SERCA2A Gene Delivery Prevents Deterioration of Global Function and Retards Remodeling in a Sheep Model of Ischemic Mitral Regurgitation

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Mitral regurgitation (MR) doubles post-myocardial infarction (MI) mortality. We have shown that moderate MR augments remodeling in an apical MI model (no intrinsic MR) with independent LV-to-LA MR-type flow, and that repair of MR after 1 month induces reverse remodeling. In particular, sarcoplasmic reticulum calcium ATPase 2 (SERCA2) levels were depressed in correlation with the degree of hypertrophy. We hypothesized that up-regulating SERCA2A levels using a gene therapy approach will prevent ischemic MR-induced ventricular remodeling in our model.

Methods: Antero-apical MIs were created, and an LV-to-LA shunt was implanted in 12 sheep (regurgitant fraction=30%). One week before MR and MI creation, all the sheep underwent percutaneous transcoronary delivery of adeno-associated virus serotype 5 encoding either for βgal as a control (AAV5. βgal- 6 sheep) or SERCA2a (AAV5.SERCA2a- 6 sheep).

Results: Sheep in the AAV5.SERCA2a group had a significantly smaller increase in **LV end-systolic volume** at 1 and 3 months (88.1 ml vs 69 ml at one month, and 99.4 ml vs 82.6 ml at 3 months, P=0.05 and P=0.03 respectively). **LV end-diastolic volumes** did not differ significantly between the groups, reflecting persistent MR-induced volume overload. **Maximal systolic dP/dT** increased significantly at 1 and 3 months in the AAV5.SERCA2a group, while decreasing in the control sheep (807.5 mmHg/sec vs 1165 mmHg/sec, P=0.002 at 1 month, and 607.8 mmHg/sec vs 877.8 mmHg/sec, P=0.006, at 3 months) . **Preload recruitable stroke work**, reflecting global systolic function, was significantly higher in the AAV5.SERCA2a sheep at 3 months (32.2 vs 48.3 ml*mmHg, P=0.003). Pro-hypertrophic and anti-apoptotic **STAT3 and pAkt** decreased significantly more in the control group (P=0.001 and P=0.007 respectively).

Conclusion: Upregulating myocardial SERCA2a using virally mediated gene delivery in an established controlled model of ischemic MR increases global systolic function and reduces end-systolic volumes, reflecting improved contractile function of the muscle. The decrease in intracellular pathways involved in compensated remodeling was smaller in the genetically modified animals. Thus, upregulating SERCA2a in ischemic MR may retard the appearance of decompensated remodeling and failure.

Platelet Responsiveness to Aspirin Loading in Patients with ST-Elevation Myocardial Infarction Undergoing Primary Percutaneous Intervention is Associated with Myocardial Reperfusion and Clinical Outcome

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Background: In patients with stable coronary artery disease, and patients undergoing elective percutaneous coronary intervention (PCI), laboratory resistance to aspirin is associated with a higher incidence of adverse events. Nevertheless, the responsiveness to aspirin in acute myocardial infarction (AMI) and its implications have not yet been investigated.
Methods: The study comprised 76 aspirin naïve patients who underwent primary PCI (PPCI) for ST-elevation MI (STEMI). Platelet reactivity was assessed 30-60 mins after a loading dose of 300mg chewable aspirin, by conventional aggregometry and Impact R, where platelet reactivity to arachidonic acid (AA) was expressed by platelet deposition under flow conditions.
Results: Patients were stratified using the median value of AA-induced platelet aggregation (PA) (49%) to good responders to aspirin (n=38), who had a median AA-induced PA of 33% (25-41), and poor responders to aspirin (n=38), who had a median AA-induced PA of 77% (70-84). Similarly, good compared with poor responders had higher surface coverage by Impact R (3.9±2.6 vs. 2.2±1.3, p=0.003). Good versus poor responders were similar regarding baseline demographic, clinical and angiographic characteristics. However, good responders were more likely to demonstrate early ST-segment resolution ≥70% after PPCI (84% vs 54%, p <0.01), suggestive of better myocardial reperfusion. Good compared to poor responders had a lower incidence of adverse cardiovascular events (re-infarction, need for re-intervention, congestive heart failure and/or death) throughout a 6-month follow-up (11% vs 24%, respectively; p<0.05).
Conclusions: Ex vivo poor platelet responsiveness to aspirin loading in STEMI patients is associated with a worse prognosis in patients undergoing PPCI.

Incidence of Early Left Ventricular Thrombus after Acute Anterior Wall Myocardial Infarction in the Primary Coronary Intervention Era

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BACKGROUND: Rapid reperfusion has been shown to decrease mortality and improve LV function recovery. Previous studies have reported that left ventricular thrombus (LVT) is a major complication of ST-segment elevation acute anterior wall myocardial infarctions (AMI). This thrombus may dislodge and emboli to brain or other tissues. There is no data on LVT in the current primary PCI (PPCI) era. We sought to demonstrate the incidence of LVT after AMI in patients (pts) treated with PPCI compared to thrombolysis or conservative treatment.

METHODS: We conducted a retrospective, single center study in 642 pts with anterior wall AMI who were treated with PPCI (n=297), Thrombolysis (n=128) or conservative treatment (n=217) between January 2000 and December 2006. A LVT was defined as an echodense mass adjacent to an abnormally contracting myocardial segment.

RESULTS: No statistical difference was found in LVT rate among the groups: 21/297 pts (7.1%) in PPCI, 10/128 (7.8%) in thrombolytics and, 9/217 (4.1%) in the conservative. This is an almost identical incidence (P=0.28) as reported in the pre-PPCI era. Those in the thrombolytics group were characterized by shorter duration from symptom start and were generally treated with heparin/LMWH.

CONCLUSIONS: This is the largest report to evaluate the incidence of LVT formation after AMI. In the current era of rapid reperfusion by PPCI, the rate of thrombus formation is similar to that reported in the past and not different than for patients treated conservatively or with thrombolysis. This may be also as a result of pts selection for PPCI.

A Comprehensive Evaluation of Drug Eluting Stents Compared with Bare Metal Stents for Patients with Acute ST Elevation Myocardial Infarction

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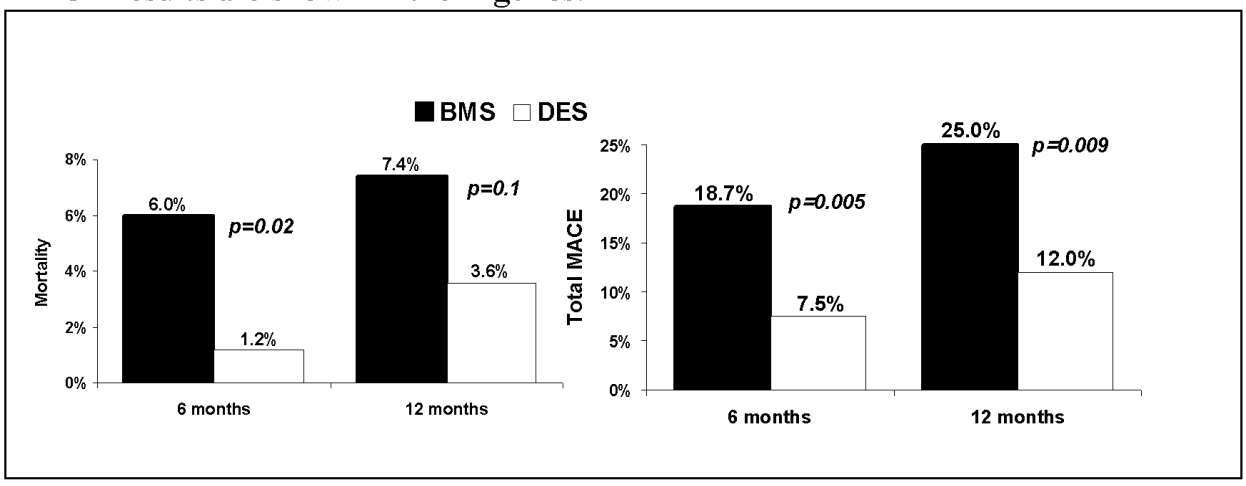
Background: The present study investigates the clinical outcomes in consecutive group of patients with ST elevation MI (STEMI) treated with either dug eluting stents (DES) or bare metal stents (BMS) at our institution.

Methods: This prospective registry included 162 patients with STEMI undergoing primary PCI within 12 hours of symptoms onset and using DES implantation (e.g. 51% Cypher, 42% Taxus, 7% Endeavor stents). The control group consisted of 897 patients implanted with BMS. Patients with cardiogenic shock were excluded from analysis. The incidences of major adverse cardiac events (MACE) including recurrent MI, angiographically proven (i.e. definite) stent thrombosis, target vessel revascularization (TVR) and target lesion revascularization (TLR) were assessed at six months and one year.

Results: STEMI patients treated using DES were somewhat younger (59±12 vs. 61±13, p=0.07) but had more anterior MI location (64% vs. 45%, p=0.0001). The prevalence of diabetes mellitus was 25% in both groups. Angiographic success was achieved in 97% of patients in both groups. At one year, the rate of definite stent thrombosis was 4.1% in the BMS group vs. 0.7% in the DES counterparts (p=0.04). TVR was remarkably lower among DES vs. BMS treated patients by one year (5.7% vs. 15.4%, p=0.002). Overall mortality and MACE results are shown in the **Figures**.



Conclusion: According to our clinical experiences, the use of DES in STEMI is safe and effective as compared to BMS. DES was not associated with an increased risk of coronary thrombosis and was effective in reducing the incidence of adverse events up to one year in patients with STEMI referred for emergent primary PCI.

The Impact of Right Ventricular Dysfunction on Long Term Mortality in Patients with Acute Myocardial Infarction

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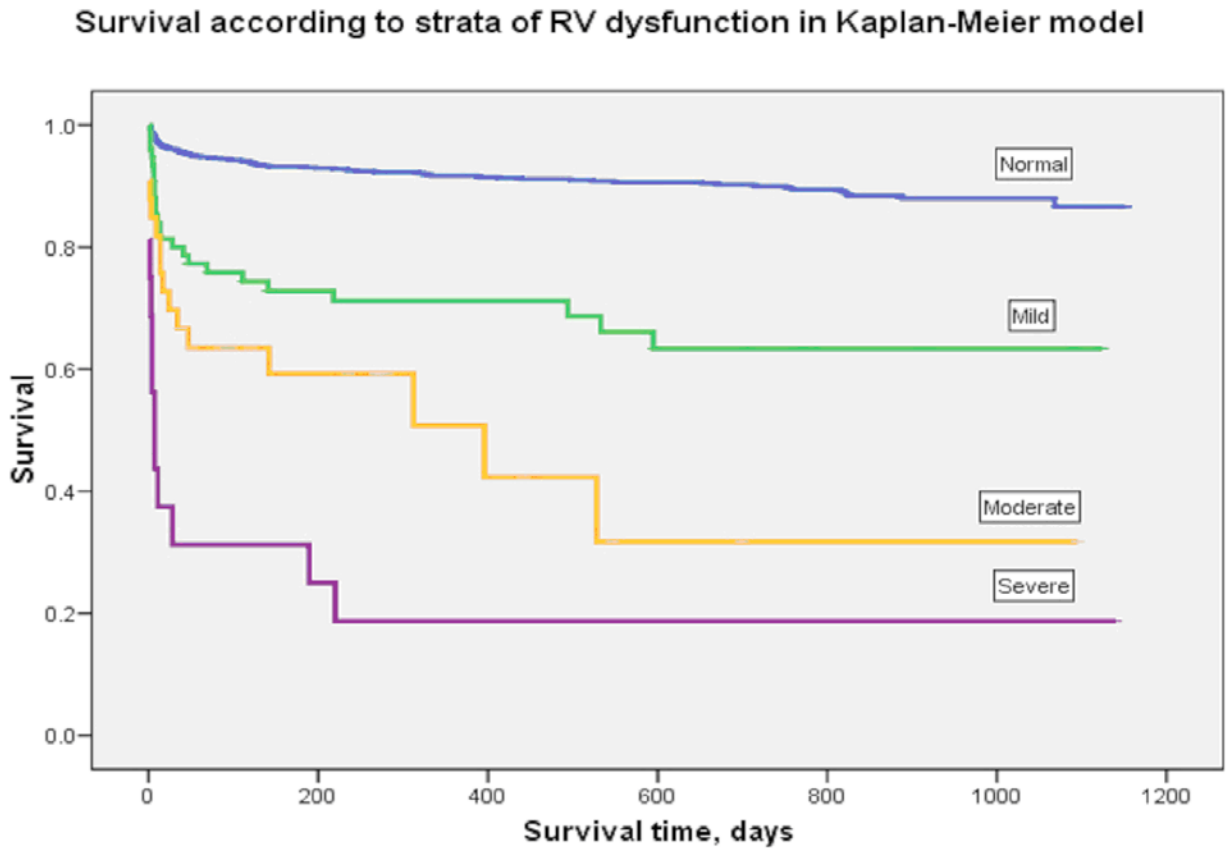
Aim: To assess the impact of right ventricular (RV) dysfunction on long-term mortality in patients with acute myocardial infarction.

Methods: We prospectively studied 1217 consecutive patients with AMI and RV function assessed by echocardiography in the first 24 hours from admission. They were followed-up for a mean of 17 months.

Results: Mild RV dysfunction was detected in 6.2%, moderate in 2.7% and severe in 1.3% of the patients. The overall mortality was 32.0%, 45.2% and 81.3% respectively, and only 9.3% in the normal RV function group ($p<0.0001$). After adjusting for age, gender, Killip class, on-admission blood pressure, diabetes mellitus, inferior wall involvement, ST-elevation AMI, creatinine clearance and left ventricular systolic function, the odds ratio for mortality were 3.07 (95% confidence interval [CI], 1.25-7.53, $p<0.01$), 3.89 (95%CI, 1.22-12.34, $p<0.02$) and 21.66 (95%CI, 3.12-150.0, $p<0.002$) for mild, moderate and severe RV dysfunction respectively, as compared to normal RV function group.

Figure 1 depicts the Kaplan-Meier cumulative survival for each group.

Conclusion: There is a graded independent association between the severity of RV dysfunction after AMI and long-term mortality. Even a mild dysfunction is associated with an increase in risk of death.



Comparison of the Predictive Value of Four Different Risk Scores for Outcomes of Patients with ST-Elevation Acute Myocardial Infarction

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Background: Accurate risk stratification has an important role in the management of patients with acute coronary syndromes (ACS). Even among patients with ST-elevation acute myocardial infarction (STEMI) for whom early therapeutic options are well-defined, risk stratification has an impact on early and late therapeutic decision-making. We aimed to compare the prognostic value of four risk scores used to evaluate patients with STEMI.
Methods: We studied 855 consecutive patients with STEMI treated with primary percutaneous coronary intervention (PCI), who were included in our primary PCI registry between 01/2001-06/2006 (age = 60.5±13 years, 19% females, 28% diabetes, 48% anterior MI). Excluded were patients with cardiogenic shock. For each patient the TIMI, CADILLAC, GRACE and PAMI risk scores were calculated using clinical variables, and for the CADILLAC score also angiographic characteristics. Thirty day and one year outcomes, including death, MI, target vessel revascularization and major adverse cardiac events (MACE) – composed of the previous three components – were assessed. The predictive value of the four risk scores was evaluated by the area under the curve (AUC) or C-statistic method.
Results: Predictive accuracy of the four risk scores for the various clinical outcomes is presented in the Table.

Risk Score	**TIMI** AUC (P trend)	**CADILLAC** AUC (P trend)	**GRACE** AUC (P trend)	**PAMI** AUC (P trend)
30 day death	0.724 (<0.0001)	0.824 (<0.0001)	0.471 (0.5)	0.742 (<0.0001)
30 day MI	0.61 (0.05)	0.685 (0.001)	0.533 (0.5)	0.64 (0.005)
30 day MACE	0.635 (<0.0001)	0.714 (<0.0001)	0.544 (0.1)	0.65 (<0.0001)
1 year death	0.747 (<0.0001)	0.813 (<0.0001)	0.475 (0.5)	0.752 (<0.0001)

Conclusions: The CADILLAC, TIMI and PAMI risk scores all demonstrated a high predictive value for mortality in patients with STEMI undergoing primary PCI. The GRACE score, which was developed from a registry of patients with a wide spectrum of ACS, had a lower predictive value. Therefore, the CADILLAC, TIMI and PAMI scores can be used effectively to risk stratify patients with STEMI.

The Impact of Glycoprotein 2b/3a Antagonist Therapy on Early and Late Clinical Outcomes in AMI Patients Undergoing Primary PCI

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Background: Glycoprotein (GP) 2b/3a inhibitors have been shown to improve clinical outcome in ACS pts undergoing PCI. Data are scarce and controversial concerning the use of GP 2b/3a in AMI pts undergoing primary PCI.

Aims: To assess the outcome of AMI pts undergoing primary PCI and stenting with or without an adjunctive therapy of Eptifibatide [Epi] as a bolus plus infusion for 8-18 hrs.

Methods: We analyzed our clinical results among pts undergoing primary PCI within 12 hours of symptoms onset of AMI. Patients with cardiogenic shock were excluded

	Epi- therapy	Control	P value
No.	**705**	**232**	
Age (yr)	59±12	65±14	<0.001
Male (%)	85	72	<0.001
Anterior MI (%)	48	47	NS
DM (%)	21	33	0.002
HTN(%)	41	53	<0.001
Smoking (%)	49	34	<0.001
Dislipidemia (%)	45	44	NS
MV CAD (%)	56	56	NS
DES (%)	15	11	NS
No Reflow (%)	5	7	NS
EF (%)	42	44	NS
CADILLAC Score	3.9±3.4	5.1±4.0	<0.001
ACT (sec)	252±53	257±57	NS
One month adverse events			
Stent thrombosis (%)	1.8	2.2	NS
Death (%)	1.7	8.6	<0.001
Six months adverse events			
Death (%)	3.7	12	<0/001
Re-MI (%)	5.2	7.5	NS
TVR (%)	8.2	11.2	NS
CABG (%)	4.0	4.4	NS
Stent thrombosis (%)	2.8	3.1	NS

Using multivariate analysis, CADILLAC Score and adjunctive GP 2b/3a therapy emerged as independent correlates with adverse clinical outcome at one month (O.R. 1.4 (1.2-1.5); p<0/001; O.R. 0.3 (0.1-0.6); p=0.001, respectively) and 6 months (O.R 1.4 (1.3-1.5); p<0.001; O.R. 0.4 (0.2-0.9); p=0.02, respectively) in pts undergoing primary PCI for AMI.

Conclusion: Our analysis shows that adjunctive therapy of eptifibatide in AMI pts undergoing primary PCI might be associated with improved clinical outcomes