

Drugs Congress

Cardiovascular Risk Management Telmisartan. Aim for More Protection

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SUMMARY

The second Pritor®/Kinzal® conference on cardiovascular risk management, held in Rome, Italy, was entitled "Telmisartan. Aim for more protection", and had a special focus on the novel angiotensin II receptor blocker (ARB), telmisartan and the importance of controlling blood pressure (BP) in the prevention of cardiovascular disease (CVD). Hypertension affects 1 billion people world-wide, causes 7 million deaths per year and is the most profound risk factor for developing CVD. Hypertension and CVD commonly occur as part of a genetically complex disorder of glucose and lipid metabolism known as metabolic syndrome with insulin resistance as a key etiological factor. At the present time, a specific drug therapy is not available for this clinical condition, which is a strong predictor of type 2 diabetes, CVD and death in affected patients. Vascular protection is the key to reducing the morbidity associated with diabetes. There is evidence that if antihypertensive treatment is based on total cardiovascular risk evaluation and the presence or absence of end organ damage (arteries, brain, heart and kidneys), and not just on level of BP, it is very effective in controlling CVD mortality. This is the treatment approach advised in the recent 2007 guidelines on the management of hypertension and CVD. Further to this, the new classes of antihypertensive agents, such as calcium-channel blockers, angiotensin-converting enzyme (ACE) inhibitors (ACEIs) and, more recently, angiotensin receptor blockers (ARBs) are equivalent to the older classes of drugs (β blockers and diuretics) in terms of BP lowering, but in addition, may provide further effects through cardiometabolic benefits and CVD control and also better tolerability. In particular, ARBs have been singled out for potential first-line treatment of hypertension, as well as a treatment of choice for diabetic patients with nephropathy. With its unique pharmacokinetic properties and receptor binding, telmisartan, indicated for the treatment of essential hypertension, is one of the most potent and long-acting antihypertensives within the ARB class, and in clinical trials, has been shown to be superior to both losartan and valsartan in terms of maintaining blood pressure control over the 24-hour period. ARBs and in particular telmisartan have also been found to exhibit their effect through peroxisome proliferator-activated gamma (PPAR- γ) receptors as well as the angiotensin receptors and modulation of the renin-angiotensin aldosterone system (RAAS); for this reason, they may reduce the onset of new diabetes. Indeed, telmisartan demonstrated significant improvement in insulin resistance, glucose and lipid metabolism compared to other drugs. It is anticipated that the ONTARGET® (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) in over 30,000 high-risk cardiovascular patients will provide further data on improving cardiovascular and renal outcomes. The trial is designed to explore whether dual RAAS blockade with telmisartan and the ACEI, ramipril, is more effective than ramipril alone and if telmisartan is comparable to ramipril in preventing cardiovascular morbidity and mortality and end-organ protection in optimally treated high-risk patients.

Telmisartan is indicated for the treatment of essential hypertension.

The views and opinions expressed in any presentations are solely those of the speakers.

PROCEEDINGS REPORT

Introduction

This was the second Pritor®/Kinzal® conference on cardiovascular risk management; the meeting was entitled "Telmisartan. Aim for more protection". As the title suggests, the conference had a special focus on the novel angiotensin receptor blocker (ARB), telmisartan, and the importance of controlling blood pressure (BP) in the prevention of cardiovascular disease (CVD). Presentations were made by an international team of European experts. The views and opinions expressed in the presentations are solely those of the speakers.

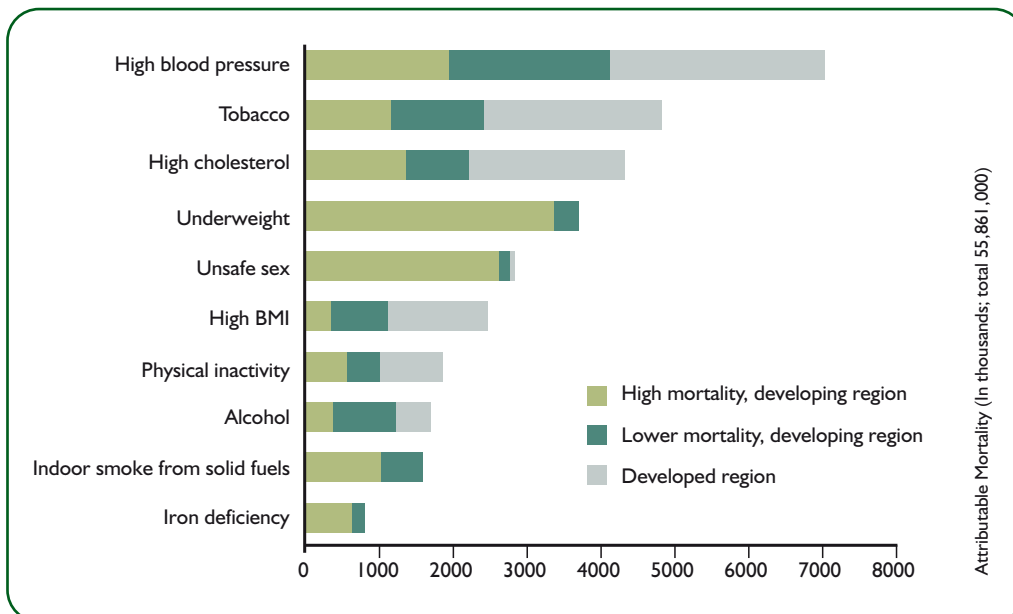
The aim of the meeting was to provide the most up-to-date scientific information on BP control and an opportunity for delegates to discuss issues in relation to their daily practice. The welcome address was given by Giuseppe Mancia, Professor of Medicine at the University of Milan-Bicocca, St Gerardo Hospital, Milan, Italy, who introduced the theme of the conference and thoughts on the aims of the day's proceedings. The main topics of the conference were as follows.

Hypertension, its Control and End Organ Protection

Professor Sverre Kjeldsen, from the Ullevaal University Hospital, Norway, and University of Michigan Hospital, USA, gave an overview of the global situation regarding hypertension, which affects 1 billion people world-wide, causes 7 million deaths per year, and is indeed a greater health risk than other risk factors such as tobacco, high cholesterol, obesity and physical inactivity (Figure 1). Hypertension is the most profound risk factor for developing CVD,¹ and the relationship between hypertension and CVD risk is continuous, consistent, and independent of all other risk factors.

The number of people with hypertension is expected to increase to 1.56 billion by 2025, and the potential consequences of this epidemic require immediate control. This is a huge undertaking, but the overwhelming evidence shows that despite ongoing campaigns for life-style changes, antihypertensive

Figure 1. Global Mortality 2000: Impact of Hypertension and Other Health Risk Factors



Reproduced with permission from Ezzati et al.¹

therapy is the single most effective way to control BP and achieve cardiovascular protection. In a meta-analysis of 29 trials in over 160,000 patients that compared different treatments or a treatment vs. placebo, there was a clear association between a reduction in BP and the relative risk of stroke, major CV disease, coronary heart disease, CV disease death and total mortality. Furthermore, the greater reductions in BP produced the greater reductions in risk.²

There is also evidence that if antihypertensive treatment is based on total cardiovascular risk evaluation and the presence or absence of end organ damage (arteries, brain, heart and kidneys), and not just on the level of BP, it is particularly effective in controlling CVD mortality. This is the treatment approach recommended in the recent 2007 guidelines for the management of arterial hypertension and CVD.³

Gianfranco Parati from the University of Milano-Bicocca further developed the theme of the importance of effective antihypertensive treatment for end organ protection, emphasizing the issues surrounding the causes of poor BP control. Despite progress in diagnosis and treatment of hypertension, the proportion of hypertensive patients with properly controlled BP is still far from satisfactory. The reasons include inadequate therapeutic approach, poor treatment compliance, resistant hypertension (e.g. obstructive sleep apnoea syndrome [OSAS], obesity), an ineffective drug regimen (e.g. poor 24-hour coverage) or a combination of these conditions.

The key way to achieve satisfactory control includes rigorous diagnosis and assessment of all risk factors, regular monitoring of BP and prescription of the most effective antihypertensive agents.⁴ Long lasting antihypertensive agents as well as antihypertensive drug combinations are considered the way forward, as shown in the recent SURGE-2 trial (Study of a hypertensive population Under treatment with telmisartan in Real clinical conditions with the Goal of controlling Early morning blood pressure rise). This study showed that coverage of 24-hour and morning BP was better when telmisartan, alone or in combination with hydrochlorothiazide, was added to the existing treatment.^{5,6}

Ambulatory BP Monitoring

Isolated clinic measurements are the traditional method of monitoring BP. However, ambulatory BP monitoring (ABPM) provides a more accurate insight into the relationship between BP changes and everyday life and an estimate of the overall BP load exerted on the cardiovascular system over 24 hours, particularly the morning surge of BP levels.^{5,8} Indeed, there is a direct and significant relationship between the daily cycle of BP and end organ damage, and longitudinal evidence for a superior predictive value of 24-hour BP mean values and variability patterns in relation to the risk of cardiovascular morbidity and mortality.

ABPM also allows assessment of the 24 hour efficacy of antihypertensives using mathematical indices such as the trough-to-peak ratio and the smoothness index.⁹ This approach has enabled the differences between drugs, particularly different ARBs to be observed. This will be discussed later.

Evolution of Antihypertensives

Evidence accumulated over the last 20 years demonstrates that new classes of antihypertensive agents, such as calcium-channel blockers, angiotensin-converting enzyme (ACE) inhibitors (ACEIs) and, more recently, ARBs are equivalent to older drugs, such as β -blockers and diuretics in terms of BP lowering effect. However, there is clear indication that newer drugs may provide benefits beyond BP control.¹⁰ Although still to be fully answered, the effects of these drugs include antagonising the progression of hypertensive disease, as monitored through the so-called "intermediate" endpoints, including the development of left ventricular hypertrophy, microalbuminuria and overt proteinuria, as discussed by Professor Massimo Volpe, from the University "La Sapienza" Rome, Italy,¹¹ and reducing cardiovascular morbidity and mortality. Furthermore, the newer drugs, especially those based on ACEIs or ARBs in combination with a low-dose thiazide diuretic, are now considered more effective and safer

than older drugs, especially in view of their better metabolic profile (reduced incidence of new-onset diabetes) and their better tolerability (fewer adverse events). In particular, ARBs have been singled out for potential first-line treatment of hypertension, as well as a treatment of choice in diabetic patients with nephropathy.

Mode of Action of ARBs

Angiotensin I is metabolised by ACE to the vasoactive peptide hormone angiotensin II. Angiotensin II plays an essential role in the physiological regulation of BP and cardiovascular and renal function mainly through 2 receptor subtypes (AT₁ and AT₂). Since increased levels of tissue ACE are a hallmark of hypertension and are induced in virtually every model of cardiac injury - volume overload, atherosclerotic plaque, infarction, post-infarction remodeling, heart failure, and aging - pharmacological modulation of the renin-angiotensin-aldosterone system (RAAS) has become the universal first-line strategy in the treatment of hypertension and CVD including type II diabetes.

The first and very well documented class of drugs modulating the RAAS consists of ACEIs that exert their beneficial effects by blocking angiotensin II formation, thus reducing the activation of both AT₁ and AT₂ receptors. ARBs belong to the second and more

recent class of RAAS modulators. ARBs, in contrast to ACEIs, also reduce the deleterious effects of angiotensin II but leave AT₂ receptors unopposed. This leads to an increase in plasma levels of angiotensin II and activation of other angiotensin II receptor subtypes. The latter may lead to important antigrowth and antitissue proliferation effects. As angiotensin II is also produced via non-ACE mediated pathways, a combination of both RAAS modulators may be more beneficial than either agent alone.

Despite evidence for additive benefits of dual RAAS blockade with ACEIs and ARBs, more compelling data are needed to evaluate the protective effects of ARBs when used alone or in combination with an ACEI in high-risk patients with controlled hypertension.^{12,13}

Telmisartan and Comparison with Other ARBs

The combination of unique pharmacokinetic properties and receptor binding, make telmisartan one of the most potent and long acting antihypertensives within the ARB class, which has been shown to be superior to both losartan and valsartan (Table I). Peter Meredith, Reader in Clinical

Table I. Comparative Pharmacokinetics of Angiotensin II Receptor Antagonists

	Telmisartan	Losartan	Irbesartan	Candesartan Cilexetil	Valsartan
Active metabolite	No	EXP3174	No	Candesartan	No
Bioavailability	40-60%	~30%	60-80%	15%	25%
Volume of distribution	500 L	12 L	15-93 L	10 L	17 L
Terminal t _{1/2}	~24h	6-9h	11-15h	5-9h	6-9h
Hepatic:renal elimination	98:2 no CYP450	65:35 CYP450	80:20 CYP450	60:40 CYP450	69:31 no CYP450
Protein binding	>99.5%	90-92%	90-92%	>99%	94-97%

Compiled data from P. Meredith.

Pharmacology, University of Glasgow, UK, presented the background to telmisartan, and the results of an important clinical study.

In the analysis of ABPM trials using the smoothness index, telmisartan and amlodipine maintained relatively consistent BP control over 24 hours, whereas losartan 50 mg and valsartan 80 mg tended to lose efficacy towards the end of the dosage interval. A direct comparison of telmisartan (40–80 mg) and valsartan (80–160 mg) demonstrated that during steady-state therapy, both treatments lowered BP to a comparable extent around the time of peak response. However, telmisartan lowered both systolic and diastolic BP to a greater extent than did valsartan over the last 6 hours of the dosing interval. In addition, on a day in which a dose was omitted from the treatment regimen (to mimic poor compliance with a missed dose), there was a notable trend for greater BP reduction during the latter part of the dosing interval with telmisartan compared with valsartan.

There is thus a volume of evidence to indicate that there are important differences between ARBs with respect to efficacy and duration of action. Are these differences of clinical relevance with respect to outcome?

The AMADEO® trial was conducted to determine whether the pharmacological differences between telmisartan and losartan would translate into larger and more durable reductions in urinary protein excretion over time in hypertensive patients with type 2 diabetes and overt nephropathy (Figure 2).¹⁴

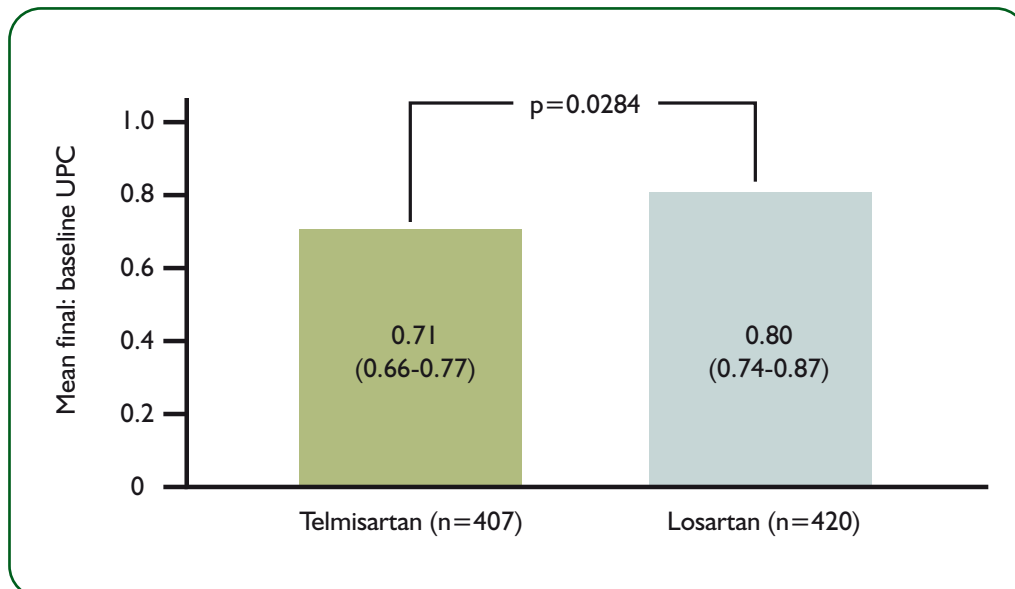
The trial showed that the mean final urinary protein: creatinine ratio (the primary outcome measure) was reduced to a significantly ($p = 0.028$) greater extent in the telmisartan group (29%) when compared to the losartan group (20%). In addition, telmisartan prolonged the time to a first cardiovascular event, although this did not achieve statistical significance.

Potential Cardiometabolic Benefits of ARBs

Thomas Unger, Center for Cardiovascular Research, Charité Hospital, Berlin, Germany and José R González Juanatey, Cardiology Department, Hospital Clínico-Universitario, Santiago de Compostela, Spain presented the cardiometabolic benefits of ARBs.

Hypertension and CVD commonly occur as part of a genetically complex disorder of the glucose and lipid metabolism known as metabolic syndrome with

Figure 2. Amadeo trial primary endpoint: mean change in urinary protein: creatinine after 1 year treatment



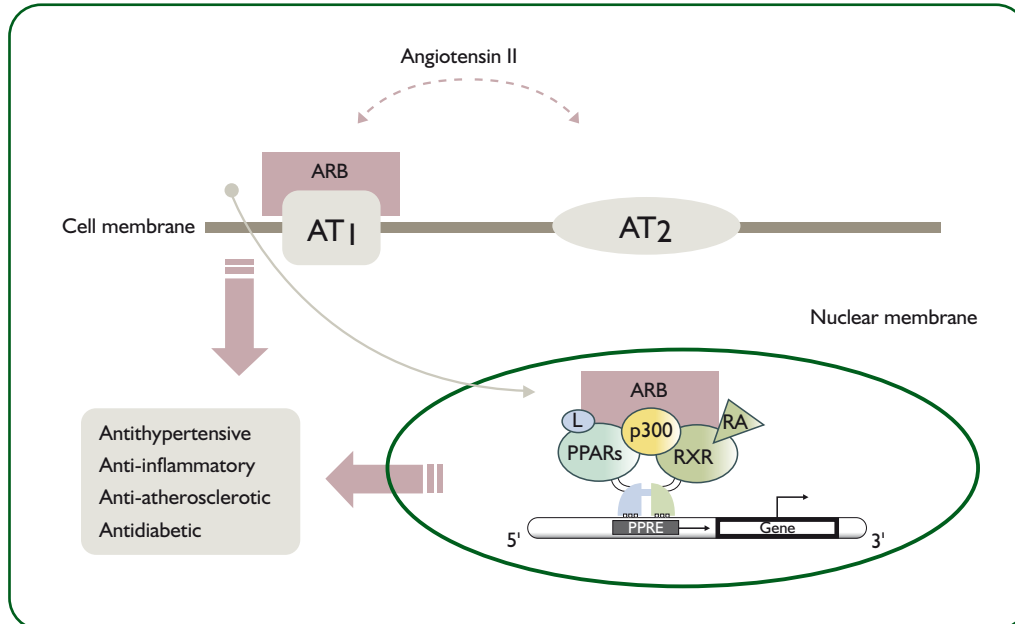
Bakris G et al.¹⁴ American Society of Hypertension 2007. Scientific Sessions; Chicago

insulin resistance as a key etiological factor. At the present time, no specific drug therapy is available for this clinical condition, which is a strong predictor of type 2 diabetes, CVD and death in affected patients.

Vascular protection is the key to reducing the morbidity associated with diabetes. Angiotensin II is known to exert a variety of deleterious effects on the vasculature, and this is likely to be a major explanation of the protective benefits observed with blockade of the RAAS. As stated earlier, RAAS blockade also appears to reduce the onset of new diabetes, which points to a fundamental effect on metabolism. Recent developments have thrown new light onto the mechanism of these effects. The importance of unopposed stimulation of the angiotensin II type 2 (AT₂) receptor in vascular protection is recognised, and recent studies have revealed that some ARBs, including telmisartan, act as selective peroxisome proliferator-activated gamma receptor (PPAR-γ) modulators in vitro (Figure 3). This effect is at least partly due to direct interaction with PPAR-γ itself, and there is a clear order of potency among the ARBs.^{14,15}

Due to its selective PPAR-γ modulating (SPPARM) activity, telmisartan is to date the most potent, and only ARB showing an effect at physiologically achievable plasma concentrations, and has demonstrated significant improvement in insulin resistance, glucose and lipid metabolism without the adverse effects seen with glitazones (fluid retention, oedema and weight gain). Accompanying the superior 24-hour BP control, a significant increase in insulin-sensitising-activity with a reduction in plasma insulin, glucose and HbA_{1c} levels have been observed in patients treated with telmisartan compared with patients randomised to other antihypertensive agents including other ARBs. Additionally, the effect of telmisartan on lipid metabolism, has resulted in a reduction in plasma triglyceride levels, an increase in energy expenditure and amelioration of the pro-inflammatory and pro-atherogenic risk profile of patients treated with this agent. These data indicate that telmisartan provides a novel approach to addressing the multifactorial components of metabolic syndrome and atherothrombotic cardiovascular risk.

Figure 3. AT₁R-Antagonism (Telmisartan) and PPARγ



Compiled from data from Benson et al,¹⁵ Schupp et al,¹⁶ Clasen et al,¹⁷ Zhao et al,¹⁸ Schupp et al,¹⁹ and Schupp et al.²⁰

ONTARGET®

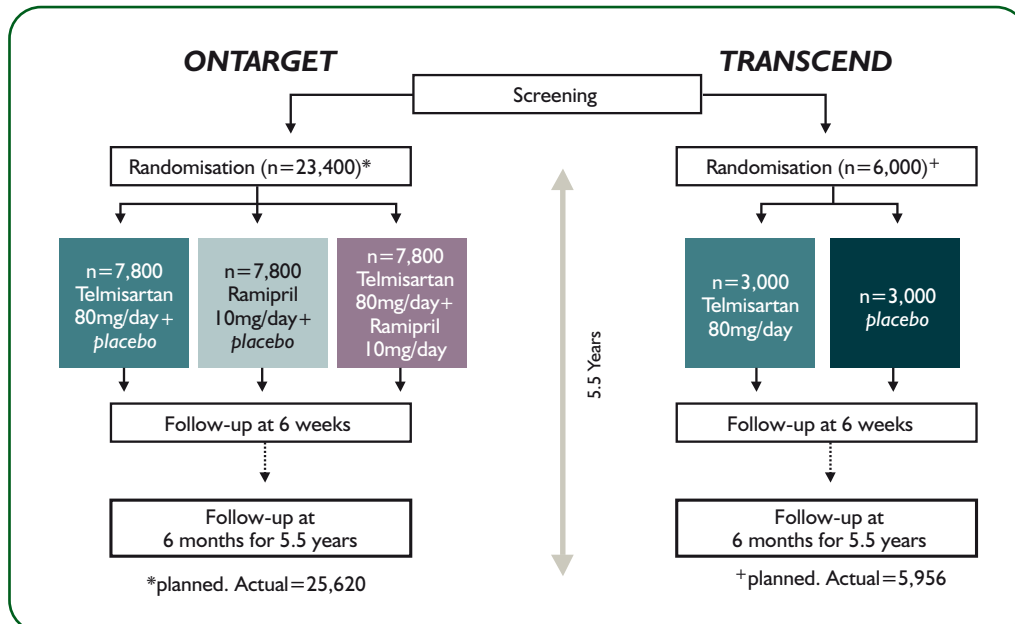
Details of the landmark ONTARGET® (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) were provided by Roland Asmar, from The Cardiovascular Institute, Paris, France. This is the largest ARB trial to date involving over 30,000 high-risk cardiovascular patients in more than 40 countries. The trial is designed to explore whether dual RAAS blockade with the ARB telmisartan and the ACEI ramipril is more effective than ramipril alone and if telmisartan is comparable to ramipril in preventing cardiovascular morbimortality and affording end-organ protection in optimally-treated normotensive high-risk patients (Figure 4). This will provide a unique opportunity to examine whether dual RAAS blockade might be more beneficial ramipril in further improving cardiovascular and renal outcomes.

The ONTARGET® findings and those of TRANSCEND® (Telmisartan Randomized AssessmeNt Study in aCE iNtolerant subjects with cardiovascular Disease) will provide further critical information on the prognostic effects of telmisartan in patients with high cardiovascular risk and the clinical relevance of the cardiometabolic actions of this drug, particularly on the new-onset of diabetes.

Evolution of the Guidelines for Controlling Hypertension

Finally, the need to calibrate antihypertensive treatment on the background of patients' total cardiovascular risk was emphasized in the 2003 European Society of Hypertension (ESH) and European Society of Cardiology (ESC) Guidelines. Further emphasis has been added by the 2007 Guidelines because of the evidence that: (1) individuals at high cardiovascular risk need treatment strategies that differ in many important aspects from those to be implemented in patients with a low or moderate risk and; (2) a high cardiovascular risk condition (i.e. a $\geq 20\%$ risk of having a cardiovascular morbid and fatal event in 10 years) is far more common in subjects with BP values above but also below 140/90 mmHg than thought only few years ago. Regarding the latter, the two main reasons are the high prevalence of multiple risk factors in many subjects and the frequency to which subclinical organ damage with adverse prognostic effects can be identified by examinations just a step beyond routine.

Figure 4. The ONTARGET Trial Programme Study design



Reproduced with permission from Teo et al.²¹

In his talk, Giuseppe Mancia reviewed the 2007 ESH/ESC guidelines concerning the identification of patients at high risk, including the new measures of subclinical organ damage proposed, the treatment strategies to be adopted under this circumstance, including the lower BP threshold and target for drug treatment and the need to expand drug treatment to non-antihypertensive drugs such as the antiplatelet and lipid lowering ones, and the paramount importance in high risk individuals with hypertension but also with BP in the high normal (or if there is a history of cardiovascular events in the normal) range to consider the combination of two antihypertensive drugs even as a first step intervention. This last part was dealt with in relation to the data that will be generated by ONTARGET[®] and by the TALENT[®] (STudy EvALuating the Efficacy of Nifedipine GITS – Telmisartan Combination in Blood Pressure Control trial), which will provide new evidence on the type of treatment that may optimise cardiovascular protection in high risk normotensive and hypertensive patients, as well as the advantage of combinations such as those of an ARB with an ACEI (for which evidence of cardiovascular protection in hypertension is limited) or a calcium antagonist.

Relevance of the Meeting to Daily Clinical Practice of Delegates

Overall, delegates considered the conference useful both in terms of helping to improve their clinical practice and also very informative from a scientific standpoint.

Almost all delegates were already aware of ONTARGET[®], mostly through the pharmaceutical companies involved in the development of telmisartan. In particular, they were aware of the CVD outcomes and end organ protection aims of the study. Moreover, these outcomes were of most interest to daily practice (Table II).

Table II. ONTARGET[®] study outcomes of most interest to delegates' clinical practice

Which ONTARGET[®] study outcomes are of most interest to your practice?

Cardiovascular protection

Cardiovascular morbimortality improvement

Prevention of diabetes

Renal and cardiovascular protection (renal and cardiovascular endpoints)

Combination therapy - more protection

Protective effect of combined therapy

Protective effect against organ damage

Effect on metabolic syndrome

Additional benefit of dual RAAS blockade

PROCEEDINGS CONTRIBUTORS

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Gianfranco Parati, Professor of Medicine, Department of Clinical Medicine and Prevention, University of Milan-Bicocca, Milan; Head of the Department of Cardiology, S. Luca Hospital, Istituto Auxologico Italiano, Milan, Italy.

Giuseppe Mancia, Professor of Medicine and Chairman, Department of Clinical Medicine and Prevention, University of Milan-Bicocca, Milan, Italy.

Peter Meredith, Reader in Clinical Pharmacology, Department of Medicine and Therapeutics, University of Glasgow, Glasgow, UK.

Thomas Unger, Chair of Pharmacology and Director, Center for Cardiovascular Research (CCR) and Institute of Pharmacology, Charité – Universitätsmedizin Berlin, Germany.

Massimo Volpe, Professor of Cardiology and Internal Medicine, and Chairman and Director of Cardiology, Faculty of Medicine, University "La Sapienza" of Rome, Sant'Andrea Hospital, Via di Grottarossa, Italy.

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