**Ranolazine reduces symptoms of palpitations and documented arrhythmias in patients with ischemic heart disease — The RYPPLE randomized cross-over trial**

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Background: Ranolazine decreases the frequency of arrhythmias during the acute phases of ischemic heart disease (IHD), but it remains unknown if it has similar effects in the chronic phase of the disease. We performed a prospective, randomized, cross-over pilot trial to test the hypothesis that chronic treatment with ranolazine can reduce the incidence of documented arrhythmias and the related symptoms of palpitation in stable patients with IHD.

Methods: We randomized 105 patients with stable IHD and symptoms of angina and palpitations already on therapy with beta-blockers and/or calcium antagonists to ranolazine (750 mg bid, N = 53) or placebo (N = 52) for 30 days (until T-1). After a wash-out period to avoid any carryover effect, cross-over was performed,and patients were switched to the other drug which was continued for 30 days (until T-2). All patients underwent symptom-limited exercise stress testing and 48-hour ECG Holter monitoring at T1 and T2. During the study period, patients were told to use a OmronN® portable ECG monitor HCG-801 device in case of symptoms of palpitations.

Results: Ranolazine reduced the number of anginal episodes more commonly than placebo (5 ± 8 episodes/30 days vs. 21 ± 24 episodes/30 day, p = 0.001) and increased exercise durations at 1 mm ST-segment depression (514 ± 211 s vs. 402 ± 287 s, p = 0.025) and at onset of angina (614 ± 199 s vs. 519 ± 151 s, p = 0.007) at stress testing.

These effects were coupled by significant decreases with ranolazine as compared with placebo treatment periods in the occurrence of frequent (>1000 beats) supraventricular arrhythmias (33% vs 52%, p = 0.01) and complex ventricular arrhythmias (17% vs 30%, p = 0.045). Complete resolution of symptoms of palpitations was significantly more common with ranolazine than placebo (31/53 vs 16/52 patients, p = 0.008). Also, portable ECG recordings showed that arrhythmias were less common during ranolazine vs. placebo, with significant decreases in number (7 ± 10 episodes/30 days vs. 23 ± 29 episodes/30 day, p = 0.001) and duration (10 ± 18 min/30 days vs. 19 ± 21 min/30 day, p = 0.021) of symptomatic arrhythmic episodes. No severe side effects were recorded during the trial period.

Conclusion: The antianginal and antiischemic properties of ranolazine are paralleled by significant decreases in the occurrence of both arrhythmias and the related symptoms of palpitations in stable patients with IHD. (ClinicalTrials.gov identifier: NCT01495520).

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**Local delivery of thrombolytics before thrombectomy in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention — The DISSOLUTION randomized trial**

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Background: Prompt reperfusion with percutaneous coronary intervention (PCI) in ST-elevation myocardial infarction (STEMI) improves clinical outcomes through salvage of myocardial tissue. Although use of thrombus aspiration with PCI can improve epicardial flow and myocardial perfusion, several unmet needs remain. The purpose of this trial was to evaluate the hypothesis that local delivery of low-dose thrombolytics can enhance the efficacy of thrombus aspiration in STEMI patients undergoing primary PCI.

Methods: A total of 102 patients with STEMI and angiographic evidence of totally occlusive thrombosis in the culprit artery were randomly assigned to receive local bolus of 200,000 units urokinase (N = 51) or saline solution (N = 51) followed by manual aspiration thrombectomy (Pronto™, Vascular Solutions, Inc., Minneapolis, Minnesota) and PCI. Both groups received abciximab (i.v. bolus + 12-h infusion). End points included final thrombolysis in myocardial infarction (TIMI) flow grade, frame count, and thrombus grade > 2, myocardial blush grade (MBG), 60-min ST-segment resolution (STR) > 70%, and 6-month clinical outcomes. All patients had echocardiography at 6-month and left ventricular ejection fraction (EF) and wall motion score (WMS) were obtained.

Results: Baseline clinical and angiographic characteristics of both groups were similar. Local urokinase was associated with post-PCI evidence of higher TIMI flow grade 3 (96% vs. 68%; p = 0.027), lower TIMI frame count (18 ± 11 vs. 25 ± 13; p = 0.045) and fewer TIMI thrombus grade > 2 (20% vs. 52%; p = 0.039). Histopathologic evaluation performed in 11 Gr. A and 11 Gr. B patients showed that aspirated thrombi after urokinase were smaller, softer and less organized than after saline. Post-PCI myocardial perfusion was slightly increased with urokinase (MBG 2/3: 88% vs. 64%; p = 0.09), with significantly more patients showing STR > 70% (80% vs 56%, p = 0.001). No differences between the two groups were subsequently seen in clinical outcomes and EF, whereas 6-month WMS was significantly lower in patients receiving local urokinase than saline (1.21 ± 0.29 vs 1.45 ± 0.32, p = 0.008).

Conclusion: Local delivery of low-dose thrombolytics before thrombectomy in STEMI patients undergoing primary PCI is associated with improved coronary flow, myocardial perfusion, and 6-month regional myocardial function. Delivery of low-dose thrombolytic agents directly to the site of thrombus might be an effective strategy to enhance efficacy of thrombus aspiration in primary PCI. (ClinicalTrials.gov identifier: NCT01568931).

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**Pharmacodynamic effects of atorvastatin vs. rosuvastatin in coronary artery disease patients with normal platelet reactivity while on dual antiplatelet therapy — The PEARL randomized cross-over study**

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Background: Levels of platelet reactivity in patients on dual antiplatelet therapy (DAPT) can potentially be influenced by concomitant treatment with statins that inhibit the CYP3A4 system involved in the activation of clopidogrel. Recent studies have shown that a high platelet reactivity during co-administration of clopidogrel and a CYP3A4-metabolized statin (i.e. atorvastatin) can be lowered by switching to a non-CYP3A4-metabolized statin (i.e. rosuvastatin). Aim of this study was to verify if atorvastatin and rosuvastatin have different pharmacodynamic effects also when they are given to patients with coronary artery disease (CAD) with baseline normal platelet reactivity while on DAPT.

Methods: A total of 100 stable CAD patients receiving DPAT (clopidogrel 75 mg plus aspirin 100 mg) who had evidence of normal