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4TH ASIAN PACIFIC  
**Congress of Heart Failure**

Heart Failure in 3D - Drugs, Devices, Diagnostics

31 January to 2 February 2008  
Melbourne Exhibition and Convention Centre  
Melbourne, Australia

Official Satellite Symposium

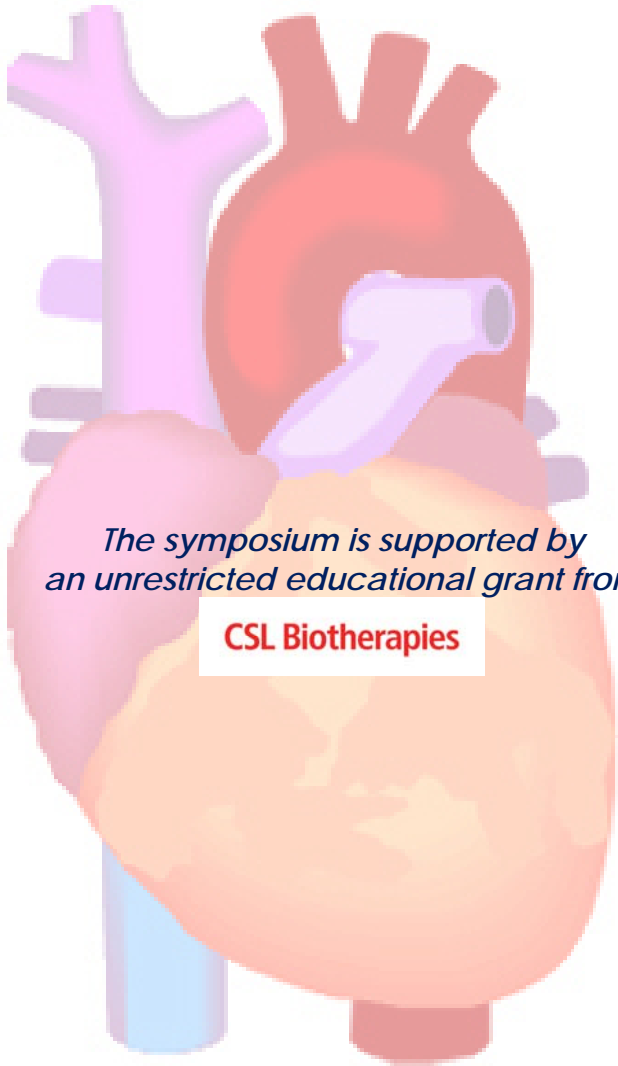
**4th Asian Pacific Congress of Heart Failure**

***“New Therapeutic Options in the  
Treatment of Heart Failure: Role of  
Third Generation  $\beta$ -Blockers”***

**Melbourne Exhibition and Convention Centre**

**Abstract Book**

**Saturday, 2<sup>nd</sup> February, 2008**



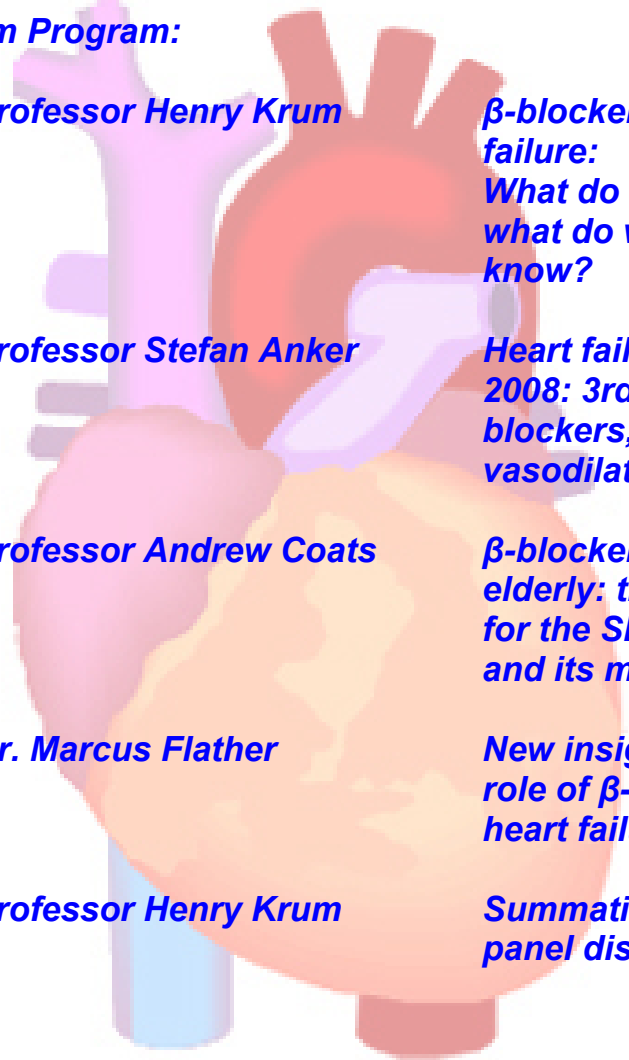
*The symposium is supported by  
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**CSL Biotherapies**

# Symposium Program

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## *Symposium Program:*

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- 4:00 PM Professor Henry Krum**      ***β-blockers in heart failure:  
What do we know and what do we still need to know?***
- 4:20 PM Professor Stefan Anker**      ***Heart failure therapy in 2008: 3rd generation β-blockers, nitric oxide & vasodilation***
- 4:40 PM Professor Andrew Coats**      ***β-blockers in the elderly: the rationale for the SENIORS study and its main results***
- 5:00 PM Dr. Marcus Flather**      ***New insights into the role of β-blockers for heart failure***
- 5:20 PM Professor Henry Krum**      ***Summation & chair panel discussion***

# Symposium Faculty

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**Prof Henry Krum**

Professor Henry Krum is a well recognised figure in the area of cardiovascular clinical pharmacology and therapeutics, attested to by his extensive professional activities in this area.

Prof Krum is also a physician at the Alfred Hospital in Melbourne and heads Clinical Pharmacology at Monash University and the Alfred Hospital. He has extensive research experience in cardiovascular diseases and clinical pharmacology, something to which his publication record testifies. His interests lie with heart failure and hypertension, and his work spans the fields of both basic and applied sciences.

Professor Krum has been a member of numerous International Steering and Executive Committees for major clinical trials in the area of cardiovascular pharmacotherapy. He is currently Principal Investigator of a number of multicentre investigator-initiated trials testing cardiovascular therapeutic strategies.



**Prof Andrew Coats**

Andrew J. Coats moved to the University of Sydney in late 2002. At Sydney he has served as Dean of the Faculty of Medicine, and Chairman of the Committee of Deans, before taking up his present Deputy Vice-Chancellor (Community) role earlier in 2006. He trained at Oxford, Cambridge and Melbourne, before joining the National Heart and Lung Institute, Imperial College School of Medicine, where he headed the Department of Clinical Cardiology as the first Viscount Royston Professor of Clinical Cardiology. From 1996-2000 he was Director of Cardiology at the Royal Brompton Hospital and until 2002 was Associate Medical Director (R+D) of the Royal Brompton and Harefield NHS Trust. Since February 1999 he has been Editor-in-Chief of the International Journal of Cardiology.

Prof Coats has been Chairman or Steering Committee Member of a number of major morbidity/mortality trials including SENIORS.

His main research interests are in the pathophysiology and therapy of chronic heart failure, in exercise physiology and in the management of hypertension.

# Symposium Faculty

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**Prof Stefan Anker**

**Stefan D. Anker** is Professor of Cardiology and Cachexia Research at the Department of Cardiology in the Charité, Campus Virchow-Klinikum in Berlin, Germany (since 2002). Dr. Anker studied medicine and obtained his M.D. (1993) from Charité Medical School in Berlin. He went on to earn a Ph.D. (1998) at the National Heart & Lung Institute (NHLI), Imperial College London, based on studies on cachexia in chronic heart failure. As part of his training, Dr. Anker was a cardiology research fellow and then team leader at the NHLI. He now is Senior Research Fellow at Imperial College London.



**Dr Marcus Flather**

**Marcus Flather** graduated from the Royal Free Medical School in 1982 and trained in general medicine and cardiology in London and Oxford. In 1988 he joined the Department of Cardiovascular Medicine and the Clinical Trial Service Unit at the University of Oxford as a British Heart Foundation Junior Research Fellow with Peter Sleight, Rory Collins and Richard Peto. During his 5 years in Oxford he was part of the team that co-ordinated the ISIS-3 and ISIS-4 studies evaluating treatments for myocardial infarction, and the Fibrinolytic Therapy Trialists Collaboration, a systematic overview of randomised trials of fibrinolytic treatment in acute myocardial infarction. In 1993 he moved to McMaster University in Hamilton, Canada, to work with Salim Yusuf as a Clinical Research Scholar on international trials in acute coronary syndromes including the OASIS programme, and undertook formal training in clinical trials and epidemiology. In 1996 he took up the post of Director of the newly established Clinical Trials and Evaluation Unit (CTEU) at the Royal Brompton Hospital, with an honorary Consultant Cardiologist position and honorary Senior Lecturer appointment at the National Heart and Lung Institute of Imperial College and Honorary. CTEU specialises in the design, co-ordination analysis and reporting of multi-centre trials in cardiovascular and respiratory diseases.

# ***β-blockers in heart failure: What do we know and what do we still need to know?***

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**Professor Henry Krum**

**Head Clinical Pharmacology Unit**

**Director, NHMRC Centre of Clinical Research Excellence in Therapeutics  
Monash University**

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Beta-blockers are now well established as mandatory therapy for all severities of systolic chronic heart failure, unless contra-indicated or not tolerated. This is based on guideline recommendations built on the strong evidence base for these agents.

In this setting it would therefore seem that most questions with regard to beta-blockers in heart failure have been answered. Whilst this is partially true, there are still many issues of uncertainty with regard to the use of these agents in this setting:

- What role may beta-blockers have in patients with heart failure and preserved systolic function?
- What is the role of beta-blockade in the treatment of patients with asymptomatic LV systolic dysfunction remote from an ischaemic event?
- Are beta-1 selective versus non-selective agents preferred in patients with obstructive airways disease? Does an evidence-base exist for this in chronic heart failure?
- Is there a role for beta-blockers in heart failure prevention in high-risk populations?
- What is the most appropriate approach to maximising clinical benefits with beta-blockers in existing indications?
  - achievement of “target” dose?
  - treatment to pre-defined heart rate reduction?
  - achievement of a target absolute heart rate level?

These are but some of the many questions that still exist with regard to the use of beta-blockers in heart failure. Given that many of these agents are now generic it is unfortunate but highly unlikely that large-scale clinical trial programs will be conducted to address them. In this context, we therefore need to carefully consider available evidence in clinical decision making with regard to the most appropriate prescribing of existing agents for proven indications.

Professor Krum has been a member of numerous International Steering and Executive Committees for major clinical trials in the area of cardiovascular pharmacotherapy. He is currently Principal Investigator of a number of multicentre investigator-initiated trials testing cardiovascular therapeutic strategies



# **Heart Failure therapy in 2008: 3rd Generation $\beta$ -blockers, nitric oxide & vasodilation**

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## **Professor Stefan Anker**

**Applied Cachexia Research, Charité Campus Virchow-Klinikum, Berlin, Germany**

**Clinical Cardiology, National Heart & Lung Institute, Imperial College London, UK**

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Chronic HF is a complex syndrome affecting many body systems. Key pathophysiologic findings in patients with chronic HF are neurohormonal activation, vasoconstriction and endothelial dysfunction as well as insulin resistance.

Modern therapy of chronic HF utilizes drugs, devices, exercise and life style advice. The corner-stone of modern HF therapy in 2008 is the use of beta-blockers. Not all beta-blockers are efficacious - there are 4 beta-blockers with established efficacy to improve morbidity and mortality in chronic HF, namely metoprolol succinate, bisoprolol, carvedilol and nebivolol.

There is large variation in pharmacological and physiological profile of these beta-blockers. Research has shown that nebivolol promotes the availability of nitric oxide (NO) in the endothelium and thereby promotes vasodilation and b) unlike other beta-blockers does not impair tissue insulin sensitivity.

These are important effects as hypertension and atherosclerosis – the most common causes of HF development – are associated with development of endothelial dysfunction, mainly due to a reduced endothelial availability of NO. The latter has anti-inflammatory and antithrombotic properties, by:

- inhibition of leukocyte adhesion,
- reduction of platelet adhesion and aggregation, and
- reduction of the expression of plasminogen activator inhibitor-1 (PAI-1), which is a prothrombotic protein.

There is now also emerging evidence that NO synthase (eNOS-)derived NO is important for the repair capacity of bone marrow-derived endothelial progenitor cells (EPCs).

These observations suggest that targeting endothelial dysfunction in HF patients – directly or indirectly – and enhancing NO availability, would be beneficial in patients at major risk for cardiovascular events. Patients with chronic HF are such patients.



# ***β-blockers in the elderly: the rationale for the SENIORS study and its main results***

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**Professor Andrew Coats**  
**Deputy Vice-Chancellor (Community)**  
**Faculty of Medicine, University of Sydney**

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Large randomized trials have shown that beta-blockers reduce mortality and hospital admissions in chronic heart failure. Two of the most commonly cited reasons for underutilization of beta-blockers are uncertainty of the benefits or tolerability of beta-blockers in patients of advanced age or with relative preservation of left ventricular ejection fraction.

In the SENIORS study we addressed these concerns. 2,128 patients aged  $\geq 70$  years with a history of heart failure were randomized to nebivolol (1,067) (titrated from 1.25 mg once daily to 10 mg once daily) and to placebo (1,061). The primary outcome was a composite of all-cause mortality or cardiovascular hospital admission (time to first event). The mean age was 76.1 years (SD $\pm$ 4.7), 38.4% were female, mean 17 ejection fraction was 36% (with 35.7% having ejection fraction  $>35\%$ ) and 68.9% had a prior history of coronary heart disease.

Despite the advanced age and high frequency of co-morbidities nebivolol, a highly selective beta-blocker with unique nitric oxide dependent vasodilatory effects, was extremely well tolerated with a mean dose at study end (mean follow-up 21 months) of 7.7 mg and of placebo 8.5 mg.

The primary outcome occurred in 332 patients (31.1%) on nebivolol compared to 375 (35.3%) on placebo (hazard ratio 0.86; 95% CI 0.74-0.99,  $p=0.039$ ). There was no significant influence of age, gender or ejection fraction on the effect of nebivolol on the primary outcome. Death (all-causes) occurred in 169 (15.8%) on nebivolol and 192 (18.1%) on placebo (hazard ratio 0.88; 95% CI 0.71-1.08,  $p=0.21$ ). When comparing patients with similar characteristics to those recruited in MERIT-HF, CIBIS-II or COPERNICUS a similar magnitude and significance of mortality reduction was seen as with the previously established beta-blockers for heart failure.

The effects of nebivolol in a wide range of cardiovascular conditions and its efficacy and good tolerability in elderly heart failure patients regardless of co-morbidity or type of ventricular disturbance mean that nebivolol can be recommended in a broad heart failure population in the Community to which the SENIORS population most closely matches of any of the major morbidity and mortality trials in heart failure.



# **New Therapeutic Options in the Treatment of Heart Failure: Role of Third Generation $\beta$ -Blockers**

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**Dr Marcus Flather**

**Cardiologist and Director of the Clinical Trials and Evaluation Unit  
Royal Brompton Hospital, London, UK**

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It is now clearly established that beta adrenergic blockade is an essential pharmacological strategy in the management of heart failure along with diuretics, ACE-inhibitors and aldosterone antagonists. The majority of heart failure in the community is found in elderly patients and therefore the SENIORS study evaluated the role of the third generation beta blocker nebivolol in the management of patients aged 70 years or older with heart failure. Nebivolol is a potent beta-1 adrenoceptor blocker and exerts a vasodilator action via a nitric oxide dependent mechanism. The SENIORS study enrolled 2128 patients and found a moderate but clinically worthwhile reduction in the incidence of the composite outcome of all-cause mortality or cardiovascular hospital admission hazard ratio 0.86, 95% CI 0.74-0.99 (P=0.04) (1) leading to the inclusion of nebivolol in the European Society of Cardiology Guidelines for the effective management of heart failure in the elderly (2). Uniquely SENIORS included patients with a wide range of ejection fraction, with one third of patient with EF >35%.

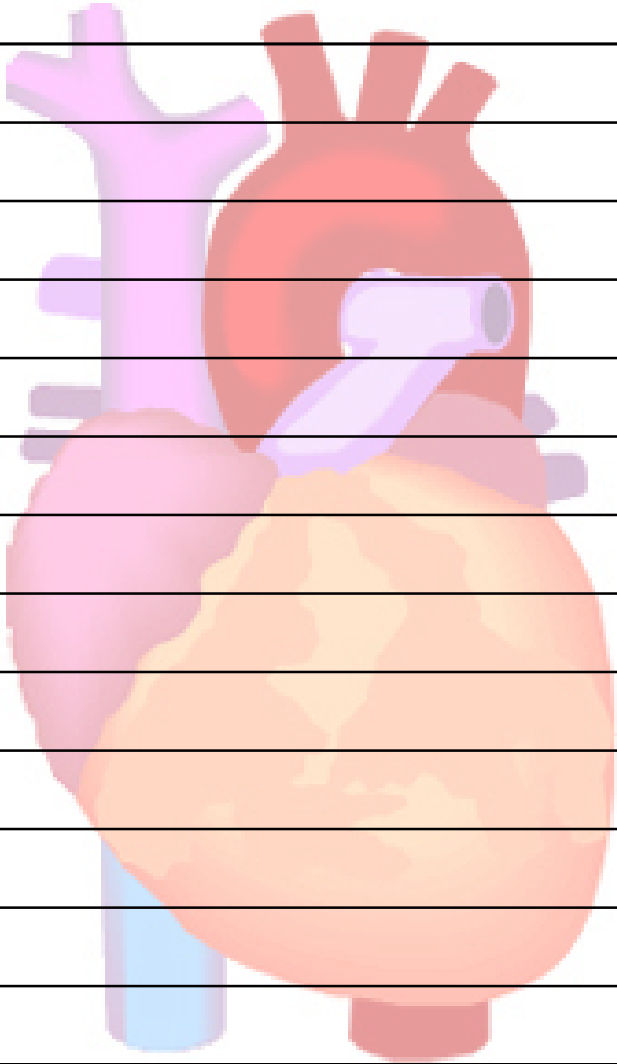
There are concerns that patients are not receiving adequate doses of evidence based therapies, and in practice the doses used are much lower than tested in the clinical trials that have demonstrated their efficacy. A post hoc analysis of the SENIORS trial indicates that there is a dose-related benefit of nebivolol (3). In SENIORS, patients received an initial dose of 1.25mg titrated up to a target of 10mg, or matching placebo over about 8-12 weeks. There was a dose dependent increase in the efficacy of nebivolol with a hazard ratio of 0.75, (95% CI 0.63-0.90) in patients receiving 10mg and 0.73 (95% CI 0.52-1.02) in those receiving 5mg, whereas apparent benefits were less in patients who received lower doses. These findings lend further support to the recommendations that patients should be encouraged to receive the highest tolerated doses of beta blockers in heart failure.

The cost effectiveness of nebivolol was also evaluated from the SENIORS trial. An individual simulation model based on a Markov modelling frame work was developed to evaluate costs and outcomes for nebivolol compared to placebo in elderly patients with heart failure receiving standard treatments over the patient's life time (4). The total cost per patient was £4,568 and £6,287 for the standard treatment and nebivolol groups respectively, and mean life-years were 7.547 and 8.378, and QALYs were 5.2 and 5.844 over the life time of patients aged 70 at the start of treatment respectively. The probabilistic sensitivity analysis provided an incremental cost of £1,720, incremental life years were 0.831, and QALYs were 0.64. Thus the incremental cost effectiveness ratio for the addition of nebivolol to standard therapy was £2,069 (95% CI 1,947 to 2,217) per life year, and £2,670 (95% CI 2,475 to 2,918) per QALY. This analysis based on the SENIORS trial indicates that nebivolol is a cost-effective treatment for a wide range of elderly patients with heart failure compared to placebo, and should be offered as a routine strategy for this patient population. These analyses will be presented and discussed in this presentation.

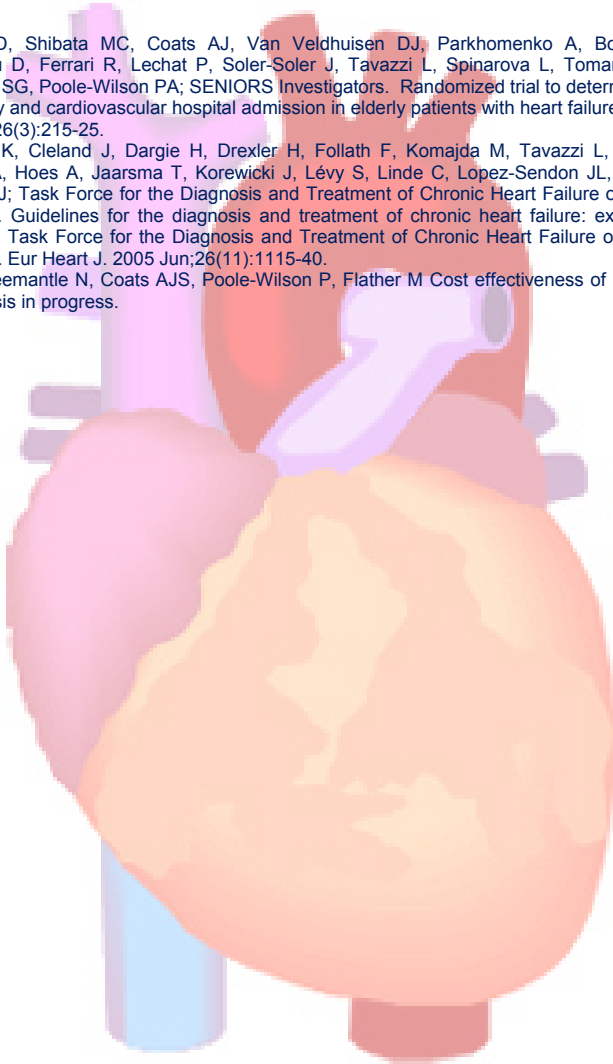
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# NOTES



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# NOTES

