HEART

Editorial

Introducing new treatments in clinical practice: the Italian approach to β blockers in heart failure

Congestive heart failure (CHF) is a growing public health problem, having a significant impact on the health care system.[1–3] Recently β adrenergic antagonists, considered in the past a potential cause of worsening heart failure, have emerged as a promising approach in the treatment of patients with CHF, reducing sympathetic activity and its deleterious consequences.[4] Several randomised clinical trials have tested the effects of carvedilol, metoprolol, and bisoprolol in patients with heart failure with different causes and severity. The results of these trials have shown that β blockers can have a favourable role in improving left ventricular function, reducing symptoms and the need for hospitalisation, delaying clinical progression of the disease, and, as a logical consequence, reducing mortality.[5–8]

However, clinical experience shows that treatment with β blockers is delicate to manage and potentially harmful in inexperienced hands. A short epidemiological study conducted in Italy in 1994 showed that β blockers were used in only 4% of Italian patients with heart failure, acknowledging that most Italian cardiologists were inexperienced in this field.[9] With such background the Italian Association of Hospital Cardiologists (ANMCO) adopted three different lines of intervention:

- to evaluate the rate of β blockers prescribed over the previous three years, analysing the data collected by the Italian network on heart failure (IN-CHF)
- to produce and implement guidelines on β blocker treatment in patients with heart failure
- to plan an observational study on β blocker treatment according to the established indications and contraindications in outpatients, and to evaluate the safety profile of widespread application of this treatment.

Epidemiological survey

From March 1995 to January 1998, data on 6428 patients was collected by locally trained clinicians from 133 cardiological centres using an ad hoc software. The rate of β blocker prescriptions in outpatients with CHF increased as follows: 7.5%, March 1995 to August 1995; 10.3%, September 1995 to February 1996; 15.9%, March 1996 to August 1996; 17.0%, September 1996 to February 1997; 18.4%, March 1997 to August 1997 and September 1997 to January 1998. The increase over time was significant ($p < 0.001$).

Mean doses of β blockers used in clinical practice tended to be lower than those generally suggested by clinical trials. Specifically mean (SD) daily doses of carvedilol, metoprolol, and atenolol were 22 (16), 75 (54), and 48 (23) mg, respectively.[10] A multivariate analysis adjusting for the main clinical and epidemiological variables showed that younger age, heart failure from idiopathic dilated cardiomyopathy, lower New York Heart Association (NYHA) class, and lack of atrial fibrillation as dominant rhythm were independently associated with more β blocker prescriptions. Sex, ejection fraction, heart rate, and other CHF causes did not affect the rate of prescriptions. The same dataset showed that one year mortality of patients enrolled in the registry was high (16.2%).[11]

Production and implementation of specific guidelines

A careful review of the evidence available in the literature was performed. The results of this search were presented and discussed at five meetings held in different Italian regions. These activities were performed over two months during the second half of 1997. Cardiologists from more than 200 centres were involved in the discussion of the results of the trials on β adrenergic antagonists, on possible indications and contraindications, and ways to monitor patients in the early phase of β blocker administration.

A final paper containing a review of the literature and the guidelines was prepared and published in the *Italian Journal of Cardiology*.[12] Table 1 summarises the recommendations for β blocker use in patients with heart failure adopted in Italy.

Table 1 Summary of the recommendations for β blocker use in patients with heart failure adopted in Italy

Which patients with congestive heart failure are suitable for β blocker treatment?
- patients with dilated cardiomyopathy of any cause, with depressed left ventricular function (ejection fraction < 40%), in NYHA class II–III, clinically stable on angiotensin converting enzyme inhibitor, diuretic, and digitalis treatment

Which patients are more likely to benefit?
- NYHA class II–III
- history of hypertension
- heart rate > 90 beats/min
- symptom duration < 24 months

Which patients are less likely to benefit?
- advanced heart failure (high wedge pressure, hypotension, cardiac index < 2.5 l/min/m^2)
- symptom duration > 24 months
- severe biventricular dysfunction
- systolic blood pressure < 100 mm Hg
- heart rate < 70 beats/min

For which patients do uncertainties still exist (scarce data from trials)?
- elderly patients (> 75 years)
- NYHA class IV
- comorbidities (diabetes, chronic obstructive pulmonary disease, renal failure, peripheral vasculopathy)
- asymptomatic left ventricular dysfunction
- heart failure caused by valvar disease or diastolic dysfunction

What are the contraindications?
- severe chronic obstructive pulmonary disease
- first degree AV block (PQ > 0.28 seconds)
- second degree AV block (Mobitz 2 or advanced)
- patients being treated with intravenous inotropes
- heart rate < 50 beats/min
- systolic blood pressure < 90 mm Hg

The outcome research study: β blockers in patients with congestive heart failure. Guided use in clinical practice (BRING-UP study)

An observational study was planned with the aim of introducing β blocker treatment into clinical practice and guiding its application in routine conditions of care. At the time of planning, β blockers were not yet approved in Italy for clinical use in patients with heart failure, and it was considered that, as soon as approval was available, cardiologists could be faced with possible marketing pressure. Further, widespread adoption of this treatment approach could also produce safety concerns. A controlled approach in introducing β blocker treatment in clinical practice appeared to be the safest solution.

The study protocol included the description of the treated population, the selected β blocker agent and dosage, timing and methods of titration, number and reasons for discontinuation, and main clinical events during one year of follow up.

The study organisation provided all participating centres with carvedilol, metoprolol, and bisoprolol at different doses. The responsible clinicians could decide whether to start β blocker treatment and which agent to use. The protocol was approved by the pertinent ethics committees; patients started on β blockers were fully informed of the study procedures and signed a consent form. The study was supported in terms of organisation and drug distribution by the pharmaceutical companies that produce the β blockers (a per patient payment was not foreseen). Data collection and analysis was done by the ANMCO Research Center in Florence. Ten experienced cardiological centres were available to serve as referents for inexperienced physicians for any clinical problems they might face during the study.

From 15 January to 18 February 1998, 3171 patients were enrolled by 206 cardiology centres, which were a good representative sample of all Italian cardiology centres. Twenty five per cent of the recruited patients were already on β blocker treatment and 27% started treatment at the enrollment visit. After the recruitment phase, 52% of the patients with heart failure were receiving β blockers. The analysis of the one year follow up period will provide data on the tolerability of treatment and, in context to outcome research, on the effects of β blockers on main clinical events.

Conclusions

Randomised clinical trials are accepted today as the best way of producing evidence that should guide clinical practice. However, while debates and investments are continuing with the aim of optimising the principles and operational aspects of randomised controlled trials, the problem of transferability of evidence to the heterogeneity and confounding aspects of routine clinical practice is left to the empirical freedom of prescribers.

The GISSI studies (Gruppo Italiano di Studio della Sopravvivenza nell'Infarto)[13–15] illustrated that the use of population trials is a powerful tool in upgrading and bridging the gap between research and routine care. ANMCO adopted a similar strategy to face the more delicate phase of translating experimental evidence into epidemiological documented effectiveness. The production of guidelines, which today is seen as a key task for scientific societies, can only be considered as a starting point: formal epidemiological research and outcome studies dealing with diagnostic and therapeutic decisions are the natural and culturally equally challenging evolution and integration of the experimental approach. The critical relevance of this strategy, both from the scientific and the public health point of view, is specifically evident in an area such as β blocker use in heart failure. Here the transferability of experimental data coincides with the adoption of a paradigm of treatment that goes against a long held belief but in which a truly favourable risk–benefit profile is expected to result from the balance of diagnostic accuracy, carefully controlled short term follow up, and comprehensive long term care.

Following this strategy, large acceptance of an evidence based treatment, namely β blocker use in CHF, was achieved in a brief period of time. The results obtained so far suggest that the strategy is attractive, applicable, and worth pursuing. It is, however, important to remember that this strategy involved patients with heart failure followed by cardiologists in Italy, which is a small part of the whole world of heart failure management. This approach could be expanded, through specific programmes, to other protagonists of the management of patients with CHF.

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