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Thèse

Pour le

DOCTORAT EN MEDECINE

Diplôme d'État
Par

Farid CHALLAL

Né le 18 décembre 1986 à MARSEILLE (13)

Peri-procedural serum fibrinogen and CRP elevation before Percutaneous Coronary Intervention significantly predict stent thrombosis and Major Cardiovascular ischemic Events at 15-months

Présentée et soutenue publiquement le lundi 17 octobre 2016

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RESUME

Pré requis

La présence d'un syndrome inflammatoire biologique est considérée comme un facteur d'augmentation du risque d'évènements thrombotique et de thrombose de stent au décours d'une angioplastie coronaire. Il n'existe pas de recommandations précises concernant le seuil de marqueurs d'inflammation au-delà duquel le rapport bénéfice risque d'une implantation de stent devient défavorable. La pratique est de repousser l'implantation de stent en cas d'élévation des marqueurs d'inflammation ce qui expose les patients à un risque d'évènement cardiaque dans l'attente de la revascularisation.

Objectif

L'objectif principal de cette étude était d'explorer la corrélation entre les taux de fibrinogène et protéine C-réactive dosés avant la réalisation d'une implantation de stent coronaire et le risque de survenue d'évènements cardiovasculaires majeurs à long terme notamment le risque de thrombose de stent, afin d'argumenter la décision thérapeutique devant la présence d'un syndrome inflammatoire chez un patient ayant une indication non urgente d'angioplastie coronaire.

Méthodes et Résultats

719 patients consécutifs (âge moyen 67,8, 72,9 % d'hommes, 56,6 % de syndromes coronaire aigus) pour lesquels avait été réalisée une angioplastie coronaire percutanée avec implantation d'au moins un stent ont été inclus rétrospectivement. Les taux de fibrinogène et de protéine C-réactive (CRP) étaient dosés en routine avant ou immédiatement après l'angioplastie.

Après un suivi moyen de 15,9 ±4,2 mois, un évènement cardiovasculaire majeur (MACE) au moins était survenu chez 71 patients (9,87%) et une thrombose de stent certaine ou probable était survenue chez 20 patients (2,78%). L'analyse multivariée montrait que le taux de fibrinogène et de CRP étaient des facteurs de risque indépendants de la survenue de MACE (OR = 2,73 [1,49 – 5,04] et 2,28 [1,32-3,91]

respectivement) pour des seuils diagnostics à 3,5g/L et 6,0 mg/L, et de la survenue de thrombose de stent certaine ou probable (OR = 6,07 [1,39-26,4 et] 4,33 [1,62-11,59] respectivement) avec de seuils diagnostics à 3,5g/L et 5,4 mg/L).

Conclusion

Des taux de fibrinogène et CRP élevés lors d'une angioplastie coronaire percutanée sont associés à risque plus élevé de survenue d'évènement cardiovasculaire majeur à long terme et de thrombose de stent. Retarder l'angioplastie ou proposer une stratégie anti-thrombotique plus intensive et/ou prolongée pourrait être proposée dans cette population à haut risque résiduel.

Mots clés : angioplastie coronaire – stent - thrombose de stent – fibrinogène – CRP - inflammation

ABSTRACT

Background

Biological inflammatory syndrome is often considered as increasing thrombotic events and stent thrombosis risk after a percutaneous coronary intervention. As of today there are no guidelines concerning a cut-off of inflammation biomarkers above which the risk benefit balance is unfavorable. Current practice is to defer the stent implantation procedure when inflammation biomarker levels are high, a revascularization deferral that may potentially increase patient's risk of ischemic events.

Objective

The objective of this study was to explore the correlation between baseline fibrinogen and C-Reactive protein (CRP) levels before proceeding to coronary stent implantation and the rate of major cardiovascular events at long term, especially the stent thrombosis risk, to argue the clinical decision behind the presence of a biological inflammatory syndrome in patient with a indicated percutaneous coronary intervention without emergency.

Methods and Results

719 consecutive patients (67,8 years, 72,9% men, 43,4% acute coronary syndrome [ACS]) who underwent PCI with implantation of a least one stent were retrospectively enrolled. Baseline fibrinogen and CRP levels were assayed in routine before or immediately after PCI. After a mean follow-up of 15,9 ±4,2 months, MACE occurred in 71 patients (9,87%) and definite or probable stent thrombosis occurred in 20 patients (2,78%).

Multivariate analysis shows that peri procedural fibrinogen and CRP levels were independent risk factors of MACE (HR = 2,73[1,49-5,04] and 2,28 [1,32-3,91] respectively) with cut-offs identified at 3,5g/L and 6,0 mg/L respectively, and of stent thrombosis (HR = 6,07 [1,39-26,4] and 4,33 [1,62-11,59] respectively) with cut-offs identified at 3,5g/L and 5,4 mg/L).

Conclusion

Peri procedural elevated serum fibrinogen and CRP are associated with higher risk of stent thrombosis and long term MACE in our population. These results advocate PCI deferral and/or more intensive and prolonged anti-thrombotic medication strategy in this higher residual risk population.

Key-words : percutaneous coronary intervention – coronary stent implantation – stent thrombosis – fibrinogen – CRP - inflammation

INTRODUCTION

Elevated serum fibrinogen is a known risk factor for short and long term major adverse cardiovascular events (MACE) in patients with atherosclerotic heart disease [1] [2] [3] [4], as well as other inflammation biomarkers including C-reactive protein and leukocytes count [5].

Elevated fibrinogen is also suspected to increase MACE after percutaneous coronary intervention (PCI) but this relation is still unclear, especially regarding stent thrombosis and early stent thrombosis, a serious complication resulting in increased mortality after PCI [6].

Of notice neither ESC and ACC/AHA Guidelines [7] [8] recommend blood serum fibrinogen or C-reactive protein levels measurements before proceeding to PCI; they do not mention them in the routine evaluation of risk to benefit ratio of performing stent implantation. Many interventional cardiology groups use to differ PCI procedures because of peri procedural increased levels of inflammation biomarkers; the reason for this deferral is early stent thrombosis risk and potential adverse events such as myocardial infarction and death.

In NSTEMI cases, interventional cardiologist may wait for several days and sometimes weeks before performing PCI. This delay may be deleterious, as patients may suffer from prolonged myocardial ischemia and adverse events that could have been prevented by early revascularization [6]. They are currently no guidelines and few data to estimate the risk to benefit of early versus delayed revascularization in NSTEMI patients with elevated inflammation biomarkers. In addition, if inflammation biomarkers elevation is indeed correlated with increased stent thrombosis and MACE risk, physician may want to take it into account when choosing antithrombotic treatment and duration after PCI.

In cases of STEMI, these levels are often unknown before performing emergency primary PCI. Inflammation markers elevation after emergency PCI is frequent in STEMI patients and is known to be associated with worst outcomes as it often results from large myocardial infarction. Nonetheless because of a well proven clinical benefit of early revascularization in STEMI, this elevation is not taken into account to estimate the risk to benefit ratio of primary PCI.

We aimed to test in our population the hypothesis that elevated fibrinogen and CRP at the time of PCI will predict higher risk of stent thrombosis and MACE. The first objective of our study was therefore to investigate the correlation between fibrinogen and CRP elevation and stent thrombosis and MACE after PCI in our population.

The secondary objective was to identify fibrinogen and CRP threshold of higher risk that should be taken into account when deciding to perform early or delayed PCI.

METHODS

Study patients

719 consecutive patients undergoing elective PCI in our University Hospital between January and October 2014 were retrospectively enrolled in this study. PCI indications were STEMI (168), NSTEMI (239), unstable angina (81) and stable angina (231). We recorded usual cardiovascular risks factors, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass grafting (CABG), left ventricular ejection function (LVEF), and platelet inhibitors used as adjuvant therapy for PCI.

Lab analysis

Peri procedural blood analyses were performed on peripheral blood sample routinely collected in patients before and/or after PCI. We recorded blood concentrations of fibrinogen and CRP before the PCI when available, or immediately after if it was the only data available.

We also recorded hemoglobin concentrations, platelet number, leukocytes number, and glomerular filtration rate using the MDRD formula. To constitute a real life population similar to daily practice, there were no exclusion criteria.

PCI procedure

All procedures were performed in the Cardiology Cath lab of Tours University Hospital.

PCI procedural data were: indication (stable angina, unstable angina, STEMI or NSTEMI, acute coronary syndrome (ACS) or not), number of diseased vessels, stenting site (Left main, LAD, Cx, RCA or CABG), number of implanted stent, number of treated coronary arteries, stent diameter, stent length, total implanted stent length and type of implanted stent (drug-eluted stent (DES), bare-metal stent (BMS) or bioresorbable stent (BVS)).

Endpoints, definitions, and follow-up

The primary endpoint was the first occurrence of major cardiovascular events (MACE) as a composite of cardiac death, myocardial infarction, definite, probable or possible stent thrombosis (ST), restenosis and stroke.

The principal secondary endpoint was the first occurrence of stent related MACE as a composite of all types of ST and restenosis.

Other secondary endpoints were definite or probable ST, definite or probable early stent thrombosis (occurring in the first month, corresponding to acute and subacute ST); stroke (from any cause); restenosis (target vessel revascularization).

Patient could experience several events during follow up (restenosis, stent thrombosis, and myocardial infarction). In this case the first event only was recorded as MACE for the analysis of correlation with inflammation markers elevation.

Cardiac death was defined as : any death due to identified cardiac cause (MI, low-output failure, fatal arrhythmia), unwitnessed death, death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment [9]. Non cardiovascular death was recorded if an unequivocal non-cardiovascular cause could be established.

Clinical restenosis was defined as the recurrence or worsening of ischemic symptoms (typical angina, MI or death) or ischemia at exercise testing (>1 mm ST segment depression) with an angiographic confirmation of the initial target vessel implication in symptoms.

The diagnosis of acute MI was based on the universal definition of MI [9]. Periprocedural or postprocedural elevations of cardiac enzymes were disregarded if ischemic signs or symptoms were absent. Stent thrombosis was assessed by the Academic Research Consortium criteria [9] with the pre-specified component of primary composite outcome being definite or probable.

Stroke, as detected by the occurrence of a new neurological deficit, was confirmed by a neurologist and on imaging.

All study endpoints were confirmed on the basis of source documentation from medical records. Clinical, procedural, and outcome data were retrospectively collected from medical records, or from the CRAC registry (Center Region Angioplasty Committee, a prospectively multicenter regional database collecting data from all PCI procedures in the Center Region of France).

Clinical follow-up after PCI was retrieved from patient's clinical file. Patients are usually seen at 3, 6 or 12 months, consultation based on the Cardiologist decision. Medical reports contain cardiac symptoms, clinical status, all interventions, outcome events, and adverse events. If needed, additional data were retrieved from other specialist's evaluation trough medical records, such as Emergencies or Neurology departments. Follow up was also assessed using the CRAC registry data. In this registry, patient's vital status, stent thrombosis and adverse events are systematically collected at 12 month by a Clinical Research Assistant.

Statistical analysis

All analysis were performed using JMP (version 12.0, SAS Institute Inc., Cary, NC, USA). Continuous variables were presented as mean ±SD, and were compared using a Student t test. Categorical variables were reported as frequencies (%) and were compared with the Fisher exact test. P values were obtained from Student t test for continuous variables and from chi-square test for proportions.

After making ROC curves to identify the best diagnosis cut-off of fibrinogen and CRP serum levels, we compared the differences between groups; these were assessed by the log-rank test.

Then, we used a Cox proportional hazards model to compare survival analysis for patients with and without elevated serum fibrinogen and elevated CRP.

A p-value < 0,05 was considered significant.

RESULTS

Population and follow-up

719 patients undergoing PCI were enrolled. Mean age was 67,8 ±13,4 years, 72,9% were men.

407 patients (56,6%) had PCI for acute coronary syndrome (ACS), including 168 STEMI (23,4%), and 239 NSTEMI (33,2%). 231(32,1%) patients had planned PCI for stable angina (or LVEF dysfunction or pre-operative evaluation) and unstable angina for 81 (11,3%) patients.

Mean follow-up was 15,9 ±4,2 months (median 15 months).

Principal patient's characteristics are reported in table 1.

Baseline Lab analysis

Peri procedural Fibrinogen values were available for 675 patients (93,9%), and CRP values for 577 patients (80,3%).

Baseline Lab analysis were reported in Table 2.

Procedural data

803 arteries were dilated in 719 patients, and a total of 1213 stents were implanted.

Stenting sites were Left main (25, 3,5%), LAD (338, 47%), Cx (175, 24,3%), RCA (256, 35,6%) and venous or arterial graft (9, 1,13%). 87,9% (1067) of implanted stent were drug eluting stent (DES), 10,7% (130) bare metal stent (BMS) and 1,3% (16) bioresorbable stent.

Procedural data were reported in Table 3.

Events during follow-up

During the 15 months follow-up, we recorded 71 MACE (9,98%). Among them, 50 stent related MACE (6,95%), 20 definite or probable ST (2,78%), 34 (4,74%) definite, probable or possible ST including 9 early ST (1,25%) and 16 coronary restenosis (2,23%).

56 patients (7,79%) died during follow-up, among them 41 from identified cardiac cause (5,7%). MACE during follow-up are reported in table 4.

There was no significant difference on MACE rate between PCI indication subgroups (stable angina 10,39%, unstable angina 9,88%, NSTEMI 9,66%, STEMI 9,52%).

MACE

Patients experiencing MACE during follow-up were older (71,4 vs 67,4 years p = 0,016), had a worst LVEF (42,3% with LVEF <40% vs 14,8% p <0,0001) and glomerular filtration rate (65,6 mL/mn vs 75,6 p =0,0146), had more previous CABG (21,1% vs 7,9% p <0,0001) and were more frequently stented on the left main coronary artery (8,5% vs 2,9% p <0,0001).

They also had lower Hb levels (128,6g/L vs 137,6g/L p <0,0001), and higher levels of Fibrinogen and CRP (4,31 ±1,10g/L vs 3,88 ±0,98g/L p = 0,001 and 17,81 ±34,43 vs 8,22 ±15,98mg/L p = 0,0002 respectively).

Univariate analysis for MACE risk factors are reported in Table 5.

After calculating a cut-off value with the highest area under the curve (0,64) of fibrinogen >3,5 g/L, multivariate analysis showed that it was an independent risk factor of MACE with a Hazard Ratio of 2,73 ([1,49- 5,04] p = 0,0005). The calculated cut-off value of CRP was 6,0 mg/L (ROC curve AUC = 0,62), and it was also a significant independent risk factor with an Hazard Ratio of 2,28 ([1,32-3,91], p = 0,003).

Adjusted MACE risk factors are reported in Table 7.

At 15 months, patients with elevated fibrinogen > 3,5g/L and elevated CRP > 5,4mg/L had a higher than two fold MACE rate (12% vs 4,9%, p = 0,0005 and 14,4% vs 7,1%, p = 0,004 respectively).

Event-free curves for MACE at 15 months in elevated fibrinogen and CRP patient's groups and in the other patient's group reported in Figure 1.

Stent related MACE

Patients who experienced stent-related MACE had a worst LVEF (37,5% with LVEF <40% vs 16,1% p = 0,0006), more often multitroncular disease (83,3% vs 55,7% p <0,0001), more previous CABG (25% vs 8% p= 0,0008) and were more frequently stented on CABG (6,25% vs 0,89% p = 0,016) and on the left main coronary artery (10,4% vs 2,9% p = 0,024).

They had lower Hb levels (128,6g/L vs 137,2g/L p = 0,0027), and significantly higher levels of Fibrinogen (4,39 ±0,99g/L vs 3,89 ±0,99g/L, p = 0,012) and statistically non-significant higher levels of CRP (18,46 ±35,02 vs 8,45 ±16, 8mg/L, p = 0,06).

Univariate analysis for stent related MACE risk factors are reported in Table 7.

After calculating a cut-off value with the highest area under the curve (0,66) of fibrinogen >3,33 g/L, multivariate analysis showed that it was an independent risk factor of stent related MACE with an Hazard Ratio of 5,29 ([1,87- 14,92] p = 0,0001). The calculated cut-off value of CRP was 5,4 mg/L (ROC curve AUC = 0,62), and it was a significantly independent risk factor with an Hazard Ratio of 2,22 ([1,32-3,91], p = 0,003).

Adjusted Hazard Ratios for stent related MACE risk factors are reported in Table 8.

At 15 months, patients who had elevated fibrinogen and CRP higher than 3,5g/L and 5,4mg/L had a significantly higher rate of stent related MACE (8,3% vs 3,0%, p = 0,0052 and 11,3% vs 4,9%, p = 0,009).

Event-free curves for stent related MACE at 15 months in elevated fibrinogen and CRP patient's groups and in the other patient's group are reported in Figure 2.

Definite and probable stent thrombosis

Patients who experienced definite and probable stent thrombosis had a worst LVEF (55,0% with LVEF <40% vs 16,5% p = 0,0001), more previous CABG (25% vs 8,7%, p = 0,035) and were more frequently stented on CABG (10,0% vs 1,0%, p = 0,02). They had higher platelet levels (233,9 ± 99 G/L vs

227,5±73,5 G/L p=0,078), and had higher levels of Fibrinogen and CRP (4,56 ±1,01g/L vs 3,90 ±0,89g/L, p = 0,002 and 26,9 ±37,7 vs 8,6 ±17,79mg/L p=0,023 respectively).

Univariate analysis for definite and probable stent thrombosis risk factors are reported in Table 9.

After calculating a cut-off value with the highest area under the curve (0,64) of fibrinogen >3,5 g/L, multivariate analysis showed that it was an independent risk factor of MACE with a Hazard Ratio of 6,07 ([1,39- 26,4] p = 0,003); The calculated cut-off value of CRP was 5,4mg/L (ROC curve AUC = 0,62), and it was a significantly independent risk factor with a Hazard Ratio of 4,33 ([1,62-11,59], p = 0,002).

The other independent predictors of definite and probable stent thrombosis after multivariate analysis were LVEF < 40% (HR = 6,21 [2,51 – 15,31], p = 0,0001), previous CABG (HR = 3,48 [1,23 – 9,92], p=0,035) and CABG stenting (HR = 10,98 [2,13 – 56,6], p = 0,02).

Adjusted Hazard Ratios for definite and probable stent thrombosis risk factors are reported in Table 10.

Early stent thrombosis

There was only 9 early stent thrombosis in our study. The only significant differences between groups concerned high blood pressure (88,9% vs 54,9%, p= 0,048), left ventricular dysfunction (55,6% vs 17%, p = 0,009), and Abciximab use (22,2% vs 5,2%, p = 0,04).

Patients experiencing early stent thrombosis had non statistically significant higher levels of Fibrinogen and CRP (4,42 ±1,29g/L vs 3,92 ±1,00g/L, p = 0,31 and 32,6 ±45,96 vs 8,89 ±18,21mg/L p=0,19 respectively).

Univariate analysis for definite and probable early stent thrombosis risk factors are reported in Table 11.

Restenosis

For 17 patients experiencing restenosis during follow-up, analysis showed few significant differences between groups : patients with restenosis had more frequently previous CABG (29,4% vs 8,7%, p =

0,016), were less frequently stented on the RCA (11,7% vs 36,3% p = 0,02), and had significantly lower Hemoglobin level (127,1 ±18 g/L vs 136,9 ±17g/L, p = 0,041).

Univariate analysis for restenosis risk factors are reported in Table 12.

Subgroup analysis

Patients who underwent urgent PCI (STEMI, and NSTEMI) had significantly higher levels of CRP (13,7 ±25,7 mg/L vs 5,2 ±7,4 mg/L, p = 0,006). There was no significant difference regarding fibrinogen level (3,94 ±1,1 vs 3,89 ±0,9 g/L, p = 0,21).

In the non-urgent PCI subgroup, patients who experienced MACE, stent thrombosis and stent related MACE had significantly higher level of fibrinogen (4,29 vs 3,85 g/L p = 0,01 ; 4,25 vs 3,88 g/L p = 0,036 and 4,25 vs 3,87 g/L p = 0,035 respectively). There was no significant difference regarding CRP level (5,76 vs 5,12 mg/L p = 0,51 ; 5,54 vs 5,17 mg/L p = 0,77 and 4,95 vs 5,21 p = 0,79 respectively).

In the urgent PCI subgroup, patients who experienced MACE, stent thrombosis and stent related MACE had significantly higher levels of fibrinogen (4,36 vs 3,89 g/L p = 0,042 ; 4,77 vs 3,9 g/L p = 0,007 and 4,54 vs 3,9g/L p = 0,014 respectively) and CRP (30,7 vs 11,6 mg/L p= 0,036 ; 42,3 vs 11,9 mg/L p = 0,029 and 33,3 vs 12 mg/L p = 0,051 respectively) for all analyzed event.

Patients experiencing restenosis in both urgent and non-urgent PCI subgroups had a non-significant trend toward higher levels of both CRP and fibrinogen.

All subgroups analysis for events in urgent and not urgent PCI subgroups are reported in tables 13 and 14.

DISCUSSION

In our retrospective study, patients with higher peri procedural fibrinogen or CRP levels experienced more MACE, stent related MACE and stent thrombosis during the 15 month post PCI follow up. Patients who experienced early stent thrombosis also had higher peri procedural fibrinogen and CRP levels, but the difference wasn't statistically significant. The small number of early stent thrombosis 9 (1,25%) in our study may explain a lack of power to detect significant difference regarding inflammation markers.

Our study is the first to investigate correlation between baseline inflammation biomarkers and long-term outcomes of percutaneous coronary intervention in a real-life population whatever the PCI indication, planned procedure for stable angina or acute coronary syndrome.

High level of baseline fibrinogen and CRP appear to significantly increase MACE, stent related MACE, definite and probable stent thrombosis, both for patients undergoing urgent or non-urgent PCI.

Patients with ACS undergoing PCI had increased baseline levels of fibrinogen and CRP. This elevation of inflammation biomarkers was also observed for patients without ACS who further experienced MACE. It suggests that MACE risk increase is partly independent of the urgent or non-urgent nature of PCI indication. Therefore, fibrinogen and CRP elevation would rather be considered as markers of atherothrombotic residual risk. This was previously suggested in several studies [10] [11] [12].

Buffon et al. [13] showed that preprocedural CRP level which is an easily measurable marker of acute phase response, was a powerful predictor of both early and late outcome in patients undergoing single vessel PCI (excluding myocardial infarction, previous PCI or CABG and LVEF dysfunction). Their data suggested that early complications and clinical restenosis were markedly influenced by the preprocedural degree of inflammatory cell activation. At one-year follow-up, clinical restenosis occurred in 63% of patients with high CRP levels and in 27% of those with normal CRP levels (cut-off = 3mg/L). However, their study population was more restricted than our study.

Our results are also in keeping with Park et al. [14] who showed an increased risk for MACE at 2 years when CRP level was > 3,0mg/L in patients undergoing non urgent PCI with a Hazard ratio = 2.81.

Regarding the putative mechanisms, C-reactive protein (CRP) increase in the blood of patients with inflammatory conditions and CRP- induced monocyte tissue factor (TF) may contribute to inflammation-associated thrombosis [15]. High levels of TF are present in atherosclerotic plaques due to their expression by macrophages and vascular smooth muscle cells and the presence of cell-derived TF-positive microvesicles [16]. CRP and TF expression is markedly increased in plaques derived from patients with ACS as compared to stable angina patients. Interestingly, statin treatment where shown to reduce vascular expression of CRP and TF suggesting one of the mechanisms involved in statin related residual risk reduction [17].

Studies previously reported significant correlations between elevated serum fibrinogen level, atherosclerotic risk factors and adverse cardiovascular events in the general population [18] [19] [20] [21].

Serum fibrinogen plays a critical role in arterial thrombosis as a key component of platelet crosslinking and clot formation [22]. Fibrinogen is increased in the response to systemic inflammation likely to be present in patients with high cardiovascular risk, existing coronary heart disease, and more acute clinical presentations. In addition, platelet activation may further contribute to release of fibrinogen stores, potentiate thrombus formation, and increase cardiovascular risk. Then interplay between these mechanisms suggests a correlation between elevated fibrinogen level and increased cardiovascular events, although a direct causal link was not established.

Mahmud E. et al showed in a recent study that elevated baseline fibrinogen level was independently associated with 6-months MACE, but in this study patients presenting with acute coronary syndrome were excluded [23].

Leukocytes count was higher in all MACE subgroups, but the differences didn’t reach statistical significance. Previous studies suggested leucocytes implication in thrombosis mechanisms.

Histopathological analysis of thrombus specimen in patients presenting with stent thrombosis after PCI showed significant focal leukocytes recruitment, particularly neutrophils. Interestingly, eosinophil recruitment was also observed, suggesting a potential allergic component in the process of ST [24].

In our study lower hemoglobin level was significantly correlated with worst outcomes including MACE and stent thrombosis. Several hypothesis may be discussed to explain this observation : lower hemoglobin level may be associated with higher risk of future anti thrombotic therapy discontinuation, one of the most powerful predictor of stent thrombosis and death [25] [26] [27]. In our retrospective study, we had no data regarding antiplatelet drug prescription and adherence during follow up.

In the Pilgrim's study, the prevalence of anemia in an unselected patient cohort undergoing PCI was high and associated with advanced age, diabetes, and chronic kidney disease [28] ; incidence of cardiac death and stent thrombosis was also significantly increased.

In our population, 110 (15,3%) of 719 patients had a hemoglobin rate < 120 mg/L.

There is a rational to explore anemia before performing PCI in these patients except for those presenting with urgent PCI indication such as STEMI patients.

In many studies, admission for ACS seems to increase stent thrombosis risk subsequently resulting in higher death rate or extensive myocardial infarction [29] [30] [31].

In our study, patients with definite or probable stent thrombosis had significantly higher levels of CRP, fibrinogen and leukocytes in both PCI indication subgroups (urgent and non-urgent PCI). Our analysis suggests that fibrinogen and CRP higher elevation in patients presenting with ACS may explain the higher incidence of events comparing to planned PCI patients.

Whatever the causes, patients with increased preprocedural levels of inflammation biomarkers are clearly more at risk of MACE, and may benefit from more intensive antithrombotic therapy. One may hypothesize that therapeutic optimization may reduce the observed residual risk in these high risk patients.

Recent studies explored the interest of a prolonged dual antiplatelet therapy (DAPT) beyond one year after coronary stent implantation [32]. Of notice Maury et al [33] shows that prolonged DAPT beyond one year after a DES implantation significantly reduced the risks of stent thrombosis and major adverse cardiovascular and cerebrovascular events but was associated with an increased risk of bleeding. Although inflammation markers were not included in the risk to benefit model derived from this study [34], we believe that their elevation may help identifying high risk patients that may benefit from prolonged DAPT.

In addition, the new powerful P2Y12 inhibitors may benefit in these high residual risk patients. Platelet inhibition with Clopidogrel was shown to be highly variable, tributary to pharmacogenetics determinants. Some cytochromes polymorphisms were shown to be associated with lower biological effect and higher rate of MACE [36 37]. The new P2Y12 inhibitors (ticagrelor and prasugrel) have been proven beneficial in ischemic events reduction including stent thrombosis in patient undergoing PCI for acute coronary syndrome [38 39].

High risk coronary artery disease patients with elevated inflammatory markers may also benefit from more intensive lipid lowering therapy using high dose statin. The JUPITER trial investigating rosuvastatin in primary prevention patients with baseline CRP >2mg/L showed significant reduction of MACE suggesting that intensive statin therapy may benefit in patients with modest elevation of inflammation biomarkers[35].

Limitations

Antithrombotic therapy is a major intervention to prevent MACE and ST. As previously mentioned, we had no data regarding antiplatelet drugs prescription and adherence during follow-up in our study. One may hypothesize that patient presenting with MACE and stent thrombosis may have discontinued their treatments [28]. To our knowledge there are no known correlation between periprocedural elevation of inflammation markers and early antithrombotic drugs discontinuation after PCI.

Other known factor of ST such as residual target lesion thrombus or dissection, intra coronary media stasis, stent under expansion or incomplete stent apposition were not reported in our study [40] [41].

Because our study was retrospective, CRP values were unavailable for almost 20% of patients. In our routine clinical practice, fibrinogen measurement is more frequently performed. Inflammation markers level at the time of MACE during follow up were not available. These data would have helped identifying whether their elevation is merely of marker of residual risk or a direct effector of acute atherosclerotic events. This is important because if they are only residual risk markers then there would be no rational to differ stent implantation in patients with elevated fibrinogen or CRP.

CONCLUSION

Peri procedural elevated serum fibrinogen and CRP were associated with higher risk of long term MACE and stent thrombosis including early stent thrombosis in our population. These markers measurement may be recommended before scheduled PCI, as they may be an efficient tool for clinician to identify high risk patients for ischemic events residual atherothrombotic risk. Whether patients with markers elevation may benefit from differed PCI is not known and still questionable. Our data support the hypothesis that they may benefit from more intensive and prolonged anti-thrombotic medication because of higher residual risk. Prospective clinical trials investigating this hypothesis are needed as well as trials testing more intensive lipid lowering strategies in these high risk patients.

REFERENCES

1. *Green, D., Foiles, N., Chan, C., Schreiner, P. J. & Liu, K. Elevated fibrinogen levels and subsequent subclinical atherosclerosis: The CARDIA Study. Atherosclerosis **202,** 623–631 (2009).*

2. *Epstein, F. H. & Ross, R. Atherosclerosis—an inflammatory disease. N. Engl. J. Med. **340,** 115–126 (1999).*

3. *Heinrich, J., Balleisen, L., Schulte, H., Assmann, G. & van de Loo, J. Fibrinogen and factor VII in the prediction of coronary risk. Results from the PROCAM study in healthy men. Arterioscler. Thromb. Vasc. Biol. **14,** 54–59 (1994).*

4. *Schwartz, R. S., Borissoff, J. I., Spronk, H. M. & ten Cate, H. The hemostatic system as a modulator of atherosclerosis. N. Engl. J. Med. **364,** 1746–1760 (2011).*

5. *Odeberg, J. et al. Influence of pre-existing inflammation on the outcome of acute coronary syndrome: a cross-sectional study. BMJ Open **6,** e009968 (2016).*

6. *Sorajja, P. et al. Impact of Delay to Angioplasty in Patients With Acute Coronary Syndromes Undergoing Invasive Management. J. Am. Coll. Cardiol. **55,** 1416–1424 (2010).*

7. *2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur. Heart J. **35,** 2541–2619 (2014).*

8. *2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction | Journal of the American College of Cardiology | American College of Cardiology Foundation. Available at: http://content.onlinejacc.org/article.aspx?articleid=2463473. (Accessed: 19th July 2016)*

9. *Cutlip, D. E. et al. Clinical End Points in Coronary Stent Trials: A Case for Standardized Definitions. Circulation **115,** 2344–2351 (2007).*

10. *Ridker, P. M. High-Sensitivity C-Reactive Protein. Circulation **103,** 1813–1818 (2001).*

11. *Koenig, W. et al. C-Reactive Protein, a Sensitive Marker of Inflammation, Predicts Future Risk of Coronary Heart Disease in Initially Healthy Middle-Aged Men. Circulation **99,** 237–242 (1999).*

12. *Jialal, I., Devaraj, S. & Venugopal, S. K. C-Reactive Protein: Risk Marker or Mediator in Atherothrombosis? Hypertension **44,** 6–11 (2004).*

13. *Buffon, A. et al. Preprocedural serum levels of C-reactive protein predict early complications and late restenosis after coronary angioplasty. J. Am. Coll. Cardiol. **34,** 1512–1521 (1999).*

14. *Park, D.-W. et al. A Point-of-Care Platelet Function Assay and C-Reactive Protein for Prediction of Major Cardiovascular Events After Drug-Eluting Stent Implantation. J. Am. Coll. Cardiol. **58,** 2630–2639 (2011).*

15. *Cai, H. et al. Serum amyloid A induces monocyte tissue factor. J. Immunol. Baltim. Md 1950 **178,** 1852–1860 (2007).*

16. *Tatsumi, K. & Mackman, N. Tissue Factor and Atherothrombosis. J. Atheroscler. Thromb. **22,** 543–549 (2015).*

17. *Andrié, R. P. et al. Increased expression of C-reactive protein and tissue factor in acute coronary syndrome lesions: Correlation with serum C-reactive protein, angioscopic findings, and modification by statins. Atherosclerosis* ***202,*** *135–143 (2009).*

18. *Kannel, W. B., Wolf, P. A., Castelli, W. P. & D'Agostino, R. B. Fibrinogen and risk of cardiovascular disease. The Framingham Study. JAMA* ***258,*** *1183–1186 (1987).*

19. *Meade, T. W. et al. Haemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study. Lancet Lond. Engl.* ***2,*** *533–537 (1986).*

20. *Lee, A. J., Lowe, G. D., Woodward, M. & Tunstall-Pedoe, H. Fibrinogen in relation to personal history of prevalent hypertension, diabetes, stroke, intermittent claudication, coronary heart disease, and family history: the Scottish Heart Health Study. Br. Heart J.* ***69,*** *338–342 (1993).*

21. *Fibrinogen Studies Collaboration et al. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant meta-analysis. JAMA* ***294,*** *1799–1809 (2005).*

22. *Ang, L. & Mahmud, E. Monitoring oral antiplatelet therapy: is it justified? Ther. Adv. Cardiovasc. Dis.* ***2,*** *485–496 (2008).*

23. *Mahmud, E. et al. Effect of Serum Fibrinogen, Total Stent Length, and Type of Acute Coronary Syndrome on 6-Month Major Adverse Cardiovascular Events and Bleeding After Percutaneous Coronary Intervention. Am. J. Cardiol.* ***117,*** *1575–1581 (2016).*

24. *Riegger, J. et al. Histopathological evaluation of thrombus in patients presenting with stent thrombosis. A multicenter European study: a report of the prevention of late stent thrombosis by an interdisciplinary global European effort consortium. Eur. Heart J.* ***37,*** *1538–1549 (2016).*

25. *Grines, C. L. et al. Prevention of Premature Discontinuation of Dual Antiplatelet Therapy in Patients With Coronary Artery StentsA Science Advisory From the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, With Representation From the American College of Physicians. J. Am. Coll. Cardiol.* ***49,*** *734–739 (2007).*

26. *Holmes Jr, D. R. et al. Stent Thrombosis. J. Am. Coll. Cardiol.* ***56,*** *1357–1365 (2010).*

27. *Yano, M. et al. Antiplatelet therapy discontinuation and stent thrombosis after sirolimus-eluting stent implantation: five-year outcome of the j-Cypher Registry. Int. J. Cardiol.* ***199,*** *296–301 (2015).*

28. *Eisenberg, M. J., Richard, P. R., Libersan, D. & Filion, K. B. Safety of Short-Term Discontinuation of Antiplatelet Therapy in Patients With Drug-Eluting Stents. Circulation* ***119,*** *1634–1642 (2009).*

29. *Leibundgut, G. et al. Stent thrombosis up to 3 years after stenting for ST-segment elevation myocardial infarction versus for stable angina--comparison of the effects of drug-eluting versus bare-metal stents. Am. Heart J.* ***158,*** *271–276 (2009).*

30. *de la Torre-Hernández, J. M. et al. Drug-eluting stent thrombosis: results from the multicenter Spanish registry ESTROFA (Estudio ESpañol sobre TROmbosis de stents FArmacoactivos). J. Am. Coll. Cardiol.* ***51,*** *986–990 (2008).*

31. *Kukreja, N. et al. The Risk of Stent Thrombosis in Patients With Acute Coronary Syndromes Treated With Bare-Metal and Drug-Eluting Stents. JACC Cardiovasc. Interv.* ***2,*** *534–541 (2009).*

32. *Park, S.-J. et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. N. Engl. J. Med.* ***362,*** *1374–1382 (2010).*

33. *Mauri, L. et al. Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents. N. Engl. J. Med.* ***371,*** *2155–2166 (2014).*

34. *Yeh RW, Secemsky EA, Kereiakes DJ & et al. DEvelopment and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA* ***315,*** *1735–1749 (2016).*

35. *Ridker, P. M. et al. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. N. Engl. J. Med.* ***359,*** *2195–2207 (2008).*

36. *Cayla, G. et al. Clinical, angiographic, and genetic factors associated with early coronary stent thrombosis. JAMA* ***306,*** *1765–1774 (2011).*

37. *Simon, T. et al. Genetic determinants of response to clopidogrel and cardiovascular events. N. Engl. J. Med.* ***360,*** *363–375 (2009).*

38. *Wiviott, S. D. et al. Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. N. Engl. J. Med.* ***357,*** *2001–2015 (2007).*

39. *Wallentin, L. et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. N. Engl. J. Med.* ***361,*** *1045–1057 (2009).*

40. *Fujii, K. et al. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. J. Am. Coll. Cardiol.* ***45,*** *995–998 (2005).*

41. *Cook, S. et al. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. Circulation* ***115,*** *2426–2434 (2007).*

Table 1. Patients Characteristics

Characteristic	Mean ± SD or n(%)
Age, yr (mean ± SD)	**67,8 ± 13,4**
Male, n (%)	524 (72,9)
BMI, kg/m² (mean ± SD)	27,2 ± 4,8
Risk Factors	
Hypertension, n (%)	399 (55,4)
Diabetes Mellitus, n (%)	187 (26)
Hypercholesterolemia, n (%)	400 (55,6)
Smokers, n (%)	370 (51,4)
Family history, n (%)	176 (24,5)
LVEF <40%, n (%)	126 (17,5)
Prior Stroke	31 (4,3)
Prior Myocardial Infarction, n (%)	127 (17,7)
Prior PCI, n (%)	214 (29,8)
Prior CABG, n (%)	66 (9,2)
platelet inhibitors	
Aspirin, n (%)	719 (100)
Ticagrelor, n (%)	280 (38,9)
Prasugrel, n (%)	5 (0,69)
Clopidogrel, n (%)	387 (53,8)
Abciximab, n (%)	39 (5,4)

SD: standard deviation; BMI: body mass index; LVEF: left ventricular ejection function; PCI: percutaneous Coronary intervention; CABG: Coronary artery bypass graft;

Table 2. Baseline Lab analysis

Lab analysis	Mean ± SD
Hemoglobin (g/L)	136,1 ±17,19
Platelet (G/L)	228,2 ±74,5
Leukocytes (G/L)	9,6 ± 3,8
CRP (mg/L)	9,22 ± 19,5
Fibrinogen (G/L)	3,92 ± 1,0
GFR MDRD (mL/mn)	75,1 ± 24,5

SD: standard deviation; CRP: C-reactive protein; GFR: glomerular filtration rate

Table 3. Indication of PCI and procedural data

	Mean ± SD / n(%)
STEMI	168 (23,4%)
NSTEMI	239 (33,2%)
Total Acute Coronary Syndrome	407 (56,6%)
Multivessels disease	414 (57,6%)
Stenting site	
- Left Main	25 (3,48%)
- LAD	338 (47%)
- Cx	175 (24,34%)
- RCA	256 (35,61%)
- CABG	9 (1,13%)
N Dilated site	1,19 ±0,51
N Stent	1,69 ±1,05
Stent diameter (mm)	2,93 ±0,46
Stent length (mm)	17,2 ±6,41
Total stent length (mm)	26,82 ±17,41
Stent type DES/BVS/BMS *	633 (88,0%) / 9 (1,3%) / 77 (10,7%)

STEMI = ST elevation myocardial infarction; NSTEMI = non-ST elevation myocardial infarction

LAD: left descending artery; Cx: circumflex artery; RCA: right coronary artery; CABG: coronary artery bypass graft;

DES = drug-eluted stent; BVS = bioresorbable stent; BMS = bare-metal stent

*803 arteries dilated in 719 patients. 1213 stents were implanted

Table 4. MACE during follow-up

Events	n	%
MACE	71	9,98
All cause death	56	7,79
Cardiac death	41	5,7
Myocardial Infarction (including ST)	46	6,39
Stent related MACE	48	6,68
Stent thrombosis (all types)	34	4,74
Early ST	9	1,25
Late	25	3,48
Definite or probable ST	20	2,78
Restenosis	17	2,36
Stroke	8	1,11

MACE = Major Cardiac Events; ST = stent thrombosis;

Table 5. Univaried analysis MACE risks factors

	MACE (mean ±SD or %)	HR	no MACE (mean ±SD or %)	P*
male	76,1%	0,93	72,6%	0,709
Age (yr)	71,4 ± 14,1		67,4 ± 13,3	0,016
BMI (kg/m²)	27,3 ± 5,2		27,2 ± 4,8	0,686
smokers	49,3%	1,01	51,5%	0,902
HTA	62,0%	1,13	54,8%	0,873
diabetes	36,6%	1,49	24,6%	0,156
hypercholesterolemia	53,5%	0,99	54,2%	0,896
LVEF < 40%	42,25%	4,2	14,81%	<0,0001
multitroncular disease	76,1%	1,37	55,4%	0,126
previous PCI	35,2%	1,22	28,9%	0,478
previous CABG	21,1%	2,68	7,9%	< 0,0001
Acute coronary syndrome	54,9%	0,93	56,8%	0,8
Platelet inhibitors				
Clopidogrel	58,6%	1,10	53,2%	0,981
Ticagrelor	32,9%	0,83	39,7%	0,739
Prasugrel	0,0%		0,6%	
Abciximab	0,071	1,36	0,053	0,074
stent implanted (n)	1,78 ±1,27		1,67 ±1,02	0,282
PCI site				
left main	8,5%	2,87	2,9%	< 0,0001
LAD	50,7%	1,08	46,7%	0,887
Cx	35,2%	1,53	23,1%	0,114
RCA	32,4%	0,86	37,6%	< 0,0001
CABG	5,53%	7,67	0,77%	0,006
dilated sites (n)	1,15 ± 0,39		1,19 ± 0,52	0,546
stent diameter (mm)	2,86 ± 0,45		2,93± 0,45	0,175
Stent lenght (mm)	16,69 ± 6,54		17,42 ± 4,72	0,653
total stent lenght (mm)	26,00 ± 15,45		26,93 ± 17,55	0,670
BMS	14,1%	1,40	10,1%	0,069
Hb (g/L)	128,65 ±16,09		137,57 ± 18,85	< 0,0001
Platelet (G/L)	233,93 ±74,06		227,52 ± 78,74	0,493
Leukocyte (G/L)	10,28 ±5,51		9,53 ± 3,59	0,114
CRP (mg/L)	17,81 ±34,43		8,22 ± 15,98	0,0002
Fibrinogen (g/L)	4,31 ±1,10		3,88 ± 0,98	0,001
GFR MDRD (mL/mn)	65,56 ±33		75,6 ±23	0,0146

MACE = Major Cardiac Events; ST = stent thrombosis; BMI = Body mass index; LVEF = left ventricular ejection function; PCI = percutaneous Coronary intervention; CABG = coronary artery bypass graft; LAD : left descending artery; Cx : circumflex artery; RCA : right coronary artery; BMS = bare-metal stent; Hb = Hemoglobin; CRP : C-reactive protein; GFR : glomerular filtration rate

*p-value for comparison of MACE and no MACE groups

Table 6. Adjusted MACE Hazard Ratios

	Adjusted HR	P*
Age > 71 years	2,11 [1,28 – 3,46]	0,003
LVEF < 40%	4,21 [2,50 – 7,07]	< 0,0001
previous CABG	2,81 [1,47 – 5,39]	0,003
PCI site		
-left main	3,05 [1,18 – 7,92]	0,036
-RCA	0,45 [0,25 – 0,81]	0,005
-CABG	7,67 [2,01 – 29,28]	0,006
Lab parameters		
-Hb < 123 g/L	3,11 [1,86 – 5,2]	< 0,0001
-CRP > 6,0 mg/L	2,28 [1,32 – 3,91]	0,003
- Fibrinogen > 3,5 g/L	2,73 [1,49 – 5,04]	0,0005
- GFR MDRD <63mL/mn	3,09 [1,88 – 5,09]	<0,0001

LVEF: left ventricular ejection function; CABG: coronary artery bypass graft; RCA: right coronary artery; PCI : percutaneous coronary intervention; Hb : hemoglobin; CRP: C-reactive protein; GFR MDRD : glomerular filtration rate MDRD; HR, hazard ratio with 95% confidence interval for comparisons between MACE and no MACE groups
*p-value for comparison of MACE and no MACE groups

Table 7. Univaried analysis stent related MACE risks factors

	Stent related MACE (mean ±SD or %)	HR	No stent related MACE (mean ±SD or %)	P*
male	72,92%	1,00	72,88%	0,99
age	70,0±13,5		67,6±13,4	0,249
BMI	28,02%		27,19%	0,30
smokers	50,0%	0,94	51,56%	0,83
HTA	64,58 %	1,51	54,69%	0,179
diabetes	35,42%	1,63	25,19%	0,129
hypercholesterolemia	62,5%	1,44	53,65%	0,23
multitroncular disease	83,33%	3,97	55,74%	<0,0001
previous PCI	41,67%	1,76	28,91%	0,068
LVEF < 40%	37,5%	3,12	16,1%	0,0006
previous CABG	25%	3,81	8,05%	0,0008
Acute coronary syndrome	52,08%	0,82	56,93%	0,51
Platelet inhibitors				
Clopidogrel	64,58%	1,61	53,06%	0,12
Ticagrelor	31,25%	0,69	39,49%	0,24
Prasugrel	0%		0,75%	
Abciximab	6,25%	1,19	5,37%	0,79
stent implanted	1,92±1,43		1,67±1,02	0,246
PCI site				
CABG	6,25%	7,39	0,89%	0,0165
left main	10,42%	3,78	2,98%	0,024
LAD	45,83%	0,95	47,09%	0,86
Cx	35,42%	1,78	23,55%	0,07
RCA	18,75%	0,39	36,96%	0,0076
n dilated sites	1,12±0,33		1,190±0,52	0,19
stent diameter	2,93±0,46		2,83±0,44	0,139
Stent length	17,34±6,51		15,81±4,54	0,053
total stent length	27,48±16,82		26,78±17,4	0,78
BMS	14,58%	1,46	10,43%	0,38
Hb (g/L)	128,58±18,5		137,26±16,9	0,0027
Platelet (G/L)	238,15±77,9		227,41±74,3	0,36
Leukocyte (G/L)	9,45±3,84		9,66±3,84	0,72
CRP (mg/L)	18,46±35,02		8,450±16,8	0,063
Fibrinogen (g/L)	4,39±0,99		3,890±0,99	0,012
GFR MDRD (mL/mn)	68,18 ±35,4		75,1 ±23,5	0,19

MACE = Major Cardiac Events; ST = stent thrombosis; BMI = Body mass index; LVEF = left ventricular ejection function; PCI = percutaneous Coronary intervention; CABG = coronary artery bypass graft; LAD: left descending artery; Cx: circumflex artery; RCA: right coronary artery; BMS = bare-metal stent; Hb = Hemoglobin; CRP: C-reactive protein; GFR : glomerular filtration rate

*p-value for comparison of stent related MACE and no stent related MACE groups

Table 8. Adjusted stent related MACE Hazard Ratios

	Adjusted HR	p
LVEF < 40%	3,13 [1,68 – 5,81]	< 0,0006
previous CABG	3,81 [1,77 – 7,75]	0,0008
Multivessels disease	3,97 [1,83 – 8,61]	< 0,0001
PCI site		
-CABG	7,39 [1,79 – 30,52]	0,017
-RCA	0,39 [0,19 – 0,83]	0,0076
Lab parameters		
-Hb < 123 g/L	2,78 [1,51 – 5,12]	0,0016
-CRP > 5,4 mg/L	2,22 [1,19 – 4,12]	0,013
- Fibrinogen > 3,35 g/L	5,29 [1,87 – 14,94]	0,0001

LVEF: left ventricular ejection function; CABG: coronary artery bypass graft; RCA: right coronary artery; PCI: percutaneous coronary intervention; Hb: hemoglobin; CRP: C-reactive protein;
HR, hazard ratio with 95% confidence interval for comparisons between stent related MACE and no stent related MACE groups

Table 9. Univaried analysis definite and probable stent thrombosis risks factors

	Definite/probable ST (mean ±SD or %)	Hazard Ratio	No definite/probable ST (mean ±SD or %)	P*
male	75%	1,119	72,8%	0,827
Age (yr)	69,8 ±14,63		67,7 ±13,4	0,368
BMI (kg/m²)	28,46 ±28,46		27,21 ±27,21	0,116
smokers	55,0%	1,15	51,4%	0,748
HTA	75,0%	2,48	54,8%	0,065
diabetes	35,0%	1,56	25,6%	0,356
hypercholesterolemia	65,5%	1,59	53,9%	0,323
LVEF < 40%	55,0%	6,21	16,45%	0,0001
multitroncular disease	75,0%	2,26	55,4%	0,099
previous PCI	45,0%	1,97	29,3%	0,144
previous CABG	25,0%	3,49	8,7%	0,035
Acute coronary syndrome	60,0%	1,15	56,51%	0,097
Platelet inhibitors				
-Clopidogrel	60,0%	1,29	53,6%	0,572
-Ticagrelor	40,0%	1,05	38,9%	0,922
-Prasugrel	0,0%		0,6%	
-Abciximab	0,0%		5,58%	
PCI site				
-left main	10%	2,87	3,1%	0,11
-LAD	45%	0,92	47,1%	0,847
-Cx	30%	1,34	24,2%	0,558
-RCA	20,0%	0,86	36,19%	0,11
-CABG	10,0%	10,98	1,0%	0,02
stent implanted	2,2 ±1,7		1,67 ±1,03	0,081
n dilated sites	1,1 ±0,31		1,19 ±0,51	0,552
stent diameter	2,81 ±0,46		2,93 ±0,48	0,217
Stent length	17,27 ±4,84		16,3 ±6,45	0,39
total stent length	27,45 ±19,96		26,69 ±17,27	0,142
BMS	10,0%	0,92	10,7%	0,916
Hb (g/L)	129,9 ±21,99		136,9 ±17,01	0,178
Platelet (G/L)	233,93 ±99		227,52 ±73,5	0,078
Leukocyte (G/L)	9,09 ±3,31		9,66 ±3,86	0,22
CRP (mg/L)	26,9 ±37,17		8,6 ±17,79	0,023
Fibrinogen (g/L)	4,56 ±1,01		3,90 ±0,89	0,0020
GFR MDRD (mL/mn)	68,19 ±35,41		75,01 ±23,51	0,19

MACE = Major Cardiac Events; ST = stent thrombosis; BMI = Body mass index; LVEF = left ventricular ejection function; PCI = percutaneous Coronary intervention; CABG = coronary artery bypass graft; LAD: left descending artery; Cx: circumflex artery; RCA: right coronary artery; BMS = bare-metal stent; Hb = Hemoglobin; CRP: C-reactive protein; GFR: glomerular filtration rate

*p-value for comparison of definite and probable stent thrombosis and no definite and probable stent thrombosis groups

Table 10. Adjusted definite and probable stent thrombosis Hazard Ratios

	Adjusted HR	P*
LVEF < 40%	6,21 [2,51 – 15,31]	0,0001
previous CABG	3,48 [1,23 – 9,92]	0,035
CABG stenting	10,98 [2,13 – 56,6]	0,02
Lab parameters		
CRP > 5,4 mg/L	4,33 [1,62 – 11,59]	0,002
Fibrinogen > 3,5 g/L	6,07 [1,39 – 26,4]	0,003

LVEF: left ventricular ejection function; CABG: coronary artery bypass graft; CRP: C-reactive protein;
HR, hazard ratio with 95% confidence interval for comparisons between definite and probable stent thrombosis and no definite and probable stent thrombosis groups
*p-value for comparison of definite and probable stent thrombosis and no definite and probable stent thrombosis groups

Table 11. Univaried analysis definite and probable early stent thrombosis risks factors

	Early ST (mean ±SD or %)	Hazard Ratio	No early ST (mean ±SD or %)	P*
male	77,8%	1,31	72,8%	0,734
age	73,2 ±13,04		67,7 ±13,3	0,241
BMI	28,1 ±3,02		27,2 ±4,86	0,421
smokers	55,6%	1,18	51,4%	0,804
HTA	88,9 %	6,56	54,9%	0,048
diabetes	22,20%	0,817	25,9%	0,8
hypercholesterolemia	66,7%	1,698	54,1%	0,446
LVEF < 40%	55,56%	6,08	17,04%	0,009
multitroncular disease	77,8%	2,606	57,32%	0,2
previous PCI	29,8%	1,336	22,3%	0,608
previous CABG	0%		9,31%	
Acute coronary syndrome	77,78%	1,15	56,34%	0,192
Platelet inhibitors				
Clopidogrel	22,22%	0,241	54,23%	0,051
Ticagrelor	66,67%	3,182	38,59%	0,09
Prasugrel	0,7%		0%	
Abciximab	22,2%	5,197	5,21%	0,041
PCI site				
left main	10%	2,87	3,1%	0,11
LAD	45%	0,92	47,1%	0,847
Cx	30%	1,34	24,2%	0,558
RCA	20,0%	0,86	36,19%	0,11
CABG	0%		1,27%	
stent implanted	1,78 ±1,39		1,68±1,04	0,849
n dilated sites	1,11 ±0,33		1,19 ±0,51	0,502
stent diameter (mm)	3,06 ± 0,46		2,92 ±0,53	0,48
Stent length (mm)	17,26 ±4,82		15,66 ±6,43	0,35
total stent length (mm)	26,84 ±16,4		26,62 ±17,37	0,89
BMS	10,0%	0,92	10,7%	0,916
Hb (g/L)	141,78 ±18,6		136,6 ±17,18	0,43
Platelet (G/L)	239,0 ±68,53		228,1 ±74,66	0,647
Leukocyte (G/L)	11,61 ±5,52		9,62 ±3,81	0,312
CRP (mg/L)	32,62 ±45,96		8,89 ±18,21	0,188
Fibrinogen (g/L)	4,42 ±1,29		3,92 ±1,00	0,314
GFR MDRD (mL/mn)	69,78 ±25,89		74,67 ±24,51	0,58

MACE = Major Cardiac Events; ST = stent thrombosis; BMI = Body mass index; LVEF = left ventricular ejection function; PCI = percutaneous Coronary intervention; CABG = coronary artery bypass graft; LAD: left descending artery; Cx: circumflex artery; RCA: right coronary artery; BMS = bare-metal stent; Hb = Hemoglobin; CRP: C-reactive protein; GFR: glomerular filtration rate

*p-value for comparison of definite and probable early stent thrombosis and no definite and probable early stent thrombosis groups

Table 12. Univaried analysis restenosis risks factors

	Restenosis mean or (%)	HR	no restenosis	P*
male	76,4%	1,21	72,8%	0,73
age	74,4 ±11,9		67,9 ±13,5	0,25
BMI	28,0 ±6,5		27,2 ±4,8	0,64
smokers	52,9%	1,06	51,4%	0,9
HTA	52,9 %	6,56	55,4%	0,84
diabetes	29,4%	1,19	25,7%	0,73
hypercholesterolemia	64,7%	1,56	53,9%	0,37
LVEF < 40%	23,6%	1,48	17,4%	0,52
multitroncular disease	76,8%	2,44	57, 2%	0,099
previous PCI	47,1%	2,14	29,3%	0,13
previous CABG	29,4%	4,38	8,3%	0,016
Acute coronary syndrome	52,2%	0,86	56,7%	0,75
Platelet inhibitors				
Clopidogrel	58,8%	1,24	53,7%	0,67
Ticagrelor	35,3%	0,85	38,9%	0,75
Prasugrel	0%		0,7%	
Abciximab	0%		5,6 %	
PCI site				
left main	5,9%	1,77	3,4%	0,61
LAD	52,9%	1,27	46,9%	0,62
Cx	41,2%	2,22	23,9%	0,12
RCA	11,8%	0,23	36,3%	0,02
CABG	0%		1,27%	
stent implanted	1,94 ±1,39		1,68±1,04	0,45
n dilated sites	1,12 ±0,33		1,19 ±0,33	0,39
stent diameter (mm)	2,84 ± 0,41		2,93 ±0,46	0,39
Stent length (mm)	17,49 ±5,73		17,23 ±6,43	0,58
total stent length (mm)	29,04 ±15,4		26,8 ±17,37	0,55
BMS	5,9%	0,52	10,8%	0,48
Hb (g/L)	127,18 ±18,6		136,9 ±17,18	0,04
Platelet (G/L)	253,0 ±98,5		227,6 ±73,9	0,64
Leukocyte (G/L)	9,98 ±3,8		9,64 ±3,84	0,36
CRP (mg/L)	16,53 ±29,41		9,02 ±18,61	0,14
Fibrinogen (g/L)	4,29 ±1,0		3,91 ±1,0	0,39
GFR MDRD (mL/mn)	70,47±19,57		74,71 ±24,62	0,39

MACE = Major Cardiac Events; ST = stent thrombosis; BMI = Body mass index; LVEF = left ventricular ejection function; PCI = percutaneous Coronary intervention; CABG = coronary artery bypass graft; LAD: left descending artery; Cx: circumflex artery; RCA: right coronary artery; BMS = bare-metal stent; Hb = Hemoglobin; CRP: C-reactive protein; GFR: glomerular filtration rate

*p-value for comparison of definite and probable early stent thrombosis and no definite and probable early stent thrombosis groups

Table 13. Non urgent PCI subgroup analysis: MACE, definite or probable stent thrombosis, all stent thrombosis type, restenosis and total stent related MACE and baseline levels of fibrinogen, CRP

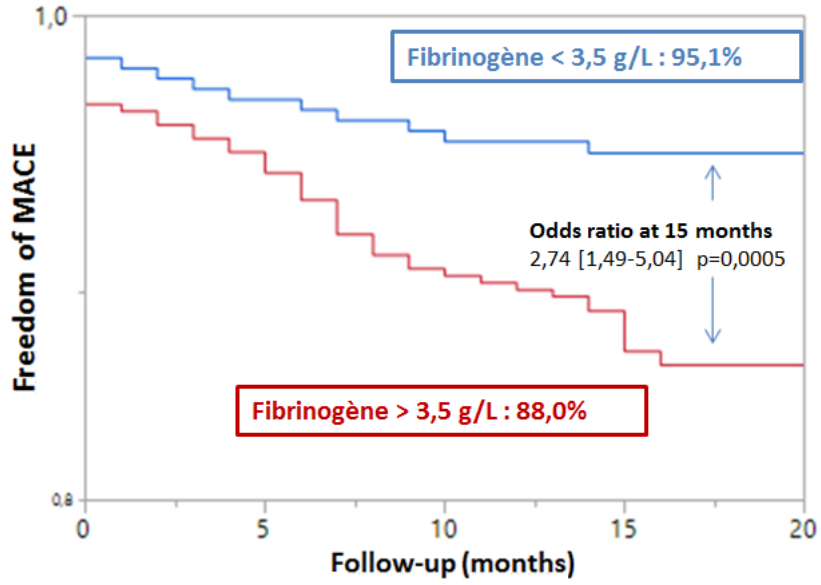
	Fibrinogen (g/L)			CRP (mg/L)		P*
MACE	no (n = 278)	yes (n = 32)		no (n = 266)	yes (n = 31)	
	3,85 ± 0,91	4,29 ± 0,87	p = 0,01	5,12 ± 7,67	5,76± 4,72	p = 0,51
stent thrombosis (definite or probable)	no (n = 302)	yes (n = 8)		no (n = 289)	yes (n = 8)	
	3,89 ± 0,92	4,11 ± 0,48	p = 0,26	5,15 ± 7,47	6,7 ± 5,27	p = 0,44
stent thrombosis (all type)	no (n = 295)	yes (n = 15)		no (n = 282)	yes (n = 15)	
	3,88 ± 0,92	4,25 ± 0,59	p = 0,036	5,17 ± 7,54	5,54 ± 4,62	p = 0,77
restenosis	no (n = 302)	yes (n = 8)		no (n = 289)	yes (n = 8)	
	3,89 ± 0,92	4,26 ± 1,11	p = 0,38	5,22 ± 7,51	3,85 ± 2,51	p = 0,19
stent related MACE	no (n=287)	yes (n = 23)		no (n = 274)	yes (n = 23)	
	3,87 ± 0,91	4,25 ± 0,79	p = 0,035	5,21 ± 7,64	4,95 ± 4,02	p = 0,79

Table 14. Urgent PCI subgroup analysis: MACE, definite or probable stent thrombosis, all stent thrombosis type, restenosis and total stent related MACE and baseline levels of fibrinogen, CRP

	Fibrinogen (g/L)			CRP (mg/L)		P*
MACE	no (n = 329)	yes (n = 36)		no (n = 239)	yes (n = 29)	
	3,89 ± 1,04	4,36 ± 1,29	p = 0,042	11,64 ± 21,28	30,73± 46,27	p = 0,036
stent thrombosis (definite or probable)	no (n = 353)	yes (n = 12)		no (n = 257)	yes (n = 11)	
	3,91 ± 1,07	4,86 ± 0,98	p = 0,006	12,5 ± 24,13	41,72 ± 43,58	p = 0,05
stent thrombosis (all type)	no (n = 347)	yes (n = 18)		no (n = 252)	yes (n = 16)	
	3,90 ± 1,06	4,77 ± 1,18	p = 0,007	11,88 ± 22,3	42,33 ± 50,28	p = 0,029
restenosis	no (n = 356)	yes (n = 9)		no (n = 260)	yes (n = 8)	
	3,93 ± 1,08	4,33 ± 0,95	p = 0,25	13,22 ± 25,2	29,2 ± 38,45	p = 0,28
stent related MACE	no (n=341)	yes (n = 24)		no (n = 274)	yes (n = 23)	
	3,9 ± 1,06	4,54 ± 1,15	p = 0,014	12,03 ± 22,5	33,29 ± 46,7	p = 0,051

*p-value for comparison of definite and probable stent thrombosis and no definite and probable stent thrombosis groups

Figure 1. Event-free curves (with 95% confidence intervals) for MACE at 15 months in the elevated fibrinogen (>3,5g/L) and CRP (>5,4mg/L) patients groups and in the other patients.



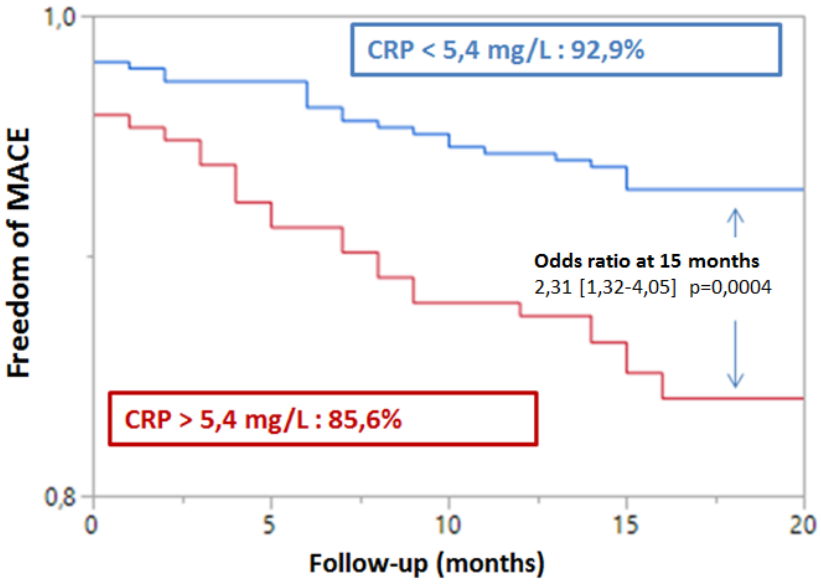
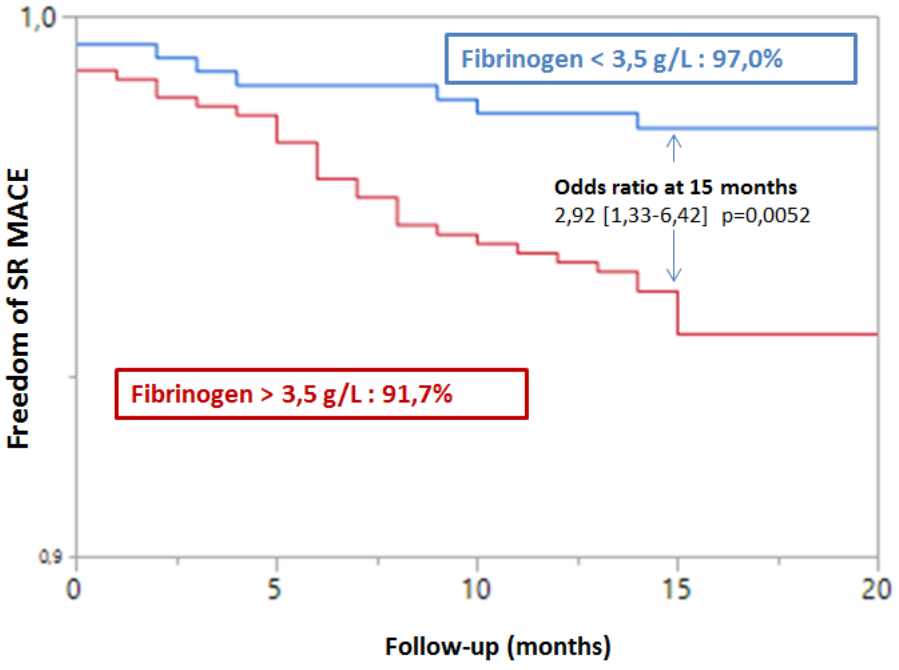


Figure 2. Event-free curves (with 95% confidence intervals) for stent related MACE at 15 months in the elevated fibrinogen (>3,5g/L) and CRP (>5,4mg/L) patients groups and in the other patients.



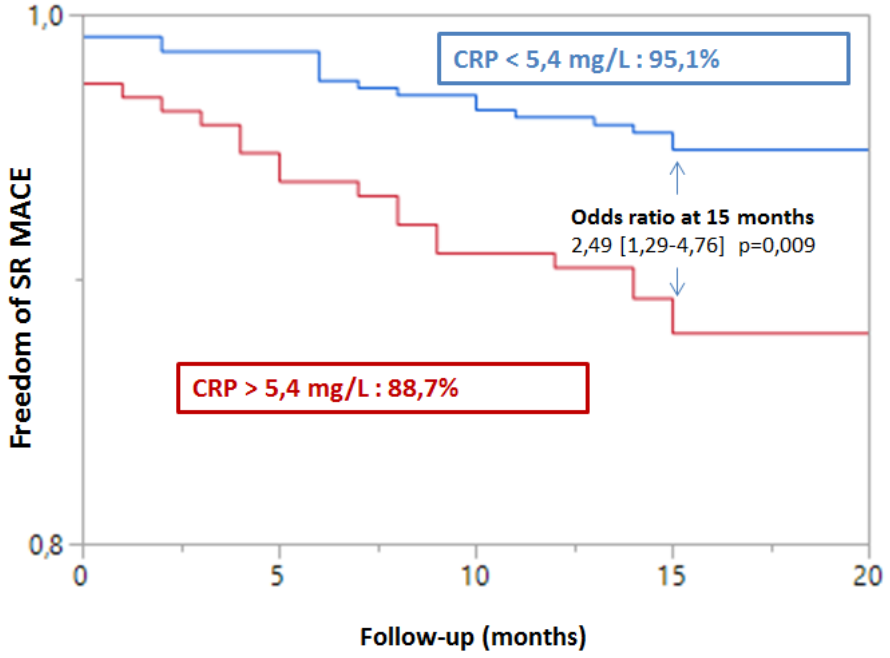
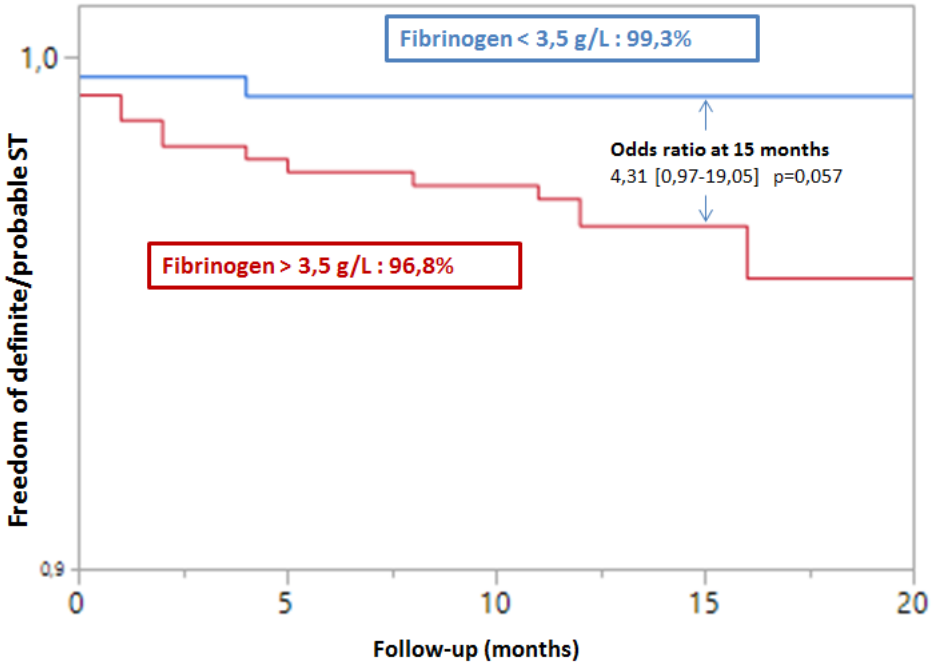
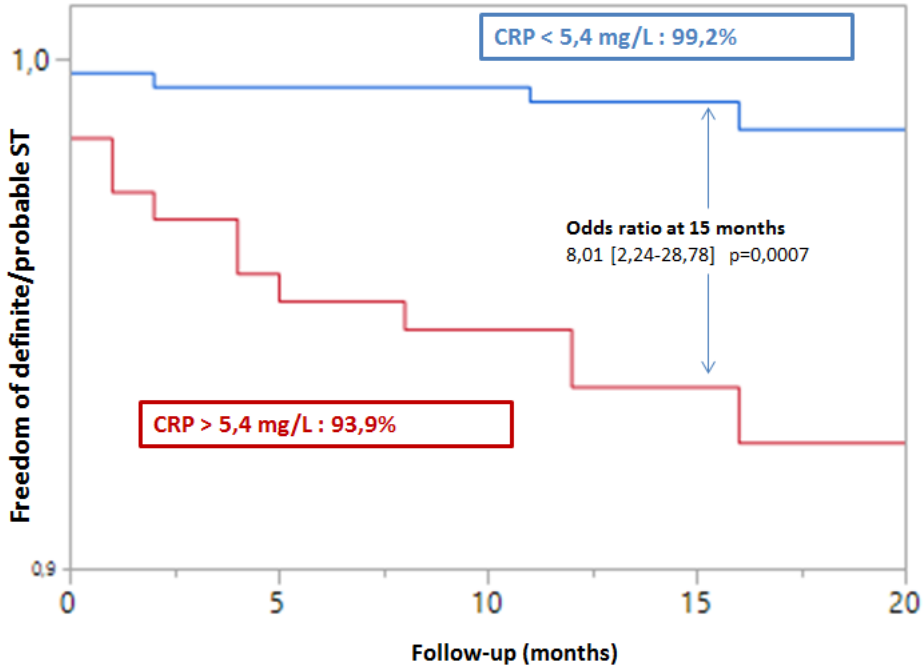


Figure 3. Event-free curves (with 95% confidence intervals) for definite and probable sent thrombosis at 15 months in the elevated fibrinogen (>3,5g/L) and CRP (>5,4mg/L) patients groups and in the other patients.





SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert d'opprobre
et méprisé de mes confrères
si j'y manque.

Farid CHALLAL

45 pages – 14 tableaux – 3 figures

Résumé : La présence d'un syndrome inflammatoire biologique est considérée comme un facteur d'augmentation du risque d'évènements thrombotique et de thrombose de stent au décours d'une angioplastie coronaire. La pratique est de repousser l'implantation de stent en cas d'élévation des marqueurs d'inflammation ce qui expose les patients à un risque d'évènement cardiaque dans l'attente de la revascularisation.
Objectif : l'objectif principal de cette étude était d'explorer la corrélation entre les taux de fibrinogène et protéine C-réactive dosés avant la réalisation d'une implantation de stent coronaire et le risque de survenue d'évènements cardiovasculaires majeurs à long terme notamment le risque de thrombose de stent.
Méthodes et Résultats : 719 patients consécutifs pour lesquels avait été réalisée une angioplastie coronaire percutanée avec implantation d'au moins un stent ont été inclus rétrospectivement. Les taux de fibrinogène et de protéine C-réactive (CRP) étaient dosés en routine avant ou immédiatement après l'angioplastie. Après un suivi moyen de 15,9 ±4,2 mois, un évènement cardiovasculaire majeur (MACE) au moins était survenu chez 71 patients (9,87%) et une thrombose de stent certaine ou probable était survenue chez 20 patients (2,78%). L'analyse multivariée montrait que le taux de fibrinogène et de CRP étaient des facteurs de risque indépendants de la survenue de MACE et de la survenue de thrombose de stent certaine ou probable.
Conclusion : des taux de fibrinogène et CRP élevés lors d'une angioplastie coronaire percutanée sont associés à risque plus élevé de survenue d'évènement cardiovasculaire majeur à long terme et de thrombose de stent. Retarder l'angioplastie ou proposer une stratégie anti-thrombotique plus intensive et/ou prolongée pourrait être proposée dans cette population à haut risque.

Mots clés : angioplastie coronaire – stent - thrombose de stent – fibrinogène – CRP - inflammation

Jury :

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