



# Cardioneurology, an emerging discipline: highlights of the Sixth Genoa Meeting on Hypertension, Diabetes and Renal Disease

Sixth Genoa Meeting on Hypertension, Diabetes and Renal Disease, Genoa, Italy, February 22–24, 2007

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The Sixth Genoa Meeting on Hypertension, Diabetes and Renal Disease was held in Genoa, Italy from February 22–24, 2007. The meeting was co-sponsored by the American Society of Nephrology, under the auspice of several Italian and international societies in the renal cardiovascular and metabolic areas, and involved more than 350 participants. The meeting provided up-to-date information regarding the tight link between cardiovascular and renal disease, and aimed at enhancing cardio-renal health education among those who study and manage the broad spectrum of kidney-heart disease. The event has grown rapidly in attendance and in scientific quality over the past few years, and thanks to its top-level faculty, it has now become an essential meeting for clinicians and researchers in this field. Herein, we report highlights of the data presented at the meeting.

## Inflammation & endothelial dysfunction

The opening symposium focused on the relationship between endothelial dysfunction, inflammation, and cardiovascular and renal disease [1]. C Zoccali (Consiglio Nazionale delle Ricerche, Reggio Calabria, Italy), current president of the Italian Society of Nephrology, emphasized how patients with

established renal disease exhibit a consistent association between renal function and biomarkers of inflammation. In a survey based on a series of 103 patients with chronic kidney disease, creatinine clearance correlated both with C-reactive protein and IL-6, with the IL-6-creatinine clearance link being fairly strong. Similarly, in a sizeable group of patients with mild-to-severe renal insufficiency attending a renal clinic in Birmingham, UK, glomerular filtration rate was associated both with low-grade inflammation and endothelial dysfunction, even among patients with moderate renal impairment. On the other hand, a *post hoc* analysis of randomized, placebo-controlled trials showed that statins prevented loss of kidney function to a higher extent in individuals with greater evidence of inflammation. Thus, inflammation and perhaps endothelial dysfunction may not only be a marker for the loss of kidney function among patients with chronic renal damage, but they may be causally involved in it.

The next speaker, P Romagnani (Excellence Center Denoche, University of Florence, Italy), provided an update on the pathophysiology of endothelial progenitor cells and their potential for future clinical use. Endothelial progenitor cells are circulating precursor cells

that have recently been implicated in vascular and cardiac regeneration. There is an ongoing discussion on the immunocytological definition of endothelial progenitor cells, based on various surface markers, and, currently, various cell types are included in the term 'endothelial progenitor cells'. Cardiovascular risk factors negatively influence endothelial progenitor cell number and function, while vascular protection (e.g., by statins, estrogens and physical activity) may be partly mediated by progenitor cells. Endogenous mobilization or injection of *ex vivo*-generated endothelial progenitor cells is associated with enhanced re-endothelialization, improved endothelial function and reduced atherosclerotic burden. However, reduced number and impaired function of endothelial progenitor cells have been linked to situations with increased cardiovascular risk and to clinical atherosclerotic diseases. Romagnani went on to describe several experimental and clinical studies on ischemic cardiovascular diseases, which suggest a therapeutic potential for endothelial progenitor cell transplantation. A better understanding of endothelial progenitor cell biology will help us to devise more effective treatment of ischemic and cardiovascular disorders in the future.

## Mild renal dysfunction: the kidney message on cardiovascular health

On Friday, the meeting opened with a Consensus Conference on the role of microalbuminuria as a marker of risk. Both of the discussants, D de Zeeuw (University of Groningen, The Netherlands) and R Trevisan (Bergamo, Italy), gave the audience a detailed overview of clinical trials supporting the prognostic value of microalbuminuria and its reduction through antihypertensive therapy. A lively debate followed, with

several scheduled statements by *ad hoc* appointees of a number of scientific societies. All the speakers agreed that adopting lower values than those currently used to define microalbuminuria might improve the sensitivity of this test and lead to a more rational and effective assessment of global risk in clinical practice [2].

The cardiovascular system is profoundly influenced by abnormalities in renal function. Recently, it has been pointed out that cardiovascular risk progressively increases as the glomerular filtration rate declines, and is already significantly elevated even in the earliest stages of renal damage. These findings are even more noteworthy when one considers that a mild reduction in renal function is relatively common in hypertensive patients. In his talk on this topic, R Pontremoli (University of Genoa, Italy), showed recent data from the Third US National Health and Nutrition Examination Survey, indicating that approximately 13% of all nondiabetic adults in the USA have a creatinine clearance of less than 60 ml/min. The presence of clinical proteinuria and low-grade albuminuria are also powerful predictors of unfavorable prognosis [3]. Optimal blood pressure control, as indicated by international guidelines, is of the utmost importance both in order to slow the progression of renal damage and to prevent cardiovascular events. However, target blood pressure levels are often very difficult to achieve in clinical practice, and most renal patients remain hypertensive despite treatment. Along the same lines, the next speaker, R Agarwal (Indiana University School of Medicine, IN, USA), pointed out that patients with chronic kidney disease should also be evaluated and treated for dyslipidemia. Dyslipidemia is a risk factor for the development and progression of kidney dysfunction in people without overt renal disease, as well as progression in those with diabetic and nondiabetic kidney disease. Although definitive randomized, controlled trials are lacking, the collective evidence suggests that

treatment of dyslipidemia is associated with less decline in renal function. The use of potent statins in high doses can lead to transient proteinuria via impairment of proximal tubular receptor-mediated endocytosis, in a dose-dependent manner. However, in the long term, the use of statins may result in a reduction in proteinuria and in the rate of decline of renal function. Several large, definitive trials, which are currently being carried out to examine the safety and efficacy of statins in cardiovascular and renal protection, should provide more definitive answers regarding the role of these drugs in this very high-risk population.

#### **Novel aspects of pharmacologic renin–angiotensin–aldosterone system blockade for cardiovascular & renal protection**

A Morganti (University of Milan, Italy) opened this session by reviewing clinical pharmacology and effectiveness of angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers, both when used alone and in combination [4]. The clinical trials that have been conducted on renal patients to date have shown that combination treatment is slightly more effective than treatment with single agents, regardless of blood pressure reduction, at least on intermediate end points such as changes in proteinuria. Optimal doses of these drugs remain to be established and more studies are clearly needed in this important area.

AV Stanton (Royal College of Surgeons, Dublin, Ireland) reported on a novel class of renin–angiotensin–aldosterone system-inhibiting drugs that is currently being placed on the market. Renin inhibitors block the renin–angiotensin–aldosterone system at the highest level, that is, at its origin, and may offer an exciting new approach for the pharmacotherapy of renal and cardiovascular protection. More recently, investigative studies have started examining the value of these drugs in heart failure, nephropathy and diabetes mellitus. There is also considerable interest in the benefits of aliskiren in combination

with diuretics, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Stanton summarized the available data on the clinical development of aliskiren, which is the only renin inhibitor that has, as yet, progressed to Phase III clinical trials.

#### **Renal & cardiovascular implications of the metabolic syndrome**

In the subsequent session, G Deferrari (Dean of the Medical School, University of Genoa, and President of the meeting) analyzed the effect of obesity and the metabolic syndrome on the kidney [5]. There is strong epidemiological and pathophysiological evidence linking these two clinical conditions to the presence of hypertension and renal damage, and the characteristic components of metabolic disorders are obvious targets for treatment in the attempt to reduce the risk of cardiovascular disease in patients with chronic kidney disease. Although no guidelines are currently available for the treatment of metabolic syndrome, the greatest emphasis should be placed on treating obesity, increasing physical activity and avoiding an atherogenic diet. The next speaker, S Del Prato (University of Pisa, Italy), reviewed the results from clinical trials in patients with the metabolic syndrome. He underlined that attempts to treat the metabolic syndrome by focusing on insulin-resistance and obesity should not detract from the importance of tackling major individual cardiovascular risk factors included in the syndrome. Statins remain first-line pharmacotherapy for dyslipidemia thanks to their efficacy at lowering low-density lipoprotein cholesterol and their anti-inflammatory properties. Since high triglycerides and low high-density lipoprotein cholesterol are common lipid disturbances in the metabolic syndrome, fibrates may also be taken into consideration. Angiotensin-converting enzyme inhibitors and angiotensin-II-receptor blockers may play a role in the treatment of the metabolic syndrome, not only because of

their blood pressure lowering action but also because of their metabolic and anti-inflammatory properties. Although the metabolic syndrome may be a useful tool for addressing the growing risk of diabetes and cardiovascular disease in our populations, until a common pathogenetic factor has been clearly identified to act as a therapeutic target, clinicians must evaluate and treat all cardiovascular disease risk factors,

regardless of whether or not the patient meets the diagnostic criteria of the 'metabolic syndrome'.

### Expert commentary & future perspective

The two and a half days of the Genoa Meeting encompassed topics such as epidemiology, pathogenesis, screening and evaluation, and several other controversial issues involved in the treatment

of hypertension- and diabetes-related renal and cardiovascular diseases. The meeting also provided up-to-date knowledge on new and rapidly expanding fields, such as the therapeutic use of stem cells. The meeting format, which allowed considerable time for lively discussion, provided opportunities for an update and insight into areas that are currently important and probably will become even more so in the future.

### Highlights

- Mild renal impairment is an often overlooked cause of increased cardiovascular mortality, especially in hypertensive patients. Its prevalence has been increasing over the last several years.
- Subclinical inflammation and endothelial dysfunction are often associated with renal impairment in hypertensive patients and could be causally related to it.
- The metabolic syndrome and obesity are also strongly associated with the presence of kidney damage. Future intervention strategies aimed at preventing these clinical conditions at the population level are needed in order to reduce cardiovascular morbidity and mortality in the near future.
- Aggressive multifactorial treatment of cardiovascular risk factors is recommended in hypertensive and/or diabetic patients with renal damage, both for cardiovascular and renal protection.
- Antihypertensive treatment, preferably by renin–angiotensin–aldosterone-blocking drugs, is a highly cost-effective approach in these patients subgroups.

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