Efficacy of trimetazidine: lessons from meta-analyses

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Abstract

Trimetazidine, a metabolic agent with anti-ischemic properties, has been used for the management of angina for more than a decade. The focus of this paper is the efficacy of trimetazidine as unveiled by recent meta-analyses. Six meta-analyses have been published on the effects of trimetazidine in the treatment of heart failure and in the management of stable angina, including nearly 20,000 patients. In patients with heart failure, trimetazidine improves ventricular function, functional capacity and may also reduce mortality. In stable angina, all meta-analyses indicate that trimetazidine improves exercise capacity and reduces angina. The stage is set for the development of large, long-term clinical trials on the effects of trimetazidine on clinical outcomes in patients with heart failure and in patients with stable angina.

Keywords: coronary artery disease; angina; heart failure; left ventricular function; functional capacity.

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Introduction

In most countries, stable angina pectoris is currently managed with anti-platelet agents, statins, β- blockers, angiotensin converting enzyme and anti-anginal medications, but a high percentage of patients also receive revascularization procedures, particularly stent implantation [1]. However, recent randomized clinical trials have consistently shown that stent implantation has no significant impact on clinical outcomes for this patient population [2]. Moreover, despite improvement in angina at one-year, stent implantation seems to have no significant effect in the control of angina in the long-term [3]. Therefore, only patients with high-risk profiles may derive benefit from percutaneous or surgical revascularization with reduction of clinical events [4]. Despite these well-established concepts, most patients with stable angina do not receive optimal medical therapy and are referred to revascularization procedures [5].

In patients with stable angina, optimal medical therapy should include medications that may impact in disease progression, such as anti-platelet agents and statins, β- blockers and angiotensin converting enzyme as well as agents that are used for the control of angina. Very few clinical trials have been conducted to evaluate the efficacy of anti-anginal agents with enough power to evaluate clinical outcomes in patients with chronic coronary artery disease without a recent myocardial infarction [6,7]. Therefore, current guidelines for the management of these patients are mostly based on meta-analysis of small, randomized

trials in which the main outcome is angina, evaluated by exercise testing, the frequency of angina attacks or the use of short-acting nitrates.

Trimetazidine, a metabolic agent with anti-ischemic properties, has been used for the management of angina for more than a decade. Several clinical trials have demonstrated its efficacy as monotherapy as well as in combination with one or even more than one anti-anginal agent [8]. Recently, several systematic reviews and meta-analysis have summarized the efficacy of trimetazidine in patients with coronary artery disease [9–14]. The efficacy of trimetazidine on quality of life has been reviewed by Marazzi et al [15] and the focus of this paper will be the efficacy of trimetazidine as unveiled by recent meta-analyses.

Meta-analyses of trimetazidine in chronic heart failure

Since patients with coronary artery disease associated with heart failure have a high incidence of clinical events, the two meta-analyses recently published were able to evaluate the effects of trimetazidine on functional variables as well as in clinical outcomes [11,14].

Gao et al. [11] reviewed 17 trials involving 955 patients and were able to demonstrate improvement in left ventricular dimensions, left ventricular ejection fraction, and functional capacity with the administration of trimetazidine. The mean improvement in left ventricular ejection fraction of 7.5 % (95% CI 6.3 to 8.7; p<0.01) is clinically relevant and favorably compares with the effects of beta-blockers. Interestingly, ejection fraction was found to improve not only in patients with ischemic etiology, but also in patients with non-ischemic etiology, raising the hypothesis that trimetazidine might exert its effects independently of the improvement of myocardial ischemia. Mean improvement in functional class was – 0.41 in New York Functional Class (CI – 0.51 to – 0.31, p<0.01), which also compares favorably with the improvement obtained by other medications, such as angiotensin converting inhibitors. Finally, the meta-analysis showed significant reductions in mortality (RR 0.29; 95% CI 0.17 to 0.49; p<0.01) and hospitalizations (RR 0.42; 95% CI 0.30 to 0.58, p<0.01), the most important outcomes in heart failure. The favorable effects of trimetazidine on left ventricular function was recently confirmed in the meta-analysis by Hu et al. [13], who evaluated 11 trials with 545 patients to compare trimetazidine with placebo, using as outcomes functional variables obtained by echocardiography or radionuclide angiography. In this later study, which did not select patients with the diagnosis of heart failure, there was improvement in ventricular volumes and ejection fraction, but trimetazidine also improved wall motion score index.

The meta-analysis by Zhang et al [14], which included 16 trials with 884 patients, presented results similar to those obtained by Gao et al [11], confirming the significant reduction in hospitalization for cardiac causes (RR: 0.43, p=0.03), but not the reduction in mortality. Moreover, New York Heart Association functional class and total exercise time on exercise testing, as well as resting left ventricular ejection fraction (mean change 6.46%, p<0.0001) were improved by trimetazidine. This meta-analysis also evaluated the effect of trimetazidine on B type natriuretic peptide levels, showing a mean reduction of 203 pg/ml (p<0.01).

Meta-analyses of trimetazidine in stable angina

Patients with chronic stable angina have a good prognosis and, therefore, there is little evidence that any anti-anginal intervention may alter outcome. For instance, the ACTION trial failed to show improvement in survival of patients with angina treated with long-acting nifedipine [6]. Likewise, a recent meta-analysis of 26 trials, including 6,108 patients, showed no significant survival benefits of beta-blockers (OR 0.92, 95% CI 0.62 to 1.38) when compared to placebo in patients with stable angina [16]. One study in which an anti-anginal agent was shown to reduce events was the BEAUTIFUL trial [7], which evaluated the effects of ivabradine, a heart rate reducing agent, in patients with coronary artery disease and left ventricular systolic dysfunction. However only patients with a resting heart rate higher than 70 bpm presented a significant reduction in admission to hospital for fatal and non-fatal myocardial infarction (0.64, 95% CI 0.49-0.84, p=0.001) and coronary revascularization (0.70, 95% CI 0.52-0.93, p=0.016). Therefore, the three meta-analysis available on the effects of trimetazidine in stable angina have evaluated as outcomes stress-induced myocardial ischemia, number of weekly angina attacks, and use of short-acting nitrates.

In 2003, Marzilli and Klein [9] published the first meta-analysis of 12 trials, including 868 patients. In this early meta-analysis, trimetazidine was found to

increase exercise duration to 1 mm ST segment depression on the exercise test, and to reduce weekly episodes of angina, both as monotherapy and as add-on therapy. Later, Ciapponni et al. [10] conducted a meta-analysis of 23 trials with 1,378 patients with stable angina. Compared with placebo, trimetazidine reduced the number of weekly angina attacks (mean difference -1.44, 95% CI -2.10 to -0.79; p<0.0001), reduced weekly nitroglycerin tablet consumption (95% CI -1.47 to -2.20, -0.73; p<0.0001) and improved exercise time to 1 mm segment depression on the exercise test (p=0.0002). At that time, only 4 small trials were available in which trimetazide was compared to other anti-anginal agents and confidence intervals were too large for appropriate interpretation.

Since current guidelines recommend beta-blockers as first choice for the treatment of stable angina [17] and ivabradine has a clinical-trial-based indication [7], it is important to compare the effects of trimetazidine with other anti-anginal drugs which do not act by reducing heart rate. This may be particularly useful when one is considering the addition of a second drug for those patients already taking beta-blockers, or for those who do not tolerate beta-blockers. In the largest meta-analysis conducted on the effects of trimetazidine, Danchin et al. [12] evaluated 218 trials with a total 19,028 patients, including the results a previously unpublished study, the VASCO trial. In agreement with the meta-analysis of Ciapponni et al. [10], trimetazidine improved exercise tolerance, weekly angina episodes, and use of short-acting nitrates when compared with placebo. For the comparison of other anti-anginal agents without an effect on heart rate, network meta-analyses were performed. This strategy allows for the evaluation of direct comparisons (A vs. B from head-to-head comparisons) and indirect comparisons (A vs. C is extrapolated from A vs. B and B vs. C), giving information about the relative efficacy of treatments that have not been compared in head-to-head trials. In these analyses, trimetazidine when compared to dihydropyridines, long-acting nitrates, nicorandil, and ranolazine, both as monotherapy and as add-on therapy, had similar anti-ischemic effects. The findings of this robust meta-analysis support the indication of trimetazidine as an effective agent for the management of stable angina.

One specific point should be mentioned on these data. Among the numerous studies included in this network meta-analysis, the VASCO trial [12] is the largest randomized study conducted with trimetazidine. In this trial, patients with stable angina receiving 50 mg q.d. of atenolol were randomized to the addition of trimetazidine MR 35 mg b.i.d., or trimetazidine MR 70 mg b.i.d., or placebo b.i.d. for a 12 week-period. In the global population of VASCO, there was no significant difference between treatment with trimetazidine and placebo on exercise test and clinical parameters. These data, which are not consistent with results reported in all other trials, were attributed to the fact that most of the patients in the VASCO trial had only mild angina, which was treated adequately by monotherapy with atenolol. This was confirmed when complementary analyses were performed in the more symptomatic patients of the VASCO trial, and showed that differences with placebo became statistically significant. Thus, these results suggest that the population of that study did not adequately represent the target population for trimetazidine. The large number of patients included in the VASCO trial confirmed the safety profile of trimetazidine MR. Indeed, there were no significant differences in adverse effects among the three groups. However, the short duration of the study (12 weeks) did not allow for the evaluation of the incidence of, for instance, extrapyramidal disorders, which have been recently associated with long-term use of trimetazidine [18].

Conclusion

Over the last decade six meta-analyses have been published on the effects of trimetazidine in the treatment of heart failure and in the management of stable angina, in total including almost 20,000 patients. In patients with heart failure, trimetazidine improves ventricular function, functional capacity, and may also reduce mortality. In stable angina, all meta-analyses indicate that trimetazidine improves exercise capacity and reduces angina. The stage is set for the development of large, long-term clinical trials on the effects of trimetazidine on clinical outcomes in patients with heart failure and in patients with stable angina. •

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