## ABSTRACTS

Abstracts for Invited Lectures:

### IL1.

#### ENDOTHELIAL DYSFUNCTION: THE COMMON CONSEQUENCE IN DIABETES AND HYPERTENSION

Y Huang
Institute of Vascular Medicine & School of Biomedical Sciences, The Chinese University of Hong Kong, Hong Kong

Endothelial dysfunction, caused by diminished impact of endothelium-derived relaxing factors and/or exaggerated influence of endothelium-derived contracting factors in the vascular wall, is the common consequence of diabetes and hypertension. The degree of endothelial dysfunction predicts future cardiovascular outcomes. We have examined the cellular mechanisms involved in endothelial dysfunction in diabetes and hypertension using *ex vivo* and *in vivo* models. We have identified an upregulation of renin-angiotensin system (RAS) components in both hypertension and diabetes. Our data show that the use of RAS blockers (including renin inhibitor, ARB and ACE inhibitors) effectively restores endothelial function in both animal models of diabetes and hypertension. Likewise, cyclooxygenase-2 (COX-2) is also implicated to be a critical player in endothelial dysfunction in both pathological conditions. Both RAS and COX mediate the detrimental effects of several risk factors on endothelium-dependent relaxations in mouse and rat arteries, including hyperglycemia, oxidative stress, inflammatory cytokines, angiotensin II, and advanced glycation end products. Recently, we have found that bone morphogenetic protein 4 (BMP4) is possibly one of the common upstream activators to induce endothelial dysfunction in both hypertension and diabetes. BMP4 activated NAD(P)H oxidases to induce oxidative stress and upregulated the expression and activity of COX-2 in endothelial cells, which could cause hypertension, impair endothelium-dependent relaxation, induce endothelium-dependent contraction, and cause endothelial cell apoptosis. Importantly, we found a crosstalk between the RAS and BMP4 in hypertension and diabetes. Better understanding of the cellular and molecular mechanisms of endothelial dysfunction shall help to identify more effective therapies to improve cardiovascular outcomes in patients with hypertensive and diabetes.

### IL2.

#### VASCULAR OXIDATIVE STRESS: THE COMMON LINK

RA Cohen, XY Tong
Vascular Biology Unit, Whitaker Cardiovascular Institute, Boston University School of Medicine, USA

Vascular disease in hypertension and diabetes is associated with systemic vascular inflammation and increased adhesion of leukocytes to activated vascular cells. Excess levels of oxidants are implicated both as a cause of damage to vascular constituents, but also as important pathogenic contributors to changes in cardiovascular cell structure and function. The excess oxidants arise from several sources including NADPH oxidase, xanthine oxidase, and mitochondria. Superoxide anion and hydrogen peroxide are produced by these systems in both leukocytes and vascular cells, and hypochlorous acid, another strong oxidant, is produced by leukocyte myeloperoxidase. Nitric oxide is also produced in excess by the inducible isoform of nitric oxide synthase in inflamed blood vessels. Peroxynitrite, formed by the rapid reaction of superoxide and nitric oxide, is another potent endogenous oxidant in hypertensive and diabetic human and animal blood vessels. These oxidants cause damage, altering protein function, introducing DNA mutations, and increasing lipid peroxidation. Unlike that to DNA and lipids, the damage to proteins is selective, affecting specific oxidant-sensitive cysteine, tyrosine, methionine, and tryptophan amino acid residues. Altered structure and function of some proteins results, and if the oxidation is irreversible, then protein degradation is required for restoration of function. With some important vascular proteins, for example endothelial nitric oxide synthase, prostacyclin synthase, and superoxide dismutase, oxidation of a single susceptible amino acid inactivates the enzyme. The beneficial effects of antioxidants, at least in animal models of hypertension and diabetes, can in part be ascribed to protection of the function of these and other proteins. The pathogenic importance of oxidation of specific cysteine residues is reflected by the fact that in some proteins, such as the sarcoplasmic reticulum calcium ATPase, expression of mutant proteins lacking the reactive cysteine thiol, recapitulates a disease phenotype, such as accelerated smooth muscle or impaired endothelial cell migration. Thus, many of the shared functional abnormalites of hypertensive and diabetic blood vessels may be caused by oxidants. Although studies using antioxidants have failed in patients, the successful treatment of vascular disease with HMG CoA reductase inhibitors, PPAR agonists, thromboxane $A_2$ antagonists, and polyphenols may depend upon their ability to decrease production of damaging oxidants.

## ABSTRACTS

Abstracts for Invited Lectures:

### IL3.

### THE TP-RECEPTOR: THE COMMON VILLAIN

M Félétou
Department of Angiology, Institut de Recherches Servier, 11 rue des Moulineaux, Suresnes, France

Thromboxane $A_2$ is the preferential physiological ligand of the TP receptor but other prostaglandins as well as some prostanoids, which do not necessarily derived from cycooxygenases (COX) such as isprostanes, are also able to activate this receptor. The stimulation of TP receptors elicits diverse physiological/pathophysiological actions, including platelet aggregation and smooth muscle contraction. Furthermore, the activation of endothelial TP receptors promotes the expression of adhesion molecules and favours adhesion and infiltration of monocytes/macrophages. In various cardiovascular diseases, the endothelial dysfunction is due to the release of endothelium-derived contracting factors (EDCF) that counteract the vasodilator effect of NO. Endothelium-dependent contractions involve the activation of COX, the production of reactive oxygen species along with that of EDCFs, which diffuse toward the vascular smooth muscle cells and activate the TP receptors. Antagonists of the TP receptor curtail the endothelial dysfunction in diseases such as hypertension and diabetes, are potent antithrombotic agents and prevent vascular inflammation. Therefore, TP receptor antagonists, because of this triple activity, may demonstrate a unique potential for the treatment of cardiovascular disorders.

### IL4.

### THE HYPERTENSION-DIABETES CONTINUUM

BMY Cheung
Department of Medicine, The University of Hong Kong, Hong Kong

Hypertension and diabetes are both common chronic conditions that affect a major proportion of the general population. They tend to occur in the same individual, suggesting common predisposing factors, which can be genetic or environmental. While the genes causing hypertension or diabetes await elucidation, the environmental causes of these diseases are well known. Obesity and physical activity are the two leading factors that predispose to both diseases. Individuals with abdominal obesity are likely to develop lipid abnormalities and elevation of blood pressure and glucose. In time, hypertension and diabetes ensue. Because of the shared aetiology, there is substantial overlap between hypertension and diabetes. In the Hong Kong Cardiovascular Risk Factor Prevalence Study, 40% of the subjects in the community had either raised blood pressure or raised blood glucose. Only 42% of people with diabetes had normal blood pressure and only 52% of people with hypertension had normal glucose tolerance. The presence of hypertension or diabetes should alert the clinician to the possibility of the other condition. Obesity, lipid abnormalities, raised blood pressure and glucose are all components of the metabolic syndrome. The syndrome therefore implies a pathological process, which is potentially reversible in the early stages. Previous efforts targeting smoking, hypertension and hypercholesterolaemia have started to bear fruit. However, obesity is on the increase in developed and developing countries. It is now time to focus on obesity and the metabolic syndrome, which require more a public health than a pharmacological approach.

### IL5.

### IMPORTANCE OF BLOOD PRESSURE LOWERING IN TYPE 2 DIABETES

J Chalmers
The George Institute for International Health, University of Sydney, Australia

The main results of ADVANCE, published in 2007 indicated major benefits of blood pressure lowering with the fixed combination of perindopril and indapamide, which reduced mortality, cardiovascular complications and renal disease, in patients with type 2 diabetes, irrespective of baseline blood pressure, whether the patients were hypertensive or not.

The findings presented at this meeting will show that these findings are remarkably consistent across a very wide spectrum of patients with type 2 diabetes. First we report that the renal benefits are similar in patients with baseline systolic blood pressures ranging from above 160 to below 120 mmHg at baseline. In absolute terms, the fixed combination of perindopril and indapamide prevented one renal event among every 20 patients treated for 5 years.

Next we demonstrate that the benefits of this treatment are similar across age groups, and that older patients over the age of 75 years derive at least as much benefit as younger subjects, with greater reductions in absolute risk and no significant increase in adverse events.

Our findings demonstrate that cognitive function at entry is an independent predictor of clinical outcomes in patients with type 2 diabetes, but that the reductions in mortality and clinical complications obtained with perindopril-indapamide are similar across sub groups defined by cognitive function at baseline.

We report that urinary albumin and estimated Glomerular Filtration Rate (eGFR) are independent risk factors for cardiovascular and renal events in patients with type 2 diabetes and that the benefits of blood pressure lowering with perindopril-indapamide are at least as great or greater in patients with renal disease at baseline.

Finally, we show that the benefits of blood pressure lowering with perindopril-indapamide are similar in all risk categories, but that the absolute risk reductions are greater in patients with type 2 diabetes with the highest initial risk as categorized according to the 2007 ESH/ESC guidelines.

In conclusion, extensive studies of the effects of blood pressure lowering the fixed dose combination of with perindopril and indapamide confirm the remarkable consistency of benefits obtained in a very broad cross section of patients with type 2 diabetes. This suggests the results are applicable to community patients with diabetes and strengthens the recommendation that this treatment with this treatment should be considered routinely for the prevention of serious complication in patients with type 2 diabetes across the world.