Impact of Old Age on Clinical and Angiographic Characteristics of Coronary Artery Spasm as assessed by Acetylcholine Provocation test

**Background:** Coronary artery spasm (CAS) is one of the important etiological factors for patients (pts) with chest pain but no coronary artery stenosis. Generally smoking and other factors were known the clinical risk factors for CAS. However, clinical aspects related to age on CAS have been seldom investigated and reported. We investigated whether there is any impact of old age on CAS and as compared with younger age by intracoronary acetylcholine (Ach) provocation test.

**Methods:** A total 2954 consecutive pts without significant coronary artery lesion who underwent Ach provocation test by injecting incremental doses of 20, 50, 100 ug into the left coronary artery between March 2004 and April 2009 were enrolled. Significant CAS was defined as focal or diffuse severe transient luminal narrowing (>70%) with/without chest pain or ST-T change on ECG. the Ach provocation test results and its associated parameters were compared between the younger pt group (<50 years old, n=1044 pts, mean age: 41.15 ± 7.4 years) and older pt group (≥50 years old, n=1910 pts, mean age: 62.06 ± 7.44).

**Results:** Baseline clinical characteristics were similar between the two groups except that more male (58.3% vs. 42.0%, p<0.001) and smoker (38.9% vs. 24.3%, p<0.001) in younger patients group whereas more diabetes mellitus (16.3% vs. 6.0%, p<0.001), dyslipidemia (21.3% vs. 13.3%, p<0.001) and hypertension (54.2% vs. 32.6%, p<0.001) in older patients group. The rate of positive Ach provocation test was higher in the older pts group. Further, older pts group showed higher incidence of diffuse and multi-vessel spasm (Table).

**Conclusion:** In our study, we found that old age predisposes towards a higher chances of significant CAS, diffuse and multivessel spasm as assessed with the intracoronary Ach provocation test. Special care should be emphasized in older age pts present with wave of depolarisation at left lower edge.

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**TCT-438**

Atorvastatin, Administered at the Onset of Reperfusion, Protects Human Myocardium Against Lethal Reperfusion Injury by Activation of the RISK pathway

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**Background:** HMG Co-A reductase inhibitor (statin) therapy has been shown to reduce peri-procedural event rates and myocardial injury in patients undergoing percutaneous coronary intervention and cardiac surgery. In experimental animal models, treatment with statins reduces myocardial infarct size by up-regulating enzymes of the Reperfusion Injury Salvage Kinase (RISK) pathway. Whether this opportunity for pharmacological cardioprotection exists in humans is unknown.

**Methods:** Right atrial appendages were harvested from consenting adult patients undergoing elective cardiac surgery. From these, individual atrial trabeculae were explanted. Trabeculae were then suspended in an organ bath and subjected to 90 minutes hypoxia followed by 120 minutes reoxygenation in order to simulate ischaemia-reperfusion injury (IRI). At the end of the protocol, recovery of contractile function was determined and compared to baseline. Trabeculae were randomised into the following groups: Control (N=14); Hypoxic preconditioning (positive control) (N=4); ATV (25μM) at reoxygenation (N=9); ATV & UO (10μM), an Erk1/2 inhibitor (N=5); ATV & LY (15μM), a PI3-K inhibitor (N=5); ATV & L-NAME (10μM), a non-specific NOS inhibitor (N=7); ATV & 1400W (5μM), a specific inducible NOS inhibitor (N=5); Inhibitors and vehicle agents alone had no effect on recovery (N=18).

**Results:** Trabeculae in the control group recovered 37.5±1.6% of baseline contractile function following simulated IRI. Treatment with ATV at reperfusion significantly improved recovery (61.1±3.8%, p<0.001). This effect was abolished by LY(29.88±3.8%), U0126(34.35±4.0%), L-NAME(34.35±4.0%) and 1400W(38.57±5.0%).

**Conclusion:** Atorvastatin, administered at reoxygenation, protects human atrial myocardium from simulated ischaemia-reperfusion injury via activation of PI3-K, Erk 1/2 and NOS, components of the RISK pathway.

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**TCT-439**

Peri-ventricular Delivery of a Nanoparticle Albumin-Bound (nab) Ramapycin Solution Reduces Luminal Stenosis in a Porcine Femoral Artery Balloon Injury Model

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**Background:** Rapamycin-based drug delivery platforms in peripheral arteries have proven to be safe and feasible but not effective in reducing intimal hyperplasia (IH). We sought to determine whether peri-ventricular delivery of ramapycin would be effective in reducing luminal stenosis in a porcine balloon injury model.

**Methods:** Femoral artery injury sites were created with a pressure-controlled endothelial denudation. Two weeks later, a 20-30% overstretch of the injury sites was performed as a functional mPTP opening was induced after 188 ±22.7 seconds of oxidative stress, providing evidence for a functional mPTP in HCM. Furthermore, pre-treatment with the known mPTP inhibitor, CsA, and atorvastatin, delayed the onset of mPTP opening by 51±10% (P<0.001) and 35±7% (P<0.05), respectively.
performed. Under fluoroscopy, nab-rapamycin (Abraxis Bioscience) (5 or 500 μg) or vehicle was delivered to the adventitia using a micro-infusion catheter (Mercator MedSystems). After 28 days, the arteries were harvested. The primary outcome was histomorphometric evidence of luminal stenosis and remodeling. Vehicle injury was scored on a validated ordinal scale.

Results: There was 100% procedural success in 16 injury sites treated with adventitial injections. Nab-rapamycin treated vessels had significantly larger GNT (p<0.01, ANOVA) and total vessel areas (p<0.005) indicating less negative remodeling. Percent luminal stenosis and maximal intimal width decreased in a dose-dependent fashion. Control vessels had significantly more fibrosis (p<0.001).

Mean values for measured and calculated metrics for 16 injured femoral segments treated with an injective vehicle or nab-rapamycin:

<table>
<thead>
<tr>
<th>Metric</th>
<th>Group</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumens (mm²)</td>
<td>Control</td>
<td>3.32 ± 5.88</td>
</tr>
<tr>
<td></td>
<td>Nab-rapamycin</td>
<td>3.81 ± 3.45</td>
</tr>
<tr>
<td>Minimal intimal width</td>
<td>Control</td>
<td>0.25 ± 5.00</td>
</tr>
<tr>
<td></td>
<td>Nab-rapamycin</td>
<td>0.00 ± 1.28</td>
</tr>
<tr>
<td>Maximal intimal width</td>
<td>Control</td>
<td>0.13 ± 5.01</td>
</tr>
<tr>
<td></td>
<td>Nab-rapamycin</td>
<td>0.11 ± 0.13</td>
</tr>
<tr>
<td>Percent stenosis</td>
<td>Control</td>
<td>19.9 ± 1.7</td>
</tr>
<tr>
<td></td>
<td>Nab-rapamycin</td>
<td>11.45 ± 0.45</td>
</tr>
<tr>
<td>Infarct area</td>
<td>Control</td>
<td>1.78 ± 0.48</td>
</tr>
<tr>
<td></td>
<td>Nab-rapamycin</td>
<td>1.68 ± 1.08</td>
</tr>
</tbody>
</table>

*p-values based on ANOVA

Conclusion: These data suggest that adventitial delivery of rapamycin decreases luminal stenosis by inhibiting IH and preventing negative remodeling. The decreased fibrosis in treated vessels suggests a mechanism by which rapamycin may affect vessel remodeling following injury.

TCT-440

Allogeneic Mesenchymal Precursor Cells Reduce Infarct Size and Preserve Cardiac Function Following Intracoronary Infusion in a Sheep Model of Acute Myocardial Infarction

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Background: Mesenchymal precursor cells (MPC) are cells that exhibit therapeutic actions in pre-clinical models of acute myocardial infarction (AMI). They are immune privileged and can be given in an allogeneic setting. The aim of the current large animal study was to assess the effect of intracoronary delivery of allogeneic MPC directly following an AMI. Methods: The 30 sheep that survived the anterior AMI were blindly randomized to the control group (n=12), in which 5 ml placebo (0,9% NaCl) was adiministred in the left anterior descending artery for 60 minutes. In all animals bivalirudin was administered intravenously. Minutes prior to reperfusion animals were randomized into the study group (n=11) in which 0,4 mg/kg dextran i.v. and reperfusion injury (RI) was undetermined.

Methods: In 23 landrace pigs STEMI was induced by the occlusion of the wire (OTW) balloon catheter in the medial left anterior descending artery for 60 minutes. In all animals bivalirudin was administrated intravenously. Minutes prior to reperfusion animals were randomized into the study group (n=11) in which 0,4 mg/kg dextran i.v. and reperfusion injury (RI) was undetermined.

Results: In the control group, global LVEF deteriorated to 36.6±2.0%, whereas it was enhanced in treated sheep to 45.4±1.4% (p=0.009). Also regional function improved, as fractional area change (FAC) in the apex increased by 39% in MPC-treated animals compared to controls (p=0.027), and FAC in the mid-ventricle increased by 30% (p=0.007). Local systolic wall thickening in the affected antero-septal wall improved from 9.6±5.5% in controls to 14.1±1.8% in treated animals (p=0.001) and in the anterior wall from 13.8±3.6% to 34.7±1.9% (p<0.001). Morphometric analysis revealed that MPC treatment resulted in a 40% reduction in infarct size from 18.2±1.7% in control animals to only 10.9±1.6% in treated sheep (p=0.001). Also, infarct (p=0.001) and border zone (p=0.011) thickness were enhanced in the treatment group. Histological analysis showed an increase in blood vessel density of >50% in the infarct (p<0.001), remote (p=0.007) and border (p=0.001) areas evoked by MPC therapy. In addition, cardiomyocyte size was smaller in border (p=0.001) and remote (p=0.002) areas, accompanied by reduced collagen contents, suggestive of decreased remodeling.

Conclusion: Intracoronary delivery of allogeneic MPC directly after the AMI resulted in preserved global and regional cardiac function, evoked by reduced infarct size, increased perfusion and reduced remodeling.

TCT-443

Systemic and Local Tissue Pharmacokinetics of Single and Overlapping NEVOSTM Sirolimus-Eluting Stents in the Porcine Coronary Artery Model

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Background: Preclinical safety and pharmacokinetics of the NEVOSTM stent, a novel sirolimus-eluting stent (SES) that uses bioreosorbable PGA and reservoirs (RES TECHNOLOGY®, Cordis Corporation, NJ), have been evaluated on single stent implants. As patients often receive multiple single or overlapping (OL) stents, we examined the influence of overlap and sirolimus dose on the systemic and local tissue pharmacokinetics of NEVOSTM stents.

Methods: Single or OL NEVOSTM stents, and OL double dose (2x) NEVOSTM stents (2.5x12 mm) were implanted in non-diseased porcine coronary arteries (n=6–

9/cohort/time point; 100% OL) for 1, 3, 8, 14, 30, or 60 days. Harvested stents, arteries, myocardium, lung, liver, kidney, and blood (4 hours, 1, 3, 5, 8, 14, 30, and 60 days post-implant) were analyzed for sirolimus content. Abnormal tissues were evaluated for histopathology.

Results: There were no early deaths or adverse clinical effects from OL 2xNEVOSTM experiment with 3 treated and 3 control subjects sacrificed at 28 days. The primary efficacy endpoint for both experiments was kidney NE tissue content. Secondary outcomes were plasma and tissue GNT levels, histological evidence of renal denervation and renal artery injury. Results: The 24 treated and 6 control renal arteries had 100% procedural success in the delivery of GNT or vehicle. Histology showed optimal healing in injected renal arteries and no deleterious endocardial or intimal fibrosis. There was no evidence of non-stenosing neointima and no or minimal medial fibrosis, with no difference between treated and control arteries (p=NS). There was a time-dependent decrease in renal NE content, dropping 20%/16% (p<0.024) at 28 days, each compared to vehicle controls at 28 days. Denervation was evident from NE drops and from histology, with reduced fiber density and endo- and peri-neurial fibrosis in GNT-injected arteries, but no neuronal changes evident in vehicle controls. PK analysis revealed GNT retention of 54 ng/g around the renal arteries at 28 days. By contrast, GNT plasma concentrations were below adrenergic blocking levels at 24 hours post-injection. Conclusion: GNT, delivered to the renal peri-adventitia resulted in a time-dependent reduction in kidney NE content and specific immune-mediated destruction of renal artery perivascular nerve tissue. Peri-adventitial drug delivery appears to be a safe and efficient mode to maximize tissue concentration while minimizing plasma spillover.