Results of Drug Eluting Stents in Diabetic Versus Non-Diabetic Patients for Diffuse In-Stent Restenosis

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Background: Drug-eluting stents (DESs) are often used for the treatment of in-stent restenosis (ISR). The clinical outcome following implantation of DES for the treatment of diffuse ISR is less well defined among patients with Diabetes mellitus (DM).

Objective*:* We sought to compare the clinical outcomes using DES treatment for ISR in DM versus non DM patients.

Methods: we studied 110 patients who were treated for diffuse ISR [Mehran class >1] using DES. We identified 52 DM patients with ISR receiving DES, and compared them to 58 non DM pts treated for ISR with DES. We compared the procedural and angiographic results and clinical outcome at 6-months.

Results*:* Clinical characteristic, long-term outcome are summarized:

	No DM (N=58)	**DM (N=52)**	**P-value**
Age (years)	63±12	66±10	0.2
Males (%)	81	58	*0.007*
GFR (<60 mL/min/1.73 m^2) (%)	14%	12%	0.7
Chronic total occlusion (%)	16%	19%	0.6
Small vessel size (<2.5mm)	2.6±0.6	2.6±0.7	0.9
Mean stents length	27±7	27±7	0.99
6 months outcome			
Death (%)	3.5	1.9	0.6
Re-AMI	0	5.8	0.06
Stent thrombosis	0	7.8	*0.03*
Target vessel revascularization (%)	3.5	17.3	*0.02*
CABG	1.7	1.9	0.9
MACE$^+$	6.9	22	*0.03*

$^+$MACE= Death, re-AMI, TVR

Conclusions*:* DES implantation for diffuse ISR is associated with increase risk for stent thrombosis, re-infarction and/or need for repeat revascularization in diabetic patients compared to non-diabetic counterparts. Thus, diffuse ISR may be associated with more 'malignant' clinical course in diabetic patients.

Perfect Stent Positioning in Bifurcations: To Kiss or not to Kiss

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Background: Kissing balloons (KB) are considered essential to prevent stent distortion when treating side branches even with provisional bifurcation stenting. Current stent deployment techniques disregard the precise deployment position of the stent and its cells in relation to the sidebranch (SB) ostium. We postulated that stent deployment with precise orientation (both longitudinally and radially) followed by SB inflation would result in a patent SB in the absence of stent distortion.

Methods: Five bifurcations were treated in 3 juvenile pigs. Using a novel fixed wire based bifurcation system, stents were advanced to the bifurcation. Based on the marker system the rotational and longitudinal orientation and positioning of the stent was confirmed with relation to the main vessel and SB. The stents were deployed and in three cases the SB was dilated with balloons on the initial side branch wire. OCT was performed in two cases.

Under fluoroscopic control in a human cath lab stents were deployed silicone phantoms with a bifurcation set at 60 degrees. The stents was advanced in the main branch (MB) and deployed with the SB access cell in the proximal or distal portion of the ostium, with perfect rotational alignment. The SB was initially inflated and then followed by kissing balloon procedure, or kissing balloon (KB) was performed immediately. Phantoms were imaged with microCT and 3D reconstructions were performed at each stage of the study.

Results: In all cases the stents could be oriented as predetermined. Angiographic results were excellent with no stenoses of side branches. OCT demonstrated an unimpeded SB ostium with no stent distortion. In the phantoms, when the stent was deployed without SB post dilation stent achitecture was undistorted wih excellent patency to the SB. With proximal positioning of the SB access cell, SB inflation resulted in reflection of stents struts back into the lumen. This was only partially corrected by KB. In the same position KB immediately post stent rendered a perfect result. However with distal positioning of the SB access cell, SB inflation alone provided a perfect result. When pefect radial aligment was used therewas no stent distortion on the wall opposing the SB. Ex vivo CT analysis of the stented pig coronary confirmed these findings.

Conclusion: Using current stent techniques KB must be the next step following MB stenting. When perfect stent positioning is used the SB can be dilated with no MB stent distortion.

Impact of Final Minimal Luminal Diameter of the Stent on Long-term Results Following Sirolimus-eluting Stent Implantation for Diffuse in-stent Restenosis

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OBJECTIVES: We assessed the predictive value of minimal luminal diameter (MLD) for long-term patency of sirolimus-eluting stents (SES) implantation for diffuse in-stent restenosis .

BACKGROUND: By IVUS studies minimum stent area is a consistent predictor of in-stent restenosis. The value of angiographic MLD as a predictive value for SES failure still limited.

METHODS: From the RMC-ISR database, 110 patients were treated for diffuse ISR [Mehran class>1] using SES {Cypher}. Baseline angiography including pre- and post stenting QCA measurement were analyzed. Post-procedure MLD [<2.5mm] were correlated with 12 months target lesion revascularization [TLR].

RESULTS: Mean age 64±11 years with 70% male, 47% with DM and 16% with recurrent ISR. At baseline, 83% of the lesions were diffuse and proliferative and 16% total occlusions. The SES implantation was successful in all patients except one. Anti GP 2b/3a was used 45% of patients. The mean balloon pressure for stent deployment was 19±4 atmosphere. The mean stents length was 27±7mm. At 12-month follow-up, the total MACE rate was 12.7% (death 4.5%, MI .2.7%, CABG 3.6%, stent thrombosis 0.9%, TVR 12%, TLR 12%). Final MLD<2.5mm was positively correlated to 12 months TLR.

In a multivariate analysis adjustment to DM, time to restenosis, MLD<2.5mm [OR=4.2, 95% CI=1.1-16, P=0.03] was significant independent predictors of 12 months TLR. DM was borderline **[**[OR=3.12, 95% CI=0.8-12, P=0.08

CONCLUSIONS: In this study, reduced restenosis in the malignant type if in stent restenosis. MLD<2.5mm is a significant angiographic predictor of 12 months TVR

Do Drug Eluting Stents Improve Outcome in Patients Undergoing Primary PCI for ST Elevation Myocardial Infarction?

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Background: The role of drug eluting stents in primary PCI (PPCI) performed for ST elevation myocardial infarction (STEMI) is controversial. While a randomized trial suggested benefit, registry data suggest these stents may be associated with increased late mortality.
Aim: To investigate the clinical outcome of patients with STEMI treated with BMS or DES during PPCI.
Methods: We performed an observational study of 327 consecutive patients affiliated with Clalit Health Services who had PPCI for STEMI between 4/04 and 10/06. We compared patients who received DES (N=60 ,age: 60±13 years) to those who received BMS (N= 209, age:62±13 years). Patient data was obtained from computerized databases. Clinical, angiographic and angioplastic characteristics and one year clinical outcome were compared between the two groups.
Results: STEMI pts with DES more frequently had diabetes mellitus (38% vs, 24%, $p<0.04$) and moderate to severe left ventricular dysfunction (73% vs. 53%, $p=0.03$). The culprit lesion was more frequent in the LAD (65% vs 44%, $p<0.001$) and more often calcified (20% vs. 11%, $p=0.05$).Vessel diameter was smaller (3±0.4 vs.3.2 ±0.4 mm, $p=0.04$) and the stents longer (24±11 vs. 22±9 mm, $p=0.05$) when DES were implanted. Direct stenting was less frequent used with DES (22% vs. 43%, $p<0.01$). Immediate success was similar with both types of stents (99% vs. 100%). After one year follow up no differences were observed between patients given BMS or DES in all cause mortality (13% vs. 12%), myocardial infarction (2% vs 3%); surgical or angioplasty revascularization (15% vs. 8%) and a combined end points of those outcomes (29% vs. 20%, p=.NS) respectively .
Conclusion: In current clinical practice DES in the setting of STEMI is more frequently used in patients with diabetes and LV dysfunction and in LAD lesions. No clinical advantage of DES was found in this study.

Percutaneous Coronary Intervention for Chronic Total Occlusions: the Rabin Medical Center experience

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BACKGROUND: Percutaneous treatment of coronary chronic total occlusions (CTO) remains one of the major challenges in interventional cardiology. Bare metal stenting is limited by high rates of restenosis. Drug-eluting stents (DES) markedly reduce the risk of restenosis of relatively simple or complex nonocclusive lesions.

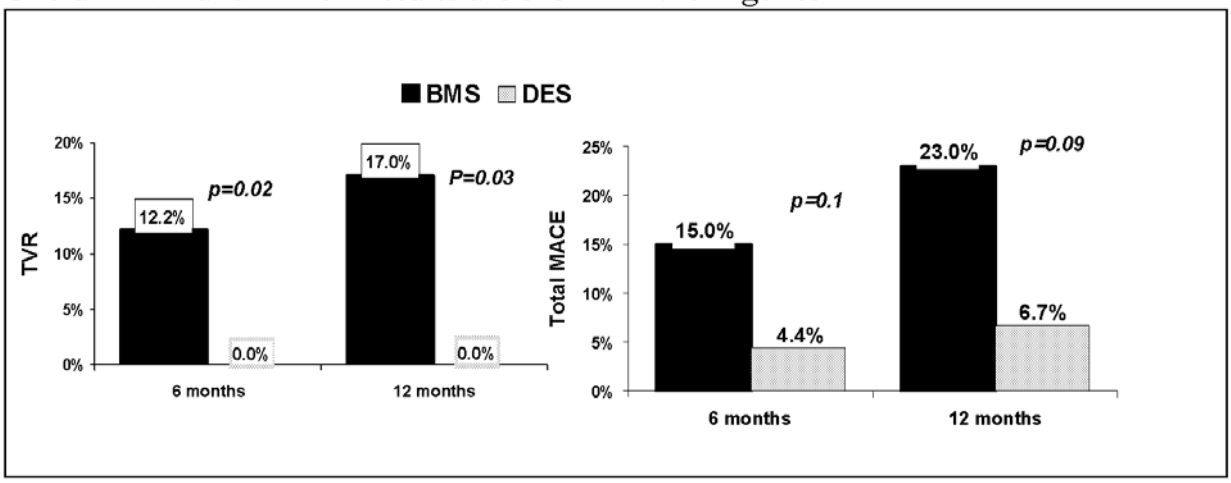
OBJECTIVE: This study sought to determine the clinical and angiographic outcomes after drug-eluting stent (DES)-supported PCI for CTO. .

METHODS: This study comprises 86 CTO lesions which were successfully treated with DES implantation [67% Cypher, 11% Taxus, 22% Endeavor stents)]. The control group consisted of 41 patients implanted with BMS only (n=26) or BMS and DES (n=15).

RESULTS:

	BMS [n=41]	DES [n=45]	P-value
Age [year]	62±12	63±12	.7
Male	90%	87%	0.5
LAD/DIAG	20%	33%	0.3
DM	34%	42%	0.4
CTO duration [m]	14±33	13±32	0.99

Overall TVR and MACE results are shown in the **Figures**



CONCLUSIONS: DES implantation for CTO is safe. Most events which are related to the need for repeat reintervention are decreased by the introduction of DES.

Aspiration During Every Stage of Primary PCI: "ADMIT"-Trial: Mid-Term Results

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Background: Distal embolic phenomena may appear during each stage of thrombus containing lesion intervention.

Aim: Assessing the role of active aspiration during each stage of primary PCI (PPCI) compared to the standard technique in a randomized prospective trial.

Material & Methods: So far, sixty nine patients eligible for PPCI were included. We excluded patients in cardiogenic shock. Demographic, clinical, angiographic, echocardiographic characteristics, ECG data and biomarkers in each group were collected. Clinical and echocardiographic records at 30 and 180 days follow – up are being investigated.

Results: The fallowing table presents the patients parameters in both groups:

*Parameter determined at the end of the procedure. N- Number of pts

Variable	Aspiration in every stage N= 34 (49.3%)	Standard –PPCI N=35(50.7%)	p-value
Age (years)	57.32±12.6	58.8±11.62	NS
Male n. (%)	30(88.2%)	27(77.1%)	NS
≥3 major risk factors	21(61.8%)	28(80.0%)	0.095
Killip FC (≥2) at admission	7(20.6%)	4(11.4%)	NS
Anterior wall infarct	18 (52.9%)	22 (64.7%)	NS
Inferior wall infarct	16 (47.1%)	12 (35.3%)	NS
*TIMI flow 3. N (%)	28(82.4%)	29(82.9%)	NS
*Mean TFC	25.23±12.2	30.4±15.8	NS
*Mean MBG 3. N (%)	22(64.7%)	15(42.9%)	0.069
Mean Peak CK	3012.7±2730	2143.9±2051	NS

Five MACE, defined as death, re- infarction and TVR had occurred during hospitalization period and 30 days follow- up. There was no significant difference between the arms.

Conclusion: This preliminary mid- term report show that performing repeated aspiration during every step of PPCI intervention neither improves nor damaging. Further data needs to be investigated as we are yet recruiting.

ADAM-15 Metaloproteinase Domain Derived Peptide as the Natural Ligand to GRP78 Receptor on Endothelial Cells for Therapeutic Angiogenesis

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ADAM15 is a membrane-anchored glycoprotein that contains a disintegrin and metalloprotease domains. The elevated levels of ADAM15 in endothelial cells prompted an evaluation of its role in neovascularization. Mice lacking the ADAM15 gene exhibit a strongly reduced angiogenic response compared to wild-type controls. It was found that neither VEGF nor bFGF induce changes in ADAM15 expression in human vascular endothelial cells.

The aim of the present study was to identify peptides derived from ADAM15 with angiogenic activity. **Results:** Three 12 aminoacid peptides were synthesized from the ADAM15 metalloprotease domain and termed ADoPep 1, 2 and 3. We studied binding, proliferation, migration and tube formation of endothelial cells under hypoxia with these peptides and found that ADoPep1 exhibited the strongest angiogenic activity invitro. In a mouse hind limb ischemia model, ADoPep1 at 0.1 microgram per mouse injected intramuscularly to the ischemic leg restored blood perfusion, as detected by laser Doppler imager. Histological examinations of the treated leg showed increase in capillary density, suggesting neovascularization. The Adam 15 derived peptides were found to bind glucose regulated protein GRP78 receptor on endothelial cells that increased after incubation with ADOPep1 under hypoxia conditions. The mean number of GRP78 positive cells was also significantly increased in ischemic limb histological sections 14 days post ADopep1 treatment. The role of ADoPep in prevention of apoptosis was studied using endothelial cell subjected to hypoxia or $CoCl_2$ induced apoptosis. ADoPep1 prevented only hypoxia induced apoptosis demonstrating that the inhibition of apoptosis by ADOPep1 is specific to the hypoxia stress conditions.

Conclusions: This study contributes to the search for new molecules for development of therapeutic angiogenesis in ischemic diseases.

Endothelial Nitric Oxide Synthase and Superoxide Dismutase are Crucial to Endothelial Progenitor Cells Function in Diabetes

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Background – Endothelial progenitor cells (EPCs), key regulators of vascular repair are impaired in diabetes. We postulate a tight crosstalk between endothelial nitric oxide synthase (eNOS) and superoxide dismutase (SOD) in regulating EPC levels and function in diabetes.

Methods – EPCs from diabetic patients and healthy subjects were compared ex vivo for their number and function. In another experiment healthy EPCs cultured under high glucose concentrations were either treated by insulin or SOD in vitro. Superoxide and NO production as well as SOD activity were assessed.

Results – EPC levels and function in diabetic patients were significantly reduced compared to those of healthy subjects ($P<0.05$). EPCs from diabetic patients produced excessive superoxide anions, lower NO levels but higher SOD activity compared to non-diabetic control subjects ($P<0.05$). NO produced from EPCs derived from diabetic patients correlated negatively with $HbA1_C$ and glucose levels ($r = -0.57$; $P = 0.003$ and $r = -0.49$; $P = 0.01$, respectively). NOS inhibition with N^G-nitro-L-arginine methyl ester (L-NAME) as well as SOD treatment attenuated superoxide generation and normalized functional capacity of EPCs treated with high glucose. Insulin treatment failed to suppress superoxide production but has restored NO bioavailability and improved EPC proliferation.

Conclusions – SOD seems to be essential for EPC regulation and may play an important role in modulating EPC function in diabetic patients.

In Vivo HIF-1 Alpha Expression in Experimental Murine Atherosclerosis

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Background **-** Hypoxia inducible factor-1 (HIF-1) regulates T cells activation, cytokine production and proliferation by inducing a shift towards T_H2-cell responses and inhibition of T_H1-cell pro-inflammatory response. T cells stimulation and cytokine secretion play a central role in the progression of atherosclerosis. We explored the effect of over-expression of HIF-1α in ApoE knockout mice lymphocytes, as a tool to regulate inflammation and atherosclerotic process.

Methods and Results –Intravenous hydrodynamic plasmid injection of empty pCDNA3 or pCDNA3-HIF-1αP564A (HIF-1α mutated stabilized construct) were performed to atherosclerosis prone Apolipoprotein E knockout mice. After 24 hours, HIF-1α over-expression in splenocytes (n=3) was validated by RT-PCR and ELISA. One week post-injection, spleens and aortas (n=3) were analyzed for expression of IL-10, INF-γ and TGF-β by RT-PCR. In addition, the cytokine profile of splenocytes was studied employing an inflammatory cytokine array. Increased expressions of IL-10 and TGF-β in splenocytes as well as a decreased expression of INF-γ in aortas were measured in HIF-1α-treated mice, compared to controls. Cytokine arrays revealed a shift of the T_H1 inflammatory response toward T_H2 cytokine expression. At day 30, systemic injection (n=8) was repeated. At day 60, animals were scarified and aortas were isolated for plaque progression assessment. Aortic sinus lesion size was significantly decreased in mice treated with pCDNA3-HIF-1αP564A and were characterized with reduced lipid cores as well as larger fibrous caps, compared with controls.

Conclusions – Over-expression of HIF-1α in mouse splenocytes is associated with attenuation of inflammatory response and attenuated plaque progression in experimental atherosclerosis.

Vitamin E Provides Renal Protection to Diabetic Mice Genetically Modified at the Haptoglobin Locus

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Background: The haptoglobin (Hp) gene is polymorphic with two classes of alleles denoted 1 and 2. Individuals with diabetes mellitus (DM) homozygous for the Hp 1 allele (Hp 1-1) are at decreased risk of developing diabetic complications, including nephropathy, as compared to individuals homozygous for the Hp 2 allele (Hp 2-2). Retrospective data from antioxidant studies suggests that vitamin E therapy provides benefit to Hp 2-2 individuals. We sought to recapitulate this pharmacogenomic effect in mice transgenic for the Hp 2 gene.

Methods: DM was induced in Hp 1-1 and Hp 2-2 mice with streptozotocin. After 3 months functional, morphometric and histochemical differences between the kidneys of Hp 1-1 and Hp 2-2 mice were assessed by measurement of creatinine clearance (CCT), albuminuria, glomerular area, glomerular collagen and iron. DM mice were treated for 10 weeks with Vitamin E at a dose of 40mg/kd/day.

Results: In the absence of DM we found no difference in any functional, morphometric or histochemical parameter between Hp 1-1 and Hp 2-2 mice. Moreover, no differences were found between Hp 1-1 mice with or without DM. However, there was a significant increase in CCT, albuminuria, glomerular area, glomerular collagen and iron in Hp 2-2 mice with DM. Vitamin E treatment prevented the functional, morphometric and histochemical changes seen in Hp 2-2 DM mice.

Conclusions: Vitamin E appears to provide protection against the development of nephropathy in Hp 2-2 DM mice.

Single Center Experience with Trans-Radial Approach for Primary PCI

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Background: More than 90% of the procedures in our Cath Lab are done as trans-radial approach. Lately we have extended this technique to primary PCI (PCI/TRA).
Methods: Since January 2007 we adopted the radial approach for all new patients with STEMI referred to primary PCI. Patients with weak radial pulse, severe dysrhythmias, CHF or hypotension were excluded. We used published world data for time table reference (NRMI, DANAMI) .
Results: 25 STEMI patients underwent primary PCI/TRA as a routine procedure (right radial all). IRA were: LAD: 11, LCX: 2, RCA: 12. Full patency restoration of the IRA was achieved in 100% of the patients. In 3 cases we used thrombus aspiration devices, in 5 patients a bifurcation PCI with kissing balloon was performed successfully. Six patients had slow reflow phenomenon resolved after IC Adenosine injection. In two cases IABP was inserted trough the femoral artery due to low blood pressure and slow reflow. There was no major bleeding, pseudo-aneurysm or fistula. In one case (treated by Integrilin Heparin and Plavix) there was a large hematoma in groin (IABP insertion site) and small one in the forearm. There were 3 more cases with minor hematoma in the forearm.
Time table:

	World data	Our experience in PCI/TRA
Symptom onset to Balloon	Median 218 min	90-840 (median 267) min
Hospital door to Balloon	83-120 (median 116) min	45-180 (median 72) min
Cath Lab door to Balloon	20-53 min	20-35 (median 27) min

Conclusions: Following a meticulous learning curve, the trans-radial approach can be applied for primary PCI with high success rate, short door to balloon interval, and low complication rate. This approach improves patient's convenience and well being. The very low vascular complication rate increases the safety margin for this procedure that involves intense use of anti-coagulation/aggregation medications.