

# THE EFFECT OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND SARTANS ASSOCIATION TO IVABRADINE VERSUS METOPROLOL ON THE MAIN DOPPLER PARAMETERS OF THE MITRAL INFLOW IN DIABETIC PATIENTS WITH PRESERVED EJECTION FRACTION

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**Keywords:** angiotensin converting enzyme (ACE) inhibitors, sartans, ivabradine, metoprolol, mitral Doppler flow

**Abstract:** Within a larger study of the effect of ivabradine versus metoprolol on the main Doppler parameters of the mitral inflow in diabetic patients with normal ejection fraction, we studied the outcome of these parameters in relation with the association or non-association of angiotensin-converting enzyme inhibitors and sartans, taken together as inhibiting medication of the same system. The results showed an independent beneficial effect of the association of these drugs to ivabradine (in some cases they even enhance its favourable action), respectively to metoprolol.

**Cuvinte cheie:** inhibitori ai enzimei de conversie, sartani, ivabradină, metoprolol, flux Doppler transmitral

**Rezumat:** Am studiat, în cadrul unui studiu mai amplu al efectului ivabradinei față de metoprolol asupra principalilor parametri Doppler ai fluxului transmitral, la pacienți diabetici cu fracție de ejeecție normală, evoluția acestor parametri în funcție de asocierea sau non-asocierea inhibitorilor de enzimă de conversie a angiotensinei și a sartanilor, considerate împreună, ca medicație inhibitoare a aceluiaș sistem. Rezultatele au indicat un efect benefic independent al asocierii acestor droguri la ivabradină (în unele cazuri acestea chiar îi amplifică efectele favorabile), respectiv la metoprolol.

## INTRODUCTION

The angiotensin converting enzyme inhibitors and the sartans participate in the physiopathological processes associated to heart failure, such as hypertension, left ventricular hypertrophy, myocardial fibrosis and endothelial dysfunction. Their use proved beneficial for the patients with systolic dysfunction of the left ventricle.

This medication contributes to the reduction of left ventricular hypertrophy in the patients with hypertension, reason for which it is widely considered to be also beneficial in the treatment of the diastolic dysfunction with preserved ejection fraction. The effect of their association to metoprolol or ivabradine on the main parameters of the Doppler mitral flow has not been studied up to the beginning of this study.

## WORKING HYPOTHESIS

We started from the hypothesis that the association of angiotensin converting enzyme inhibitors and sartans could enhance the benefits of the use of ivabradine, respectively metoprolol in the treatment of the diastolic dysfunction with preserved ejection fraction in diabetic patients, reflected in the better Doppler mitral flow parameters.

## PURPOSE

The purpose of this study was to evaluate the utility of the association of angiotensin converting enzyme blockers and sartans to ivabradine, respectively to metoprolol in the treatment of the diastolic dysfunction with preserved ejection fraction in diabetic patients.

## METHODS

We undertook an experimental study on diabetic patients with preserved ejection fraction, coming from the

ambulatory of the Diabetes and Nutritional Diseases of the Sibiu Clinical County Emergency Hospital, cardiologically unexamined before, under treatment with metoprolol, of which in a subgroup, metoprolol was replaced by ivabradine in equivalent doses as sinus rate reduction, for a period of three months.

There resulted two subgroups: an experimental one, treated with ivabradine and a control subgroup, which continued the treatment with metoprolol. Both subgroups had similar structure in terms of age, gender, initial Doppler aspect, morbidity and drug association.

For these two subgroups, we determined the main parameters of the Doppler mitral inflow at the initial moment and after three months and we evaluated the effects of the association of angiotensin converting enzyme inhibitors and sartans to each of them. The medication was administered according to the international guidelines. The patients of the two subgroups who gave up the treatment out of various reasons were excluded from the study.

For statistics we used the SPSS v.10. program. In order to compare the quantitative variables, we used the media equality test (independent T test) and for comparison of the qualitative variables, we used the Crosstabs association table.

The treatment with angiotensin converting enzyme inhibitors, respectively sartans was homogenously distributed within the two subgroups, allowing their comparison. From the experimental subgroup, 33 (66%) patients were treated with drugs belonging to these classes and from the control subgroup, 24 patients (60 %). Their antihypertensive effect, of reducing the cardiovascular hypertrophy and the endothelial dysfunction had a similar action on the patients of both subgroups (Likelihood ratio  $p=0,558$ ).

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### RESULTS

The subgroup treated with angiotensin converting enzyme inhibitors and sartans associated to ivabradine and metoprolol showed a statistically insignificant enhancement of the E wave velocity at the start of the A wave after 3 months, while the subgroup treated without this association showed no change at all of this parameter. At the initial and final moment, there were no significant differences between the two subgroups.

For the subgroups treated with ACE inhibitors and sartans association, a statistically insignificant prolongation of the isovolumic relaxation time was seen after 3 months of treatment ( $p=0,243$  respectively  $p=0,436$ ), the differences between the subgroups remaining statistically insignificant for the subgroup treated with ACE inhibitors and sartans ( $p=0,985$  respectively  $p=0,371$ ) as for the subgroup treated without ACE inhibitors or sartans ( $p=0,919$  respectively  $p=0,983$ ).

For the experimental subgroup, treated with ivabradine associated to ACE inhibitors and sartans, the mean value of the mitral deceleration time was statistically insignificantly prolonged ( $p=0,635$ ) and for the control subgroup with association of ACE inhibitors and sartans to metoprolol, the mean value of the mitral deceleration time was insignificantly shortened ( $p=0,276$ ). In time, the two subgroups showed no significant differences between each other, neither at the initial moment ( $p=0,997$  respectively  $p=0,947$ ), nor at the final moment ( $p=0,747$  respectively  $p=0,626$ ).

In the subgroup with ACE inhibitors and sartans associated to ivabradine, the A wave duration was significantly prolonged after 3 months ( $p=0,005$ ), while in the subgroup treated with ACE inhibitors and sartans associated to metoprolol, the A wave duration had an insignificant prolongation ( $p=0,578$ ). At the initial moment, the two subgroups did not differ significantly ( $p=0,630$  respectively  $p=0,781$ ) but at the final moment, there was a significant difference between the two subgroups ( $p=0,004$  for the ACE inhibitors and sartans treated and  $p=0,445$  for those without this association).

In conclusion, it may be said with 95% level of certitude that the association of ACE inhibitors or sartans to the treatment with ivabradine is beneficial for the diastolic function of the left ventricle with preserved ejection fraction in diabetics.

No significant enhancement of the maximum velocity of the E wave was seen neither in the subgroups treated with association of ACE inhibitors or sartans to ivabradine, nor to metoprolol. There were not significant differences between the subgroups at the initial and at the final moment concerning the E wave maximum velocity.

The association of ACE inhibitors or sartans to ivabradine, respectively to metoprolol did not significantly influence the maximum velocity of the A wave. The non-association of ACE inhibitors or sartans to ivabradine produces an insignificant favourable reduction effect of the A wave maximum velocity in the patients with altered relaxation, while the non-association of these drugs to metoprolol does not influence the A wave maximum velocity. At the initial and final moment the two subgroups did not differ significantly concerning the A wave maximum velocity.

This study showed a beneficial effect on the main parameters of the Doppler mitral inflow of the association of ACE inhibitors and sartans to ivabradine respectively to metoprolol in diabetic patients with preserved ejection fraction, confirming the previous data. There was seen a beneficial effect especially for increasing the action of ivabradine of A wave duration enhancement, the only parameter on which ivabradine was superior to metoprolol in this study.

### CONCLUSION

The association of ACE inhibitors and sartans to the treatment with ivabradine, respectively metoprolol, in diabetic patients with preserved ejection fraction is beneficial and independent on the majority of the main Doppler parameters of the mitral inflow.

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