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High prevalence of marijuana smokers in acute coronary syndromes in young people

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Background: Despite marijuana is the most frequent drug use worldwide, there is no prospective clinical data of its implication in acute coronary syndromes (ACS). The aim of this study was to evaluate the prevalence of marijuana smokers in young people admitted to intensive unit care for ACS.

Material and Methods: From September 2010 to Mars 2011, we prospectively included all patients below 50 years old admitted for ACS at the University Hospital of Toulouse, France and assessed their use of Marijuana by medical questioning and systematic urinary assay. Patients were divided into 2 groups (marijuana smokers and no marijuana smokers) according to the presence of marijuana in urines. Parametric and non-parametric tests were used for groups comparison.

Results: 63 patients were included. Mean age was 42±7 years old and 52 (82.5%) patients were male. In this cohort, 23.8% (15) were recognized as marijuana smokers (MS). There was no difference in classical cardiovascular risk factors, age and gender between the two groups. Interestingly, MS present significative more non ST elevation myocardial infarction than non MS patients (67% vs 29.2%; p=0.009). There was no difference in the coronary status but a high frequency of multivessel coronary disease (respectively 46.6% and 45.8%, p=0.95) in the two groups. There was no death in MS group whereas two in the non MS group. No difference was observed in left ejection fraction at hospital discharge (55% vs 52%, p=0.291). Marijuana addiction is characterized by an 86.7% use in the 24 hours preceding the ACS and 73.3% in the last three hours.

Conclusion: Marijuana use is frequent, especially in the few hours preceding the event, and probably underdiagnosed in ACS of people below 50 years old. Clinical presentation of ACS is different in this group with less ST elevation suggesting a more complex coronary artery disease. Multicentric study should be achieved to assess epidemiology and pathophysiolgical role of marijuana use in ACS.

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Clinical, angiographic and genetic determinants of early coronary stent thrombosis: the ONASSIST study

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Objectives: To perform a comprehensive analysis of all determinants of definite early stent thrombosis (ST) to identify the risk and the modifiable factors of early ST.

Methods: Using a web-based case collection and reporting system, 123 patients with definite EST on dual antiplatelet therapy were matched 2:1 according to age and gender with 246 controls. All patients were genotyped for 23 genetic variants involved in clopidogrel metabolism (CYP2C19, CYP2C9, CYP2B6, CYP3A5, POR, ABCB1, PON1), platelet receptor function (P2Y12, ITGB3), and the coagulation and fibrinolytic system (MTHFR, Factor V, Fibrinogen, Prothrombin, PAI1 and VKORC1).

Results: CYP2C19*2 (ORund=2.53, 95% CI [1.61-3.97], p<0.0001) and ABCB1 TT3435 (ORund=2.01, 95% CI [1.22-3.30], p=0.006) carriers were more frequent among patients with EST than controls while CYP2C19*17 (ORund=0.53, 95% CI [0.31-0.88], p=0.01) and ITGB3 PlA2 (ORund=0.50, 95% CI [0.29-0.87], p=0.01) carriers were less frequent. The accuracy of the clinical model to discriminate between EST and controls (AUC 0.72, 95% CI [0.66-0.77] did not differ significantly from the genetic model (AUC 0.68, 95% CI [0.62-0.73] (p=0.34), although combining both led to a significant improvement in the discriminatory power of the model (AUC 0.78, 95% CI [0.73-0.83], p=0.004). Among all independent predictors of early ST, the use of high clopidogrel loading doses (OR=0.73, 95% CI[0.57-0.94], p=0.01) and proton pump inhibitors (OR=2.19, 95% CI [1.28-3.72], p=0.004) were the only modifiable factors.

Conclusion: In addition to established clinical and angiographic factors, three genes involved in clopidogrel metabolism and platelet receptor function (CYP2C19, ABCB1, ITGB3) were significantly significantly improved the ability to predict early ST. PPI use and clopidogrel dose were both independently correlated with the risk of early ST, suggesting that the final amount of active metabolite generated is a major factor of prevention.

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Impact of the time of presentation on the management and in-hospital outcome of patients with STEMI: insights from the MIRAMI registry

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Background: The impact of the timing of presentation of patients with acute myocardial infarction (AMI) and the subsequent effect on management and prognosis have not been fully investigated.

Methods and results: A total of 1315 patients admitted for AMI between January 1995 and December 2010 were included in our MonastIR AMI (MIRAMI) registry. We deliberately excluded from the analysis patients who presented late and therefore did not receive a reperfusion strategy. A total of 768 patients did receive one of the two reperfusion strategies (thrombolysis or primary angioplasty) and therefore were included in this analysis. There were no significant differences on the frequency of AMI between the different periods of the day and particularly between working and off-work hours. (p=0.92). Primary angioplasty was more frequently performed between 8 and 12 a.m (p=0.03). Thrombolysis was more given between 8 and 12 p.m (p=0.03). AMI was more frequent during winter (31.7% with p= 0.007) but mortality was higher during autumn (p=0.008). There were no differences in mortality and heart failure according to the hour of presentation (p=0.77 and p=0.44 respectively).

Conclusion: The time of presentation of patients with AMI did have an impact on the selection of the reperfusion strategy but not on the in-hospital outcome. There is clearly an impact of the season with a higher in-hospital mortality during autumn.

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High doses of clopidogrel to overcome genetic resistance: the randomized cross-over CLOVIS-2 study

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Background: Carriers of the loss-of-function CYP2C19*2 genetic variant have lower active metabolite levels and diminished platelet inhibition after clopidogrel loading.

Objectives: To determine the pharmacokinetic (PK) and pharmacodynamic (PD) responses to two LDs (LD) of clopidogrel according to carriage of CYP2C19*2 genetic variant.

Methods: Young post-MI patients heterozygous (wt/*2, n=43) or homozygous (*2/*2, n=8) for the CYP2C19*2 genetic variant were matched with patients not carrying the variant (wt/wt, n=58). All patients were randomized to 300mg or 900mg clopidogrel LD. The relative reduction in residual platelet aggregation (RR-RPA in %) and the area under the plasma concentration (AUC0-6) – time curve of active metabolite) from baseline to six-hours post loading were compared according to both LD and CYP2C19*2 carriage.

Results: The 300 mg LD led to a gene-dose effect for RR-RPA (–65.7±35.9% in wt/wt vs. –48.0±38.4% in wt/*2 vs.-14.6±32.4% in *2/*2; overall p-value=0.003, p=0.03 for wt/wt versus wt/*2, p=0.04 for wt/*2 versus *2/*2)

with minor effect in *2/*2 carriers. After 900mg LD, the effect of the CYP2C19*2 variant on platelet inhibition was fully compensated in wt/*2 carriers but not in *2/*2 carriers (–83.6±25.8% in wt/wt vs. –77.2±26.9% in wt/*2 vs. –29.5±26.8% in *2/*2; overall p-value=0.0003, p=0.20 for wt/wt versus wt/*2, p<0.001 for wt/*2 versus *2/*2). A similar pattern was observed for the active metabolite AUC0-6 and there was a significant correlation between PK and PD responses irrespective of the LD.

Conclusion: Carriers of CYP2C19*2 display significant lower responses to clopidogrel with a gene dose-effect. Clopidogrel resistance can be overcome by increasing the dose in heterozygous carriers but not in homozygous carriers.

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Switching patients from clopidogrel to prasugrel at the early phase of an acute coronary syndrome: impact of prasugrel reloading

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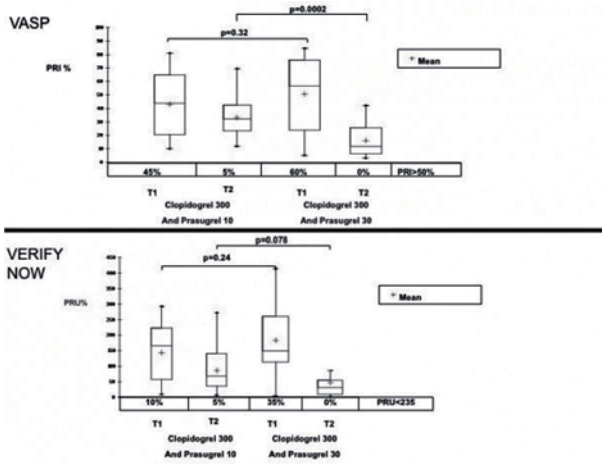
Purpose: There is no consensus on how to manage the switch from clopidogrel to prasugrel immediately after a clopidogrel loading dose (LD). The aim of this study was to evaluate the pharmacodynamic response of switching patients in this situation and comparing two prasugrel reloading doses (RD) by using three laboratory tests. Methods: Patients hospitalized for acute coronary syndrome (ACS) who received a 300 mg LD of clopidogrel before admission were referred for inclusion. Their platelet response to the P2Y12 inhibitor was tested with vasodilator-stimulated phosphoprotein phosphorylation (VASP), Verify Now assay and light transmission aggregometry (LTA) on admission (T1). Then, patients were immediately randomized for 2 RD of prasugrel (10 mg or 30 mg) and platelet response was tested again by the same methods (T2). Results: 20 patients were included in each group. All T1 and T2 analyses were performed during the first 24 hours after hospitalization. Compared with a 300 mg LD of clopidogrel, the proportion of patients with platelet hyporesponsiveness for VASP to the P2Y12 inhibitor was lower after the prasugrel RD: 8 vs 1 (p<0.001) in the 10 mg prasugrel group and 12 vs none (p<0.001) in the 30 mg prasugrel group. Late adenosine diphosphate-induced platelet aggregation (LPA), by LTA was lower after a 30 mg prasugrel RD compared with a 10 mg RD (mean LPA 8 +/–9 vs 14 +/–12; p<0.001). Similar results were found using VerifyNow P2Y12 (mean PRU 38 +/–60 vs 87 +/–71; p < 0.001) and VASP assays (mean PRI 17 +/– 12 vs 33 +/–15; p<0.001). No bleeding events were reported during the hospital stay.

Conclusions: For patients receiving 300 mg clopidogrel therapy after an ACS, a 30 mg RD of prasugrel compared to a 10 mg RD is associated with further reduction in platelet function and markedly decreases the proportion of P2Y12 inhibitors low responders.



Platelet inhibition tested by Verify Now and VASP

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Long-term dual antiplatelet treatment and clinical outcome of diabetic patients treated with drug-eluting stents

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Background: Despite encouraging short and mid-term results with drug-eluting stents (DES) in diabetic (DM) patients (pts) with coronary artery disease, the long-term efficacy is controversial. We assessed the influence of long-term dual antiplatelet treatment (DAPLT) with aspirin and clopidogrel on clinical outcome of DM pts treated with DES.

Methods: The study included 610 consecutive DM pts (male 80%, mean age 65±9 years) that had been treated with DES. Five years clinical follow-up (FU) obtained in 584/610 (96%) of them. At the end of follow-up, 341 (58%) pts were on DAPLT and 243 (42%) on single antiplatelet treatment (SAPLT). The primary end-point was the combination of death (D), non-fatal myocardial infarction (MI) and cerebrovascular accident (CVA), and was considered as hard end-point (HEP). Stent thrombosis (ST) occurring -12 months after DES implantation was considered as early (EST), and for >12 months, as late (LST). The ARC definition for ST was used.

Results: There was no difference in gender, age, risk factors profile, unstable coronary artery disease, insulin treatment, extent of coronary artery disease, and systolic left ventricular function between the two groups. At 12 months post PCI 546 (92%) pts were on DAPLT; the incidence of EST (definite or probable) was 0.8%. The incidence of LST (definite or probable) was 0.7%. There was no difference in the incidence of ST in pts treated with DAPLT vs. SAPLT (1.4% vs. 1.6%, p: ns). At FU, HEP was observed in 18% vs. 13%, in pts on DAPLT vs. SAPLT (p: ns).

Conclusion: Long-term DAPLT in DM pts treated with DES implantation is not associated with better clinical outcome or lower risk of definite or probable ST.

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Incidence and predictors of coronary stent thrombosis: evidence from an international collaborative meta-analysis including 32 studies, 222,752 patients, and 4490 thromboses

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Background: Stent thrombosis remains among the most feared complications of percutaneous coronary intervention (PCI) with stenting. However, data on its incidence and predictors are sparse and conflicting.

Objective: We aimed to perform a collaborative systematic review on incidence and predictors of stent thrombosis. PubMed was systematically searched for eligible studies from the drug-eluting stent (DES) era (1/2002-12/2010).

Methods: Studies were selected if including ≥2,000 patients undergoing stenting or reporting on ≥25 thromboses. Study features, patient characteristics, incidence and predictors of stent thrombosis were abstracted and pooled, when appropriate, with random-effect methods (point estimate [95% confidence intervals]).

Results: A total of 32 studies were identified (222,752 patients, 4,490 thromboses), with DES used in 89%. After a median of 22 months, definite, probable, or possible stent thrombosis had occurred in 2.3% (2.0%; 2.6%), with acute in 0.3% (0.2%; 0.5%), subacute in 1.1% (0.9%; 1.3%), late in 0.5% (0.4%; 0.6%), and very late in 0.6% (0.4%; 0.7%). Similar figures were computed for studies reporting only on DES, except for lower rates of acute ST (0.2% [0.1%; 0.2%]). From a total of 47 candidate variables, the most reliable predictors of definite/probable stent

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