Authors[1]: TOMCSÁNYI J.

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COMPARISON OF THE EFFICACY OF TRIMETAZIDINE IN REVASCULARIZED AND NONREVASCULARIZED STABLE ANGINA PATIENTS BASED ON THE ONECAPS STUDY

SUMMARY (Author's summary)

Introduction: The recently published ATPCI study resulted in the safety of trimetazidine administered immediately after successful revascularization but was not more effective (cardiovascularis death, recurrence of angina, hospitalization for cardiac event) than the randomized double-blind placebo.

Objective: A retrospective analysis of our previously published ONECAPS open-label observational study was performed to determine whether there was a difference in the efficacy of trimetazidin prolong in the angina patients according to whether or not they had previously undergone revascularization.

Method: Of the 1670 angina patients, 1008 were not revascularized, while 662 had previously undergone revascularization. There was no difference in age or comorbidity between the two groups. Patients were examined for changes in weekly angina, short-acting nitroglycerin use and angina severity during once-daily administration of trimetazidine prolong 80 mg in revascularized and non-revascularized study groups.

Results: In both the revascularized and non-revascularized group, trimetazidine resulted in a significant reduction ($p<0.0001$) in both weekly angina count and short-acting nitroglycerin use. In addition, the proportion of angina with Canadian Cardiovascular Society (CCS) I increased and the proportion of CCS III and CCS IV decreased in both patient groups as well. All of this effect was achieved with statin, ACEI/ARB, and beta-blocker use above 90% in revascularized patients.

Conclusion: Trimetazidine prolong 80 mg once daily significantly reduced the number of angina per week, the use of short-acting nitroglycerin per week, and the severity of angina. This effect is independent of whether the patient has previously received revascularization.

ABBREVIATIONS

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; ATPCI = efficacy and safety of trimetazidine after percutaneous coronary intervention; MR = modified release

Not long ago, the results of the long-awaited ATPCI study were announced at the 2020 European Society of Cardiology Congress. Between 2014 and 2016 they enrolled patients that had previously undergone successful percutaneous coronary intervention for either stable coronary artery disease or non-ST-elevation acute coronary syndrome in a randomised study [1, 2]. Although the long-term twice daily administration of trimetazidine to 6007 randomised patients was deemed safe, it did not result in significant improvements with regard to the

[1] Adresse permettant de contacter les auteurs

primary efficacy endpoint, which was the composite of cardiac death; hospitalisation for a cardiac event; recurring angina or increasing in the intensity of antianginal treatment. The study was met with criticism [3, 4], the most significant of which was that current angina or documented ischaemia were not requirements for the introduction of trimetazidine therapy. Patients were enrolled in the study directly after successful catheter intervention.

It is with regard to these critical considerations that we completed a retrospective analysis of the patient population of the ONECAPS study [5] in order to determine, with exclusive regard to angina, whether trimetazidine was as effective for angina patients that have previously undergone revascularisation as for the study group that had not undergone revascularisation.

PATIENTS AND METHOD

The ONECAPS study was an open-label, prospective, observational study of patients with stable angina pectoris [5]. A total of 1,701 patients took part in the study. However, information on revascularisation was only known for 1,670 patients. In all cases, revascularisation took place at least 6 months before recruitment. Due to the fact that this variable was not a criterion of the original study, the average amount of time since revascularisation is not known. The revascularisation of patients was defined as either a coronary bypass surgery (156 cases), or percutaneous coronary angioplasty (506 cases). In our retrospective analysis, we examined the effect of the once-daily administration of 80 mg trimetazidine prolong as adjunctive treatment in previously revascularised and non-revascularised patients separately. Our analysis examined the change in weekly angina count, the use of short-acting nitroglycerin, and the change in the severity of angina in the two subgroups.

The demographic data of revascularised and non-revascularised patient populations are shown in Table 1. The data in the table demonstrate that both study groups were large enough for the examination of the efficacy of the once-daily administration of trimetazidine prolong 80 mg.

Table 1. Demographic data of the subgroups of the examined patient population

	Revascularised (n = 662)	Not revascularised (n = 1,008)
Age (years)	68	68
Male (%)	59	43
Start of angina pectoris (year)	7.2	7.0
Hypertension (%)	93.7	93.4
Hyperlipidaemia (%)	90.2	73.5
Smoking (%)	63.4	51.2
Previous infarction (%)	58	7
Diabetes mellitus (%)	41.8	34.2
Atrial Fibrillation (%)	16	14
Stroke/Transient ischemic attack (%)	14	15
Peripheral vascular disease (%)	22	14

RESULTS

The only difference between the treatment of revascularised and non-revascularised angina patients in the study was that a greater number of revascularised patients received dual platelet aggregation inhibitors, statin therapy, as well as long-acting nitrate therapy, and a higher proportion of revascularised patients received ivabradine (Table 2).

Table 2. Importance of the application of drug groups to the respective subgroups with regard to coronary artery disease

	Revascularised (n = 662)	Not revascularised (n = 1,008)
Platelet aggregation inhibitors	78%	92%
ACE inhibitors/ Angiotensin II receptor blockers	88%	92%
Statins	69%	90%
Beta-blockers	85%	92%
Ivabradine	25%	11%
Calcium antagonists	51%	47%
Long-acting nitrates	24%	35%

The once-daily administration of trimetazidine 80 mg adjunctive therapy over the course of 3 months resulted in an equally significant reduction in weekly angina count and in the weekly short-acting nitroglycerin requirement in both the non-revascularised and revascularised study groups (Figures 1 and 2). The change in the severity of angina was similar in the two subgroups (Figure 3). The figure demonstrates that as a result of the trimetazidine prolong, there was a gradual increase in the proportion of mild angina cases, and there was a reduction in cases of severe angina in both study groups.

Figures 1 and 2. Changes in average weekly angina count and short-acting nitrate requirements in the non-revascularised patient group (figure 1, left) and revascularised patient group (figure 2, right)

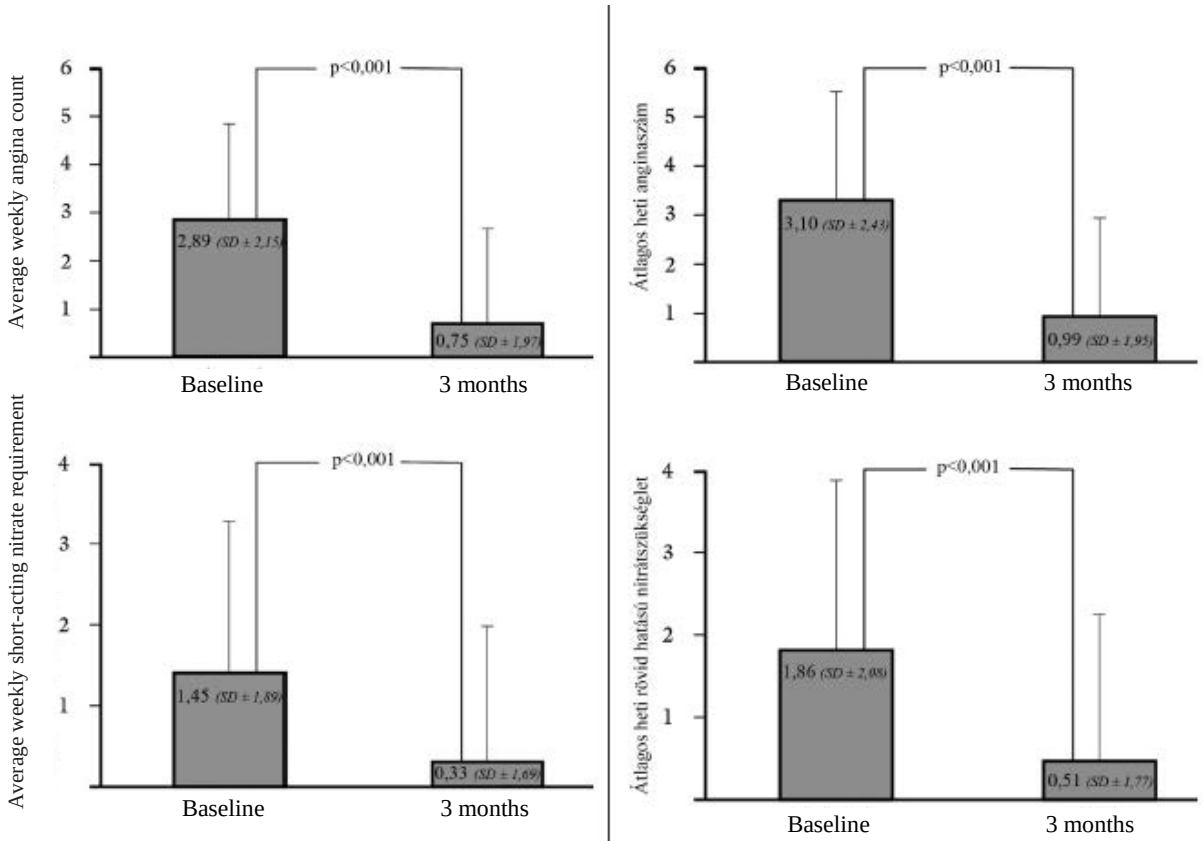
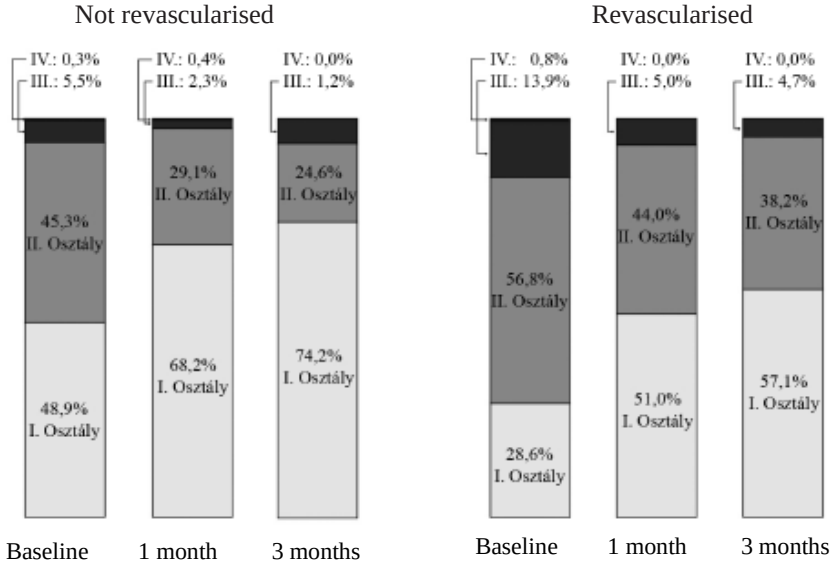


Figure 3. Changes in the severity of angina in non-revascularised and revascularised study groups according to the classifications of the Canadian Cardiovascular Society (CCS)



Number of patients

I. Osztály	389	302	193	150	153	97
II. Osztály	360	129	64	298	132	65
III. Osztály	44	10	3	73	15	8
IV. Osztály	2	2		4		

Osztály = Class

DISCUSSION

Based on the results of our study, the once-daily administration of 80 mg trimetazidine to patients with angina symptoms significantly reduced their angina count and severity of angina, regardless of prior revascularisation.

When compared with the results of the recently published ATPCI study [2], it can be said that the "recommended" treatments received by the revascularised study group recruited to the ONECAPS study did not derogate significantly from that of the ATPCI study. In other words, a large proportion of patients received statin, ACEI or ARB therapy, and beta-blocker treatment. As a result, the two studies are comparable, and it can be deduced that the ONECAPS study was successful with regard to efficacy due to the fact that the presence of angina was required as a prerequisite of trimetazidine treatment. This factor appears more important than the fact that the patients of the ONECAPS study received the more up-to-date once-daily dose of trimetazidine prolong 80 mg treatment, meanwhile the patients of the ATCPI study received twice daily doses of trimetazidine 35 mg MR preparation. It is very difficult to demonstrate the efficacy of a preparation with regard to cardiovascular mortality if the examined study group is low risk. As a matter of fact, this was the case with trimetazidine in the ATPCI study. The yearly cardiovascular mortality rate of the placebo group was 0.6 %/year. This is understandable if the risk status of patients is considered based on the TIGRIS register or COURAGE study [6, 7]. The results of the ATPCI study do not demonstrate the ineffectiveness of trimetazidine, instead they are an example of a wrongly selected study group for the purpose of demonstrating efficacy.

Finally, it must be noted that while the efficacy of trimetazidine prolong was demonstrated in both reducing angina count and angina severity, the rate of change of these two criteria was not uniform. The cause of this is not known. From data in scientific literature, it is known that the severity of angina is predictive of both the total mortality rate and revascularisation [8, 9].

CONCLUSION

1/ Trimetazidine is an excellent, metabolically effective, anti-ischemic preparation which is capable of reducing the incidence of angina symptoms and their severity in all forms and across all ages [10, 11].

2/ As the previous prospective [12] and current retrospective studies have demonstrated that, insofar as patients have angina symptoms, trimetazidine is effective with regard to angina recurrence even after having undergone revascularisation.

LIMITATIONS OF THE STUDY

The present study has a number of limitations, the most important of which are as follows:

- The retrospective and observational nature of the study can never be as authoritative as a randomised prospective study.
- We cannot determine the exact amount of time that passed between revascularisation and enrolment into the study.
- We did not examine the efficacy of trimetazidine prolong in relation to cardiovascular death or hospitalisation for a cardiac event. We only examined its efficacy in relation to angina recurrence.
- We could not determine what the incidence of neurovascular disease was, or what the left ventricular function of patients was like.

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