currently, two ways of assessing morning BP are available: ABPM and home BP measurement. Non-invasive ABPM allows the recording

of BP every 15–30 minutes during the day and night. Different methods of assessing morning BP from ABPM have been described. The one we prefer is simply to ask the patient to take a BP measurement at the time he gets up in the morning or, better still, to use a position sensor that automatically triggers this measurement (Figure). We were able to show in the Bordeaux cohort of hypertensive patients that the difference between the systolic blood pressure (SBP) on rising and the SBP measured while lying within the 30 minutes before rising was a significant predictor of future cardiovascular events independent of average 24-hour BP and age.³ Another study⁴ using ABPM has shown the good predictive value of high morning BP in elderly hypertensive patients.

For practical reasons, home BP measurements are increasingly more widely used. It allows the patient to measure BP immediately after getting up. BP measurements must be taken in the sitting position, approximately 5 minutes after rising. It is recommended to take 3 consecutive measurements and average them. These morning measurements of BP are shown to be more closely related to the prevalence of complications than office BP in diabetic patients.⁵ The underlying pathophysiological mechanism of an excessive morning surge in BP is not fully understood. In our opinion, interest in this mainly stems from its relationship with



increased BP variability.⁶ However, some other factors may influence BP on rising, such as the activity of the sympathetic nervous system and, in our experience, aldosterone plasma levels, linked in most instances to RAAS activity.

The morning coincides with the trough period of most antihypertensive drugs

Recently, it was shown that morning hypertension, indicating hypertension especially in the morning but not in the evening, is a good predictor of stroke, especially in patients using antihypertensive medication.⁷ If we accept the possible causal link between the increase in morning BP and the occurrence of cardiovascular complications, we must then consider morning BP as a therapeutic target. Usually, antihypertensive drugs are taken in the morning after rising, so that the BP surge on rising occurs at the time when the treatment taken the previous day is likely to be less effective. Consequently, we should favour the use of medication with a long duration of action, 24 hours and beyond.

Blocking the RAAS is the best way to protect renal function in diabetic patients

One of the main mechanisms leading to renal failure in diabetic patients is the increased glomerular capillary pressure, which mainly depends on the BP in the afferent artery and on the tonus of the efferent artery, influenced by the activation of the RAAS. Drugs that inhibit the RAAS are more likely to reduce glomerular capillary hypertension through reduction of BP and efferent arteriolar vasoconstriction.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) have been shown to reduce proteinuria and the

incidence of renal failure in diabetic patients.⁸ So, a long-acting drug from these two classes is certainly the first choice with which to treat a patient with diabetic nephropathy and a high morning BP. Telmisartan, an ARB with the longest duration of action of any available ARB,⁹ has a proven efficacy over the entire 24-hour period between doses, including the critical early-morning period.^{10,11}

However, BP goals are frequently difficult to achieve in hypertensive diabetic patients with nephropathy. Sometimes 2 or 3 drugs are needed to control BP: on top of a RAAS inhibitor such as telmisartan, a diuretic or a calcium-channel antagonist can be added. Most of these patients usually require the combination of these 3 classes of drugs as the target office BP must be below 130/80 mmHg, which means an even lower BP target for average daytime or home BP.

In some patients with severe proteinuria, high doses of an ARB or even a combination with an ACE inhibitor may be considered. The efficacy of this treatment should be verified with ABPM or home measurements to check that BP control is optimal, especially in the morning hours. ◀

Figure. 24-Hour ABPM in a patient with excessively high morning BP. 24-Hour ABPM is performed with a device equipped with a position sensor placed on the patient's chest. BP measured in the lying position is in blue, in sitting or standing position in red. Heart rate is shown in green. When the sensor detects a change in position (from lying to standing, after at least 1 hour of lying) it automatically triggers a BP measurement, as shown when the patient gets up in the morning.

ABPM = ambulatory blood pressure monitoring; BP = blood pressure.

References

1. Suzuki H, Nakamoto H, Okada H, et al. Clin Exp Hypertens. 2002;24:249-60.
2. Suzuki H, Kanno Y, Nakamoto H, et al. Clin Exp Hypertens. 2005;27:129-38.
3. Gosse P, Lasserre R, Minifie C, et al. J Hypertens. 2004;22:1113-8.
4. Kario K, Pickering TG, Umeda Y, et al. Circulation. 2003;107:1401-6.
5. Kamoi K, Miyakoshi M, Soda S, et al. Diabetes Care. 2002;25:2218-23.
6. Gosse P, Schumacher H. J Clin Hypertens (Greenwich). 2006;8:584-9.
7. Asayama K, Ohkubo T, Kikuya M, et al. Hypertension. 2006;48:737-43.
8. Parving HH, Andersen S, Jacobsen P, et al. Semin Nephrol. 2004;24:147-57.
9. Burnier M, Maillard M. Blood Press Suppl. 2001;1:6-11.
10. Giles TD. J Hypertens Suppl. 2006;24:S11-6.
11. Gosse P. Vasc Health Risk Manag. 2006;2:195-201.



Hans-Christoph Diener

Hans-Christoph Diener, MD, Chairman and Professor, Department of Neurology, University of Essen, Essen, Germany, is recognized for his work in the study of neurological diseases. A past president of the Germany Society of Neurology (DGN), he is currently Chairman of its Guideline Commission. In addition to the research he has conducted on stroke, he is among the leading experts on migraine and has published on a number of other neurological diseases. He is one of the co-authors of the influential textbook *Neurological disorders: course and treatment*. Dr Diener received his medical degree from the University of Freiburg in Germany and received specialist training at the University of Tübingen in Germany, before joining the teaching staff at the University of Essen. In addition to his research and clinical work, Dr Diener played an instrumental role in establishing the first acute stroke unit in Germany.

Prospects for better prevention of stroke: the RAS system

14

When considered independently from other vascular diseases, stroke is the second most common cause of death worldwide after cardiovascular events.¹ Death rates within 30 days of an initial stroke approach 10%.² About two-thirds of stroke survivors 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 Although it has been reported that approximately one-third of patients achieve full recovery after stroke, subtle signs of impairment, such as partial cognitive loss, may be underappreciated. In a study that compared stroke survivors to age- and sex-matched controls, the risk of dementia over a subsequent 10-year period was increased two-fold.⁵

Progress has been made in the acute treatment of stroke by introducing thrombolysis and establishing stroke units. Benefit depends on reaching a medical facility that has an emergency response system capable of rapidly confirming the diagnosis and initiating treatment.⁶ For this reason and the potential of major disability in patients who survive stroke,

which some consider worse than a fatal event,⁷ the best approach to containing stroke morbidity and mortality remains in prevention. Moreover, it is important to recognize that patients who survive a first stroke are at substantial risk of having a second vascular event, compounding the risk of the primary event. In a study that followed 1,923 primary-stroke survivors, 11.8% had a second stroke, and 7.7% had a cardiac event within 2 years.⁸

Modifiable risk factors for stroke

The modifiable risk factors for stroke have been outlined by several guidelines. In general, the factors that increase risk of stroke also increase risk of myocardial infarction (MI) and other vascular events. The European Stroke Initiative has listed the modifiable risk factors for stroke as high blood pressure, high serum cholesterol levels, smoking, diabetes, hyperhomocysteinaemia, obesity, physical inactivity, heavy alcohol use, atrial fibrillation, and history of other vascular diseases such as previous MI and peripheral arterial disease.⁹ With little variation, the same modifiable risk factors were listed by the most recent

Interview with
Hans-Christoph Diener,
Department of Neurology,
University of Essen, Essen,
Germany
By Ted Bosworth

American Heart Association/American Stroke Association guidelines.¹⁰

Of these modifiable risk factors for stroke, hypertension is the most predictive and one of the most prevalent.¹ A condition that increases with age, hypertension affects about two-thirds of individuals who reach the age of 65 years.¹¹ The correlation between increasing degrees of hypertension and increasing rates of stroke is linear and independent of other risk factors.¹² It is estimated that up to 44% of strokes can be prevented with hypertension control.¹³ In one meta-analysis using data from primary-prevention studies, each 10-mmHg decrease in systolic blood pressure was associated with a 33% relative reduction in stroke among people between the ages of 60 and 79 years.¹⁴

In guidelines for primary prevention, blood pressure 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 blood pressure is < 140/90 mmHg. However, a meta-analysis of prospective studies with data on 1 million patients suggest optimal blood pressure levels are < 120/80 mmHg.¹⁵ For patient groups at high risk of stroke and cardiovascular events, such as those with diabetes or prior MI, most guidelines identify the target as < 130/80 mmHg.^{12,16}

There has long been a debate on whether antihypertensive drugs differ in relative protection from stroke independent of blood pressure control. Although beta-blockers and diuretics were the first antihypertensive drug classes to be associated with protection from stroke, subsequent studies have now associated calcium-channel antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs) with reductions in risk of both cardiovascular events and stroke.^{13,17–20} Large placebo-controlled trials – such as the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) and the Heart Outcomes Prevention Evaluation (HOPE) study,^{21,22} which were conducted with ACE inhibitors alone or in combination with other antihypertensive drugs – have been credited with showing reductions in the risk of stroke even in high-risk patients without significant hypertension. This has suggested that some antihypertensive drugs may offer protection by mechanisms independent of blood pressure control.²³ Although the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) provided the basis for suggesting that antihypertensive drugs may differ in their specific protection from stroke,²⁴ such studies as the Losartan Intervention For

Endpoint reduction in hypertension (LIFE) and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) have substantiated measurable differences in more rigorous comparative trials.^{25,26}

Stroke protection from RAAS inhibitors: conflicting data

Upregulation of the renin-angiotensin-aldosterone system (RAAS) is suspected of having an important role in the pathophysiology of vascular diseases leading to a range of cardiovascular events, including stroke. One result of upregulated RAAS is progressive arterial stiffness, which increases with age and is a major driver of hypertension in the elderly.²⁷ While arterial stiffness has been shown to be a predictor of stroke independent of mean blood pressure,²⁸ RAAS inhibitors have been identified as particularly well suited to control this pathogenic process.²⁸ However, the data evaluating the protective effects of the two major classes of RAAS inhibitors – ACE inhibitors and ARBs – have not been wholly consistent. While trials with ARBs have almost uniformly demonstrated robust reductions in stroke risk, the studies with ACE inhibitors have generated conflicting results, including some studies that have associated ACE inhibitors with increased risk.

The trials with ACE inhibitors include HOPE, which was conducted in high-risk patients who did not necessarily have hypertension at baseline. In HOPE, the ACE inhibitor was associated with a 32% reduction in the risk of stroke (3.4% vs 4.9%; $p = 0.001$).²² In PROGRESS, there was a 24% reduction in the risk of stroke ($p < 0.001$), but much of the stroke protection from an ACE inhibitor in PROGRESS was attributed to the additive effects of a diuretic.²⁹ The multicentre CAPtopril Prevention Project (CAPPP) associated an ACE inhibitor with an increased risk of stroke relative to diuretics or beta-blockers.³⁰ In the ASCOT study, the ACE inhibitor perindopril combined with the calcium-channel antagonist amlodipine was associated with a 23% risk reduction in stroke ($p = 0.0003$) relative to atenolol and the thiazide diuretic bendroflumethiazide.²⁶ However, there was a modest difference in blood pressure control in the ASCOT study favouring the perindopril/amlodipine combination. Although the authors concluded that the greater risk reductions with the perindopril/amlodipine combination could not be fully explained by the blood pressure differences, it is uncertain whether protection should be attributed to the ACE inhibitor, the calcium-channel antagonist, or both.

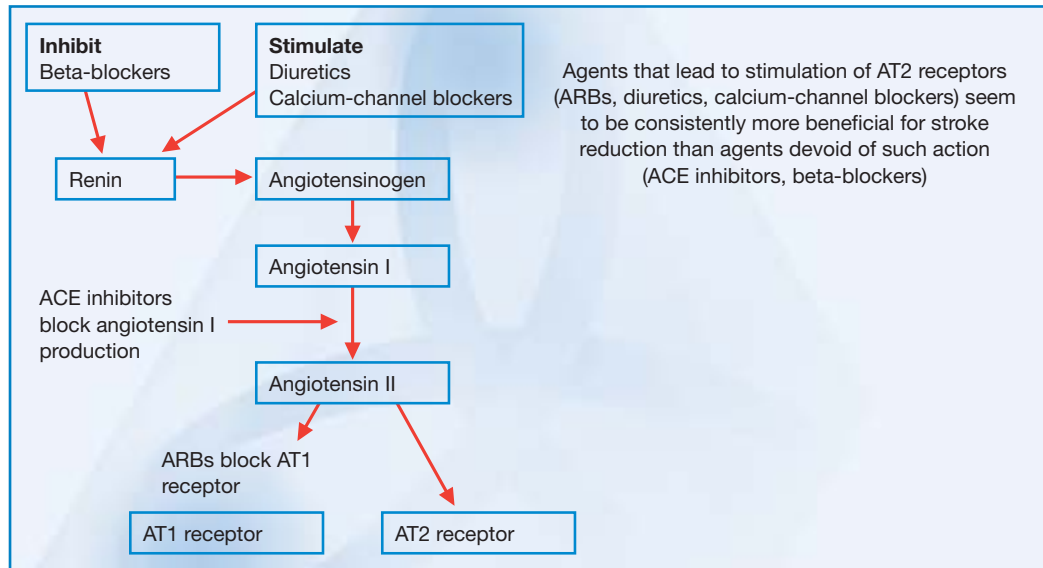


Figure. All drugs that increase angiotensin II formation, such as diuretics, calcium-channel antagonists, and ARBs, appear to reduce the risk of stroke. ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker.

Unlike ACE inhibitors, the cerebrovascular protection from ARBs in clinical trials has been relatively consistent and more likely to be attributed to the blood-pressure-independent effects of these drugs. One of the most compelling studies to show differences in outcome overall and stroke in particular was the LIFE study,²⁵ which compared the ARB losartan to the beta-blocker atenolol. For the endpoint of stroke, losartan was associated with a 25% reduction ($p = 0.001$) relative to atenolol when both drugs were titrated to provide the same blood pressure control. The proportion of patients who received a diuretic to reach target blood pressures in LIFE was similar in the two arms. In addition to the relative benefit of the ARB over the beta-blocker in LIFE, ARBs have been found to be superior for the prevention of stroke relative to another active blood-pressure-lowering therapy in the Study on COgnition and Prognosis in the Elderly (SCOPE) and the MORbidity and mortality after Stroke, Eprosartan compared with nitrendipine for Secondary prevention (MOSES) trial.^{31,32} There was also a non-significant advantage for the ARB over the calcium-channel antagonist in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial despite differences in blood pressure favouring the calcium-channel antagonist.³³

Stimulation of angiotensin II: potential stroke protection

One potential explanation for a difference between ACE inhibitors and ARBs is their relative effects on angiotensin II. The hypothesis that angiotensin II has a role in stroke reduction was first proposed in 1986.³⁴ Several experimental studies have been supportive of this hypothesis. For example, stimulation of angiotensin II type

2 (AT2) receptors by angiotensin was found to provide protection against cerebral ischaemia and improve survival in animal models.³⁵ Unlike ACE inhibitors, which block angiotensin II production, ARBs inhibit binding at the AT1 receptor, increasing circulating angiotensin II for stimulation of the AT2 receptor.³⁶ The same mechanism may be relevant to differences in stroke protection with other antihypertensive drug classes. In one review, it was noted that all drugs that increase angiotensin II formation, such as diuretics (which stimulate renin through sodium depletion), calcium-channel antagonists (which activate the sympathetic nervous system), and ARBs, appear to reduce the risk of stroke (Figure).³⁷ This may explain their relative advantage over ACE inhibitors and beta-blockers, which do not have a mechanism likely to increase AT2 receptor stimulation.

More data are needed to establish the optimal pharmacological regimen for protection against stroke, which may involve combination strategies not only to improve blood pressure control but also for the potential of blood-pressure-independent effects. Such combinations may include an ARB with an ACE inhibitor to provide independent mechanisms of action for reducing overall vascular risk, particularly in very-high-risk patients such as those included in the HOPE trial, a study in which an ACE inhibitor did lower risk of stroke. It may also be appropriate to evaluate different drugs within a class. Among ARBs, those drugs with a long half-life or tight tissue binding might provide relative advantages for sustaining relative benefits, such as inhibition of the AT1 receptor.

Several ongoing studies are expected to provide new information about the relative efficacy of different strategies to prevent stroke. One of

the most promising is the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial / Telmisartan Randomized Assessment Study in aCE-iNtolerant subjects with cardiovascular Disease (ONTARGET/TRANSCEND) programme, which is now more than halfway towards completion.³⁸ Both the ONTARGET trial, which randomized patients to the ARB telmisartan, the ACE inhibitor ramipril, or a combination of the two, and the placebo-controlled TRANSCEND trial in ACE-inhibitor-intolerant patients are designed to look at a variety of cardiovascular events, but stroke is part of the primary end-point. Moreover, cognitive decline and dementia have been prospectively identified as secondary end-points. The study population in both of these studies is similar to the high-risk patients randomized in the HOPE trial and includes patients with a history of cardiovascular or cerebrovascular disease or diabetes. The ONTARGET trial randomized 25,620 patients, while the TRANSCEND trial randomized 5,926 patients. The ONTARGET comparison of ramipril, telmisartan, or the combination is of particular interest due to the established benefit of ramipril in HOPE and the favourable features of telmisartan, which include a particularly high selectivity for the AT1 receptor and a 24-hour half-life that should maintain strong inhibition of the AT1 receptor over the full 24-hour dosing period.³⁹

Blood-pressure-independent mechanisms of benefit may also be derived from studies now underway in secondary prevention of stroke in which antihypertensive drugs are being added in patients already at target blood pressure levels. One such multinational trial, the Prevention Regimen For Effectively avoiding Second Strokes (ProFESS), randomized 20,000 stroke survivors in a two-by-two trial design to one of two antiplatelet drugs or to an ARB or placebo. The antiplatelet drugs are clopidogrel or a combination of aspirin plus extended-release dipyridamole. The ARB is telmisartan. Both study arms will explore the possibility of reducing the risk of stroke by mechanisms independent of blood pressure reductions. In addition, the study will investigate whether telmisartan can decrease the severity of strokes and prevent the development or the progression of vascular dementia.

Conclusion

The importance of tight blood pressure control for reducing the risk of stroke is unequivocal. Hypertension is the most powerful risk factor for stroke, and reductions in the risk of stroke

have been demonstrated with a wide variety of antihypertensive drug classes. However, relative protection against stroke, as relative protection against other vascular events, may differ by the mechanism with which blood pressure is controlled. This has now been suggested by numerous studies, particularly those in which an ARB has been directly compared with another antihypertensive drug providing similar blood pressure reductions. This may be explained by the importance of inhibition of the RAAS, although new data suggest that stimulation of the AT2 receptor may offer some degree of cerebrovascular protection. Several large studies now underway, such as the ONTARGET/TRANSCEND programme, should generate significant new information about the importance of the mechanism of action of blood pressure control as well as point to new strategies for risk reduction. ◀

References

- World Health Organization. The World Health Report 2002. Geneva: World Health Organization; 2002. Available from: www.who.int/whr/2002/en/whr02_en.pdf.
- Rosamond WD, Folsom AR, Chambless LE, et al. Stroke. 1999;30:736-43.
- Prencipe M, Ferretti C, Casini AR, et al. Stroke. 1997;28:531-6.
- American Heart Association. Heart Disease and Stroke Statistics—2004 Update. Dallas, Texas: American Heart Association; 2003.
- Ivan CS, Seshadri S, Beiser A, et al. Stroke. 2004;35:1264-8.
- Adams HP Jr, Brott TG, Furlan AJ, et al. Circulation. 1996;94:1167-74.
- Samsa GP, Matchar DB, Goldstein L, et al. Am Heart J. 1998;136:703-13.
- Brown DL, Lisabeth LD, Roychoudhury C, et al. Stroke. 2005;36:1285-7.
- European Stroke Initiative. Stroke prevention [cited 2006 Oct 28]. Available from: www.eusi.org/prevention.php?cid=7.
- Goldstein LB, Adams R, Alberts MJ, et al. Stroke. 2006;37:1583-633.
- Burt VL, Whelton P, Roccella EJ, et al. Hypertension. 1995;25:305-13.
- Chobanian AV, Bakris GL, Black HR, et al. JAMA. 2003;289:2560-72.
- Neal B, MacMahon S, Chapman N. Lancet. 2000;356:1955-64.
- Lawes CM, Bennett DA, Feigin VL, et al. Stroke. 2004;35:1024.
- Lewington S, Clarke R, Qizibash N, et al. Lancet. 2002;360:1903-13.
- European Society of Hypertension-European Society of Cardiology Guidelines Committee. J Hypertens. 2003;21:1011-53.
- ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. JAMA. 2002;288:2981-97.
- Black HR, Elliott WJ, Grandits G, et al. JAMA. 2003;289:2073-82.
- Dahlof B, Devereux RB, Kjeldsen SE, et al. Lancet. 2002;359:995-1003.
- Turnbull F. Lancet. 2003;362:1527-35.
- Fransen M, Anderson C, Chalmers J, et al. Stroke. 2003;34:2333-8.
- Yusuf S, Sleight P, Pogue J, et al. N Engl J Med. 2000;342:145-53.
- Padma V, Fisher M, Moonis M. Expert Rev Cardiovasc Ther. 2004;2:867-76.
- ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. JAMA. 2002;288:2981-97.
- Dahlof B, Devereux RB, Kjeldsen SE, et al. Lancet. 2002;359:995-1003.
- Dahlof B, Sever PS, Poulter NR, et al. Lancet. 2005;366:895-906.
- Roman MJ, Ganau A, Saba PS, et al. Hypertension. 2000;36:489-94.
- Laurent S, Boutouyrie P. CNS Drugs. 2005;19:1-11.
- Wennberg R, Zimmermann C. BMJ. 2004;329:968-70.
- Hansson L, Lindholm LH, Niskanen L, et al. Lancet. 1999;353:611-6.
- Papademetriou V, Farsang C, Elmfeldt D, et al. J Am Coll Cardiol. 2004;44:1175-80.
- Schrader J, Luders S, Kulschewski A, et al. Stroke. 2005;36:1218-26.
- Julius S, Kjeldsen SE, Weber M, et al. Lancet. 2004;363:2022-31.
- Brown MJ, Brown J. Lancet. 1986;2:427-9.
- Fernandez LA, Caride VJ, Stromberg C, et al. J Cardiovasc Pharmacol. 1994;24:937-40.
- Chrysant SG. Hippokratia. 2005;9:99-105.
- Fournier A, Messerli FH, Achard JM, et al. J Am Coll Cardiol. 2004;43:1343-7.
- Sleight P. Acta Diabetol. 2005;42 Suppl 1:S50-6.
- Zimmermann M, Unger T. Expert Opin Pharmacother. 2004;5:1201-8.





Causal role for plasma glucose levels in cardiovascular event development?

Fasting plasma glucose was found to be an independent predictor of several cardiovascular events, including cardiovascular death, myocardial infarction (MI), stroke, and hospitalization for congestive heart failure (CHF), even after adjustment for multiple risk factors including diabetes. Patients were recruited from two ongoing parallel trials evaluating telmisartan (ONTARGET [ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial] and TRANSCEND [Telmisartan Randomized AssessmeNt Study in aCE-iNtolerant subjects with cardiovascular Disease]) in high-risk patients with coronary, peripheral, or cerebrovascular disease, or with diabetes mellitus with end-organ damage. The first trial recruited 25,620 patients and the second recruited 5,926 patients.

An interim analysis, at a mean 886 days of follow-up, compared baseline fasting plasma glucose to the adjusted cardiovascular event rate. Known diabetes mellitus was recorded in 37% of patients at follow-up, compared with only 3.2% at baseline. During follow-up, 2,882 primary events occurred. A 1 mmol/L rise in fasting plasma glucose was related to an increased risk of the primary outcome (composite of cardiovascular death, non-fatal MI, stroke, or hospitalization for CHF) with a relative risk of 1.04 ($p < 0.0001$) and each individual outcome after multivariate adjustments.

Held C, Gerstein H, Zhao F, et al. Fasting glucose as a predictor of cardiovascular events in high-risk patients.

Eur Heart J. 2006;27 (Abstract Supplement):171.

Platelet effects of Aggrenox® plus telmisartan versus clopidogrel plus aspirin in patients with diabetes

The antiplatelet potency of clopidogrel plus aspirin was stronger and faster than that of Aggrenox® plus telmisartan in this small study, but the latter produced delayed, delicate downregulation of multiple major activation-dependent platelet receptors. The study recruited 40 patients with diabetes mellitus who were randomized to receive either clopidogrel 75 mg plus aspirin 325 mg, or Aggrenox® twice daily plus telmisartan 80 mg. Platelet function biomarkers were assessed at baseline and at days 15 and 30 by conventional aggregometry, flow cytometry, and rapid analysers.

Clopidogrel plus aspirin produced fast, sustained inhibition of adenosine diphosphate

(ADP)-induced platelet aggregation at day 15 ($p = 0.0003$), and collagen-induced aggregation at day 30 ($p = 0.002$). Expression of platelet/endothelial cell adhesion molecule-1 (PECAM-1) ($p = 0.02$), glycoprotein (GP) IIb/IIIa activity ($p = 0.03$), reduced platelet activation, and formation of platelet-leucocyte microparticles were reduced by day 15. Aggrenox® plus telmisartan was associated with delayed reduction (mostly at day 30) of platelet receptor expression, including GP IIb/IIIa activity ($p = 0.04$), GP Ib ($p = 0.0002$), vitronectin receptor ($p = 0.01$), P-selectin ($p = 0.007$), and lysosome-associated membrane protein ($p = 0.009$). The Prevention Regimen For Effectively avoiding Second Strokes (PRoFESS) trial is currently comparing these two therapeutic strategies.

Serebruany VL, Malinin AI, Ziai W, et al. Effects of Aggrenox and telmisartan versus clopidogrel and aspirin in combination on platelet activation and major receptor expression in diabetic patients: Relevance to the PRoFESS trial.

Eur Heart J. 2006;27 (Abstract Supplement):233.

Telmisartan added to ACE inhibitors reduces morbidity and mortality in patients with heart failure receiving haemodialysis

Congestive heart failure (CHF) is common in patients with end-stage renal disease, and its presence increases the risk of rehospitalization and mortality. In patients with CHF receiving dialysis ($n = 303$), telmisartan added to angiotensin-converting enzyme (ACE) inhibitor therapy has been shown to reduce morbidity and mortality compared with placebo.

In a placebo-controlled double-blind study, patients received telmisartan at a target dose of 80 mg/day in addition to ongoing ACE inhibitor and other therapy. Mean follow-up was 35 months. Compared with placebo, telmisartan reduced the incidence of all-cause mortality (58.3% vs 73.1%, relative risk reduction [RRR] 20.2%, $p < 0.01$), cardiovascular death (39% vs 49.3%, RRR 20.9%, $p < 0.001$), and CHF hospitalization (37.7% vs 66.4%, RRR 44.9%, $p < 0.0001$). No interaction between outcome and treatment with ACE inhibitors, beta-blockers, or the combination was observed. The incidence of withdrawals was 13.2% in the telmisartan group and 10.7% in the placebo group, and the incidence of hypotension was 6.1% and 4.3%, respectively.

Cice G, Benedetto AD, D'Isa S, et al. Effect of telmisartan added to angiotensin converting enzyme inhibitors in reducing morbidity and mortality in haemodialysis patients with chronic heart failure.

Eur Heart J. 2006;27 (Abstract Supplement):22.

Good 24-hour blood pressure control and insulin sensitivity with telmisartan

Telmisartan provided superior 24-hour blood pressure control compared with enalapril in patients with hypertension and metabolic disturbances. In addition, telmisartan may improve insulin sensitivity and have a positive effect on the lipid profile in these patients. The open-label, parallel-group study recruited 50 patients with mild-to-moderate hypertension. Patients were randomized to receive either telmisartan 40–80 mg/day (n = 25) or enalapril 10–20 mg/day (n = 25) for 8 weeks.

After 8 weeks, a 24-hour mean diastolic blood pressure of < 85 mmHg was observed in 72% of the telmisartan-treated patients and only in 48% of the enalapril-treated patients (p < 0.05). Telmisartan also reduced fasting plasma glucose by 7% (p < 0.05), fasting plasma insulin by 8% (p < 0.05), homeostasis model assessment of insulin resistance (HOMA-IR) by 21% (p < 0.05), and glycosylated haemoglobin by 8% (p < 0.05). Telmisartan also significantly reduced plasma total cholesterol by 17% (p < 0.01), low-density lipoprotein cholesterol by 13% (p < 0.01), and triglyceride levels by 25% (p < 0.05). Enalapril did not have a meaningful effect on these parameters. These effects may be explained by telmisartan's partial peroxisome-proliferator-activated receptor gamma (PPAR- γ) activity.

Demin AA, Bondar IA, Medvedeva O, et al.

PPAR(γ)-activating angiotensin type-1 receptor blocker telmisartan in treatment of arterial hypertension with metabolic disturbances.

Eur Heart J. 2006;27 (Abstract Supplement):118.

Telmisartan and ramipril have favourable effects on endothelial cell function in diabetes

Vascular endothelial function is involved in blood pressure control and can be assessed by measuring flow-mediated dilation (FMD) of the brachial artery. Both telmisartan and ramipril were shown to improve FMD and to have an even greater effect when used in combination in this double-blind crossover trial of patients with type 2 diabetes (n = 45).

All patients (mean age 57 years) had well-controlled type 2 diabetes, free of micro-albuminuria, hypertension, and coronary artery disease. Patients were randomized to receive ramipril 2.5 mg/day, or telmisartan 40 mg/day, or combination treatment for 3 months. Subsequently they were crossed over to alternative regimens and all patients received all three regimens with a 2-week wash-out period between treatments. FMD was measured at rest and 1 minute after sphygmomanometric cuff inflation to suprasystolic pressure, and was expressed as the change in post-stimulus diameter as a percentage of the baseline diameter. All treatments increased FMD. FMD was $9 \pm 3.2\%$ at baseline, $13.01 \pm 3.6\%$ with ramipril, $17.89 \pm 7.3\%$ with telmisartan, and $19.04 \pm 5.9\%$ with combination treatment (p < 0.001).

Symeonides P, Vratsista E, Triantafyllou K, et al.

The effect of angiotensin converting enzyme inhibitor versus angiotensin receptor blocker therapy on endothelial function of diabetic patients without overt cardiovascular disease; a comparative study.

Eur Heart J. 2006;27 (Abstract Supplement):496.

The Israeli Ischemic Heart Disease study: BP indices as predictors of long-term mortality

Weitzman D, Goldbourt U. The significance of various blood pressure indices for long-term stroke, coronary heart disease, and all-cause mortality in men: the Israeli Ischemic Heart Disease study. *Stroke*. 2006;37:358-63.

Studies of blood pressure (BP) indices as disease predictors have offered conflicting conclusions. We compared pulse pressure (PP), systolic and diastolic blood pressures (SBP and DBP), and mean arterial pressure (MAP) as risk markers for long-term mortality with emphasis on stroke.

Male civil servants (aged 40–65 years; n = 9,611) were examined in 1963 and followed up for mortality until 1986. Cox regression analysis was used to assess the association between BP indices and subsequent death due to all causes, coronary heart disease (CHD), and stroke. Due to the violation of the proportional-hazards assumption, stroke mortality was analysed separately for men who were initially normotensive (SBP ≤ 140 mmHg, and DBP ≤ 90 mmHg), hypertensive (SBP > 140 mmHg, and DBP > 90 mmHg), and men with isolated systolic hypertension (ISH; SBP > 140 and DBP ≤ 90 mmHg).

During follow-up 3,167 men died, including 932 due to CHD, and 339 due to stroke. The strongest associations between BP indices and age-adjusted mortality were found for stroke mortality. A 4.8-fold increase in risk of stroke mortality was found comparing the lowest and highest SBP quintiles. A 2.9-fold risk was found for the corresponding quintiles of DBP. PP was associated with a 4.6-, 2.3-,

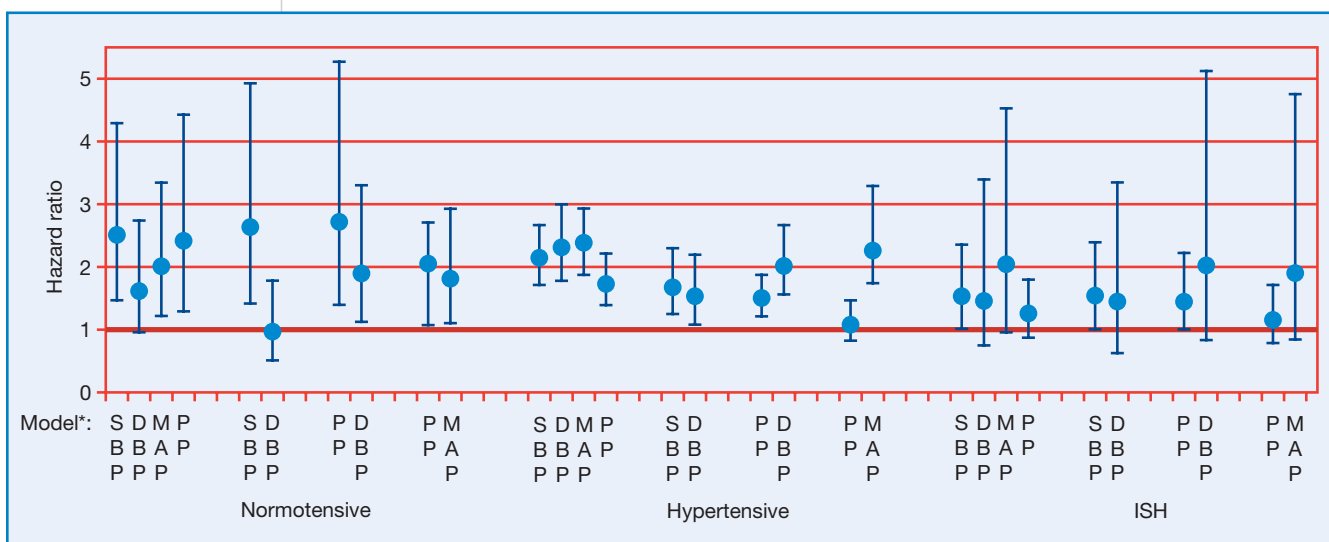
and 1.9-fold increase in age-adjusted stroke, CHD, and all-cause mortality rates, respectively (p ≤ 0.015 for linear trend for BP indices and all causes of mortality).

All 4 BP indices were predictive of fatal stroke in hypertensive and normotensive men (hazard ratios [HRs] ranged between 1.59 and 2.51, adjusted for diabetes, smoking, and socioeconomic status, and corrected for regression dilution bias). In models with 2 BP indices in normotensive men, SBP, but not DBP, remained a predictor of stroke mortality. MAP and PP were both independent predictors of stroke mortality. In the hypertensive men, SBP and DBP were independent predictors of stroke mortality (HR = 1.68 and 1.51, respectively). MAP, but not PP, remained a predictor of stroke mortality. In men with ISH, the 4 BP indices predicted fatal stroke with HR values between 1.24 and 2.04.

The 4 BP indices were also predictive of CHD and all-cause mortality. HR ranged between 1.40 and 1.63 for CHD mortality, and between 1.47 and 1.86 for all-cause mortality. These associations were adjusted for diabetes, smoking, serum cholesterol, and socioeconomic status, and were corrected for regression dilution bias. In models with 2 BP indices, SBP and DBP were independent predictors of CHD and all-cause mortality with HR values ranging between 1.23 and 1.39. MAP, but not PP, remained a predictor of CHD and all-cause mortality with HR values of 1.59 and 1.73, respectively.

SBP, DBP, MAP, and PP were predictors of stroke mortality in hypertensive and normotensive men, with DBP possibly the weaker predictor among the latter. Models with 2 BP indices yielded complex associations with

Figure. Hazard ratios and 95% confidence intervals for stroke mortality, associated with 1 standard-deviation increments in baseline blood pressure (BP) indices, corrected for regression dilution factor, and adjusted for age, diabetes, smoking, and socioeconomic status. *For each BP group, 4 models with 1 BP index each, and 3 models with 2 BP indices each are shown. ISH = isolated systolic hypertension.



stroke mortality. CHD and all-cause mortality were predicted by all 4 BP indices. In models with 2 BP components, both SBP and DBP

remained predictors of CHD and all-cause mortality. MAP, but not PP, remained a predictor of CHD and all-cause mortality.

Non-enzymatic modification of proteins by reducing sugars, a process also known as the Maillard reaction, progresses at an extremely accelerated rate in diabetes, thus leading to the formation of advanced-glycation end-products (AGEs). Recent understanding of this process has revealed that the receptor system for AGEs (RAGE) has a central role in the pathogenesis of diabetic vascular complications such as cardiovascular disease.

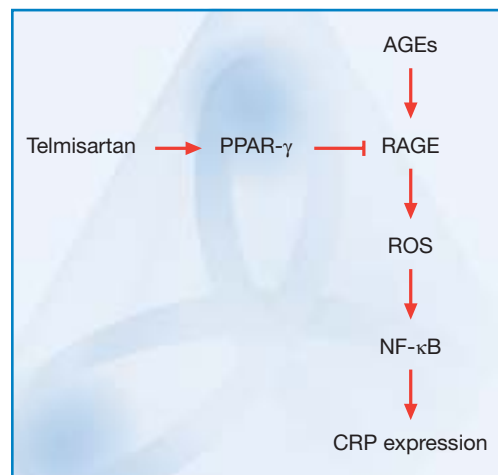
C-reactive protein (CRP) is an acute-phase reactant mainly produced by the liver in response to pro-inflammatory cytokines. Numerous studies have shown that CRP is one of the most powerful predictors of future cardiovascular events. In addition, CRP elicits endothelial dysfunction, pro-inflammatory reactions, and vascular smooth-muscle cell proliferation, thereby directly contributing to the development and progression of atherosclerosis. However, the molecular mechanism for the elevation of CRP in diabetes is not fully understood. Given that cross-talk between the AGE-RAGE system and angiotensin II has been proposed in the pathogenesis of accelerated atherosclerosis in diabetes, we examined whether and how telmisartan, a unique angiotensin II type 1 receptor blocker (ARB) with peroxisome-proliferator-activated receptor-gamma (PPAR- γ)-modulating activity, could inhibit the AGE-induced CRP production in a human hepatoma cell line, Hep3B.

Gene expression was analysed with quantitative real-time polymerase chain reaction. RAGE protein levels were determined with western blot analysis. CRP released in the medium was measured with enzyme-linked immunosorbent assay. Intracellular formation of reactive oxygen species (ROS) was measured using a fluorescent probe CM-H₂DCFDA.

Telmisartan, but not candesartan, another ARB, downregulated RAGE mRNA levels in a dose-dependent manner. Telmisartan decreased basal as well as AGE-induced RAGE protein expression in Hep3B cells. Furthermore, telmisartan, but not candesartan, dose-dependently inhibited the AGE-induced ROS generation, and subsequent CRP gene and protein induction in Hep3B cells (Figure).

Telmisartan inhibits advanced glycation end-products-induced C-reactive protein production

An anti oxidant, *N*-acetylcysteine; a glutathione peroxidase mimic, ebselen; or an inhibitor of nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase, diphenylene iodonium, also blocked the AGE-induced upregulation of CRP mRNA levels in Hep3B cells. AGE increased nuclear factor (NF)- κ B promoter activity; and curcumin, an inhibitor of NF- κ B, decreased CRP mRNA levels in AGE-exposed Hep3B cells. GW9662, an inhibitor of PPAR- γ , blocked the inhibitory effects of telmisartan on RAGE expression and its downstream signalling in Hep3B cells. In addition, troglitazone and ciglitazone, full agonists of PPAR- γ , modestly, but significantly, suppressed RAGE mRNA levels in Hep3B cells, whereas GW9662 alone increased them.



Our present study provides evidence of a unique beneficial aspect of telmisartan: it could work as an anti-inflammatory agent against AGEs by suppressing RAGE expression via PPAR- γ activation in the liver, and may have a protective role in vascular injury in diabetes.

Yoshida T, Yamagishi S, Nakamura K, et al. Telmisartan inhibits AGE-induced C-reactive protein production through downregulation of the receptor for AGE via peroxisome proliferator-activated receptor-gamma activation. *Diabetologia*. 2006;49:3094-9.

Figure. Possible molecular mechanism by which telmisartan inhibits the AGE-induced C-reactive protein expression in Hep3B cells. AGE = advanced-glycation end-product; NF- κ B = nuclear factor κ B; PPAR- γ = peroxisome-proliferator-activated receptor gamma; RAGE = receptor for AGEs; ROS = reactive oxygen species.

Reducing the risk of cardiovascular disease

Fonseca VA. Insulin resistance, diabetes, hypertension, and renin-angiotensin system inhibition: reducing risk for cardiovascular disease. *J Clin Hypertens.* 2006;8:713-20.

Diabetes mellitus is a growing problem and patients with diabetes are at an increased risk of cardiovascular (CV) disease. Among patients aged 35 years and older with diabetes, the prevalence of CV disease was 37% in 2000. Death from heart disease or stroke is 2–4 times more common among adults with diabetes than those without diabetes, and 66–75% of all patients with diabetes die from heart or vascular disease. The presence of hypertension in diabetes dramatically increases CV risk.

The development of diabetes is believed to be preceded by peripheral insulin resistance, which is often associated with mildly elevated glucose levels (impaired fasting glucose or impaired glucose tolerance) – a key component of the metabolic syndrome. The metabolic syndrome is a constellation of closely related abnormalities associated with significant risk for heart and vessel disease. Although there are several definitions, all include some degree of insulin resistance and blood pressure elevation. Other components include abdominal obesity and dyslipidaemia. All CV risk factors should be identified and treated aggressively and individually. Targets of interventions include lifestyle changes, improving glucose tolerance, increasing insulin sensitivity, reducing elevated lipids, and lowering blood pressure.

The recommendations of the Diabetes Prevention Program (DPP) Research Group include weight loss of 7% of body weight through dietary modifications and increased physical activity, which should total 150 minutes of moderate exercise per week. Lifestyle modifications have been more effective than metformin in lowering the incidence of new-onset diabetes, but although they are effective, patients often have difficulty adhering to them, and the cost-effectiveness of some programmes remains in question.

Metformin reduces glucose production and increases insulin sensitivity and has reduced the risk of progression to diabetes, but is not sufficiently effective as monotherapy. Thiazolidinediones (the glitazones) are insulin-sensitizing medications that have been shown to lower the risk of new-onset diabetes. The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) showed a non-significant reduction in the primary

composite end-point (all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, cardiac or leg revascularization, and amputation above the ankle). The secondary end-point of all-cause mortality, myocardial infarction, or stroke was, however, significantly decreased ($p = 0.027$).

Patients with impaired glucose tolerance may be treated with antihyperglycaemic medications, such as the alpha-glucosidase inhibitor acarbose or thiazolidinediones. The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) demonstrated that acarbose treatment of glucose intolerance significantly reduced the risk of CV events compared with placebo ($p = 0.02$).

All the major classes of antihypertensive agents effectively lower blood pressure while also reducing the risk of CV events. Based on data from 27 randomized trials, the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) showed that total CV events were reduced to a comparable extent in the short-to-medium term in patients with and without diabetes by regimens based on angiotensin-converting enzyme inhibitors, calcium channel blockers, angiotensin receptor blockers, and diuretics/beta-blockers. Some antihypertensive agents have been associated with metabolic side-effects that increase the risk of diabetes. Diuretics, particularly thiazides, and beta-blockers with the exception of carvedilol, may increase insulin resistance. Long-acting calcium channel blockers appear to ameliorate insulin sensitivity in hypertensive patients with and without obesity.

Given the possible risks associated with new-onset diabetes, some antihypertensive agents, such as those that antagonize the renin-angiotensin system (RAS), may be more appropriate for the treatment of hypertension in patients at risk for developing diabetes. RAS blockade has been shown to decrease the risk of developing diabetes when compared with other antihypertensive agents and to improve CV outcomes in patients with diabetes. Experimental study results suggest that the benefits of RAS blockade may be attributable to multiple interactions between insulin and angiotensin II.

Significant CV morbidity and mortality are associated with insulin resistance, diabetes, and hypertension. Evidence suggests that target-organ damage begins early in the process, leading to diabetes, with microalbuminuria, carotid artery abnormalities, and increased left-ventricular mass occurring at a higher rate

among non-diabetic patients with the metabolic syndrome than in those without the metabolic syndrome. While intensive lifestyle modification is effective in decreasing the progression to diabetes, it may be too costly to implement on a societal level, but should be initiated in all patients at high risk. Pharmacotherapy targeted at delaying progression to diabetes, lowering blood pressure, and preventing macrovascular complications will be necessary for many

patients. Clinical-trial data support the use of antihyperglycaemic agents for improving insulin sensitivity, and RAS inhibition has been shown to prevent or delay new-onset diabetes and reduce CV complications in patients with diabetes. In most patients, combination therapy, such as a combination of a RAS inhibitor and a diuretic, is necessary to reduce blood pressure and decrease CV events.

Ambulatory blood pressure (ABP) monitoring devices are now widely used for determining 24-hour blood pressure (BP) profiles and heart rate (HR). Subjects who fail to show a nocturnal decrease in BP are known to be at greater risk of cardiovascular events than those who do. The occurrence of strokes, cardiac infarcts, and subarachnoid haemorrhage is unevenly distributed during the day, with the highest incidence in the morning when BP is increasing from low overnight values.

A method of analysis that provides a non-symmetrical approximation curve representative of the circadian rhythm has been developed. The new method involves combining an S-shaped logistic curve and its mirror image. The six-parameter, double-logistic equation has a plateau with each day and night period but the duration is not fixed and is determined by the individual data. There are two independent estimates of slope, one for evening and one corresponding to the changes in the early morning. Thus, the method can estimate the early morning BP increase independently of the values obtained at other times. The method has been validated and has shown that women have more rapid reductions in evening BP than men. The aim of this study was to assess whether subjects with high BP have a greater rate of increase in morning BP than normotensive subjects.

The study obtained 528 ABP recordings from a cardiovascular risk assessment clinic and compared the upper quartile ($n = 132$) with the lower quartile ($n = 132$) based on daytime systolic BP (SBP), diastolic BP (DBP), and mean BP (MBP). Those showing higher night BP than daytime BP were not included. For clock times, day was 7 a.m. to 10 p.m. and night was 10 p.m. to 7 a.m. Subjects were also classified by SBP dipping status where the day-night difference was 10–20% (dippers), 0–10% (non-dippers), and < 0% (risers).

Hypertension and rapid morning blood pressure increase

MBP distribution was the most effective measure for classifying patients as all hypertensive (BP > 135/85 mmHg) in the upper quartile (100%) and virtually all as normotensive (BP < 135/85 mmHg) in the lower quartile (97.7%). The percentage of hypertensives with daytime DBP more than 87 mmHg (90–93 mmHg to adjust for difference between clinic and ambulatory values) was 28% and identical to the general population (about 28%), suggesting a good representative sample.

Both groups showed a qualitatively similar diurnal pattern of higher day and lower night BP and HR. However, the day-night difference was 1.8 times greater for MBP ($p < 0.001$) and 1.2 times greater for HR ($p < 0.05$) in the hypertensive compared to normotensive subjects. The maximum and minimum average values estimated by the double-logistic equation were higher in the day and lower during the night period compared to the values estimated by strict clock times in both hypertensive and normotensive subjects. The difference in day and night plateaus for SBP, DBP, MBP and HR was 1.8–2.4 times greater than that calculated by the clock method in the normotensive subjects and similar in the hypertensive subjects. The length of the daytime MBP plateau was longer for the hypertensive compared with the normotensive subjects (14.1 vs 12.3 hours, $p < 0.001$).

Using the double-logistic equation, BP patterns in normotensive subjects were symmetrical, but hypertensive subjects had a 21% faster rate of decrease in MBP in the evening compared to the rate of morning increase ($p < 0.05$). The

Head GA, Reid CM, Shiel LM, et al. Rate of morning increase in blood pressure is elevated in hypertensives. *Am J Hypertens.* 2006;19:1010-7.

rate of morning increase in SBP, MBP, and DBP was also greater in the hypertensive group compared with the normotensive group (+42%, +35%, +30%, respectively; $p < 0.05$). In the evening period, the hypertensive group had a 69%, 84%, and 73% greater rate of decline in SBP, MBP, and DBP, respectively ($p < 0.01$). The best predictor of morning increase in MBP was the rate of evening decrease ($r = 0.2$, $p < 0.01$). An overall effect of dipping status in predicting the rate of morning increase in SBP was seen ($p < 0.001$) and was more pronounced with the double-logistic assessment than with clock times. The rate of morning increase in HR was 1.8- and 1.6-fold greater than the rate of evening

decrease for the normotensive and hypertensive groups, respectively ($p < 0.001$), but with no significant difference between groups.

This analysis of 24-hour ABP recordings by a new logistic curve method reveals distinct asymmetrical circadian patterns of cardiovascular changes in normotensive (lower quartile) and hypertensive (upper quartile) subjects. The main finding was that the method detected a 30–40% greater rate of morning increase in BP in the hypertensive subjects, which may contribute to the greater cardiovascular risk at this time.

This new analytical method may prove useful for identifying subjects at high risk of cardiovascular events.

21.04 – 25.04.2007 Rio de Janeiro (Brazil)**2007 World Congress of Nephrology (WCN)**

Information: WCN 2007, ISN c/o MCI Suisse SA,
Rue de Lyon 75, 1211 Geneva 13, Switzerland,
tel: +41 223399589, fax: +41 223399621,
email: wcn2007@mci-group.com, internet: www.wcn2007.com



22.04 – 25.04.2007 Budapest (Hungary)
15th European Congress on Obesity (ECO)

Information: EASO, 231 North Gower
Street, London NW1 2NR, UK,
tel: +44 2076911900,
fax: +44 207387 6033,
email: eco2007@easoobesity.org,
internet: www.eco2007.org/

25.04 – 28.04.2007 Barcelona (Spain)

**2nd International Congress on "Prediabetes" and the
Metabolic Syndrome: Epidemiology, Management and
Prevention of Diabetes and Cardiovascular Disease**

Information: Kenes International, 17 Rue du Cendrier,
PO Box 1726, 1211 Geneva 1, Switzerland, tel: +41 229080488,
fax: +41 227322850, email: prediabetes2007@kenes.com,
internet: www.kenes.com/prediabetes2007/

26.04 – 29.04.2007 Nicosia (Cyprus)

**17th European Chapter Congress of the International Union
of Angiology (EUROCHAP)**

Information: Congresswise Ltd, PO Box 57468, 3316 Limassol,
Cyprus, tel: +357 25720554, fax +357 25721644,
email: congress@congresswise.com,
internet: www.scs.com.cy/eurochaptercyprus



19.05 – 23.05.2007 Chicago (USA)
**22nd Annual Scientific Meeting of the
American Society of Hypertension (ASH)**

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

21.06 – 24.06.2007 Barcelona (Spain)

**44th Congress of the European Renal Association & the
European Dialysis and Transplant Association (ERA-EDTA)**

Information: ERA-EDTA Congress Office, Via Spolverini 2,
43100 Parma, Italy, tel: +39 0521989078, fax: +39 0521959242,
email: congress@era-edta.org, internet: www.eraedta2007.org/

24.06 – 27.06.2007 Lisbon (Portugal)

**EUROPACE: The Meeting of the European
Heart Rhythm Association (EHRA)**

Information: EUROPACE 2007, 2035 Route
des Colles, BP 179, Les Templiers,
06903 Sophia Antipolis Cedex, France,
tel: +33 492947600, fax: +33 492947601,
email: europace@escardio.org,
internet: www.escardio.org/congresses/
Europace/Europace07/

**06.07 – 12.07.2007 Geneva (Switzerland)**

**21st Congress of the International Society on Thrombosis
and Haemostasis (ISTH)**

Information: MCI Suisse SA, Rue de Lyon 75, 1211 Geneva 13,
Switzerland, tel: +41 223399587, fax: +41 223399621,
email: isth2007@mci-group.com, internet: www.isth2007.com

01.09 – 05.09.2007 Vienna (Austria)

2007 Congress of the European Society of Cardiology (ESC)

Information: The European Heart House, 2035 Route des
Colles, BP 179, Les Templiers, 06903 Sophia Antipolis, France,
tel: +33 492947600, fax: +33 492947601,
internet: www.escardio.org

17.09 – 21.09.2007 Amsterdam (Netherlands)

**43rd Annual Meeting of the European Association for the
Study of Diabetes (EASD)**

Information: EUROCONGRES, Jan van Goyenkade 11,
1075 HP Amsterdam, Netherlands, tel: +31 206793411,
fax: +31 206737306, email: easd@eurocongres.com,
internet: www.easd.org

25.10 – 27.10.2007 Berlin (Germany)

**5th International Symposium on Obesity & Hypertension
(ISOH)**

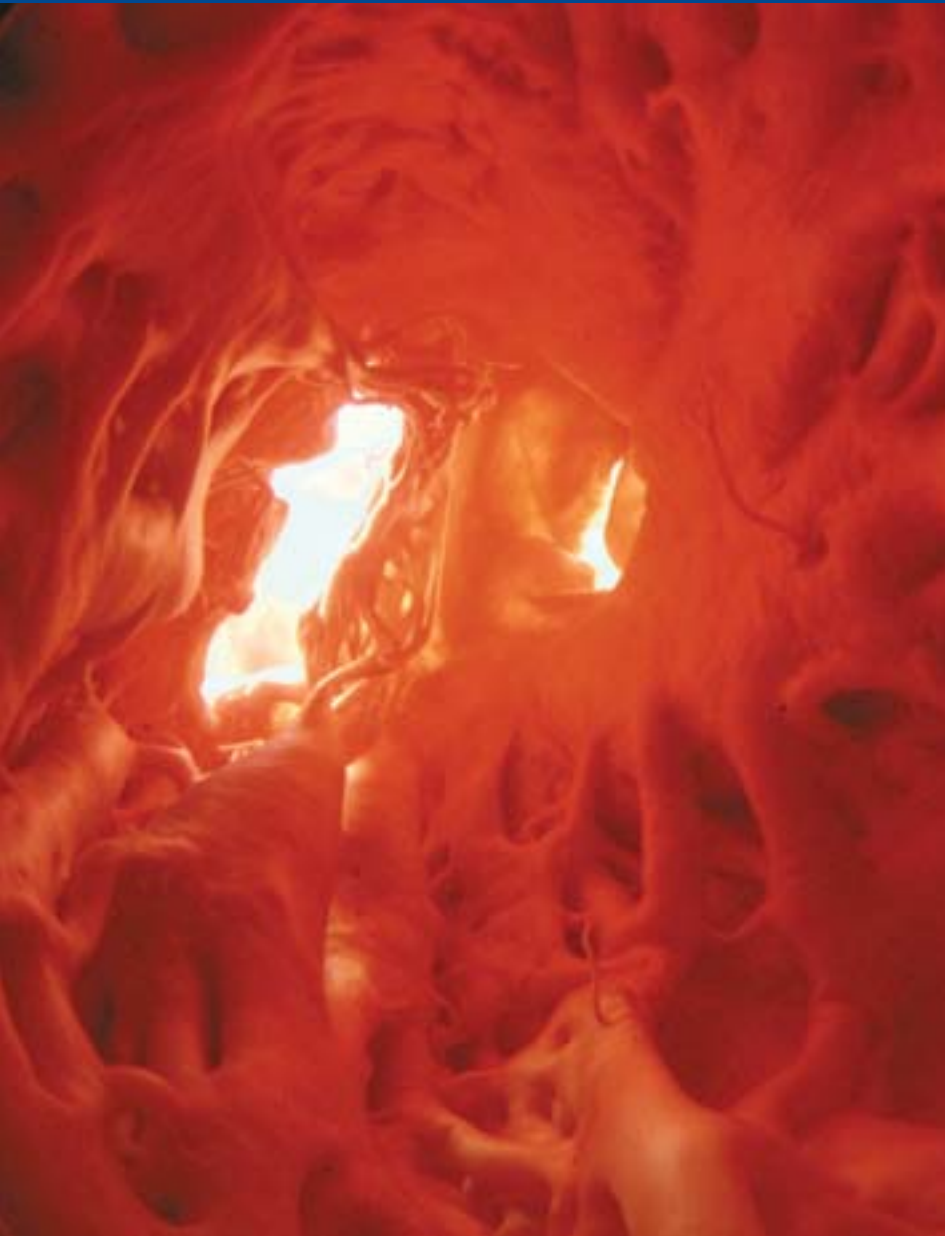
Information: CTW, Congress Organisation Thomas Wiese
GmbH, Hohenzollerndamm 125, 14199 Berlin, Germany,
tel: +49 3085996222, fax: +49 3085079826,
email: mail@isoh.de, internet: www.isoh.de

2008**30.08 – 03.09.2008 Munich (Germany)**

**2008 Congress of the European Society of
Cardiology (ESC)**

Information: The European Heart House,
2035 Route des Colles, BP 179, Les
Templiers, 06903 Sophia Antipolis, France,
tel: +33 492947600, fax: +33 492947601,
internet: www.escardio.org





Produced by Excerpta Medica
and supported by an educational grant
from Boehringer Ingelheim



**Boehringer
Ingelheim**