Preprocedural Levels of C-Reactive Protein, 
Plaque Composition, Neointima, 
and Long-Term Prognosis Following Coronary Stenting: Results From the GENERATION Study

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Background: Elevation of creatin kinase-MB (CK-MB) often occurs after coronary stent-placement. In a previous study, we found that this neointima mainly consists of vascular smooth muscle cells. In the present study, we evaluated the prevalence of CK-MB release and its relationship to long-term outcomes after successful CS in patients enrolled in the GENERATION study.

Methods: The GENERATION study was designed to evaluate the incidence of several serum markers (CRP, IL-6, and homocysteine) and neutrophilia for chronic inflammation obtained upon admission on the long-term cardiovascular morbidity and mortality and the restenosis rate after coronary stenting. For the purpose of this study, a total of 426 consecutive patients, treated for stable or unstable coronary syndromes, were recruited.

Results: Of 465 patients with normal pre-intervention CK-MB levels, 39 (39/465 6.6%) presented with CK-MB release per se. CRP (5.9 ± 2.5 versus 4.0 ± 1.7 ng/ml, p < 0.001) and baseline plasma CRP values (p < 0.001) were the only significant predictors of CK-MB release. By univariate analysis 3-fold CK-MB release was significantly associated with increased risk for the composite endpoint of cardiac death, non-fatal myocardial infarction, revascularization for unstable angina (HR:0.66, 95%CI:0.45-0.91, p = 0.017) during the 3-year follow up. However, after adjustment for baseline plasma CRP values, post-procedural 3-fold CK-MB release did not predict the long-term composite endpoint (HR: 0.99, 95%CI:0.93-1.05, p = 0.91).

Conclusion: Elevated CK-MB following successful CS may reflect the complexity of inflammatory status of the treated lesions. These factors may contribute to microembolization and subsequent silent myocardial necrosis. Therefore, an increased risk of long-term adverse clinical outcomes may be associated with these factors and not the CK-MB release per se.

Time Relation of the Amount of Macrophages in the Plaque During the Chronic Phase of In-Stent Restenosis

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Background - Inflammation plays an important role in the acute phase of in-stent restenosis. But in the chronic phase, after approximately 30 days, the neointimal plaque consists mainly of vascular smooth muscle cells. In a previous study, we found that this neointima still contains small clusters of macrophages. In this study we investigated the relation between the amount of macrophages in the in-stent restenotic plaque and the time after the placement of the stent.

Methods - Biopsies from human coronary in-stent restenotic lesions were obtained with a pullback atherecomtery catheter and immediately frozen in liquid nitrogen (n=19). The time between the placement of the stent and the biopsy varied from 69 till 465 days. The biopsies were immunostained for smooth muscle cells, macrophages and ACE, and a semi-quantitative score was applied: 0 for no macrophages, 1 for a few or clusters of cells, 2 for <10% of cells positive, 3 for 10-50% of cells positive and 4 for >50% of the cells positive. Results - As shown in the figure, an inverse correlation was found between the amount of macrophages and the time between the biopsy and the stent placement (p < 0.01). Therefore, the amount of ACE also decreases during time (p < 0.001). Conclusion - During the chronic phase of in-stent restenosis, the amount of macrophages in the neointima decreases, as well as the amount of ACE. This indicates that inflammatory cells play a role in the process of chronic in-stent restenosis, especially in the first phase.

Good Collaterals Increase the Risk of Reocclusion After Recanalization of a Chronic Coronary Occlusion?

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Background - The presence of a well developed collateral circulation in chronic coronary occlusions (CCO) is considered a potential determinant of reocclusion. The present study directly assessed collateral circulation at the time of recanalization by i.c. Doppler and pressure recordings in order to relate it to the risk of reocclusion.

Methods - In 98 consecutive patients a TCO duration >2 weeks was recanalized with stenting. Before PTCA average peak velocity distal to the occlusion (APV), distal coronary pressure (Pc) and arterial pressure (PA) were measured, and a collateral resistance index (RCR = Pc/PA) was calculated. Collateral function was assessed before the first balloon inflation. At the end of the procedure, the coronary flow velocity reserve (CFVR hyperemic APV/baseline APV) was measured after i.c. adenosine (20-40µg) in the recanalized artery.

Results. During follow-up of 6 months 14 reocclusions (16%) occurred. In patients with recocclusion the minimum lumen diameter (MLD) was lower. There was no difference in parameters of collateral function, or microvascular function as evidenced by a similar CFVR (see Table). The angiographic result remained the best predictor of recocclusion in the subgroup analysis of patients with recent and long-term occlusions, and with and without regional ventricular dysfunction.

Conclusion. The risk of recocclusion after recanalization of a TCO was determined by a low MLD, but not by the quality of collateral function or microvascular function.

Enhanced Suppression of Inflammation After Coronary Stenting (ESIS): A Randomized Clinical Trial Comparing Abciximab and Eptifibatide

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Background - Inflammation after coronary stenting portends adverse outcomes. Abciximab (A) and eptifibatide (E) are reported to alter inflammation after coronary intervention, but no randomized trial has compared their efficacy. We compared the effect of A and E on inflammation after stenting.

Methods - Patients undergoing coronary stenting were randomized to treatment with A (n=24) or E (n=26). Blood samples were obtained before stenting, and after 10 min, 1 hr and 18-24 hr. C-reactive protein (CRP, µg/ml), intereukin-6 (IL-6, pg/ml) and interleukin-1 receptor antagonist (IL-1Ra, pg/ml) were measured by ELISA. Changes in each marker after treatment with A or E were analyzed by repeated measure analysis of variance. Logistic transformation was performed to limit effects of inter-individual variability.

Results: Of the 50 patients enrolled, 86% had acute coronary syndromes. The groups (A and E) had similar clinical features, and baseline values of CRP, IL-6, and IL-1Ra. CRP, IL-6 and IL-1Ra increased after stenting despite administration of A or E (see table) and covariance increases were seen at each treatment. After logarithmic transformation, greater suppression in IL-1Ra but not CRP or IL-6 was seen after E compared with A (p < 0.03).

Conclusions: In this randomized trial, inflammation after coronary stenting persists despite treatment with A or E. A uniform benefit was seen only when the other was not seen. Enhanced suppression of inflammation after stenting is a potential therapeutic target.

Preprocedural C-Hepatic Protein Levels Are Not Associated With Restenosis After Successful Coronary Stenting: Results From the GENERATION Study

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BACKGROUND High plasma C-reactive protein (CRP) levels, has been associated with adverse prognosis in pts with coronary artery disease. However, the impact of preprocedural CRP levels on the risk of in-stent restenosis (ISR) after successful coronary stenting (CS) has not been clarified. METHODS The GENERATION study was designed to evaluate the impact of several serum markers estimated upon admittance (CRP, LPA, homocysteine and seropositivity for chlamydial infection) on the long-term prognosis and ISR rate after CS. For the purpose of this study a total of 493 consecutive patients who underwent successful CS due to stable or unstable coronary syndromes were recoulned. Complete clinical follow up was obtained from 465 (93.5%) pts in a period of 3-years. Results: By year 1, 121 patients (121/465 26.1%) developed recurrence of symptoms. ISR was observed in 106 (106/309 35%) pts. The distribution of restenosis among the 3 groups (A, B and C) was similar. The impact of CRP was significant (p=0.05). During this 3-year time period, 309 (309/465 66.5%) patients underwent angiographic restenosis study, including 114 (114/412 94.2%) symptomatic and 195 (195/244 51.5%) asymptomatic. Pts were classified into four groups according to the quartiles of CRP values. ISR was observed in 106 (106/200 53%) pts. The distribution of restenosis among the 4 groups of CRP is presented in Table. There was no statistically increased risk of ISR with increasing of CRP quartiles (p=0.89).