

Jean-Philippe Collet - 20+ years of research on thrombosis

Pr Johanne SILVAIN, MD-PhD

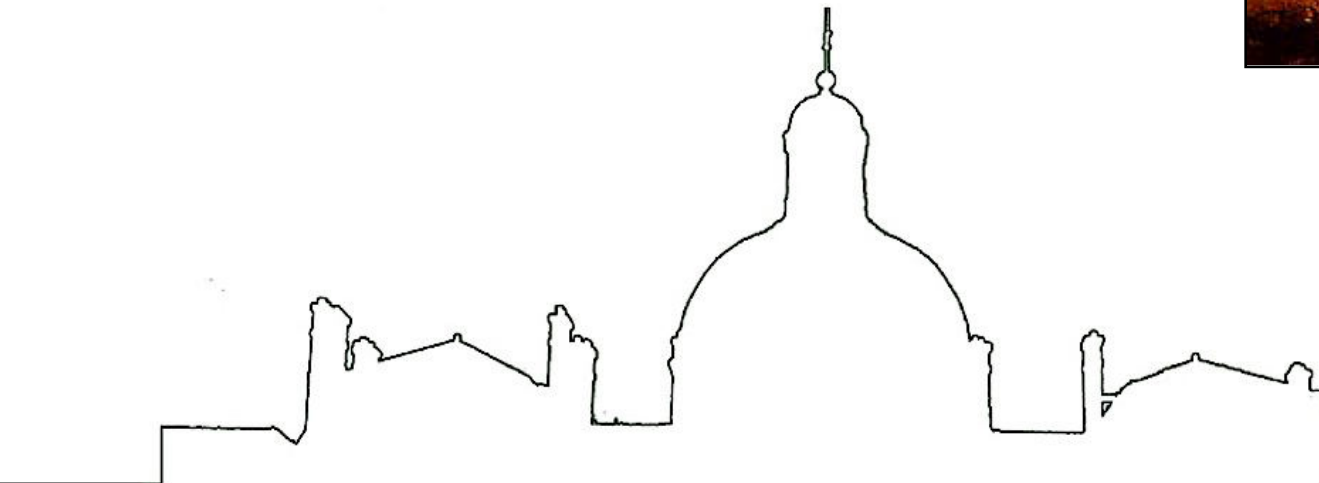
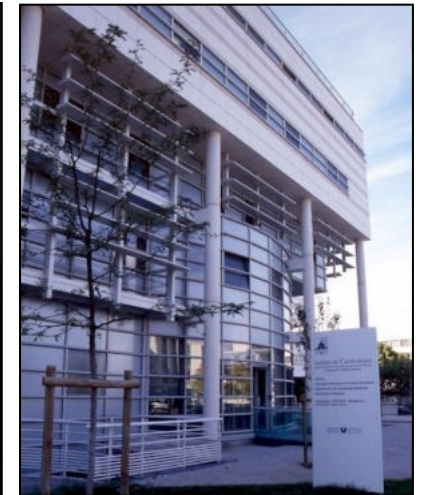
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² *ACTION Cœur study group*

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⁴ *Institut de Cardiologie (APHP)*



Academic Research Organization

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PITIE-SALPETRIERE UNIVERSITY HOSPITAL

Low molecular weight heparin after mechanical heart valve replacement.

Montalescot G, **Collet JP et al. – 2000**

PCI after **subcutaneous enoxaparin** pretreatment in patients with unstable angina pectoris.

Collet JP et al – 2001

Effects of **Abciximab** on the architecture of platelet-rich clots in patients with acute myocardial infarction undergoing primary PCI

Collet JP et al – 2001

Acute release of **plasminogen activator inhibitor-1** in ST-segment elevation myocardial infarction predicts mortality.

Collet JP et al – 2003

Anti-Xa activity relates to survival and efficacy in unselected acute coronary syndrome patients treated with enoxaparin.

Montalescot G, **Collet JP et al. – 2004**

Impact of prior use or recent **withdrawal of oral antiplatelet agents** on acute coronary syndromes.

Collet JP et al – 2004

Architecture of intracoronary thrombi in ST-elevation acute myocardial infarction: time makes the difference.

Beygui F, **Collet JP et al – 2006**



JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Thrombosis



Effects of various **anticoagulant treatments** on **von Willebrand factor** release in unstable angina.

Montalescot G, **Collet JP et al. – 2000**

A unique, low dose of intravenous enoxaparin in elective percutaneous coronary intervention.

Chousat R, **Collet JP et al – 2002**

Eptifibatide provides additional platelet inhibition in NSTEMI patients already treated with aspirin and clopidogrel. Results of the PEACE study.

Dalby M, **Collet JP et al – 2004**

Percutaneous coronary intervention after **fibrinolysis**: a multiple meta-analyses approach according to the type of strategy.

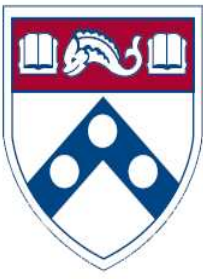
Collet JP et al – 2006

Enoxaparin anticoagulation monitoring in the catheterization laboratory using a new bedside test.

Silvain J , **Collet JP et al – 2010**

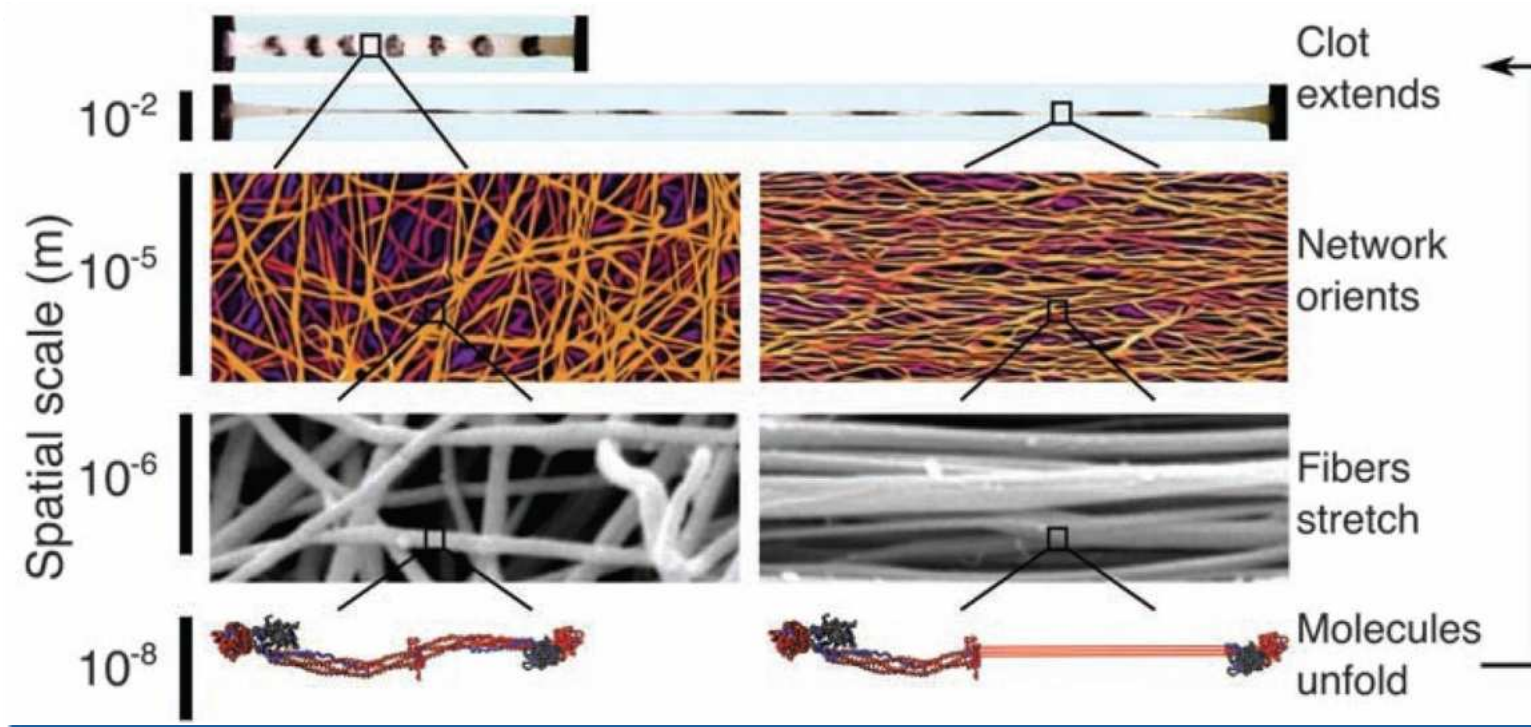
Slow response to clopidogrel predicts low response.

Bellemain-Appaix A, **Collet JP et al. – 2010**



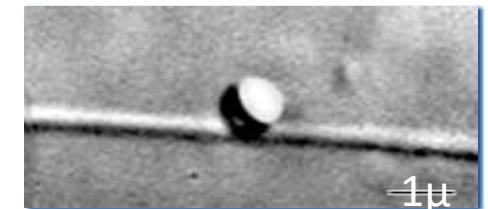
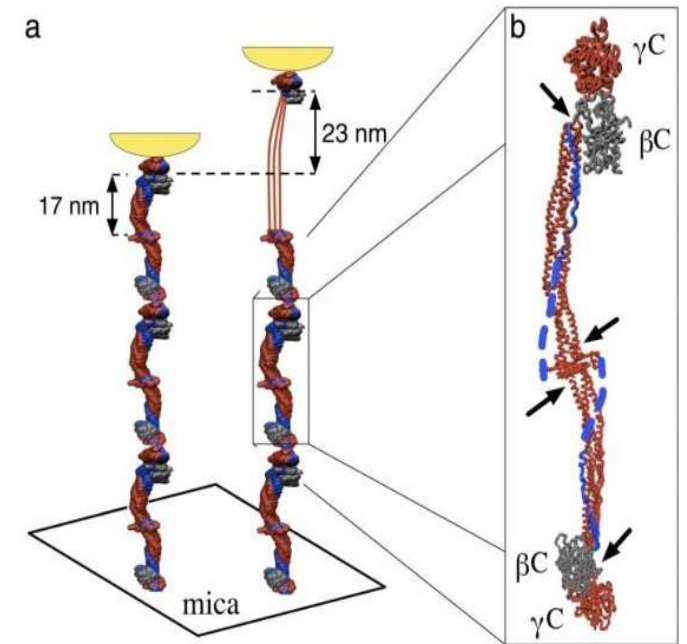
Thrombosis

Fibrin architecture

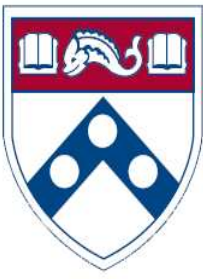


Collet JP et al . PNAS 2005

Weisel JW et al . Science 2009

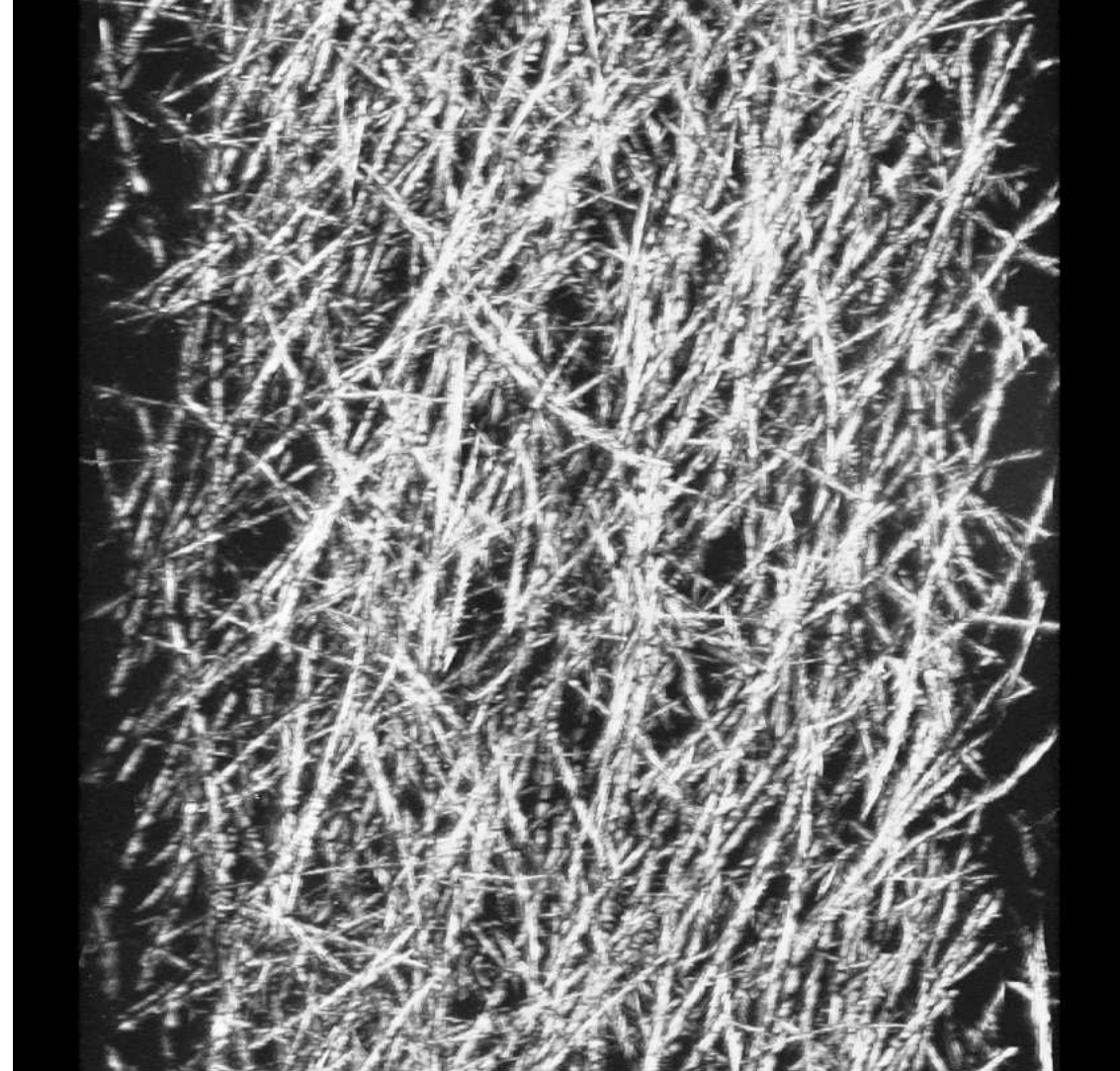
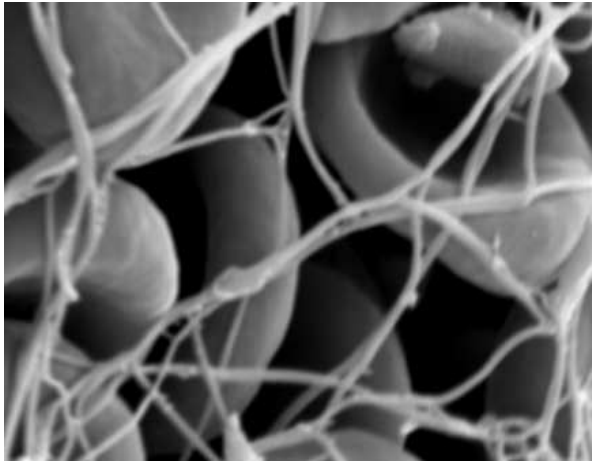


Brown et al . Science 2009

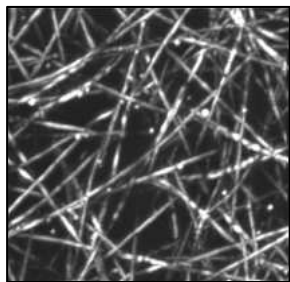


Thrombus

Fibrin architecture

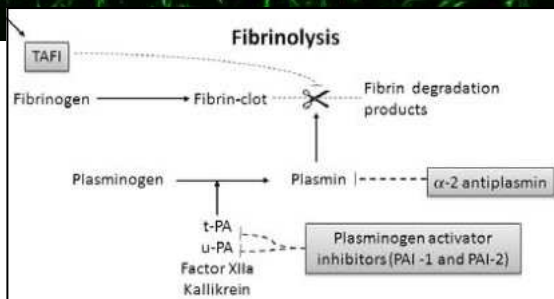
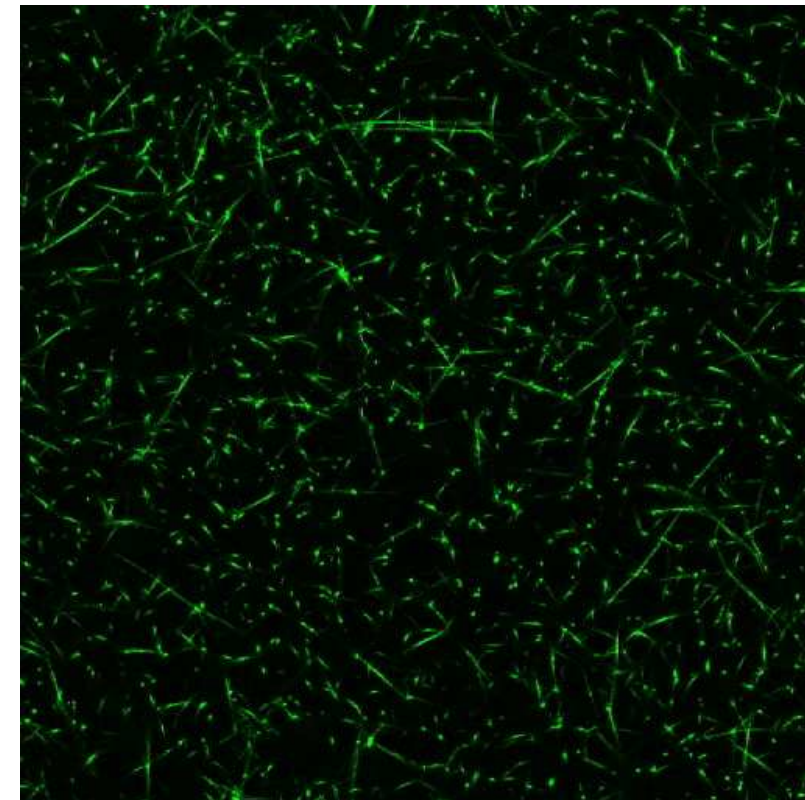
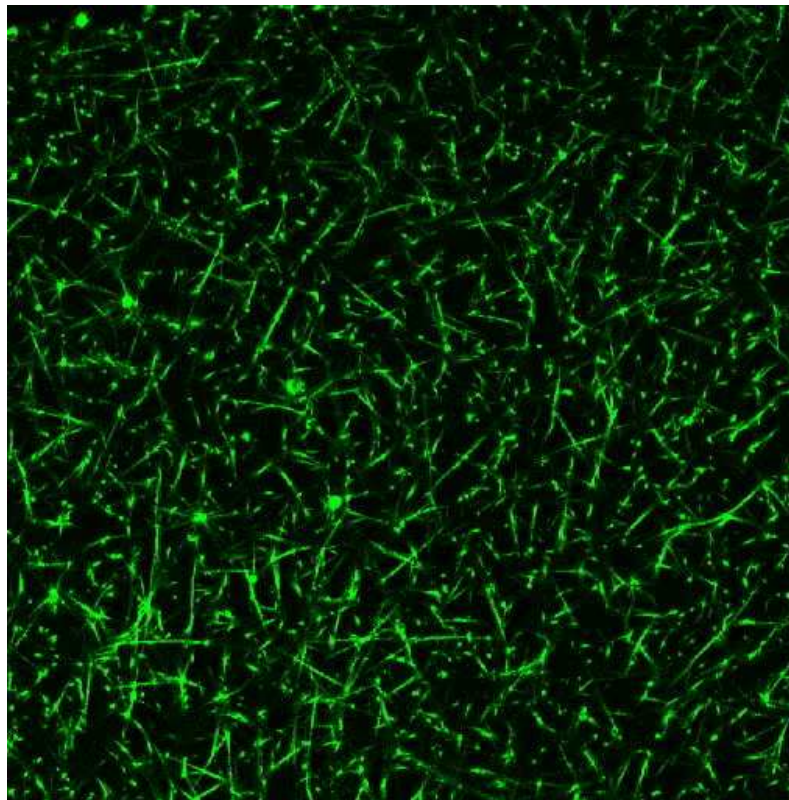
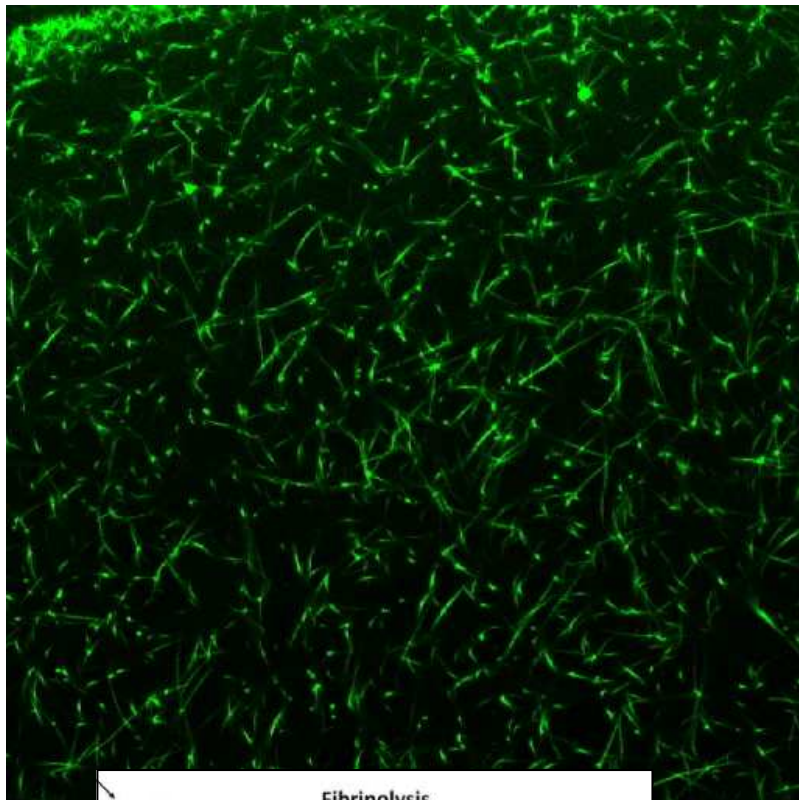
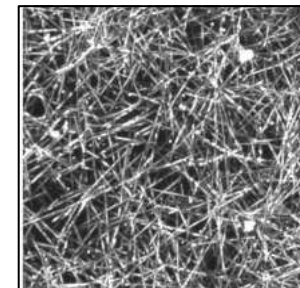


Silvain J , Collet JP et al . UPENN 2006



Thrombus Inhibition

Fibrinolysis depends on fibrin phenotype



Collet JP et al. Arterioscler Thromb Vasc Biol. 2000

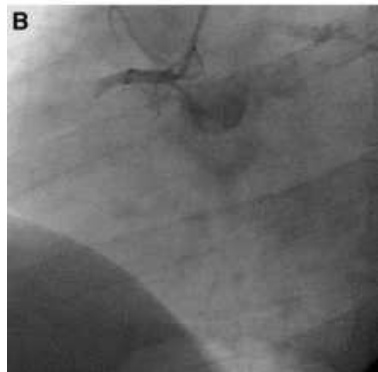
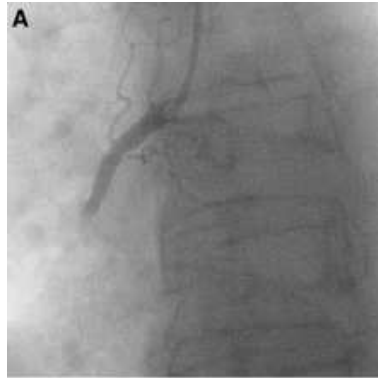
Collet JP et al. Arterioscler Thromb Vasc Biol. 2006

Silvain J, Collet JP et al. Thromb Haemost. 2011

Thrombus composition

Generation of the Hypothesis ... “Time make the difference”

60 min

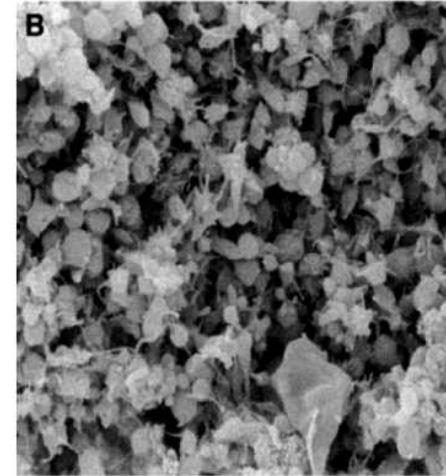


6 Hours

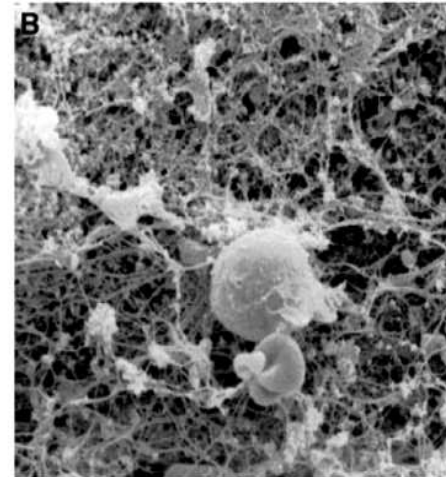


Figure 4. White (A) and red (B) thrombus trapped in the Spider filters in patients 1 and 2.

EARLY OCCLUSION

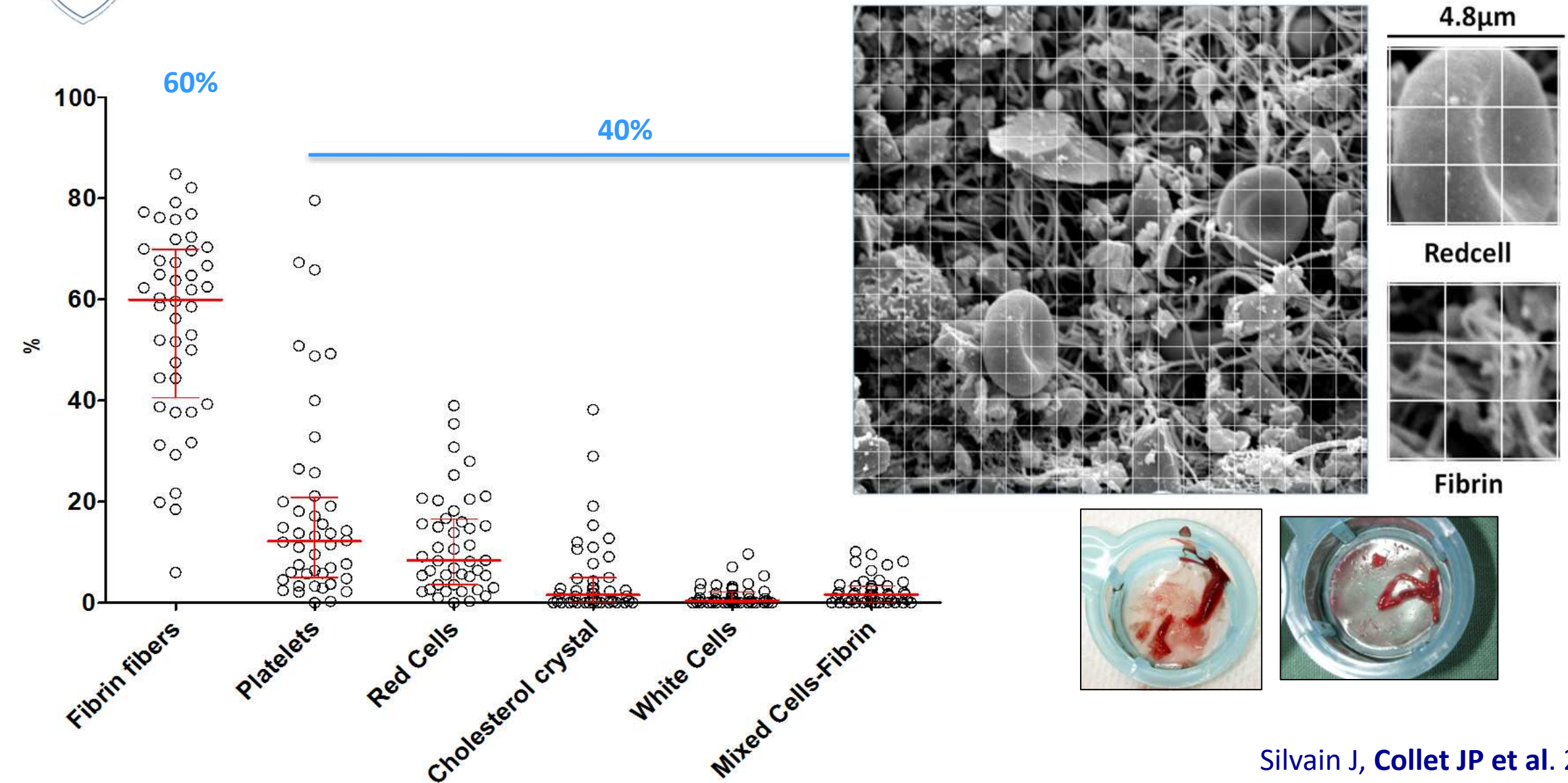


LATE OCCLUSION





Thrombus composition in MI



Dose effect of clopidogrel reloading in patients already on 75-mg maintenance dose: the RELOAD study..

Silvain J, **Collet JP et al – 2008**

Can we override **clopidogrel resistance?**

Pena A , **Collet JP et al. – 2009**

High on-treatment platelet reactivity as a risk factor for secondary prevention after PCI : A landmark analysis of the ARCTIC study.

Montalescot G , **Collet JP et al – 2014**

Coronary revascularization in the diabetic patient.

Silvain J, **Collet JP et al – 2014**

Pretreatment with P2Y12 inhibitors in non-ST-Segment-elevation acute coronary syndrome: an outdated and harmful strategy..

Collet JP et al – 2014

Platelet function test-guided strategy: lost in translation?

Collet JP et al. – 2015

Efficacy of ex vivo autologous and **in vivo platelet transfusion** in the reversal of P2Y12 inhibition by clopidogrel, prasugrel, and ticagrelor: the APTITUDE study.

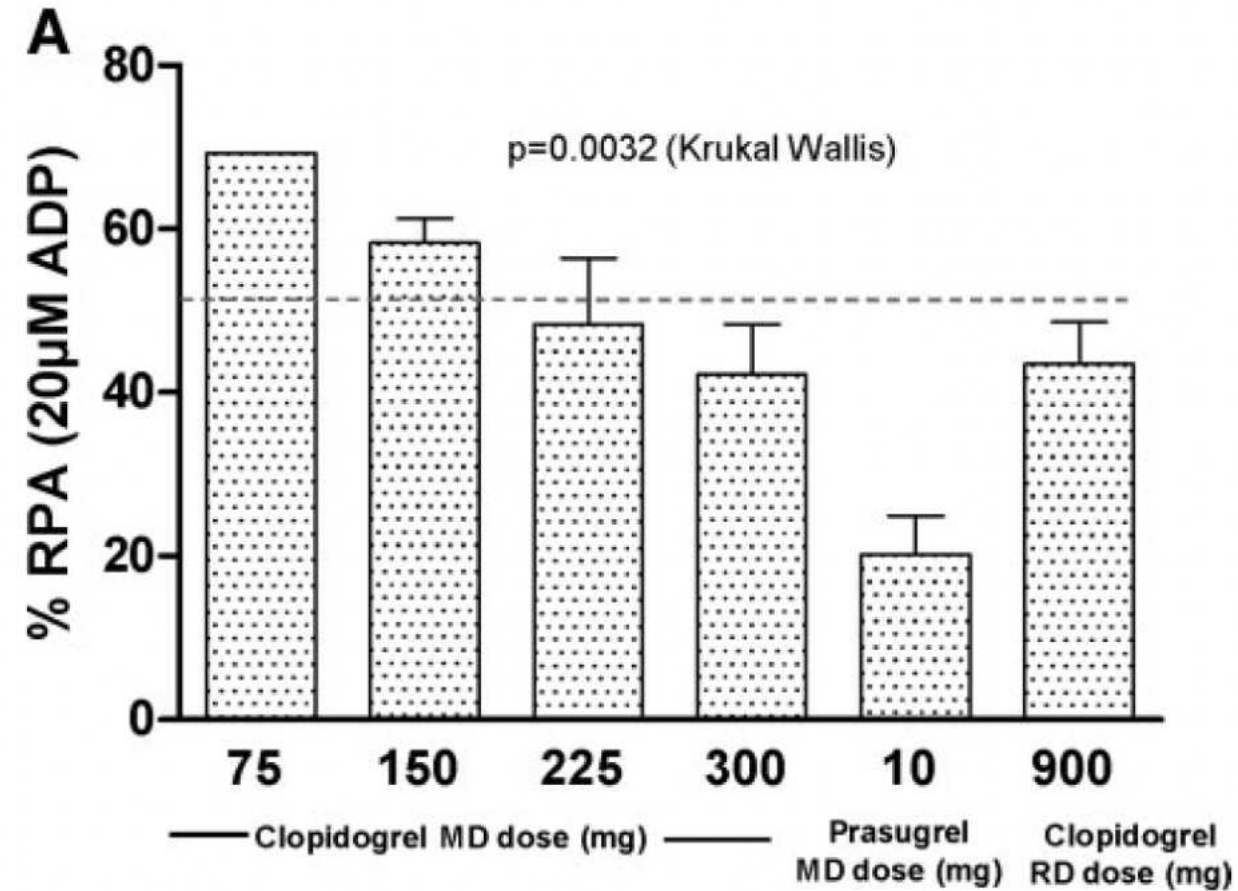
O'Connor S, **Collet JP et al – 2015**

Reasons for the Failure of Platelet Function Testing to Adjust Antiplatelet Therapy: Pharmacodynamic Insights From the ARCTIC Study.

Lattuca B , **Collet JP et al – 2019**

Stent Thrombosis

Can we override **clopidogrel resistance**?





Cardiovascular risk in **clopidogrel-treated patients** according to cytochrome P450 2C19*2 loss-of-function allele or PPI coadministration: a systematic meta-analysis.

Hulot JS , **Collet JP et al. – 2010**

Consensus and future directions on the definition of **high on-treatment platelet reactivity** to adenosine diphosphate.

Bonello L., **Collet JP et al – 2010**

New P2Y12 inhibitors versus clopidogrel in percutaneous coronary intervention: a meta-analysis.

Bellemain-Appaix A , **Collet JP et al – 2004**

Composition of coronary thrombus in acute myocardial infarction.

Silvain J, **Collet JP et al – 2006**

High doses of clopidogrel to overcome genetic resistance: the randomized crossover CLOVIS-2

Silvain J , **Collet JP et al – 2011**

Switching acute coronary syndrome patients from **prasugrel to clopidogrel**.

Kerneis M , **Collet JP et al. – 2013**

Platelet Function Testing

Collet JP et al – 2009

THE LANCET

Articles

Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study

Summary
Background Clopidogrel and low-dose aspirin have become the mainstay oral antiplatelet ischaemic events after acute coronary syndromes or stent placement. The first 681 G>A (%2) of cytochrome P450 2C19 (CYP2C19) is an important contributor individuals of the antiplatelet effect of clopidogrel. We assessed whether the C long-term prognosis of patients who were chronically treated with clopidogrel.

Methods Between April 1, 1996, and April 1, 2008, 259 young patients (aged <45 years infarction and were exposed to clopidogrel treatment for at least a month, were enrolled underwent CYP2C19 genotyping. The primary endpoint was a composite of urgent coronary revascularisation occurring during exposure to clopidogrel. Follow-up secondary endpoint was stent thrombosis proven by angiography.

Findings Median clopidogrel exposure time was 1.07 years (IQR 0.28–3.0). Based between carriers (heterozygous %1/%2, n=64; homozygous %2/%2, n=9) and non-carriers (HR) 3.69 [95% CI 1.69–8.05], p=0.0005, as did stent thrombosis (eight vs five p=0.0009). The detrimental effect of the CYP2C19%2 genetic variant persisted initiation up to the end of follow-up (HR 3.00 [1.27–7.10], p=0.009). After multigenetic variant was the only independent predictor of cardiovascular events (HR 4.00 [1.27–12.70], p=0.02).

Interpretation The CYP2C19%2 genetic variant is a major determinant of prognosis in clopidogrel treatment after myocardial infarction.

Funding Délégation à la Recherche Clinique, Assistance Publique-Hôpitaux de Paris

Jean-Philippe Collet, Jean-Sebastien Hurlot, Anne-Pierre, Eric Villard, Jean-Baptiste Eder, Johannes Silvain, Guillaume Cayla, Farzin Beygui, Gilbert Bessieres, Christian Funck-Brentano, Gilles Montalescot

Summary
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Interpretation The CYP2C19%2 genetic variant is a major determinant of prognosis in clopidogrel treatment after myocardial infarction.
Funding Délégation à la Recherche Clinique, Assistance Publique-Hôpitaux de Paris

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Montalescot at the Institut de Cardiologie, Bureau 2-236, Centre Hospitalier Universitaire Pitié-Salpêtrière, 47 Blvd de l'Hôpital, 75013 Paris, France, or at gilles.montalescot@psl.ap-hop-paris.fr.

*Additional investigators in the Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting (ARCTIC) trial are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on November 4, 2012, at NEJM.org.

N Engl J Med 2012;367:2106-8.
DOI: 10.1056/NEJMoa1209899

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THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bedside Monitoring to Adjust Antiplatelet Therapy for Coronary Stenting

Jean-Philippe Collet, M.D., Ph.D., Thomas Cuisset, M.D., Ph.D., Grégoire Rangé, M.D., Guillaume Cayla, M.D., Ph.D., Simon Elhadad, M.D., Christophe Pouillot, M.D., Patrick Henry, M.D., Ph.D., Pascal Motreff, M.D., Ph.D., Didier Carrié, M.D., Ziad Boueri, M.D., Ph.D., Loïc Belle, M.D., Eric Van Belle, M.D., Ph.D., Hélène Rousseau, Ph.D., Pierre Aubry, M.D., Jacques Monségou, M.D., Pierre Sabournet, M.D., Stephen A. O'Connor, M.B., B.Ch., Jérémie Abtan, M.D., Mathieu Kernels, M.D., Christophe Saint-Etienne, M.D., Olivier Barthélémy, M.D., Farzin Beygui, M.D., Ph.D., Johanne Silvain, M.D., Ph.D., Eric Vicaud, M.D., Ph.D., and Gilles Montalescot, M.D., Ph.D., for the ARCTIC Investigators*

BACKGROUND
Patients' responses to oral antiplatelet therapy are subject to variation. Bedside monitoring offers the opportunity to improve outcomes after coronary stenting by individualizing therapy.

METHODS
We randomly assigned 2440 patients scheduled for coronary stenting at 38 centers to a strategy of platelet-function monitoring, with drug adjustment in patients who had a poor response to antiplatelet therapy, or to a conventional strategy without monitoring and drug adjustment. The primary end point was the composite of death, myocardial infarction, stent thrombosis, stroke, or urgent revascularization 1 year after stent implantation. For patients in the monitoring group, the VerifyNow P2Y12 and aspirin point-of-care assays were used in the catheterization laboratory before stent implantation and in the outpatient clinic 2 to 4 weeks later.

RESULTS
In the monitoring group, high platelet reactivity in patients taking clopidogrel (34.5% of patients) or aspirin (7.6%) led to the administration of an additional bolus of clopidogrel, prasugrel, or aspirin along with glycoprotein IIb/IIIa inhibitors during the procedure. The primary end point occurred in 34.6% of the patients in the monitoring group, as compared with 31.1% of those in the conventional-treatment group (hazard ratio, 1.13; 95% confidence interval [CI], 0.98 to 1.29; P=0.10). The main secondary end point, stent thrombosis or any urgent revascularization, occurred in 4.9% of the patients in the monitoring group and 4.6% of those in the conventional-treatment group (hazard ratio, 1.06; 95% CI, 0.74 to 1.52; P=0.77). The rate of major bleeding events did not differ significantly between groups.

CONCLUSIONS
This study showed no significant improvements in clinical outcomes with platelet-function monitoring and treatment adjustment for coronary stenting, as compared with standard antiplatelet therapy without monitoring. Funded by Alliances in Cardiovascular Trials Initiatives and Organized Networks and others; ARCTIC ClinicalTrials.gov number, NCT00827411.

Collet JP et al – 2012

THE LANCET

Dual-antiplatelet treatment beyond 1 year after drug stent implantation (ARCTIC-Interruption): a randomised controlled superiority trial

Summary
Background Optimum duration of dual antiplatelet treatment (DAPT) after coronary stenting remains an unknown efficacy to safety ratio of extended treatment leading to discrepancies between trials and clinical practice. We assessed whether DAPT continuation beyond 1 year after coronary stenting improves outcomes.

Methods This analysis was a planned extension of the previously published ARCTIC-Monitoring trial, which randomly allocated 2440 patients to a strategy of platelet function testing with antiplatelet treatment (conventional strategy after coronary stenting with drug-eluting stents [DES]) or to a conventional strategy without monitoring and drug adjustment. The primary end point was the composite of death, myocardial infarction, stent thrombosis, stroke, or urgent revascularization 1 year after stent implantation. For patients in the monitoring group, the VerifyNow P2Y12 and aspirin point-of-care assays were used in the catheterization laboratory before stent implantation and in the outpatient clinic 2 to 4 weeks later.

Results Between Jan 4, 2011, and March 3, 2012, 1259 eligible patients were randomly allocated to the interruption group (n=635) or the continuation group (n=624). The primary end point occurred in 27 (4%) patients in the interruption group and in 34 (5%) patients in the continuation group (hazard ratio [HR] 1.17 [95% CI 0.68–2.03], p=0.58). STEEP events occurred more often in the continuation group (34%) compared with the interruption group (25%) (p=0.03). Major or minor bleedings were also more frequent in the continuation group compared with the interruption group (12 [2%] patients vs three [0%] patients; HR 0.15 [0.02–1.20], p=0.073). Major or minor bleedings were also more frequent in the continuation group compared with the interruption group (12 [2%] patients vs three [0%] patients; HR 0.15 [0.02–1.20], p=0.073).

Interpretation Our findings suggest no apparent benefit but instead harm with extension of DAPT beyond 1 year after coronary stenting. No conclusion can be drawn from this study. No conclusion can be drawn from this study. No conclusion can be drawn from this study.

Funding Alliances in Cardiovascular Trials Initiatives and Organized Networks (ACTION Study Group), French Ministry of Health, Sanofi-Aventis, Corbis, Medtronic, Boston Scientific, Fondation SGAM.

Introduction
The recommended duration of dual antiplatelet treatment (DAPT) for elective coronary implantation of a DES in stable patients, although duration in the control groups of these studies was variable and not always reflecting the 12-month recommendation of DAPT duration after DES implantation.^{1,2,3,4}

The ARCTIC (Assessment by a Double Randomization of a Conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and of Treatment Interruption versus Continuation 1 year after stenting)-Interruption trial is the second phase of the previously published ARCTIC-Monitoring study.^{5,6} In which we randomly allocated 2440 patients to either platelet function testing with antiplatelet treatment adjustment or conventional antiplatelet treatment after coronary stenting with a DES.

Collet JP et al – 2014

THE LANCET

Articles

Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial

Summary
Background Elderly patients are at high risk of ischaemic and bleeding events. Platelet function monitoring offers the possibility to individualise antiplatelet therapy to improve the therapeutic risk-benefit ratio. We aimed to assess the effect of platelet function monitoring with treatment adjustment in elderly patients stented for an acute coronary syndrome.

Methods We did this multicentre, open-label, blinded-endpoint, randomised controlled superiority study at 35 centres in France. Patients aged 75 years or older who had undergone coronary stenting for acute coronary syndrome were randomly assigned (1:1), via a central interactive voice-response system based on a computer-generated permuted block randomisation schedule with randomly selected block sizes, to receive oral prasugrel 5 mg daily with dose or drug adjustment in case of inadequate response (monitoring group) or oral prasugrel 5 mg daily with no monitoring or treatment adjustment (conventional group). Randomisation was stratified by centre. Platelet function testing was done 14 days after randomisation and repeated 34 days after treatment adjustment in patients in the monitoring group. Study investigators and patients were not masked to treatment allocation, but allocation was concealed from an independent clinical events committee responsible for endpoint adjudication. The primary endpoint was a composite of cardiovascular death, myocardial infarction, stroke, stent thrombosis, urgent revascularisation, and bleeding. Academic Research Consortium-defined bleeding complications (types 2, 3, or 5) at 12 months' follow-up. We did analysis by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01552846.

Findings Between March 27, 2012, and May 19, 2015, we randomly assigned 877 patients to the monitoring group (n=442) or the conventional group (n=435). The primary endpoint occurred in 128 (29%) patients in the monitoring group compared with 125 (29%) patients in the conventional group (hazard ratio [HR] 1.003, 95% CI 0.75–1.28; p=0.98). Rates of bleeding events did not differ significantly between groups.

Interpretation Platelet function monitoring with treatment adjustment did not improve the clinical outcome of elderly patients treated with coronary stenting for an acute coronary syndrome. Platelet function testing is still being used in many centres and international guidelines still recommend platelet function testing in high-risk situations. Our study does not support this practice in these recommendations.

Funding Eli Lilly and Company, Daiichi Sankyo, Servier, Actavis Diagnostics, Medtronic, and Fondation Coeur et Rhythme.

Introduction
Elderly people represent an increasing proportion of the acute coronary syndrome population, accounting for up to a third of patients.^{1,2} These frail patients have frequent comorbidities, including renal or hepatic dysfunction, and receive multiple medications, exposing them to an increased risk of iatrogenic complications. Moreover, elderly patients are underrepresented in clinical trials and few randomised studies of coronary artery disease have been dedicated to this population.^{3,4}

Platelet function monitoring offers the possibility to individualise antiplatelet therapy to improve the therapeutic risk-benefit ratio. We aimed to assess the effect of platelet function monitoring with treatment adjustment in elderly patients stented for an acute coronary syndrome, which is an

Cayla G et al – 2016



Jean-Philippe Collet - 20+ years of research on thrombosis

Pr Johanne SILVAIN

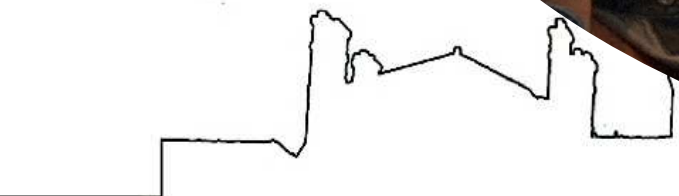
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