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EDITORIAL

Chronic heart failure: a look through the rear view mirror

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This editorial refers to 'Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies'†, by S.J. Pocock *et al.*, on page 1404

Heart failure is now the most common condition that leads to hospital admission in industrialized nations. Although the overall prognosis for patients with chronic heart failure is still gloomy, and similar to that of many of the most common forms of cancer,[1] a combination of pre-clinical and clinical research conducted over the past 25 years has led to five significant advances, each of which has received a IA recommendation in the European Society of Cardiology Guidelines for the treatment of heart failure with reduced ejection fraction.[2] These advances, well known to cardiologists, are: (i) blockers of the renin–angiotensin system [angiotensin-converting enzyme (ACE) inhibitors or angiotensin II type I receptor blockers (ARBs)]; (ii) beta-adrenergic blockers; (iii) aldosterone antagonists; (iv) implantation of cardioverter-defibrillators; and (v) the application of cardiac resynchronization therapy in patients with QRS prolongation. Each has been shown to reduce mortality in patients with heart failure. As a consequence, the cumulative benefits of these therapies has improved the prognosis in these patients quite substantially.[3]

The development of a management plan for individual patients with heart failure (as is the case with many conditions) requires an assessment of prognosis. This has been a challenging task in patients with chronic heart failure. A number of risk scores have been established since 2003 to aid physicians in this task.[4] These scores have been of varying size and clinical value.

In a very ambitious and far-reaching effort, Pocock and colleagues have formed the Meta-analysis Global Group in Chronic Heart Failure (MAGICC). They now report an analysis of individual data on almost 40 000 patients with chronic heart failure enrolled into 30 cohort studies, six of which were clinical trials and the remainder registries.[4] These patients were followed for a median of 2.5 years, providing almost 100 000 patient-years of observation, with almost 16 000 deaths! Certainly, this represents the largest number of patients and deaths ever investigated in heart failure. Among these 30 cohorts, the seven largest cohorts contributed 78% of the patients (and deaths) to this meta-analysis (see supplementary table S1 in Pocock *et al.*[4]).

The authors identified 13 highly significant individual predictors of mortality. Not surprisingly, age, ejection fraction, New York Heart Association class, serum creatinine, diabetes, male gender, and chronic obstructive pulmonary disease were confirmed as independent predictors of mortality. Quite appropriately, the authors separated patients into the two haemodynamically major subgroups of heart failure by the level of ejection fraction. Interestingly, lower systolic pressure was more predictive of mortality in chronic heart failure patients with reduced ejection fraction than it was in those with preserved ejection fraction; the opposite was the case with age. Surprisingly, atrial fibrillation did not emerge as an independent predictor of risk.

Pocock *et al.* then created a model which combined all 13 independent predictors of mortality into an integer score, which, in turn, was linked to the probability of dying within 1 year and 3 years. The stated goal was to 'create a generalizable, easily used risk score for mortality in heart failure'. The authors accomplished this and should be congratulated on their prodigious efforts.

However, the score has five limitations. First, the inclusion of, as two of the 13 independent predictors of mortality, the lack of administration of an ACE inhibitor/ARB and of a beta-blocker is puzzling. These two classes of drugs, as already pointed out, are now routine in the treatment of heart failure and it is difficult to understand why they should be included in a risk score that is to be used to evaluate future patients with this condition. The second limitation is that the concentration of natriuretic peptides, which have been shown to be useful predictors of mortality in heart failure, were not considered as potential risk predictors.[5,6]

The third limitation is the considerable amount of missing data. Only two of the 13 variables that were entered into the model—age and gender—were available in all patients. Five variables (body mass index, systolic pressure, chronic obstructive pulmonary disease, creatinine, and heart failure duration) were each missing in $>$ 10 000 patients; and three others were not available in between 6500 and 10 000 patients. The fourth is the authors' statement that there were 'substantial between-study differences

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in mortality risk not explained by predictors in our model'. They thought that these differences 'may be due to geographic variation or unidentified patient selection criteria varying across the cohorts'. Despite the extensive statistical gymnastics, including 'sophisticated computer-intensive multiple imputation methods', that were performed, it may require true MAGICC to deal with these problems, especially in the absence of external validation of the risk score (which the authors felt was unnecessary).

The last, and probably the most serious, limitation is that of the five above-mentioned guideline Class IA indications for the treatment of heart failure, only one—blockade of the renin–angiotensin system—was utilized in two-thirds of the patients with reduced ejection fraction which were entered into the seven largest cohorts. The use of beta-blockers ranged from 0% in the largest trial, the DIG trial, conducted before the widespread use of these agents in prolonging life in patients with chronic heart failure,[7] to 5–55% of patients entered into the other six large cohorts. An aldosterone antagonist was administered in only four of the seven largest cohorts (to between 13% and 50% of the patients) and apparently not at all in the other three cohorts, which were conducted before the routine use of these agents for the treatment of heart failure was advocated. Even in the small minority of patients in whom these three life-prolonging drugs were used, it is not known whether the doses were adequate. Furthermore, there is no mention in Pocock's paper, or the papers describing the individual cohorts, that any patients received devices—implanted cardioverter-defibrillators or cardiac resynchronization pacemakers—despite the well-established life-prolonging effects of these therapies. Again, these cohorts were studied before these important therapies came into general use. In short, it does not appear that the patients entered into this meta-analysis received what would be considered to be optimal current guideline-approved therapy.

For decades, there were few improvements in the treatment of chronic heart failure, and a risk score having the sophistication and size of the MAGICC score might easily have stood the test of time. Fortunately, the care of patients with chronic heart failure and reduced ejection fraction, while still far from ideal, is at last improving. Therefore, the creation of an instrument to estimate risk in future patients presenting with chronic heart failure in a field that is as dynamic as this one is quite challenging. Such a score that is based on observations in patients receiving what would be considered to be inadequate therapy by contemporary standards, and that does not consider a key prognostic measure that is widely used, is analogous to trying to discern the road ahead by peering through a rear view mirror.

Conflict of interest: none declared.

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