

TOPIC 01-4 – Coronary angioplasty

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0076

Impact of the type of stent on 1 year outcomes after PCI in 'real life'

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Aim: To compare clinical outcomes in consecutive patients treated by percutaneous coronary intervention (PCI) according to the type of stent used: 1) BMS vs. DES, 2) Sirolimus- (SES) vs. Paclitaxel- (PES) vs. Zotarolimus- (ZES) vs. Everolimus eluting stent (EES).

METHODS Among 2334 PCI performed over two years, consecutive patients treated successfully with only one kind of stent were included. Patients with MI, cardiogenic shock or out-of-hospital cardiac arrest were excluded.

We compare the occurrence of 1) TVF (CV death, Target vessel MI, TVR), 2) Target Lesion Revascularization (TLR) and 3) definite Stent Thrombosis (ST) at one year.

Results: Twelve hundred sixty patients fulfilled inclusion criteria, 615 (49%) had BMS, 645 (51%) DES. Among the DES group, 187 (29%) had SES, 171 (27%) PES, 206 (32%) ZES, 67 (10%) EES and 14 (2%) others.

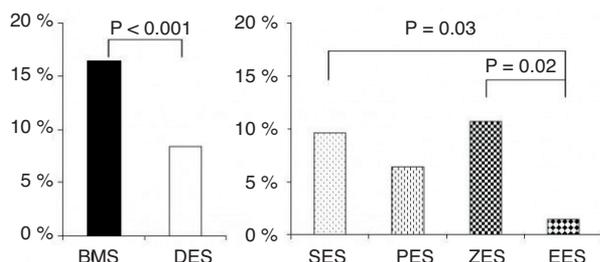
Patients in the BMS group were older, had more comorbidities, the mean stent length was lower and the average stent diameter higher, compared to DES.

Clinical and procedural characteristics were well matched between the different type of DES, except for a lower mean and total stent length in the PES group,

TVF according to the type of stent are shown in the figure. TLR was higher after BMS implantation (9.9% vs. 4.3%, $p=0.002$) without any difference between the different type of DES. The definite stent thrombosis rates were comparable whatever the stent used.

Independent predictors of TVF were BMS (OR 2.089; 95%CI 1.345-3.115, $p<0.001$), EES (OR 0.127; 95%CI 0.017-0.956, $p=0.045$) as hypertension, prior PCI and renal failure.

Conclusions: In 'real life', BMS appears to be independently correlated with an excess of TVF, partly explained by the higher risk feature of the population. All kind of DES are similarly associated with a lower TLR rate without any excess of stent thrombosis at one year. EES appears independently associated with the absence of TVF.



TVF rates according to the type of stent

0430

Percutaneous coronary intervention for refractory spasm: a monocentric retrospective study

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Between 5 and 30% of variant angina are refractory to a maximal vasodilator medication; however the prognosis could be strong. In case of focal spasm, stenting could be an alternative therapeutic. We decided to analyse this population who required a percutaneous coronary intervention (PCI), to determine whether it would be possible to identify factors in their clinical, angiographic characteristics.

Retrospectively, we included 173 patients between 2004 and 2010 in the hospital Cochin, who were diagnosed for a variant angina by a spasm provocative test: positive test was defined by the reduction of >50% of lumen arteries'. In a second time, we compared the patients who are well controlled by vasodilator drug (n=81) with the population who required a PCI because of a focal refractory spasm (n=18): persistence of a vasoreactivity during the challenge test under maximal medication. The population included majority men (62%), with a medium age of 55.6 +/- 11.7 years old. In our practice, most, 90% of the coronary angiography and challenge test were performed by radial access. The patients with focal refractory spasm had most frequently a non significant atheroma lesion. In this group, the patients were admitted in a more critical presentation: 12.5% cardiac arrest (vs 2.7%), 12.5% STEMI (vs 0%). The three coronary arteries were equally affected by spasm with a mean diameter of 3.8 +/- 0.65mm. The median time between the first challenge test and the PCI was around seven days. Drug eluting stents (DES) as bare metal stents (BMS) were equally implanted. None of the patient died during the follow-up (median 14.7 months, maximal 4 years). After PCI, 2 patients kept symptoms because of a intrastent restenosis, and 2 with a new positive challenge test (one on an other artery, one with medical treatment interruption).

To our knowledge, we report the most important serie of focal variant angina treated by PCI. There was no factor identified as predictive of the medication efficiency; a systematic control of reversibility of the challenge test under medical therapy have to be done. PCI for focal refractory spasm could be effective and safe.

0339

Accuracy of the Door-to-Balloon time for assessing the result of interventional reperfusion strategy in acute ST-segment elevation myocardial infarction

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Clinical guidelines recommend that primary percutaneous coronary intervention (PCI) should be performed within 90 minutes of hospital admission in patients with acute ST-segment elevation myocardial infarction (STEMI). The Door-to-Balloon time (D2B) is widely used to measure the performance of interventional centres.

The aim of this study is to evaluate the clinical accuracy of D2B in primary PCI.

From January 2007 to March 2008, 173 patients were admitted within 24 hours of a STEMI in our institution, and 87 were referred <12 hours for a direct coronary angiography (47 by mobile medical emergency unit, 40 by the emergency department of the institution).

The median time from the onset of pain to the first medical contact was 96 minutes (interquartile range [IQR] 41-220 minutes), and the time

from first medical contact to admission in the cathlab (Door) was 81 minutes (IQR 55-123 minutes). Median times of interventional coronary procedures were as follows:

Time	Door-Puncture	Puncture-Wire placement	Wire-Balloon	Door-to-Balloon (D2B)	Door-to-TIMI 3 flow
Number of patients	87	65	65	65	83
Median (IQR) in minutes	20 (15-25)	23 (16-28)	10 (5-17)	51 (44-66)	45 (30-57)

D2B was unavailable in 22 patients (25%), because of a spontaneous TIMI 3 flow reperfusion without indication for immediate PCI in 18 (20.8%), contra-indication for PCI in 3 (3.4%)(distal occlusion, culprit vessel diameter <2 mm), and failure in the guide wire crossing of the occlusion in 1 patient (1.1%). In contrast, Door-to-Reperfusion time, assessed by a TIMI 3 flow without no-reflow, was available in 83 patients (95%), and shorter than D2B.

Conclusion: Although it is a feasible and reproducible process performance measure, D2B time is weakly associated with the outcome of the interventional reperfusion strategy in acute STEMI. This performance measure should be associated with an outcome performance measure, such as the rate of TIMI 3 flow achieved by primary PCI, or the Door-to-TIMI 3 flow reperfusion time.

0289

Implication of the Notch pathway in the regulation of the Adenyl Cyclase (AC) 8 expression marking vascular smooth muscle cell (VSMC) trans-differentiation

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VSMC transdifferentiation, or their switch from a contractile/quiescent to a secretory/inflammatory/migratory state, is known to play an important role in pathological vascular remodelling including atherosclerosis and post-angioplasty restenosis. Several reports have established the Notch pathway as tightly regulating VSMC response to several stress factors through growth, migration, apoptosis and de-differentiation. More recently, we showed that alterations of Notch pathway also govern VSMC acquisition of the inflammatory state (Clement, 2007), one of the major events accelerating atherosclerosis. In 2006, we evidenced that the inflammatory context of atherosclerosis triggers a de novo expression of AC isoform 8, and showed, over the past several years, that there is a cause to effect relationship between this phenomenon and the properties developed by transdifferentiated VSMCs (Clement, 2006; Gueguen, 2010). The importance of AC8 de novo expression in atherosclerosis has been further highlighted by our preliminary data obtained in [AC8 x ApoE] double KO mice compared to [ApoE] KO mice indicating that AC8 deficiency compromises atherosclerosis development in pro-atherogenic [ApoE] animals. As an initial approach to understanding the regulation of AC8 expression, we examined the role of the Notch pathway. We show that the inhibition of Notch pathway (using a potent inhibitor of γ -secretase-complex, or a siRNA silencing Notch receptors or their target genes) enhances IL-1 β 's effect on AC8 expression; conversely, Notch activation achieved by coculturing IL1 β -treated VSMCs with murine cells expressing Notch ligand Jagged1 resulted in blocking AC8 transcript expression. In the balloon-injury rat carotid model of restenosis AC8's de novo expression coincided with the down-regulation of Notch3 pathway. The impact of reintroducing Notch3 (adenovirus strategy) on AC8 expression and neointimal formation occurring in this model is currently being explored.

0461

Prevailing effects of tissue cortisol compared to aldosterone in human atherosclerotic remodeling

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Our objective was to characterize the expression of corticoid system components and their main target genes in arterial wall as well as the regulation of this expression in VSMC with contractile or adipocyte-dedifferentiated phenotype.

The carotid endarterectomy samples of 42 patients were dissected in the atheroma plaque and the macroscopically intact tissue (MIT). Real time RT-PCR, western blotting and radioimmunoassay were used to assess the expression of genes of interest. The cortisol and fludrocortisone treatments of VSMC were carried out.

The GR α and 11 β HSD1 expression was several times higher than MR and 11 β HSD2 ones within the carotid wall, and this difference was more marked in the atheroma compared to MIT, resulting from a decrease in MR expression and an increase in 11 β HSD1 one in the atheroma. Cortisol increased the GR α and 11 β HSD1 mRNA levels in VSMC and diminished the MR one. Fludrocortisone only decreased the MR mRNA level. The MCP-1 and collagen I were up-regulated only by glucocorticoids. In presence of carbenoxolone, the responses of MCP-1 and collagen I to cortisol remained only GR α -dependant. After adipocyte dedifferentiation of VSMC the 11 β -HSD1 was increased while the MR and 11 β -HSD2 were markedly decreased. The collagen I mRNA was this time up-regulated in response to both cortisol and also fludrocortisone.

The glucocorticoid pathway expression and activity is higher than mineralocorticoid ones particularly in the atheroma plaque or in adipocyte-dedifferentiated VSMCs, likely due to the cortisol property to up-regulate its own production and action with simultaneous down-regulation of aldosterone ones. The prevailing glucocorticoid involvement is confirmed by cortisol-dependent up-regulation of the collagen I and MCP-1 mRNAs whereas fludrocortisone stimulates the collagen I expression only after adipocyte dedifferentiation of VSMCs. There is no «illicit» cortisol-dependent activation of MR-receptor.

0108

CB1 cannabinoid receptor antagonism inhibits balloon-induced neointima formation in atherosclerosis-prone mice

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Balloon-induced arterial injury stimulates vascular smooth muscle cell proliferation and inflammatory cell recruitment, which may result in restenosis of the diseased vessel. Increasing evidence suggests an increase of endocannabinoid levels in different pathological processes, leading to enhanced activation of their corresponding cannabinoid receptors, CB₁ and CB₂. The protective effects of CB₁ receptor antagonism in atherosclerotic mice and in vitro inhibition of vascular smooth muscle cell proliferation and migration point to a potential interest of CB₁ receptor blockade in restenosis. The objective of this study was to investigate the therapeutic benefit of the selective CB₁ receptor antagonist AM281 in balloon-induced neointima formation.

We performed left common carotid balloon distension injury in weight-matched (25-30g) male apolipoprotein E-deficient (ApoE^{-/-}) mice fed on high cholesterol (1.25%) diet for 8 weeks before the intervention. Littermates were randomly assigned to receive daily intraperitoneal injection of either the synthetic CB₁ antagonist AM281 (10 mg/kg) or vehicle control (n=6 per group), with the first injection given 30 minutes before balloon injury. After 7 days, we found significantly reduced numbers of medial nuclei (vehicle: 141.1±14.57; AM281: 86.44±19.35; p=0.0239) and intimal nuclei compared to vehicle treatment (vehicle: 44.94±5.933; AM281: 29.94±5.815; p=0.0506) in injured vessels of AM281-treated mice, indicating reduced medial smooth muscle cells proliferation. Immunohistochemical analysis revealed significantly reduced staining for CD68-positive macrophages (vehicle: 3836±1887; AM281: 987.3±486.1; p=0.0206) within dilated arteries of AM281-treated mice.

Our data indicate a critical role of CB₁ receptors in neointima formation in response to acute arterial injury. The putative effects of CB₁ receptor inhibition on endothelium regeneration after injury remain to be investigated.

0463

In vivo detection of non-occlusive thrombi in drug-eluting stents by scintigraphy and radio-labelled Annexin V in a rabbit model

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Introduction: Non occlusive thrombi are often in contact with non re-endothelialized stent struts of drug-eluting stent (DES) and could favor stent thrombosis. Annexin V radio-labelled with ^{99m}Tc is a radio-tracer with a high affinity for activated platelets.

Objectives: Our objectives were to develop an animal model of non-occlusive thrombosis of stents and to evaluate the ability of annexin V ^{99m}Tc for the detection of in-stent thrombi using scintigraphy.

Methods: Right carotid arteries of NZW rabbits (n=14) fed a high cholesterol diet were implanted with DES. Nuclear imaging was performed 10 (n=7) or 28 days (n=7) after stent implantation. Rabbits underwent a first scintigraphy 2 hours after injection of radio-labelled annexin V ^{99m}Tc. At the end of the first scintigraphy, a suture was placed surgically proximal to the injured carotid arteries in order to induce a thrombus-prone flow limiting stenosis. Four days later, a second scintigraphy was performed. After the second scintigraphy, stents were excised, imaged *ex vivo* and then fixed for histological examination and scanning electron microscopy (SEM).

Results: Activities measured *in vivo* in the stented carotid arteries after injection of annexin V ^{99m}Tc increased on the second scintigraphy after creation of a surgical stenosis as compared to the first scintigraphy (1.2 vs. 1 respectively; p<0.05). On the second scintigraphy, activities were higher at 14 vs. 32 days after stent implantation (22 vs. 11 counts/pixel/ MBq, respectively; p<0.05). DES were re-endothelialized only 32 days but not 14 days after implantation on histological sections and SEM. High activities measured *ex vivo* in stents by scintigraphy were associated with the detection of thrombi on corresponding histological sections.

Conclusions: In this study, we developed a rabbit model of non-occlusive thrombosis of non re-endothelialized DES in carotid arteries. In this model, in-stent thrombi could be detected using annexin V ^{99m}Tc scintigraphy.

0174

Non adherence to aspirin in patients undergoing coronary stenting: associated factors and implications for intervention and clinical management

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Background: Premature discontinuation of antiplatelet therapy or reduced adherence has been identified as major risk factors for stent thrombosis and poor prognosis after acute coronary syndrome.

Purpose: This study aimed at identifying correlates of non adherence to aspirin among patients undergoing coronary stenting.

Methods: We prospectively included all patients undergoing coronary stenting in our institution. Response to aspirin was assessed during hospital phase with arachidonic acid-induced platelet aggregation (AA-Ag) and good responders to aspirin (AA-Ag<30%) were included in the study for longitudinal assessment. (N=308). Response to aspirin was reassessed one month after hospital discharge and non responders received a directly observed intake of aspirin to exclude definite biological non response due to bioavailability problems. After excluding patients with bioavailability problems, response to aspirin based on platelet function testing was used to estimate non adherence to aspirin after coronary stenting. A logistic regression model was used to identify predictors of non adherence.

Results: Non adherence to aspirin concerned 14% of the study sample (n=43). After adjustment for age, migrants reported the highest risk of non adherence to aspirin (OR[95% CI]: 8.3[3.5-19.8] followed by patients receiving treatment for diabetes (4.5[1.9-10.9]). Individual reporting smoking habits had a threefold risk of non adherence (3.1[1.4-6.9]).

Conclusions: Non adherence to aspirin is relatively frequent in a population at high risk of cardiovascular events. Appropriate case management and special interventions targeting these at higher risk groups need to be implemented to avoid fatal events and assure long term response to treatment.

0419

Five-Year Clinical Outcome in Patients with Small Vessel Disease Treated with Drug-Eluting Versus Bare-Metal Stenting

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Objective: To assess the clinical impact of drug-eluting stents (DES) vs. bare-metal stents (BMS) in the treatment of small coronary vessel lesions.

Background: Stenting is known to be more effective than balloon angioplasty in patients with small vessel coronary disease. However it remains unclear if DES are more efficacious than BMS in this setting.

Methods: From January 2004 to December 2008, all patients were treated with percutaneous coronary intervention and stenting in native small coronary vessels (defined as a reference vessel diameter<3mm) were enrolled irrespective of indication. Patients were divided into two groups according to type of stent used: BMS group and DES group. Procedural and long-term clinical outcomes were compared between the both groups.

Results: A total of 645 patients were enrolled (368 treated with BMS, 277 with DES). Clinical follow up was obtained in 99.3% (median follow-up: 3.3±1.2 years; range to 12-60 months). At five years, patients treated with DES showed significantly higher five-year major adverse cardiac events (MACE)-free survival (HR 0.45, 95%CI 0.29-0.72, log-rank P=0.001) and target vessel revascularization (TVR)-free survival (HR 0.44, 95%CI 0.25-0.78, log-rank P=0.005). There were no significant differences between the two groups regarding death, acute myocardial infarction and peri procedure-myocardial infarction. The incidence of stent thrombosis was also similar in both groups.

Conclusions: DES is more effective than BMS in reducing MACE and TVR in small vessel disease. However, the use of BMS does not increase mortality or re infarction and so is reasonable to consider in selected cases.