incorporation of the therapeutic procedure into the real world\(^\text{[13]}\), populated by old, fragile subjects who constitute most of the universe of heart failure patients.

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**Beta-blockers, ventricular arrhythmias, and sudden death in heart failure: not as simple as it seems**

See page 1259 for the article to which this Editorial refers

The recent experience with beta-blockers in randomized trials in patients with chronic heart failure has been nothing short of remarkable. Four out of the five currently completed trials were stopped prematurely because of highly significant reductions in mortality [USCP (United States Carvedilol Programme), CIBIS II (Cardiac Insufficiency Bisoprolol Study), MERIT-HF (Metoprolol CR/XL Randomised Intervention Trial in Heart Failure), and COPERNICUS (Carvedilol Prospective Randomised Cumulative Survival Trial)]\(^\text{[1–3]}\). The fifth, BEST (Beta-blocker Evaluation Survival Trial), did not show a reduction in all-cause mortality and interpretation of this discrepant finding awaits the publication of full details of the study\(^\text{[4]}\). All of the three fully published trials reported a substantial reduction in the risk of sudden death (by 55% in USCP; 44% in CIBIS II, \(P=0.0011\) and 55%, \(P=0.0002\) in MERIT-HF)\(^\text{[1–3]}\). It is, therefore, tempting to see the report of Cice *et al.* in the current issue as offering mechanistic support for the effect of beta-blockers on sudden death in chronic heart failure\(^\text{[6]}\). There are, however, a number of problems with this interpretation.

Cice *et al.*\(^\text{[6]}\) report an ‘on treatment’ rather than ‘intention to treat’ analysis, excluding 20/155 (13%) of patients who did not complete the double-blind phase of the study. Secondly, ‘within group’ rather and ‘between group’ comparisons were made. Both these limitations reduce the certainty that carvedilol really did reduce ventricular arrhythmias in their patients. Indeed, even though beta-blockers are widely perceived to have an antiarrhythmic action, supporting data from properly controlled trials are sparse\(^\text{[7–9]}\).

Even if we do accept that carvedilol really did reduce the prevalence of ventricular premature beats...
and non-sustained ventricular tachycardia in the present study, should we further accept this as an important explanatory mechanism for the effect of beta-blockers on sudden death, as implied by Cice et al.? The answer must still be no, for two reasons. Firstly, there is a very poor correlation between these arrhythmias and sudden death\[10–14\]. Though some studies (but not all) show a relationship between the frequency of ventricular premature beats (and tachycardia) and death not all do and these arrhythmias do not predict sudden death\[10–14\]. Secondly, and possibly explaining the last finding, sudden death need not be due to a primary electrical event. Myocardial infarction, stroke, pulmonary embolism and ruptured abdominal aortic aneurysm are all causes of sudden death recognized by anyone serving on an end-point committee for a clinical trial in chronic heart failure. Even electrical death has diverse causes including bradyarrhythmias and complete atrioventricular block\[14,15\].

What conclusions can we draw from the study of Cice et al.\[6\] and the broader literature on beta-blockers? Clearly, these drugs now have an important place in the routine treatment of patients with chronic heart failure due to left ventricular systolic dysfunction, along with ACE inhibitors. Beta-blockers are indicated irrespective of the presence or absence of ventricular arrhythmias. An anti-arrhythmic action may be an important component of the unknown mechanism or mechanisms of action of these drugs in chronic heart failure but the case remains unproven. Indeed it is likely to remain so given the complex interrelationships between ventricular dysfunction, neurohumoral activation, myocardial ischaemia and electrical instability.

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References