EDUCATIONAL HIGHLIGHTS FROM DATA PRESENTED AT THE

EUROPEAN SOCIETY OF CARDIOLOGY (ESC) CONGRESS 2008

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FROM HYPERTENSION TO PROTECTION: CONTRIBUTION OF ANGIOTENSIN RECEPTOR BLOCKERS IN THE FIGHT AGAINST CARDIOVASCULAR DISEASE

Despite multiple therapeutic advances, cardiovascular disease (CVD) remains a significant cause of premature death throughout the world. There is no doubt of the significant benefit that effective antihypertensive therapy can have in lowering the risk of CVD and renal outcomes in patients with high blood pressure. However, over the past few years it had become increasingly apparent that blocking the renin–angiotensin–aldosterone system (RAAS) using angiotensin II receptor blockers (ARBs) may have further benefits beyond blood pressure control.

At a satellite symposium held during the European Society of Cardiology (ESC) Congress 2008, the importance of RAAS blockade in preventing cardio-renal events was highlighted, and the significant contribution that ARBs continue to play in the fight against CVD discussed.

Reducing CVD: getting more by getting to goal

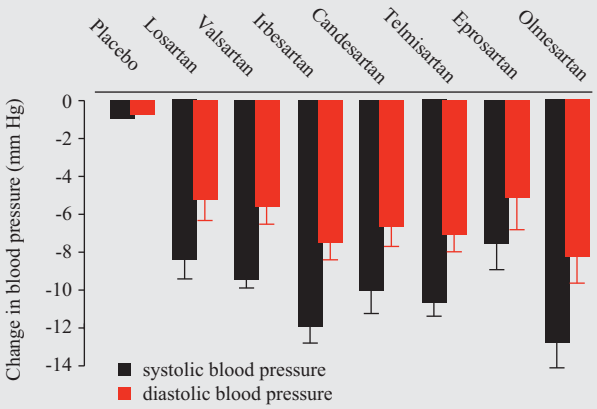
The recent ACCOMPLISH, ONTARGET, and TRANSCEND trial data highlight increasing awareness among the medical profession that ARBs may have a wider cardiovascular (CV) protective role than their proven beneficial effects in the management of hypertension, said Roland E. Schmieder (Department of Hypertension and Nephrology, Friedrich-Alexander-Universität, Erlangen-Nürnberg, Germany) who co-chaired the symposium. The first speaker, Josep Redon (Hypertension Clinic, Internal Medicine, Hospital Clinico, University of Valencia, Spain), then highlighted the problem of CVD, noting that more than 4.3 million deaths occur each year in Europe, and almost half of these deaths are due to coronary heart disease or stroke.

CVD is a continuum of disease, Prof. Redon stressed, which starts with well-known risk factors. Indeed, there is much evidence that CV risk factors, such as hypertension, account for increasing CV mortality in both developed and developing countries. There is also evidence that patients with high normal blood pressure are at significant risk of developing CVD[1].

In 2007, the European Society of Hypertension (ESH) and ESC published joint guidelines on the management of blood pressure, giving definitions of hypertension and suggesting targets for treatment[2]. The goal for most patients is to achieve a blood pressure of less than 140/80 mm Hg, but lower if this can be tolerated and if there is an underlying condition such as diabetes or renal dysfunction.
"Control of blood pressure may be one of the main manoeuvres that we can do to reduce cardiovascular risk," Prof. Redon said. There are various ways to assess blood pressure, he noted, whether this be in the clinic, at home or by ambulatory blood pressure monitoring (ABPM). The latter is established as being perhaps the best means of determining CV risk due to blood pressure, he suggested[3]. Furthermore, data show that ABPM, particularly at night-time, predicts CV outcome better than clinic blood pressure measurement[4].

The 2007 ESH–ESC guidelines[2] also recommend different blood pressure thresholds depending on the mode of blood pressure measurement: for office or clinic blood pressure the target is 140/90 mm Hg, but for 24-hour monitoring a

Figure 1 **ANTIHYPERTENSIVE ACTIVITY OF ARBS: BLOOD PRESSURE REDUCTIONS OVER 24 HOURS**



Values are mean (SE) adjusted by initial blood pressure, dose age and sex of subjects

Source: Adapted from Fabia MJ. J Hypertens 2007;25:1327–1336.

lower target of between 125–130/80 mm Hg, and lowering night-time blood pressure to 120/70 mm Hg, and daytime/home measured blood pressure to 130–135/85 mm Hg.

A recent meta-analysis (Figure 1) highlighted the variability in blood pressure reduction over 24 hours achieved with the available ARBs, but that several (irbesartan, telmisartan, and olmesartan) remain effective in the last 4 hours of the dosing schedule[5]. These data suggest that the greatest change in blood pressure can be achieved with olmesartan compared with other ARBs.

Despite the knowledge that hypertension treatment can significantly reduce the chances of CV events and the availability of effective anti-hypertensive agents, blood pressure remains inadequately controlled in a large number of patients. This is a global problem, Prof. Redon stressed, with around 18–55% of patients treated for hypertension actually achieving blood pressure goals.

Data show that a number of drugs may be required to achieve blood pressure goals, with two or more drugs being necessary in some patients. Choosing the right combination of agents is important and the ideal is to use those that complement each other, such that their effects on the mechanisms controlling blood pressure produce the maximum benefits with the minimum of side effects. The 2007 ESH/ESC guidelines[2] recognise the need for combination therapy and suggest that certain combinations of drugs are preferred over others. For instance, an angiotensin-converting enzyme (ACE) inhibitor or ARB may be used in combination with a calcium channel blocker (CCB) or a thiazide diuretic, while a CCB may be used in combination with a beta-blocker or thiazide diuretic.

Prof. Redon then highlighted data showing that a combination of an ARB (olmesartan) plus CCB (amlodipine) was more effective than either agent alone in lowering systolic blood pressure after just eight weeks of therapy [6]. Importantly, the addition of olmesartan to amlodipine in this study reduced the incidence of oedema seen with using the CCB alone by around 50%.his suggests a synergy in using these two drugs together, Prof. Redon said. An alternative is to use an ARB in combination with a thiazide diuretic such as hydrochlorothiazide (HCTZ) and there is again evidence of greater blood pressure lowering with an ARB + HCTZ combination than with either agent alone [7]. Furthermore, simplifying regimens by used fixed combinations may improve patient adherence and help patients to achieve target blood pressures.

"Combing agents with complementary activities increases efficacy without affecting tolerability," Prof. Redon said during his conclusion. "The most important message is that by using the right combination, nearly all patients can achieve guideline-recommended blood pressure goals."

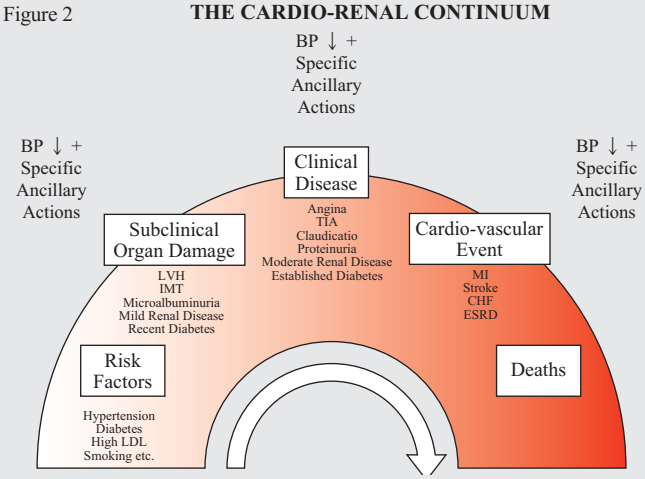
Blocking the RAAS — impact of treatment choice

Discussing the development of antihypertensive therapies over the past few decades, Enrico Agabiti-Rosei (Clinica Medica, Department of Medical and Surgical Sciences, University of Brescia, Italy) noted that there has been a "continuous improvement" in the approaches taken to reduce high blood pressure, with increasing efficacy and tolerability. "There is no doubt that ARBs are the best tolerated out of all the antihypertensive drugs," he said. However, it has become increasingly apparent that how you lower blood pressure by blocking the RAAS is important for preventing the chain of events that constitute the cardio-renal continuum (Figure 2).

While it is certainly important to use an agent that lowers blood pressure quickly and effectively, drugs that have a potent effect on angiotensin II by blocking the AT1-receptor are potentially more likely to have effects beyond blood pressure control. This is because angiotensin II plays a central role in vascular damage. In addition to having detrimental effects on the endothelium, angiotensin II is involved in endothelin and aldosterone stimulation, collagen and elastin formation, lipoprotein peroxidation, cytokine and growth factor activation, and smooth muscle proliferation. All of these, if left unchecked, may result in vascular damage, highlighting the need to target angiotensin II.

ARBs are an effective means of targeting the AT1-receptor, a fact that is now recognised by the latest ESH/ESC guidelines[2] on hypertension. These state that there are several conditions that favour the use of ARBs over other antihypertensive agents, including: heart failure, post-myocardial infarction, diabetic nephropathy, proteinuria/microalbuminuria, left ventricular hypertrophy, atrial fibrillation, metabolic syndrome, and in patient intolerant to ACE inhibitors (e.g. due to ACE-inhibitor-induced cough). Prof. Agabiti-Rosei commented: "European guidelines emphasise target organ damage assessment, overall cardiovascular risk stratification and treatment, with a major role for ARBs." Prof. Agabiti-Rosei highlighted data on the use of olmesartan noting that "experimental and clinical studies show that the ARB olmesartan combines antihypertensive efficacy and a high degree of vascular protection, and is appropriate for patients at risk of

Figure 2 **THE CARDIO-RENAL CONTINUUM**



BP = blood pressure; LVH = left ventricular hypertrophy; IMT = carotid intima-media thickening; TIA = transient ischaemic attack; MI = myocardial infarction; CHF = congestive heart failure; ESRD = end-stage renal disease

Source: Zanchetti A. J Hypertens. 2005;23:1113-1120.

cardiovascular events." Specifically, he showed data from the MORE[8], VIOS[9], and EUTOPIA[10] studies, as well as looking at the role of ARBs in the prevention of new-onset diabetes.

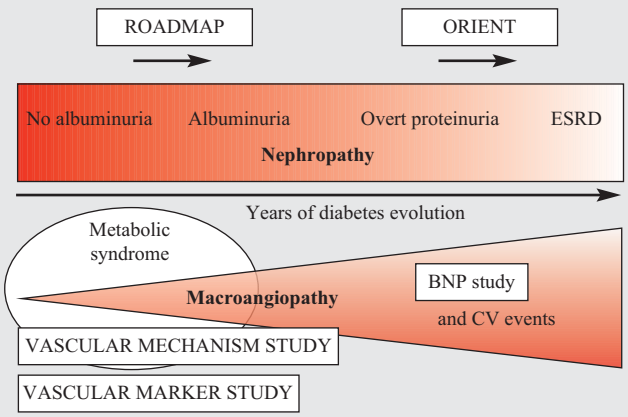
In the MORE study[8], the effects of olmesartan and atenolol on atherosclerosis progression — as measured by carotid intima-media thickness and plaque volume — were studied in over 160 patients with established coronary artery disease. After two years of treatment with these agents, a greater reduction in plaque volume was seen in patients with a larger baseline plaque volume if they were given the ARB rather than the beta-blocker.

Morphological changes in the small resistance arteries are considered an early step in the cardio-renal continuum, and evidence suggests that an increased media-to-lumen ratio in these arteries is predictive of both fatal and non-fatal CV events in patients with hypertension and other CV risk factors. In the VIOS study[9], the effect of olmesartan on vascular function was assessed in comparison to atenolol in 100 patients with stage I or II hypertension. The primary end point was the change in wall-to-lumen ratio of small resistance arteries. Olmesartan was found to decrease the wall-to-lumen ratio after one year of treatment, such that values were similar to those seen in normotensive individuals.

The EUTOPIA study[10] looked at the effects of antihypertensive therapy with an ARB with or without a statin on inflammatory markers in patients with hypertension and microinflammation and either atherosclerosis, diabetes or dyslipidaemia. After six weeks of treatment, olmesartan alone resulted in significant decreases in levels of high sensitivity (hs) C-reactive protein, hs tumour necrosis factor-·, interleukin-6 and monocyte chemotactic protein-1 as compared with placebo.

With regards to the development of new-onset diabetes, recent data from a meta-analysis of antihypertensive therapies suggest that ARBs may be associated with a lower incidence than other classes of agents[11]. The significance of this is that patients with hypertension who develop diabetes may be at greater risk of atrial fibrillation and hospitalisation for heart failure, as suggested by data from the VALUE trial[12]. Experimental data also suggest that ARBs may improve insulin signalling, Prof. Agabiti-Rosei said. He showed data from his own research indicating that olmesartan was more effective than enalapril in restoring insulin signalling in the skeletal muscle of spontaneously hypertensive rats[13]. Antihypertensive treatment with either agent also prevented microvascular rarefaction.

Figure 3 **ONGOING AND FUTURE STUDIES WITH OLMESARTAN**



ESRD = end-stage renal disease; BNP = brain-natriuretic peptide; CV = cardiovascular

Source: Laurent S. Data presented at the European Society of Cardiology (ESC) Congress 2008. Munich, Germany, 2008.

Understanding the cardiovascular continuum - new areas of research

ESH President Stéphane Laurent (Department of Pharmacology, George Pompidou Hospital and Department of Pharmacology, Paris-Descartes University, Paris, France) looked at the progress made to date in understanding the underlying pathogenesis of the cardio-renal continuum and outlined some new areas for research to further improve upon the knowledge gained (Figure 3). He began by looking at the mechanisms of endothelial dysfunction in CVD and the central role of angiotensin II in the development of target organ damage. A good example of the detrimental effects of angiotensin II on the target organs is in diabetic nephropathy where nephropathy develops over time, and is evidenced by progression from no albuminuria to albuminuria, overt proteinuria, and end-stage renal disease (ESRD).

There is good evidence from the IDNT and RENAAL trials that ARBs reduce the risk of ESRD, and from the IRMA2 trial that they can prevent the earlier step of progression from albuminuria to overt proteinuria, Prof. Laurent said. However, there are currently no data showing a benefit of ARBs at an earlier point in the scale, although these data exist for the ACE inhibitors (e.g., the BENEDICT trial[14]). This is why the ROADMAP study is being conducted. ROADMAP is a multicentre, placebo-controlled, double-blind, parallel-group trial that will compare the effects of a once-daily, 40-mg olmesartan dose with placebo on the development of microalbuminuria in 4,400 patients with type 2 diabetes[15]. The study aims to run for five years and will provide some of the first data on the role of ARBs at a very early stage in the development of diabetic nephropathy. ROADMAP will also provide data on CV morbidity and mortality, the development of ESRD, and retinopathy.

Prof Laurent presented other new studies with olmesartan include the 'Vascular Mechanism Study' and the 'Vascular Marker Study'. Both of these are looking at the early stages of vascular disease in patients with the metabolic syndrome, when aortic stiffening is known to occur and this may be an early warning sign of future CV events. The Vascular Mechanism Study is a phase IIIb investigation of 240 men and women with the metabolic syndrome and who will be treated with olmesartan 20–80 mg or placebo for one year. The aim is to see if the ARB can dose-dependently decrease the aortic stiffness that is expected to occur in these patients. The Vascular Marker Study, meanwhile, will look at the effects of olmesartan and amlodipine on changes in inflammatory markers in patients with the metabolic syndrome.

Two other new studies being conduced with olmesartan include ORIENT[16] and the OLME BNP study. ORIENT is investigating the benefits of ARB therapy in the prevention of ESRD in Asian patients, an understudied population of patients to date with a higher predisposition to diabetic nephropathy and ESRD. In this trial olmesartan (40 mg once daily) will be compared with placebo in the prevention of diabetic nephropathy, with a target accrual of 400 Japanese and Hong Kong Chinese patients with type 2 diabetes. The OLME BNP study will investigate the effects of olmesartan versus candesartan on the development of end-stage heart disease in patients with symptomatic heart failure. This is a 24-week, multicentre, randomised, double-blind, controlled, parallel-group non-inferiority trial designed to assess the effects of the two ARBs on brain-natriuretic peptide (BNP) levels, a prognostic biomarker.

"Altogether, these studies should provide new insights into the mechanisms of target-organ damage along the cardio-renal continuum in patients with hypertension and/or type 2 diabetes," Prof. Laurent concluded. In addition, these studies should provide evidence of the link between target-organ damage and CV events and "the possibility to reduce both by specifically blocking the angiotensin II receptor with olmesartan."

Beyond blood pressure control

Concluding the symposium, Carlos M. Ferrario (Hypertension and Vascular Disease Center, Wake-Forest University School of Medicine, Winston-Salem, NC, USA) said that anti-hypertensive therapy was clearly important in reducing CV risk and that using fixed-dose combinations have been shown to increase efficacy without affecting tolerability. He noted that blockade of the RAAS appears to provide CV benefits beyond blood pressure reduction "at all stages of the cardio-renal continuum." As such, the goal of treating patients is beginning to move beyond pure blood pressure control, he suggested, with cardio-renal and vascular protection all being important additional targets. The results of ongoing studies with the ARB olmesartan will help provide new insight into how RAAS blockade may achieve these new targets of therapy, and Prof. Ferrario suggested that the mechanism of action of ARBs may not all be the same. Olmesartan has several unique pharmacological properties that may lead to its preferential use in the future. These unique properties include the way in which olmesartan binds to and disassociates from the AT1 receptor[17], and the suggestion that it may lead to a reduction in the plasma concentration of angiotensin II and perhaps stimulate the expression of ACE2 in the heart and arteries.

Trial acronyms

ACCOMPLISH - Avoiding Cardiovascular Events through COMbination Therapy in Patients LIving with Systolic Hypertension

BENEDICT - BErgamo NEphrologic DIabetes Complications Trial

EUTOPIA - EUropean Trial on Olmesartan and Pravastatin in Inflammation and Atherosclerosis

IDNT - Irbesartan in Diabetic Nephropathy Trial

IRMA2 - IRbesartan in Patients with Type 2 Diabetes and MicroAlbuminuria

MORE - Multicentre Olmesartan atherosclerosis Regression Evaluation

OLME BNP - OLMEsartan Brain-Natriuretic Peptide Study

ONTARGET - ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial

ORIENT - Olmesartan Reducing Incidence of Endstage renal disease in diabetic Nephropathy Trial

RENAAL - Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan

ROADMAP - Randomised Olmesartan And Diabetes MicroAlbuminuria Prevention Study

TRANSCEND - Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease

VALUE - Valsartan Antihypertensive Long-term Use Evaluation Trial

VIOS - Vascular Improvement with Olmesartan medoxomil Study

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