

Cardiology & Diabetes at the Limits 26-28 March 2010

Prof Lionel Opie and **Prof Derek Yellon**, respectively from the Hatter Institutes of the University of Cape Town and University College London, once again produced an academic programme of outstanding quality in Cape Town, this being the 12th at the Limits meeting and the first to include diabetes along with cardiology. The meeting was attended by delegates from 22 countries amongst which were several African states.

The meeting opened on Friday evening with presentations by **Dr Richard Horton**, the editor of The Lancet, and **Dr Roberto Ferrari**, current President of the European Society of Cardiology. Horton addressed the need to reach agreement on the relationship between the medical profession, their patients and the pharmaceutical industry to ensure productive, continuing support of research in the best interests of all the parties. Ferrari delivered a wide-ranging and entertaining discussion on the Mediterranean diet, emphasizing the lack of precision in its definition as well as the cultural concomitants of that style of eating in contrast to Northern European dietary customs. He presented evidence of the beneficial effects of a diet high in vegetables and fruit with fish as an important source of protein. He pointed to the central role of olives and olive oil in the Mediterranean diet though he expressed concern about the salt content of preserved olives.

Dr Barry Maron was the first speaker on Saturday morning, discussing newer concepts around hypertrophic cardiomyopathy (HCM). He defined HCM as "primary" left ventricular hypertrophy due to a gene mutation in 1 in 500 of the general population, many of whose HCM will remain unidentified. The HCM phenotype is expressed by a variety of heterogeneous mutations. 80% of cases are due to abnormalities in beta-myosin heavy chain and myosin binding protein. Although sudden death (SD), heart failure, progression to end-stage disease and atrial fibrillation-stroke are all complications of HCM, the average survival of the condition does not differ from the general population with a mortality of 1.2% per year.

Turning to SD, he considered the arrhythmogenic substrate to be the myofibre disorganization and the accompanying fibrosis. The risk of SD is highest in the young but continues throughout life. Though SD is unpredictable, its risk factors include a family history of SD, syncope, massive hypertrophy, non-sustained ventricular tachycardia and an abnormal BP response to exercise. ICD implantation is recommended for this high risk group. Defibrillating shocks from ICD's occur in 11% p.a. in patients following a prior event and in 4% p.a. in high risk cases without history of a prior event.

Non-sarcomeric phenocopies of HCM are LAMP2, PRKAG2, Fabry's disease and mitochondrial myopathy. An example of the importance of identifying these

as separate conditions is LAMP2 in which ICD's are ineffective, survival beyond 25 years of age is unlikely and the appropriate therapy is heart transplantation.

With the availability of commercial genetic testing in the US, a group of individuals has emerged that is genotypically positive yet phenotypically negative for HCM. Certain of these individuals have been found to have diastolic dysfunction, an abnormal ECG or an elongated mitral valve. It is unknown whether such individuals progress to LVH or whether they have a risk for SD.

The athlete's heart (AH) can be difficult to separate from HCM as 3% of cases have a wall thickness that would qualify them for a diagnosis of HCM. They can usually be identified on the basis of their pattern of LVH, LV cavity size and regression to normal when not exercising. However, rare cases have been described in which HCM developed in individuals with AH over 7-16 years of follow-up.

Prof Steve Humphries discussed genetic testing for ischaemic heart disease. Based on the Northwick Park study, he pointed out that conventional risk factor testing will detect only 14% of individuals who will eventually have a myocardial infarction (MI). However the addition of a single genetic marker improves detection by only 3%. Employing a gene scoring system that includes some 10 single nucleotide polymorphisms (SNPs) gives greater power of detection. He proposed using the combination of gene profiling and the classical risk factors to improve the identification of at-risk subjects so as to more accurately counsel them on risk factor control. A major benefit of genetic testing is that, irrespective of the result, it improves patient compliance with life-style changes and adherence to treatment.

HDL cholesterol (HDLc), its role in atherosclerosis and the prospects for improving outcomes with HDL-raising therapies was the subject of **Prof John Chapman's** presentation. He emphasized the wide spectrum of HDLc's activity which includes countering inflammation, atherogenesis, thrombosis, apoptosis, oxidation and proteolysis as well as the promotion of endothelial repair. Recent evidence indicates that alcohol intake has no independent effect upon HDLc but is correlated with socio-economic status. The ideal LDLc:HDLc ratio appears to be unity. Even though low LDLc levels were achieved in the TNT study which compared high vs. low doses of atorvastatin in secondary prevention, these lower levels did not eliminate the risk associated with low HDLc. HDLc becomes dysfunctional in inflammatory states. However, Chapman did not accept that certain sub-classes of the HDL family might promote atherogenesis. Agents under investigation to evaluate the effects of raising HDLc on cardiovascular outcomes are nicotinic acid, niacin-laropiprant and newer CETP inhibitors.

Prof Ayodele Falase, Ibadan, Nigeria, and **Prof Karen Sliwa**, newly-appointed Professor of Cardiovascular Research and Head of the Hatter Heart Research Institute in Cape Town, respectively discussed cardiomyopathy and heart failure

in Africa. Both pointed to hypertension as the predominant cause of heart failure in Africa. Falase proposed a new classification for heart muscle disorders that moved away from cardiomyopathy as a grab-bag diagnosis for many cases of heart failure. Sliwa discussed peri-partum cardiomyopathy, defining its molecular etiology, and the current collaborative international research into the effects of inhibiting the abnormal prolactin that is present with bromocriptine.

The current treatment of diabetes is complicated by the occurrence of severe hypoglycaemia, weight gain, progressive loss of beta-cell function and secondary treatment failure. Recent studies have emphasized the importance of avoiding hypoglycaemia which has been associated with increased mortality and cognitive decline. The glucagon-like-peptide 1 (GLP1) agonists and their potential role in cardioprotection in diabetics were discussed by **Prof Wolfgang Schmidt** (University of Ruhr, Germany) He pointed out that diabetics not only suffer beta-cell dysfunction and apoptosis but also develop alpha-cell hypertrophy which leads to an excess of glucagon and hyperglycaemia. GLP1 agonists reduce beta-cell dysfunction and diminish the effect of glucagon. Their effect is to decrease blood glucose levels without inducing hypoglycaemia and to reduce glucagon levels once normoglycaemia is achieved. The incretin mimetics are classed as either GLP1 agonists (eg. exenatide and liraglutide) which are stable peptide analogues or dipeptidyl peptidase-4 (DPP4) inhibitors, which augment endogenous GLP1 (sitagliptin, vildagliptin and saxagliptin). Although instances of pancreatitis and pancreatic carcinoma have been found experimentally with the analogues, neither condition has appeared in clinical experience. Trials are underway to discover whether long term treatment with GLP1 agonists or DPP4 inhibitors will reduce cardiovascular events.

Prof Eberhard Standl from Munich addressed whether the combined effects of diabetes and heart disease could be controlled. He pointed out that projections were that about 1 billion people worldwide would be affected by glucose intolerance by 2030; approximately 50% with diabetes and 50% with impaired glucose tolerance. There was no significant difference in frequency between the genders. Although little difference in cardiovascular outcome was observable within the first 5 years of diagnosis, the prognosis worsened rapidly in the diabetic group within the subsequent 5 years. There was a gradient in the incidence of cardiovascular disease going from normoglycaemia through impaired fasting glucose / impaired glucose tolerance to new-onset diabetes to known diabetes. The obverse of the coin is that 2/3 to 3/4 patients with coronary artery disease in the Euro Heart Survey were found to be hyperglycaemic. The onset of diabetes can be predicted effectively by risk engines such as the FINDRISK or UKPDS scores. Certain studies have shown that prognosis is not affected by the detection and treatment of silent myocardial ischaemia. On this basis Standl recommended that it was not necessary to screen entirely asymptomatic diabetic patients for the presence of myocardial ischaemia.

Dr Kenneth Chien of Massachusetts General Hospital and Harvard Medical School presented his group's research on the development of cellular therapies to replace cardiac tissue, to produce "spare parts" for the heart and to grow disease-specific stem cells. Their long-term aim is to grow cells in which to evaluate disease mechanisms *in vitro* and to screen the effect of drug therapies. His laboratory has developed techniques to grow pluripotent stem cells from epithelium. "Master" heart stem cells are then produced from the pluripotent cells which are able to differentiate into myoblasts, mesenchymal cells and precursors of vessels. Hypothetically, such cells could be developed into tissues that would provide spare parts for diseased hearts. The work from his laboratory has shown that there are different cellular precursors for right and left ventricular myocardium.

At the session held on Sunday morning **Dr Bernard Gersh** spoke on revascularization in diabetics. On the basis of the DIAD trial, he agreed with Standl that the routine screening of low risk diabetic patients for ischaemia was unnecessary. However patients with established vascular disease do not fall into this category. The interpretation of both the COURAGE and BARI 2D trial results had to be understood in the light of every participant having undergone angiography before randomization, thus eliminating the patients with the highest risk anatomic lesions. Gersh cautioned that it was thus difficult to extrapolate the COURAGE and BARI 2D results to patients who have not already undergone angiography. These trials agreed in their finding that optimal medical therapy was appropriate treatment in chronic stable angina and that the results with revascularization were no better.

In BARI 2D the group of patients revascularized by CABG had more severe disease. In this sub-group the time to first MI was delayed in the CABG group compared to the medically treated group. Gersh highlighted the difficulty in interpreting the BARI trial, showing that though the results of the randomized group showed a benefit for CABG rather than PCI, the registry results, derived from eligible patients who decided against entering the trial and in whom the "normal" decision processes of both the treating physician and the patient came into play, CABG and PCI yielded similar results. Sub-group analysis of the SYNTAX trial indicates the expected higher mortality in diabetics in comparison to non-diabetics. However 1- and 2-year follow-up data demonstrate significant advantage of CABG over PCI in the incidence of adverse cardiac in non-diabetics with a SYNTAX score in the highest tertile and in diabetics in both the intermediate and highest tertiles.

Prof Christopher McGregor from The Heart Hospital, UCL, discussed the impact of technological developments on cardiac surgery. With the advent of more and more percutaneous techniques, robotics and miniaturization amongst others, the surgeon's role was changing. He proposed the reorganization of departments into cardiovascular medicine units to ensure integration of the various fields of activity, synergy and cooperation between the traditional

“surgical” and “medical” arms and the incorporation of imaging services which have traditionally been run separately. Care needed to be specifically patient-focused. The reorganization would require both business and financial modeling and ultimately change the nature of undergraduate training to raise cardiovascular specialists rather than cardiologists and cardiac surgeons as is presently the case.

The last presentation of the morning was by **Prof Christian Hamm**, previously a trainee in Prof Opie’s laboratory and now from Bad Nauheim concerning antiplatelet therapy. He discussed the role of aspirin, clopidogrel and glycoprotein IIb/IIIa inhibitors in acute coronary syndromes. Problems surrounding resistance to anti-platelet agents, bleeding as a consequence of treatment and the issue of triple anti-platelet therapy and concomitant warfarin treatment were mentioned. Both of the newer agents, prasugrel and ticagrelor, may offer solutions to anti-platelet drug resistance. Despite higher bleeding risk, GPIIb/IIIa inhibitors still offer benefit on a background of dual antiplatelet therapy (DAP). The combination of DAP with warfarin is subject to individualized clinical judgment and exposure to the combination should be limited to the shortest possible time.

The Monday morning programme consisted of a discussion between **Prof Lionel Opie** and **Prof Stefano Del Prato** from Pisa on whether there should be tight glycaemic control in diabetics. Del Prato’s arguments centered on the need for early tight control to avoid the ultimate microvascular and renal damage. In the early stages fewer drugs are needed, so side-effects are less than at later stages requiring several drugs associated with side-effects such as weight gain and hypoglycemic episodes. The arguments against tight control related to (1) the concept of a more realistic and lenient range of blood glucose values, which from trial data often extended well above the ideal “aim” of 6.5% HbA1c, above and below which there were problems; and (2) to a greater need for control of the BP and serum lipid than for tight glycaemic control. Hence diabetes is now a disease that challenges not only diabetologists but also cardiologists.