Optimising therapeutic efficacy in acute and chronic cardiac disease states.

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Background.

Disease states affecting the heart represent a major and costly burden to both society and to the individual. In this context, both intermediate coronary syndrome and chronic congestive heart failure are associated with unacceptably high levels of morbidity and mortality; especially among certain “high-risk” individuals. The studies described in this thesis were designed to identify and address (through the application of relatively novel and potentially useful adjunctive therapeutic strategies) some of the determinants of sub-optimal therapeutic response in both of these conditions.

Observational studies of perhexiline maleate therapy in intermediate coronary syndrome.

Perhexiline is a relatively novel pharmacological agent that has been recently shown to have “oxygen-sparing” effects via inhibition of carnitine palmitoyl transferase-1 and which has been previously used in the management of chronic angina pectoris refractory to conventional therapy. In a preliminary examination of the acute use of perhexiline in the management of “high risk” patients admitted to a coronary care unit with intermediate coronary syndrome and symptoms refractory to conventional therapy (n = 40), we demonstrated that perhexiline has incremental anti-anginal effects over those of standard treatment. Moreover, it is shown that in a similar cohort of individuals (n = 40), that perhexiline maleate is associated with an overall improvement in platelet responsiveness to the anti-aggregatory effects of the “direct” nitric oxide donor, sodium nitroprusside (as measured by ex vivo ADP-induced aggregation) and that such an improvement is strongly correlated with resolution of ischaemic symptoms.

These studies support the use of perhexiline maleate in the management of acute coronary syndromes and raise the possibility of developing analogous, but less complex, agents that also improve platelet (and possibly vascular) responsiveness to nitric oxide; thereby providing
significant clinical benefits to the sub-set of "high risk" patients who currently fail to respond (completely) to conventional pharmacotherapy.

*Randomised controlled studies of multidisciplinary, home-based intervention in chronic congestive heart failure.*

We initially examined the effects of a relatively unique home-based intervention among a large cohort of older, chronically ill patients with and without cardiac disease discharged to home following acute hospital care (n = 762): demonstrating an overall benefit as regards subsequent unplanned readmission and mortality at six months. Its particular effects on the sub-set of chronic congestive heart failure patients (n = 98) participating in the study were subsequently examined. Consequently, it was demonstrated that this intervention was particularly useful in limiting hospital-use among such patients. Moreover, it was demonstrated that its apparent beneficial effects are sustained in the medium-term.

A subsequent study, undertaken to prospectively examine the effects of this type of intervention among chronic congestive heart failure patients (n = 200), demonstrated a significant reduction in hospital-use associated with the study intervention, in addition to prolonged event-free survival, prolonged survival overall and generally improved health-related quality of life. As such, it represents the first time that a non-pharmacological intervention of this type has been shown to simultaneously improve such outcomes among chronic congestive heart failure patients discharged to home post acute hospitalisation.

These studies suggest that the widespread application of this type of intervention, especially if targeted towards "high risk" patients with chronic congestive heart failure, will provide significant benefits to both the individual and the health-care system overall.