# Znižanje srčne frekvence z ivabradinom zmanjša periproceduralno poškodbo srčne mišice po koronarnem posegu in izboljša simptome angine pektoris pri bolnikih s stabilno koronarno boleznijo

# Heart rate reduction using ivabradine protects against periprocedural myocardial injury and angina symptoms in patients with stable coronary disease undergoing coronary intervention

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**Ključne besede:**
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## Izvleček

***Namen:*** *V literaturi zaenkrat ni podatkov, ki bi dokazovali, da znižanje srčne frekvence zmanjša periproceduralno poškodbo miokarda pri bolnikih, ki imajo opravljen perkutani koronarni interventni poseg. Ivabradin je uveljavljeno protiishemično zdravilo, ki znižuje srčno frekvenco in posledično izboljša simptome angine pektoris. V pričujoči raziskavi nas je zanimalo, ali znižanje srčne frekvence z ivabradinom zmanjša periproceduralno poškodbo miokarda.*

***Metode:*** *40 bolnikom s stabilno angino pektoris in utripom v mirovanju nad 70 udarcev na minuto smo predpisali ivabradin 2x5 mg dnevno. V kontrolni skupini je bilo 40 bolnikov z*

## Abstract

***Purpose:*** *There are no data demonstrating that a decrease in heart rate reduces periprocedural myocardial injury (PMI) in patients undergoing elective percutaneous coronary intervention (PCI). Ivabradine is an established anti-ischemic drug that reduces heart rate (HR) and subsequently alleviates symptoms of angina. The present study sought to determine whether HR reduction via ivabradine attenuates PMI.*

***Methods:*** *Forty patients with stable angina and a resting HR of >70 bpm were administered 5 mg of ivabradine twice daily. The control group consisted of 40 patients with a resting HR of >70 bpm. All patients were monitored for*

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*utripom v mirovanju nad 70 udarcev na minuto. Vsi bolniki so bili vključeni mesec dni pred predvidenim posegom. Vrednosti troponina I smo določili pred posegom in 24 ur po posegu. Spremljali smo tudi simptome angine pektoris v obeh skupinah.*

***Rezultati:*** *Med obema skupinama bolnikov ni bilo statistično pomembnih razlik. Opažali smo pomembno znižanje srčne frekvence in pomembno manj simptomov angine pektoris v skupini, zdravljeni z ivabradinom (62.3±7.1 utripov na minuto vs.79±10.2 utripov na minuto; P<0.05 in 0.5±0.1 vs. 2.4±2.1; P<0.05). Vrednosti troponina I so bile pomembno nižje v skupini, zdravljeni z ivabradinom v primerjavi s kontrolno skupino (0.12±0.03 ng/mL vs. 0.44±0.08 ng/mL; P<0.05). Ko smo dodatno analizirali faktorje vpliva, smo ugotovili da na periproceduralno poškodbo miokarda vplivata le srčna frekvenca pod 70 utripov na minuto (razmerje obetov 7.0; interval zaupanja od 1.2 od 41.7; P=0.03) in število vstavljenih žilnih opornic (razmerje obetov 4.4; 95% interval zaupanja 1.1 to 17.3; P=0.03).*

***Zaključek:*** *Znižanje srčne frekvence z ivabradinom zmanjša periproceduralno poškodbo miokarda pri bolnikih ob opravljenem perkutanem koronarnem interventnem posegu.*

*one month before the scheduled intervention. After admission, troponin I levels were measured before and 24 h after the procedure. Data on any change in symptoms were also collected in both groups.*

***Results:*** *There were no significant differences between the groups. A significant reduction in HR and angina episodes per week was noted in the ivabradine group (62.3±7.1 bpm vs.79±10.2 bpm; P<0.05 and 0.5±0.1 vs. 2.4±2.1; P<0.05). The mean troponin I levels after the procedure were significantly lower in the ivabradine group compared to the control group (0.12±0.03 ng/mL vs. 0.44±0.08 ng/mL; P<0.05). When analyzing patients after coronary intervention, heart rate of <70 bpm (OR 7.0; CI 1.2 to 41.7; P=0.03) and number of deployed stents (OR 4.4; 95% CI 1.1 to 17.3; P=0.03).were the only significant predictors of PMI after adjustment for potential confounders in a multivariable logistic model.*

***Conclusion:*** *HR reduction achieved by ivabradine reduces PMI in patients undergoing elective PCI.*

## INTRODUCTION

Periprocedural myocardial injury (PMI) is frequent in patients undergoing elective percutaneous coronary intervention (PCI). The main reasons for this collateral damage are occlusion of small side branches during stent deployment and peripheral embolization via dislodged debris that also takes place during stent positioning and balloon inflation (1). It has been previously demonstrated that the extent of troponin leakage after the procedure is associated with a worse patient prognosis (2). PMI is defined in the latest universal definition of myocardial infarction as an elevation of troponin above the 99$^{th}$ percentile

of the upper level of normal (ULN) in the case with normal preprocedural values (3). Among risk factors associated with PMI, previous reports have mentioned age, N-terminal–pro-brain natriuretic peptide, hemoglobin, number of target vessels, type of lesion (B2 or C), number of stents, and presence of aortic valve calcification, just to name few (1,4,5,6). In terms of the other established atherosclerosis risk factors, it has been shown that preprocedural non-high-density lipoprotein cholesterol levels are associated with PMI (7). However, there are no data showing that heart frequency is connected to PMI. It was previously shown that elevated heart frequency is involved in atherosclerosis progression, although the pathophysiologic rationale for this phenomenon is still lacking (8). The present study hypothesized that heart rate (HR) reduction in patients with elevated heart frequency of >70 bpm attenuates PMI.

## MATERIALS AND METHODS

Patients scheduled for elective PCI were evaluated in this study, which was approved by the Institutional Ethics Committee. Inclusion criteria included suspected or preestablished coronary artery disease, presence of sinus rhythm, and resting heart frequency of >70 bpm. Exclusion criteria included previous pacemaker implantation, symptoms and signs of heart failure, left ventricle ejection fraction of <50%, creatinine levels above ULN, and prior ivabradine treatment. Patients were invited to participate in the study after the inclusion criteria were satisfied. Informed consent was obtained, and patients were instructed to come for the first time one month before the planned procedure. The heart rate was reassessed at the first visit. Patients were asked about their usual therapy adherence and then instructed to rest for 5 min. A twelve-lead electrocardiogram (ECG) was recorded and eligible (HR>70 bpm) patients were then randomly assigned to one of two groups. Patients in group 1 were prescribed 5 mg of ivabradine twice daily on top of their standard therapy. Patients in group 2 received no additional treatment. Patients were reassessed upon admission and data including history of angina and any ivabradine side effect symptoms were obtained. A twelve-lead ECG was recorded and resting heart frequency was measured.

Fasting state blood was collected upon admission using standard medical techniques. Additional blood samples were obtained 24 h after the procedure. Troponin I levels were analyzed using cardiac troponin I assay (Siemens Healthcare Diagnostics) with a limit of detection of 0.006 µg/L, 99$^{th}$ percentile cut-off point of 0.04 µg/L, and coefficient of variation of <10% at 0.03 µg/L as specified by the manufacturer (9,10).

PCI was performed by an experienced interventional cardiologist who was blinded to the study protocol. Femoral or radial approach was used. All patients received unfractionated heparin at a standard dosage (30–100 IU/kg). The drug dosage and material selection were left to the operator's discretion. The target lesions were pinpointed and PCI was performed after the coronary angiogram. Troponin I was reassessed 24 h after the procedure in all patients. PMI was defined as an elevation of troponin above the 99$^{th}$ percentile of ULN in the case of normal preprocedural values. This definition is in accordance with the 4th universal definition of myocardial infarction (3).

Student's t-test was used to evaluate the differences between continuous variables. Chi-square test was used for analysis of categorical variables. Continuous data were expressed as mean ± standard deviation (SD), whereas categorical variables were expressed as percentages. Simple logistic regression method was used to assess the correlation between HR and PMI. Multivariate logistic regression was then used to adjust the significance for other potential confounders. Statistical analysis was performed using the SPSS statistical package.

## RESULTS

There were slightly more patients with arterial hypertension in the ivabradine group. Otherwise, no significant differences were noted between the groups (Table 1: Clinical characteristics of both groups). A significant reduction in HR and angina episodes per week was present in the ivabradine group (62.3±7.1 vs.79.3±10.2 bpm; P<0.05 and 0.5±0.1 vs. 2.4±2.1; P<0.05; Table 2: Clinical effects of ivabradine treatment after one month). The mean troponin I levels after the procedure were significantly lower in

the ivabradine group compared to the control group (0.12±0.03 ng/mL vs. 0.44±0.08 ng/mL; P<0.05; Table 3). Logistic regression model showed a positive correlation between HR≥70 bpm and PMI (odds ratio (OR) 5.8; 95% confidence interval (CI 1.2–26.9; P=0.01). In a multivariate model including all of the variables, the only significant predictors of PMI were HR≥70 bpm (OR 7.0; CI 1.2–41.7; P=0.03) and the number of deployed stents (OR 4.4; 95% CI 1.1–17.3; P=0.03; Tables 1, 3).

***Table 1.*** *Clinical characteristics of both groups*

| Baseline parameters | Ivabradine group (N=40) | Control group (N=40) | P value |
|---|---|---|---|
| Age (years) | 56±13 | 57±11 | 0.9 |
| Sex (Female) | 17(42%) | 16(40%) | 0.9 |
| Weight (kg) | 88.8±16.5 | 83.2±21.6 | 0.2 |
| Height (cm) | 168.9±8.3 | 170.3±11.3 | 0.5 |
| Pulse (per min) | 79.4±10.2 | 78.3±7.9 | 0.6 |
| Hypertension | 36 (90%) | 28 (70%) | 0.05 |
| Diabetes | 11 (27%) | 11 (27%) | 1.0 |
| Dyslipidemia | 22 (55%) | 27 (68%) | 0.4 |
| Antiagregation therapy | 35 (87%) | 30 (75%) | 0.3 |
| Beta-blockers | 25 (62%) | 22 (55%) | 0.6 |
| Statins | 23 (58%) | 26 (65%) | 0.6 |
| ACE inhibitors | **31 (75%)** | **30 (78%)** | **1.0** |
| Trimetazidine | 6 (15%) | 1 (3%) | 0.1 |
| Cholesterol (mmol/L) | 5.0±1.4 | 4.9±1.5 | 0.7 |
| Hemoglobin (g/L) | 142.3±11.4 | 142.9±16.5 | 0.9 |
| LDL cholesterol (mmol/L) | 3.2±1.3 | 3.0±1.3 | 0.7 |
| Troponin levels (ng/mL ) | 0.03±0.01 | 0.02±0.01 | 0.7 |

*ACE – angiotensin converting enzyme*
*LDL – low density lipoprotein.*

***Table 2.*** *Clinical effects of ivabradine treatment after one month*

| Ivabradine group | I$^{st}$ visit | After I month | P value |
|---|---|---|---|
| Angina episodes per week | 2.4±2.1 | 0.5±0.15 | 0.00 |
| Nitroglycerin per week | 0.8±0.14 | 0.2±0.09 | 0.04 |
| CCS Scale | 2.1±0.6 | 1.5±0.5 | 0.08 |
| Beats per minute | 79.3±10.2 | 62.3±7.1 | 0.00 |

*CCS – Canadian Cardiovascular Society*

## DISCUSSION

The present study showed that heart frequency has an impact on PMI in patients with coronary disease

***Table 3.*** *Periprocedural and postprocedural parameters in both groups*

| After procedure | Ivabradine group | Control group | P value |
|---|---|---|---|
| Troponin I levels (ng/mL) | 0.12±0.03 | 0.44±0.08 | 0.02 |
| Creatinine levels (µmol/L) | 86.9±26.9 | 81.0±19.8 | 0.3 |
| Number of lesions per patient | 1.1±0.3 | 1.1±1.0 | 0.9 |
| Lesion location –LAD | 9 (23%) | 8 (20%) | 0.8 |
| Lesion location –LCX | 4 (10%) | 7 (18%) | 0.5 |
| Lesion location RCA | 7 (18%) | 4 (10%) | 0.3 |
| Lesion location other | 1 (3%) | 2 (5%) | 1.0 |
| Type B2/C lesion according to American Heart Association (AHA) | 12 (31%) | 14 (35%) | 0.8 |
| PCIs per patient | 0.4±0.05 | 0.6±0.05 | 0.1 |
| Stents per patient | 0.5±0.08 | 0.6±0.08 | 0.5 |
| Cummulative mean stent length (mm) | 30.1±16.1 | 24.6±9.7 | 0.2 |
| Cummulative mean stent diameter (mm) | **3.0±0.4** | **2.7±0.7** | **0.1** |
| Maximum pressure (atm) | 15.8±4.4 | 15.5±4.9 | 0.8 |
| Ballon inflation duration (sec) | 29.1±16.9 | 27.0±14.3 | 0.7 |
| Duration of procedure (min) | 35.3±24.6 | 37.4±16.6 | 0.7 |

*LAD – left anterior descending*
*LCX – left circumflex*
*RCA – right coronary artery*
*LDL – low density lipoprotein.*

undergoing PCI. There were no significant differences between the groups that could severely influence established results. The numbers of coronary lesions between both groups were comparable and there were no major differences in other angiographic and procedural parameters. Moreover, the included patients were all undergoing elective procedures. They had normal troponin I levels before the procedure and no signs of kidney failure before or after the procedure causing troponin I elevation. In addition, no differences in hemoglobin and low-density cholesterol levels were present between both groups, even though it was recently shown that these two factors can have an influence on PMI. Therefore, it was suggested that reduced HR has an impact on troponin I level elevation after the procedure.

Previous studies have established that different factors mirroring endothelial damage (like microalbuminuria and hypercholesterolemia) are associated with PMI (7,11). It was also shown that patients with a greater myocardial enzyme leak during interventional procedures are prone to higher complication rates and worse prognosis (2). In addition, it was demonstrated that lesion complexity and stent position affect the post-procedural prognosis (12). Consequently, it would be of benefit to highlight different factors correlated with PMI. Since heart frequency is easy to measure and relatively simple to tackle, it is also of clinical benefit to know that lower HR is associated with better outcomes after PCI.

It has been shown that elevated heart frequency in patients with established coronary disease is associated with a worse prognosis (8). The BASKET PROVE trial tried to elucidate whether HR in patients after PCI upon discharge from the hospital is associated with a worse outcome. It was demonstrated that patients with a higher HR had a higher all-cause mortality rate as well as a higher rate of myocardial infarction. Results were similar in groups of patients with acute coronary syndrome and in those with stable angina (13). However, positive results from large trials showing a possible benefit of HR reduction for prognosis of patients with heart disease are still lacking. The Signify Trial randomly assigned patients to the ivabradine or placebo groups to reduce HR to 55–60 bpm. After a median follow up of 27.8 months, there were no clinical benefits from the ivabradine treatment, with a higher rate of bradycardia, atrial fibrillation, and QT prolongation observed in the treated group (14). However, subsequent subgroup analysis demonstrated that treatment with ivabradine reduced the frequency of angina episodes, which was also confirmed in the present study (15). Studies which address pathophysiological effects are urgently required as data on HR reduction using ivabradine are still conflicting as far as clinical benefits are concerned. Dillinger et al. have tried to evaluate the impact of HR reduction using ivabradine on central aortic blood pressure and myocardial perfusion. They showed that reduced HR improves the myocardial perfusion index and diastolic perfusion time without an effect on central aortic blood pressure (16). O'Connor et al. have studied the effect of HR reduction with ivabradine on left ventricular remodelling measured by echo strain imaging in a pre-clinical setting. They were able to demonstrate that HR reduction attenuated infarct expansion and preserved remote-zone contractile function and synchrony in a mouse model of myocardial infarction (17).

There are several limitations in this study. Because a placebo arm was not present, the clinical benefit could be biased by intention to treat. However, this did not influence biomarkers and troponin I levels in both groups. The study sample was also relatively small, although there were no large heterogeneities between the groups. We also could not measure other biomarkers of cardiac necrosis, such as creatine kinase enzyme, which could give further insight into myocardial damage after the procedure. Finally, it is also possible that other unidentified factors confounded the study results. To the best of our knowledge, all parameters previously demonstrated to have an impact on PMI were included in the study.

## CONCLUSIONS

In conclusion, we were able to show that HR reduction via ivabradine reduces PMI in patients undergoing elective PCI. Further clinical studies are needed to clarify this issue.

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