There have been significant global strides in implementing reductions in dietary salt, primarily tackling processed foods and launching public-education initiatives with 60 initiatives implemented during the past four years alone. These efforts have been successful with significant effects. For example, Finland, which has one of the longest-running public salt-reduction initiatives, lowered salt intake by 15% between 1979 and 2007, from 12.8 g to 9.0 g. Likewise, The UK reduced intake by 15% between 2001 and 2011, from 9.5 g to 8.1 g, saving an estimated 8500 lives per year. The Session clearly identified the reduction of salt intake as a major global initiative for the reduction of cardiovascular disease and stroke, and an effort with great potential impact on world health.

Inaugural Renin-Angiotensin Aldosterone System Meeting:

"Putting the A back into RAAS"

Santorini, Greece, 10-12 June 2014
Official Satellite to 2014 ESH/ISH Meeting, Athens, Greece

Anastasia Susie Mihailidou and Louise Burrell

This meeting report for our Investigator-Initiated Satellite is provided on behalf of our Organising Committee members: Anthony Ashton, George Bakris, Robert Carey, Mark Cooper, Kate Denton, Carlos Ferrario, Toshiro Fujita, Peter Fuller, John Funder, Stephen Harrap, Frederic Jaisser, Colin Johnston, Martin Reincke, Michael Stowasser, Rob Widdop, Morag Young and our Secretariat, Jennifer Seabrook.

As indicated by the name, the renin-angiotensin-aldosterone system (RAAS) has three important components, renin, angiotensin and aldosterone. The RAAS is an integrated system that not only regulates blood pressure, electrolyte and fluid balance, the classical actions of RAAS, but is also involved in cardiovascular disease, metabolic syndrome and many other conditions. Our focused meeting provided the ideal interactive forum for the latest research developments by leaders in this field as well as opportunity for young investigators and students to present their research. Clinical and basic research into the regulation of RAAS in the brain, vessels, kidneys, heart and primary aldosteronism were presented. Novel techniques for both advancing research and clinical diagnosis stimulated discussion and facilitated new collaborations. Our report highlights some of these developments which were presented by our invited speakers.

It was truly an international meeting with over 50 delegates travelling from 14 countries – Australia, Austria, Canada, China, Denmark, France, Germany, Greece, Ireland, Italy, Japan, Sweden, United Kingdom and United States - to present their research, exchange ideas and establish new friendships. Securing funding was challenging and we thank our sponsors, European Society of Endocrinology, Daiichi Sankyo, Attoquant Diagnostics, Dia Sorin, Mitsubishi-Tanabe, Servier, seed funding from Dr John Funder and the COST Network for their support, which enabled this meeting to be held.

As an Official Satellite of ESH/ISH Hypertension 2014, the first presentation was appropriately "Hypertension Management in the 21st Century: Is there a role for renal denervation?" by Dr George Bakris who provided an overview of hypertension management. Although there are 9 distinct classes of antihypertensive medications, five of which influence the RAAS, control of hypertension continues to be a challenge, with NHANES 2010 reporting that only 53% of patients with hypertension achieve goal BP <140/90 mmHg. Lack of control can be due to patient non-adherence due to either side effects/tolerability of medications or refusal to accept treatment for hypertension, a silent disease. Therefore other options have been investigated such as baroreceptor activation therapy (BAT) and renal denervation. Although early studies suggested that renal denervation would provide benefit to reduce BP, the results of the SYMPLICITY HTN-3 trial failed to confirm this. Trials of BAT in hypertension and heart failure are ongoing, and early results appear promising.

The increasing aging population globally will place an enormous burden on health services. Understanding the changes in the body's homeostatic mechanisms with advancing age is paramount for targeted treatment. Exciting data from the laboratories of Dr Kate Denton and Dr Iris Jaffe identify important changes in RAAS with aging. Males have low renal angiotensin type 2 receptor (AT2R) expression throughout life, whereas in females AT2R expression is high during puberty and then declines with advancing age. Impaired vascular function with advancing age may indicate changes in smooth muscle cell (SMC) mineralocorticoid receptors (MR) or "aldosterone receptors." Mice in which MR was selectively deleted from SMC had decreased blood pressure with advancing age and reduced vascular myogenic tone and agonist-dependent contraction.

RAAS also has an important role in mediating innate and adaptive immune responses during cardiovascular disease, which Dr Ernesto Schiffrin highlighted in his presentation. Experimental studies mirror the changes observed in humans, suggesting new therapeutic approaches to improve outcomes in hypertension and cardiovascular disease. MR also have an important role in the hypothalamic paraventricular nucleus (PVN) shown in studies conducted by Dr Elise Gomez-Sanchez where activation of MR within pre-autonomic neurons in the PVN directly participate in regulation of sympathetic nervous system drive.

It is certainly an exciting period in RAS research with selective non-peptide AT2 receptor (AT2R) agonists now identified. Dr Robert Widdop provided results from their studies with CGP42112, Compound 21 or angiotensin peptides that showed cardiovascular protection in various models such as cardiac fibrosis and atherosclerosis. This was followed by Dr Robert Carey presenting his studies showing activation of intra-renal AT2R with intravenous Compound 21 increased urinary Na^+ excretion and renal proximal tubule cell apical membrane AT2R protein, while lowering BP in Ang II-dependent hypertension and a potential therapeutic target for the treatment of fluid retaining states and hypertension. Interesting computer modelling studies of ATR and the potential for developing novel ligands were presented by Dr Andreas Tzakos. The importance of identifying common pathways in pathologies other than cardiovascular disease was highlighted by Dr Ulrike Muscha Steckelings. Anti-inflammatory and immune-modulatory actions of the AT2R attenuate inflammation and cartilage destruction in rheumatoid arthritis and can reduce neurological symptoms in experimental autoimmune encephalomyelitis. In both studies, treatment of mice with an AT2R agonist modified T-cell response reducing TH1-TH17 T cells and increasing regulatory T-cells. Another potential application for AT2R stimulation is in the field of dermatology with beneficial effects of AT2 agonists in psoriasis. Various agonists for AT2R and the MAS receptor are now in preclinical and clinical development for a variety of diseases, both cardiovascular and non-cardiovascular.

Convergent pathways between Ang II and aldosterone were highlighted by Dr David Pearce and Dr Toshiro Fujita. Dr Pearce's laboratory has shown SGK1 is an important regulator of ion transport in multiple segments throughout the kidney and at the transcriptional level, regulated by aldosterone. Their recent data shows that its activity is also regulated by Ang II through an mTOR dependent phosphorylation. Interestingly, Ang II-induced phosphorylation is specific to SGK1; the serine-threonine kinase, Akt, a close relative of SGK1 is not phosphorylated in response to Ang II. Dr Fujita has identified Rac1, a member of the Rho-family of small GTP binding proteins, as a novel ligand-independent modulator of MR activity. Renal Rac1 is activated by salt loading in Dahl salt-sensitive rats and AII-overexpressed mice, leading to MR activation despite suppressed serum levels of aldosterone, leading to elevated BP and renal injury. The renal actions of RAAS continued with presentations by Dr Marc Lombes. MR are highly expressed in the distal nephron where there are large variations in extracellular fluid tonicity, establishing an osmotic gradient which regulates ion and water transport, modulated during renal development and possibly various kidney diseases. Novel findings by Dr Lombes' laboratory show that hypotonicity increases renal MR abundance and further studies are in progress to determine whether this may indicate a pathophysiological role in kidney disease, hypertension or mineralocorticoid resistance.

Similar to the exciting new research developments in selective non-peptide AT2R agonists and angiotensin peptides and their application, there is increasing interest in understanding MR structure and the determinants for tissue and ligand-specific activation. Dr Peter Fuller and his team have identified proteins which interact in the presence of ligand, either aldosterone or cortisol but not both and confirmed coactivators for the full-length human MR. Ongoing studies are planned to identify ligand-specific interactions as well as antagonism for MR which may lead to developing tissue specific agents. Dr Frederic Jaisser highlighted the new developments in activation of aldosterone and MR signaling pathways in

endothelial and vascular smooth muscle function.

Primary aldosteronism (PA) is recognized as the most common cause of secondary hypertension for 2-10% of patients with hypertension. The latest developments were presented by many of the leaders in this field in a dedicated session. Dr Maria-Christina Zennaro has established a genome-wide strategy to explore the genetics and genomics of aldosterone-related disorders and provided the introduction to this stimulating session. Dr Martin Reincke followed with presentation of his interesting research into examining the specificity and sensitivity of recently proposed prediction tests for unilateral PA in the clinic and compared the clinical prediction score which includes imaging, serum potassium and glomerular filtration rate to the combination of visible unilateral adenoma on imaging and age <40 years. The results confirmed that adrenal venous sampling continues to be a requirement in the majority of patients.

Detection of PA requires measurement of the aldosterone-renin-ratio (ARR) despite limitations in selectivity, sensitivity and interference from several antihypertensive agents. Novel methods for increasing the accuracy and improving diagnosis of PA screening

were presented by Dr Marko Poglitsch. This approach is in the validation phase and provides great promise. Confirmatory tests are also required to document aldosterone production independent of regulation via angiotensin II and include sodium loading manoeuvers such as fludrocortisone suppression testing (FST) and saline suppression testing (SST). Dr Michael Stowasser and his team have observed that recumbent SST lacks sensitivity compared to seated SST and initiated a pilot study to compare the traditional RSST protocol to SSST. The results from this study show that seated SST had better sensitivity than recumbent SST in confirming PA, was well tolerated by the patients, simple and quick to perform without hospital admission required and comparable reliability. Once the aldosterone-producing adenomas are excised, there has been interest by several research teams in developing antibodies to the enzymes involved in aldosterone biosynthesis, CYP11B1 and CYP11B2. Dr Celso Gomez-Sanchez has developed a specific mouse monoclonal antibody against CYP11B2 and a specific rat monoclonal antibody against the CYP11B1 enzyme and presented initial validation studies which show variable staining pattern in aldosterone producing adenomas and multiple different pathological patterns.

A common theme throughout the satellite was that RAAS is an integrated system. Adipocytes express all components, with overexpression of angiotensinogen (ATG) leading to increased fat mass, adipose inflammation, glucose intolerance and insulin resistance, whereas ATG knockout mice had reduced fat mass. Dr Massimiliano Caprio and his team have shown functional MR in adipose tissue, which mediate regulation of adipogenesis and adipose expansion. Addition of MR antagonists improved glucose tolerance in diet-induced obese mice, and counteracted the effects of high-fat diet on white adipose mass. Translating this to patient management, Dr Gail Adler and her team have shown that dysregulated aldosterone physiology predicts the metabolic syndrome in normotensive and hypertensive adults, without other cardiovascular risk factors. Patients with type 2 diabetes mellitus receiving MR blockade had improved coronary flow reserve, which is a measure of coronary microcirculatory function. Activation of RAAS contributes to the pathogenesis of myocardial infarction (MI) and progression to heart failure. Large randomized clinical trials have shown the benefits of targeting blockade of MR, although the exact mechanisms have not been defined. Dr Anthony Ashton presented recent findings from collaborative research with the laboratory of Dr Anastasia Susie Mihailidou demonstrating integrated activation of non-genomic and genomic MR pathways during experimental MI to promote myocardial damage.

It is an exciting time for RAAS research and we look forward to the next integrated RAAS meeting, possibly as a satellite to the 26th Scientific Meeting of the ISH to be held in Seoul, South Korea in September 2016.

Anastasia Susie Mihailidou and Louise Burrell

Glasgow secures prestigious ESH/ISH Joint Scientific Congress in 2020

The European Society of Hypertension and the International Society of Hypertension (ESH/ISH) Joint Scientific Congress 2020, which will take place at the Scottish Exhibition + Conference Centre (SECC) in Glasgow, Scotland.

The bid was delivered in partnership with the University of Glasgow, the British Hypertension Society, Glasgow City Marketing Bureau (GCMB) and the SECC.

Glasgow is widely recognised as a Centre for Excellence in hypertension research, making it the perfect host city for the ESH/ISH Joint Scientific Congress 2020; with a long, distinguished record in cardiovascular research, blood pressure and hypertension. This is evidenced by the unique situation where the President of the European Society of Hypertension, Prof Anna Dominiczak and the President of the International Society of Hypertension, Prof Rhian Touyz are both from the University of Glasgow.

Glasgow has a long history of healthcare innovation, pioneering revolutionary medical technologies to world-wide audiences and the city looks forward to a bright future of ground-breaking life science research tackling public health issues head-on.

Glasgow is one of Europe's most vibrant, dynamic and friendly cities. Easy to get to and easy to get around, the city is the location of the award-winning Scottish Exhibition and Conference Centre (the venue for 2020). Glasgow has a proud history of academic excellence with its universities internationally renowned as centres of learning and research with the second largest student population in the UK.

Delegates can also enjoy Glasgow's many parks, museums and art galleries, many of which are free of charge. Its unique and warm hearted character make it a hit with visitors, and the city's excellent track record in hosting major conferences mean that you can look forward to a congress to remember.

Scotland's cultural capital looks forward to welcoming the ISH and ESH delegates in 2020!