COMMENTARY

β blockers in heart failure

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This issue of *The Lancet* reports two novel and completely different studies of β blockers in heart failure. COMET addresses the heterogeneity of properties among β blockers with respect to outcome, while CHRISTMAS investigates possible mechanisms of improvement in myocardial function induced by β blockers.

In COMET, a randomised trial of 3029 patients with chronic heart failure, carvedilol reduced mortality by 17% relative to metoprolol ($p<0·0017$). The estimated increase in life expectancy achieved (1·4 years on average with carvedilol) is considerable in a condition in which mortality remains high despite modern treatment. Inevitably, the key issue is whether this is a pharmacological triumph for carvedilol over metoprolol and, by analogy, other β1-selective β blockers; or simply a timely reminder that the dose prescribed is, literally, of life or death importance.

The unexpectedly high 65% mortality reduction found in the US carvedilol heart-failure trials[1] suggested that the additional β-blocking activity of carvedilol, vasodilatation through α1 blockade, and antioxidant activity could confer benefit beyond β1 blockade alone. However, there are several reasons why these features might not explain the results of the US trials or of COMET. First, the pathogenic effects of the increased sympathetic nerve activity to which the myocardium is subjected in heart failure are largely β1-receptor-mediated.[2] Second, molecular effects in the myocardium are similar when equipotent doses of carvedilol and metoprolol, in respect of exercise-induced tachycardia (the accepted clinical index of β1 blockade), are compared.[3] Third, there is no supportive outcome data from large clinical trials in heart failure for benefit of α1 blockade or antioxidant activity.

For these reasons, the question of dose has to be seriously considered. Doses in COMET aimed for comparable reductions in resting heart rate between the two groups and, happily, the heart-rate reduction of 13 beats per minute in COMET with 50 mg carvedilol a day was precisely that achieved in the US carvedilol studies on which the dose was based.[1] However, the heart-rate reduction with the dose of 100 mg metoprolol tartrate a day chosen in COMET (actual mean dose 85 mg) was only 11·7 beats per minute compared with 15 beats per minute seen with 150 mg a day in the Metoprolol Dilated Cardiomyopathy trial[4] on which the dose was based (actual mean dose 108 mg metoprolol tartrate). However, the major study of metoprolol in heart failure that addressed outcome was the later MERIT-HF study,[5] which enrolled 3991 patients. The preparation used in MERIT-HF was metoprolol succinate in a controlled release/extended release formula (metoprolol CR/XL). In that study the target dose was 200 mg daily, the mean dose actually taken was equivalent to 106 mg metoprolol tartrate, and the mean reduction in heart rate was 14 beats per minute, very similar to that in the MDC trial.[4]

Therefore, it is difficult to be sure that in COMET, metoprolol exerted a similar degree of β1 blockade to carvedilol. However, it is also inappropriate to place too much emphasis on small changes in resting heart rate, and comparisons of actual outcome may be more persuasive in deciding whether the dose of metoprolol in COMET was adequate.

In MERIT-HF, metoprolol produced a 34% reduction in mortality compared with placebo, very similar to the figures for bisoprolol in CIBIS II (34%),[6] and for carvedilol in COPERNICUS (35%),[7] compared with placebo. Moreover, the annual mortality in the metoprolol group in COMET of 10% seems high compared with 7·2% for metoprolol in MERIT-HF and 8·8% for bisoprolol in CIBIS II, in broadly similar patient groups. Indeed these mortality rates resemble more closely the 8·3% annual mortality of the carvedilol group in COMET.

Undoubtedly, carvedilol was superior to metoprolol in COMET. But that this resulted from pharmacological effects other than β1 blockade cannot be conclusively inferred from a trial in which equivalent β1 blockade was not ensured. Nevertheless the COMET investigators are to be congratulated for tackling a difficult and important question. The onus would now seem to be on the makers of β1-selective blockers to respond to the challenge thrown down by COMET. Perhaps a pragmatic trial of carvedilol, metoprolol, and bisoprolol titrated to the maximum individually tolerated dose in a cohort of patients reflective of those encountered in clinical practice would satisfy most clinicians. It would also be a great service to patients with heart failure and their carers to know the truth about β blockers and mortality in heart failure.

The CHRISTMAS study concentrates on the interaction of carvedilol with its substrate, the myocardium. Rather than depressing cardiac function in heart failure, as might be expected, β blockers substantially improve function as reflected in a significant increase in the ejection fraction. This effect is less consistent in ischaemic heart disease than in dilated cardiomyopathy,[8] and the CHRISTMAS investigators hypothesised that improvement in left-ventricular ejection fraction would be associated with the extent of hibernating or reversibly ischaemic myocardium. Inevitably this study had a complex protocol and involved multiple investigations, including echocardiography, myocardial-perfusion imaging at rest and during a symptom-limited exercise test, and radionuclide ventriculography.

The clearest result from CHRISTMAS was the surprising finding that the significant majority (66%) of patients with heart failure due to coronary heart disease have evidence of hibernating myocardium or of reversible ischaemia in two or more segments of the myocardium. Treatment with carvedilol was associated with a significant increase in left-ventricular ejection fraction, but there was

a less clear effect of carvedilol on left-ventricular ejection fraction according to hibernation status (which was the primary endpoint of the study). The primary endpoint of the study was not met, but in prespecified analyses, carvedilol treatment was an independent predictor of the increase in left-ventricular ejection fraction and there was also a linear correlation between the volume of hibernating myocardium and the rise in left-ventricular ejection fraction with carvedilol. The study also provides insights into the natural history of hibernation and myocardial stunning, demonstrating a decline in myocardial viability with time from the start of the trial, which was delayed by carvedilol.

The implications of the CHRISTMAS study are potentially large because in many countries, especially the UK, patients are not routinely investigated for hibernation status—or indeed for reversible ischaemia in the absence of angina.[9] However, there are no epidemiological data to support the frequency of potentially reversible ventricular dysfunction found in CHRISTMAS. Nor is there evidence from appropriately powered clinical trials that investigation would lead to treatment other than conventional medical therapy since, although advocated, the possible benefit of revascularisation remains unproven. Certainly CHRISTMAS provides a further stimulus to the use of β blockers in heart failure and ischaemic heart disease, but there is a pressing need for a trial of revascularisation to answer this important question. Two such trials have been started, HEART-UK[10] in the UK and STICH in the US. Unfortunately, both trials are threatened by slow recruitment—probably for several reasons. In the US there is already widespread advocacy for revascularisation in this group of patients,[11] while in the UK expertise in, and resources for, the investigation of hibernation and reversible ischaemia are not readily available. However, it is to be hoped that such randomised trials can continue in order that the very important issue of revascularisation and reversible myocardial dysfunction can be addressed.

COMET and CHRISTMAS are very different trials but together they provide further insights into the benefits of β blockade in heart failure. They are also timely, because although the history of β blockers in heart failure is one of sustained revelation and success, their uptake in clinical practice is disappointing. The EuroHeart survey revealed that not only was the prescription rate in eligible patients only 37%, the doses being taken were far below those recommended on the basis of clinical trials.[12] Action is required if the results of clinical research are to be translated into clinical practice.

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Innate immunity and coeliac disease

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Coeliac disease is an inflammatory disorder of the small intestine that is triggered by dietary gluten (the storage proteins of wheat) and related cereals like rye and barley. T-cell infiltration in the intestinal epithelium and the underlying stroma can lead to complete destruction of the microscopic villi of the small intestine, with consequent malabsorption of nutrients, vitamins, and minerals. Whilst the classic presentation of coeliac disease with diarrhoea and malabsorption has become relatively rare (prevalence from 1 in 2000 to 1 in 10 000 in the west), atypical, oligosymptomatic, or even asymptomatic manifestations (with patients having villous flattening of various degrees) are frequent, with an estimated prevalence of 1 in 200 in Europe and the USA, making coeliac disease one of the most common inherited disorders. Untreated patients with oligosymptomatic or asymptomatic coeliac disease are of concern, since they might have an increased risk of disease exacerbation later, secondary autoimmune disorders, and gastrointestinal or haematological cancers.[1,2]

Coeliac disease is the best understood HLA-linked disorder, and several features of the disorder make it a model for immunological diseases that have a defined trigger.[3] First, intestinal inflammation is driven by ingestion of certain gluten peptides, and inflammation usually remits on a strict gluten-free diet. Second, coeliac disease only manifests in patients who carry the HLA-class II molecules DQ2 or DQ8. And third, coeliac disease is tightly associated with circulating mucosal (IgA-class) autoantibodies to tissue transglutaminase, which are almost 100% predictive for active disease.[1] These features are interdependent. Thus certain gluten peptides are preferentially bound to HLA-DQ2 or HLA-DQ8 on antigen-presenting cells, such as macrophages, dendritic, or B cells, which cause proliferation and production of pro-inflammatory cytokines by T cells in the lamina propria. Tissue transglutaminase, the autoantigen, is a ubiquitous intracellular enzyme which is released from fibroblasts, endothelial, and inflammatory cells during mechanical irritation or inflammation. Once secreted, tissue transglutaminase can crosslink glutamine-rich proteins, in particular gluten proteins from wheat (in which glutamine represents 30–50% of the aminoacids), with lysine groups of other proteins. At acidic pH, which occurs with inflammation, tissue transglutaminase can also simply deamidate some of the glutamine residues in gluten to glutamic acid. Deamidation introduces a negative charge into the gluten peptides that can increase the binding affinity to HLA-DQ2 or HLA-DQ8, with consequent potentiation of their capacity to stimulate T cells.[1,3]