

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.

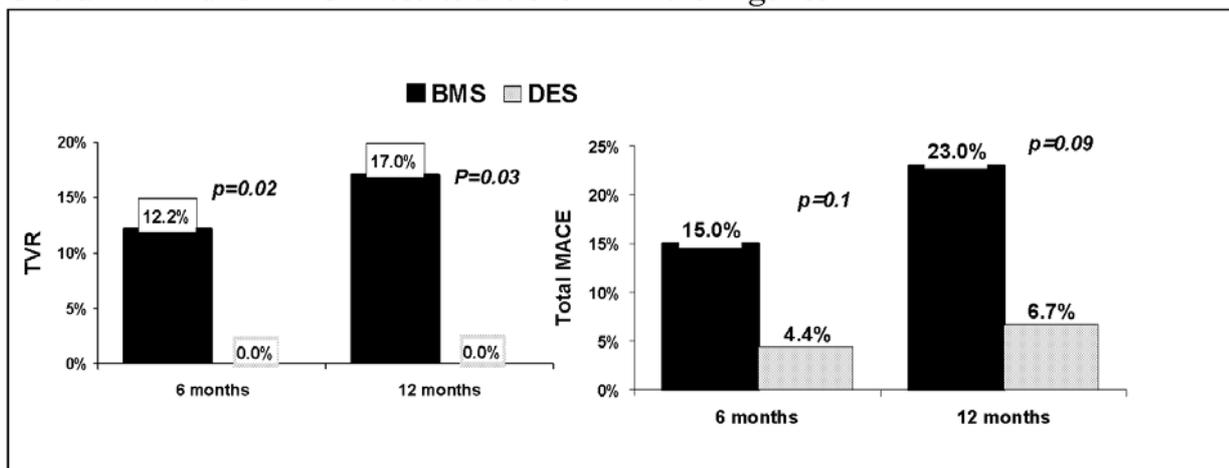
OBJECTIVE: This study sought to determine the clinical and angiographic outcomes after drug-eluting stent (DES)-supported PCI for CTO. .

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 following 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 Metalloproteinase 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 CoCl₂ 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 HbA_{1c} 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-1 α 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-1 α P564A (HIF-1 α mutated stabilized construct) were performed to atherosclerosis prone Apolipoprotein E knockout mice. After 24 hours, HIF-1 α 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-1 α -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-1 α P564A and were characterized with reduced lipid cores as well as larger fibrous caps, compared with controls.

Conclusions – Over-expression of HIF-1 α 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 through 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.

Long Term Results of Mitral Valve Repair Using Autologous Pericardium Annuloplasty

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Objectives: Use of autologous pericardium for annuloplasty during mitral valve is controversial. We therefore sought to evaluate our long-term results using this technique.

Methods: We retrospectively reviewed 173 consecutive patients aged 19 years to 92 years (59.6 ± 16.25 years) who underwent mitral valve repair complemented by annuloplasty between January 1998 and December 2003. Major causes of mitral regurgitation were annular dilatation and prolapse of the posterior leaflet. Annuloplasty was performed in all the patients using a strip of pericardium treated in glutaraldehyde 0.6% for 10 minutes. Two rows of continuous horizontal mattress Gore-Tex suture were used to secure the pericardium to the mitral annulus. Follow-up was performed in 100% of the patients, and the mean follow-up was 5.25 ± 1.62 years (range, 1.97 to 9.43 years).

Results: There were 3/173 (1.7%) 30 days deaths. Five (2.9%) patients with mitral regurgitation, with or without mitral stenosis underwent reoperation. Mean interval period between operation and reoperation was 3 ± 2.7 years. Actuarial survival rate was 92.5% at 7 years after operation. Freedom from reoperation was 97.1% at 7 years after the initial operation. Follow-up echocardiography was performed on in 160 of the 160 patients (100%). No mitral regurgitation was detected in 34 patients (21.2%), 88 (55%) had grade 1 mitral regurgitation, 35 (21.8%) had grade 2, 3 (1.8%) had grade 3 and none had grade 4.

Conclusions: Our results indicate that autologous pericardium mitral annuloplasty is an effective technique. It provides a durable, reproducible annuloplasty of the mitral valve and avoids the use of foreign materials.

Sternal Wound Infection and Mediastinitis – The End of the "Sternectomy and Muscle Flaps" Era

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BACKGROUND: Postoperative deep sternal wound infection carries a high mortality, a high morbidity, and a poor cure rate. The prevailing approach of sternectomy and pectoralis muscle or omental flaps coverage significantly disrupts the heart's natural chest wall protection and the patients' quality of life. Besides increased mortality and morbidity rates, nearly all patients find it cosmetically repulsive. We present our 5-year experience of a new conservative approach which was gradually developed to improve the outcome of these patients.

METHODS: From January 2003 to November 2007, 2.5% of our patients (n=112) were treated for sternal wound infection and mediastinitis following open heart surgery. We have gradually developed treatment protocol entailing: early hospitalization, drainage and debridement of the sternal wound using the vacuum assisted closing (VAC) system, IV antibiotics administration, macrophages injection into sternal wound margins, and home discharge with IV antibiotics and granulation promoting dressings.

RESULTS: Sternectomy rates dropped down from 43% (n=12) during 2003 to 5% (n=1) in 2007 ($P < 0.001$), macrophages administrations increased from 18% to 95% ($P < 0.001$), and the mortality of the patients with deep sternal infection and mediastinitis dropped down from 39% to 0% ($P < 0.001$).

CONCLUSION: Our newly developed standard conservative protocol for the treatment of deep sternal infections and mediastinitis is effective and highly recommended. It spares the sternum, cures the infection, and leaves the patient physically functional without the use of soft tissue flaps. This treatment was associated with a dramatic reduction in mortality and a significant improvement in patients' quality of life.