

# Additive beneficial effects of beta blockers in the prevention of symptomatic heart failure

## *Effetti additivi favorevoli dei beta bloccanti nella prevenzione dello scompenso cardiaco sintomatico*

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**ABSTRACT:** *Additive beneficial effects of beta blocker in the prevention of symptomatic heart failure. A. Genovesi Ebert, F. Colivicchi, M. Malvezzi Caracciolo, C. Riccio.*

The prevention of symptomatic heart failure represents the treatment of patients in the A and B stages of AHA/ACC heart failure classification. Stage A refers to patients without structural heart disease but at risk to develop chronic heart failure.

The major risk factors in stage A are hypertension, diabetes, atherosclerosis, family history of coronary artery disease and history of cardiotoxic drug use. In this stage, blockers hypertension is the primary area in which beta blockers may be useful. Beta blockers seem not to be superior to other medication in reducing the development of heart failure due to hypertension.

Stage B heart failure refers to structural heart disease but without symptoms of heart failure. This includes patients with asymptomatic valvular disease, asymptomatic left ventricular (LV) dysfunction, previous myocardial infarction with or without LV dysfunction. In asymptomatic valvular disease no data are available on the efficacy of beta blockers to prevent heart failure. In asymptomatic LV dysfunction only few asymptomatic patients have been en-

rolled in the trials which tested beta blockers. NYHA I patients were barely 228 in the MDC, MERIT and ANZ trials altogether. The REVERT trial was the only trial focusing on NYHA I patients with LV ejection fraction less than 40%. Metoprolol extended release on top of ACE inhibitors ameliorated LV systolic volume and ejection fraction. A post hoc analysis of the SOLVD Prevention trial demonstrated that beta blockers reduced death and development of heart failure.

Similar results were reported in post MI patients in a post hoc analysis of the SAVE trial (Asymptomatic LV failure post myocardial infarction). In the CAPRICORN trial about 65% of the patients were not taking diuretics and then could be considered asymptomatic. The study revealed a reduction in mortality and a non-significant trend toward reduction of death and hospital admission for heart failure.

**Conclusions:** beta blockers are not specifically indicated in stage A heart failure. On the contrary, in most of the stage B patients, and particularly after MI, beta blockers are indicated to reduce mortality and, probably, also the progression toward symptomatic heart failure.

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The prevention of symptomatic heart failure coincides with the treatment of patients in stage A and B of the AHA/ACC heart failure classification, in which symptoms are absent [1]. Thus the issue of this paper is to review the usefulness of betablockers in preventing the progression towards symptomatic heart failure in Stage A and B.

### Stage A

Among the risk factors which are reported in Stage A there is no doubt that hypertension plays a major role especially because of the high prevalence of hypertension among adult population [2].

It is well known that an appropriate treatment of hypertension reduces incidence of stroke, MI and left ventricular failure. A meta-analysis of 12 hypertension trials that included the development of heart failure demonstrated treatment benefits [3]. The incidence of heart failure was reduced by 52%

(CI 41-62%) compared to the control or placebo subjects. It is clear that the benefits in reducing heart failure in placebo-controlled trials are comparable, if not superior, to the reductions in stroke and coronary heart disease quantified in meta-analysis of all trials [4].

Betablockers have been evaluated in the treatment of arterial hypertension, but are they useful in preventing the progression towards symptomatic heart failure in hypertensive patients?

The STOP [5] and the SHEP investigators [6] evaluated in large randomized studies the effect of beta-blockers in preventing cardiovascular events and specifically also their ability in preventing heart failure. A relative risk reduction of heart failure of about 50% was observed in the follow up which was of 25 months and 4.5 years, respectively. However, due to the complex treatment protocol it is difficult to separately evaluate the effect of diuretics and beta-blockers.

In the STOP trial 4 active treatment were evaluated: atenolol 50 mg, hydrochlorothiazide 25 mg +amiloride 2,5 mg, metoprolol 100 mg or pindolol 5 mg. If blood pressure remained higher than 160/95, diuretic therapy was added to beta-blockers and vice-versa.

In the SHEP trial patients were randomised to placebo or chlortalidone 12,5 mg. The goal blood pressure was 160 mmHg for those patients whose initial systolic blood pressure was higher than 180 mmHg or a reduction of at least 20 mmHg for those with initial blood pressure of 160-179 mmHg. Dose doubled if the goal BP was not reached and then atenolol 50 mg or placebo was added. Therefore, in this trial which drugs, diuretics or beta-blockers, were active in preventing heart failure remains an unsolved question.

In the STOP 2 trial beta-blockers were compared to ACE inhibitors and to calcium channel blockers. This study showed that beta-blockers, again with diuretics, were no significantly worse than ACE inhibitors, which in turns are significantly better than calcium channel blockers [7].

Similar results arise from a large meta-analysis reported in Lancet [8]. Also in this study, however, the effect of beta-blockers plus diuretics, and not simply those of beta-blockers, was compared to other drugs. Therefore, the question of which drug was beneficial remains unsolved.

Another important topic in hypertension is left ventricular hypertrophy, which has been reported to be a strong predictor of events in hypertensive patients [9]. Left ventricular hypertrophy is not merely a marker of risk, since several trials suggested that its regression is beneficial. A recent meta-analysis demonstrated an omogeneous beneficial effect of LVH regression [10].

Beta-blockers are able to reduce left ventricular hypertrophy but are less effective than other classes of antihypertensive agents. A recent meta-analysis of 80 randomised, double blind, controlled trials involving more than 4000 patients suggests that beta-blockers reduce LV mass of about 6% whereas ACE Inhibitors, AT II blockers and Calcium channel blockers are able to reduce LV mass of 10, 13 and 11%, respectively [11].

Moreover, in comparison with AT II receptors blockers, beta-blockers, at least atenolol, increase significantly the new onset of diabetes [12]. Diabetes in facts means a two fold risk of heart failure in men and five fold in women and mortality from heart failure is increased in diabetic patients [13, 14]. The poorer prognosis is probably due to an underlying diabetic cardiomyopathy exacerbated by hypertension and ischaemic heart disease.

Taken together the effects on LVH regression and on diabetes in comparison to other class of drugs, particularly AT II antagonist, raises some concern on the use of beta-blockers as first class drug in hypertension.

Unfortunately its well known that often an association of several drugs are needed to reach the target blood pressure. Beta-blockers thus probably should be considered a second line drug to prevent heart failure in hypertensive patients in order to get the target blood pressure level, but may be-

come the drug of choice if other condition are present together with hypertension such as arrhythmias, angina, or previous MI [15].

## Stage B

### 1) *post MI patients*

In the Norwegian trial with timolol, which enrolled in the 80s nearly 2000 patients, a very significant reduction of death or MI was observed. The trial enrolled patients with transient HF as indicated by pulmonary crackles, a third heart sound, or radiological evidence of pulmonary congestion. Overall 33% had a history of HF but, unfortunately, the progression toward heart failure was not an end point of this trial [16].

In the Beta-blocker in heart attack trial (BHAT) with propranolol, a significant reduction of the mortality but no significant differences in heart failure was observed [17, 18].

The COMMIT trial evaluated metoprolol in suspected acute MI setting both with and without ST elevation. This was the largest trial on beta-blockers in the literature involving more than 45.000 patients and 1.250 hospitals in China [19]. The vast majority of the patients had STEMI and 54% received fibrinolysis. Patients treated with primary PCI were excluded. The results indicate that the use of metoprolol intravenous and then orally in unselected acute MI patients has a neutral effect on mortality because on one hand it reduces ventricular fibrillation, arrhythmia and reinfarction, but on the other hand it increases cardiogenic shock and new onset heart failure. However, it should be emphasized that this was a trial on acute MI and the mean follow up was 15 days.

Indeed, it is accepted that in the chronic post MI patients beta-blocker are very useful.

The metanalysis of 31 randomized controlled trial of Freemantle *et al.* indicates that treating 42 patients with beta-blocker for 2 years saves one life [20]. Moreover Phillips *et al.* calculated that the systematic treatment with beta-blockers of post MI population along 20 years would save billions of dollars, and thousands of lives [21].

We can conclude that in post MI beta-blockers have not a documented effect on the prevention of symptomatic heart failure but they are anyway indicated because of their ability of reducing mortality rate.

### 2) *Asymptomatic left ventricular dysfunction*

In this setting there is a strong rationale for the use of beta-blockers, since adrenergic activation seems to have a major role in the progression towards overt heart failure [22], and the vicious circle of positive adrenergic feed-back is interrupted by beta-blockers.

The effectiveness of beta-blockers in slowing the progression of heart failure is well assessed in NYHA classes II to IV as shown in cornerstone trials on beta-blockers in heart failure [23-25]. In these trials which tested beta blockers in heart failure few asymptomatic patients had been enrolled. NYHA I patients were 2,5% in the MDC [26] trial, 0,5% in the MERIT [23] trial and 30%

in the ANZ trial [27], summing up to barely 228 patients.

However other data obtained in post MI patients with LV dysfunction could support the indication of beta-blockers to prevent heart failure in still asymptomatic post MI patients. The SAVE trial enrolled 2231 patients with EF < 40% and no clinical evidence of heart failure or ongoing ischemia; the main issue of the study was the evaluation of Captopril in post MI LV dysfunction [28]. A post hoc analysis evaluated the effect of beta-blockers, which resulted effective in reducing cardiovascular events and also heart failure with a statistically significant reduction of progression towards severe heart failure of 27% [29].

The CAPRICORN study evaluated Carvedilol in AMI patients with left ventricular dysfunction (LVEF < 40%). The NYHA class was not specified but we can assume that most of the patients were asymptomatic because 65% of them did not require diuretics. The study showed a significant reduction of death and of the composite end point including heart failure [30]. Moreover an echo sub-study indicated a favourable effect of Carvedilol on left ventricular volumes and function [31].

Unfortunately, the hospitalization for heart failure and the death due to heart failure were not statistically affected. Thus in this prospective trial the results of the SAVE post hoc analysis were not confirmed. On the other hand, an observational study of Aronow *et al.* evaluated elderly post MI patients treated with ACE inhibitors, beta-blockers, both or none. A 60% reduction of episodes of heart failure was observed in the follow up [32].

Some data are available also in patients with left ventricular dysfunction not post MI.

The SOLVD prevention trial evaluated Enalapril in asymptomatic patients with LV dysfunction (67% NYHA I) [33]. It should be mentioned that 80% of them had a previous MI; moreover, 24% were treated with beta-blockers. A post hoc analysis of the SOLVD Prevention trial demonstrated that patients on beta-blockers had a significant reduction of death and development of heart failure [34]. This analysis suggests that beta-blockers reduce both mortality rate and pump failure rate with a number needed to treat respectively of 75 and 200. In addition, the adjusted survival analysis showed that trial participant receiving both beta-blocker and Enalapril had an independent significant reduction in the risk of death, notably arrhythmic and pump failure death, and a slower progression to symptomatic heart failure as assessed by the composite end point of death and hospitalisation for heart failure.

Only recently a trial focusing prospectively on beta blockers in NYHA I patients with LV ejection fraction less than 40% has been published. The REVERT trial demonstrated that metoprolol extended release ameliorates LV systolic volume and LV ejection fraction on top of ACE inhibitors [35]; similar results were obtained with Carvedilol in CARMEN study which, however, enrolled 63% of NYHA II patients and only 8% of NYHA I [36].

Taking into account all these data, beta-blockers seem to be probably indicated in asymptomatic left ventricular dysfunction.

In conclusion, beta-blocker are not a first line treatment in hypertension at all, and particularly to prevent heart failure.

In post MI data the preventive effect on heart failure are not conclusive but beta-blockers are indicated to reduce mortality and reinfarction.

In asymptomatic left ventricular dysfunction, although not assessed in large prospective trials, an additive effect of beta-blockers in preventing the progression to symptomatic heart failure is very likely.

### Riassunto

*La prevenzione dell'insufficienza ventricolare sinistra sintomatica consiste nel trattamento degli stadi A e B della classificazione AHA/ACC dell'insufficienza cardiaca nei quali appunto i sintomi non sono ancora presenti. Lo stadio A è costituito da situazioni a rischio di insufficienza cardiaca ma senza alterazioni strutturali, quali l'ipertensione arteriosa, il diabete mellito, la storia familiare di cardiopatia ischemica e l'uso di farmaci cardiotossici. Tra questi l'ipertensione arteriosa rappresenta il principale campo di impiego dei betabloccanti che non sembrano tuttavia più efficaci degli altri farmaci ipotensivi nel prevenire l'evoluzione verso l'insufficienza cardiaca sintomatica. Lo stadio B è costituito da situazioni in cui sono presenti alterazioni strutturali cardiache senza tuttavia sintomi di insufficienza cardiaca. Non sono disponibili dati relativi all'utilità dei betabloccanti nella prevenzione dello scompenso cardiaco nelle disfunzioni valvolari asintomatiche. Nell'insufficienza ventricolare sinistra asintomatica i grandi studi sull'utilità dei betabloccanti nell'insufficienza cardiaca hanno arruolato poco più di 220 pazienti in classe NYHA I. Lo studio REVERT che ha arruolato specificamente pazienti in classe NYHA I ha tuttavia dimostrato che la terapia con betabloccanti produce un miglioramento della frazione di eiezione in pazienti già in terapia con ACE inibitori ed una analisi post hoc dello studio SOLVD prevenzione suggerisce che la terapia con betabloccanti ridurrebbe la probabilità di morte e di progressione verso lo scompenso. Osservazioni simili provengono da uno studio post hoc dello studio SAVE, che per quanto riguarda l'insufficienza ventricolare sinistra postinfartuale legata al betabloccante non ha raggiunto la significatività statistica nel sottogruppo di pazienti che non assumendo diuretici potevano essere considerati in classe NYHA I.*

*In conclusione, il trattamento con betabloccanti non ha indicazioni specifiche nella prevenzione della progressione verso lo scompenso nei soggetti nello stadio A dell'insufficienza cardiaca. Viceversa nella maggior parte delle condizioni dello stadio B, ed in particolare nel post infarto, i betabloccanti sono indicati per ridurre la mortalità e probabilmente anche la progressione verso lo scompenso cardiaco.*



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