



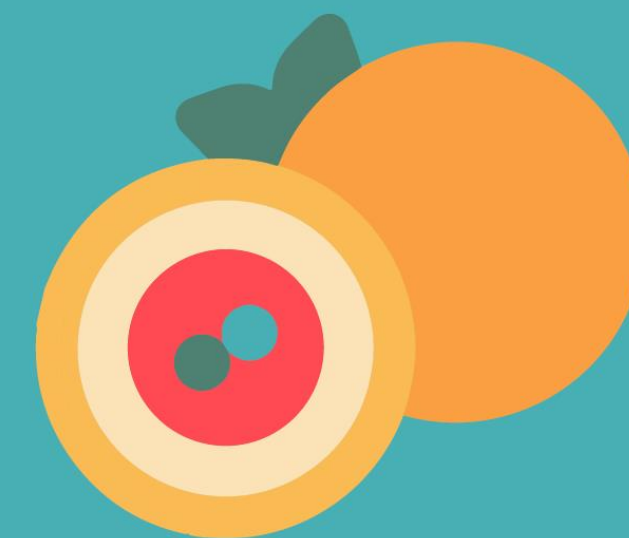
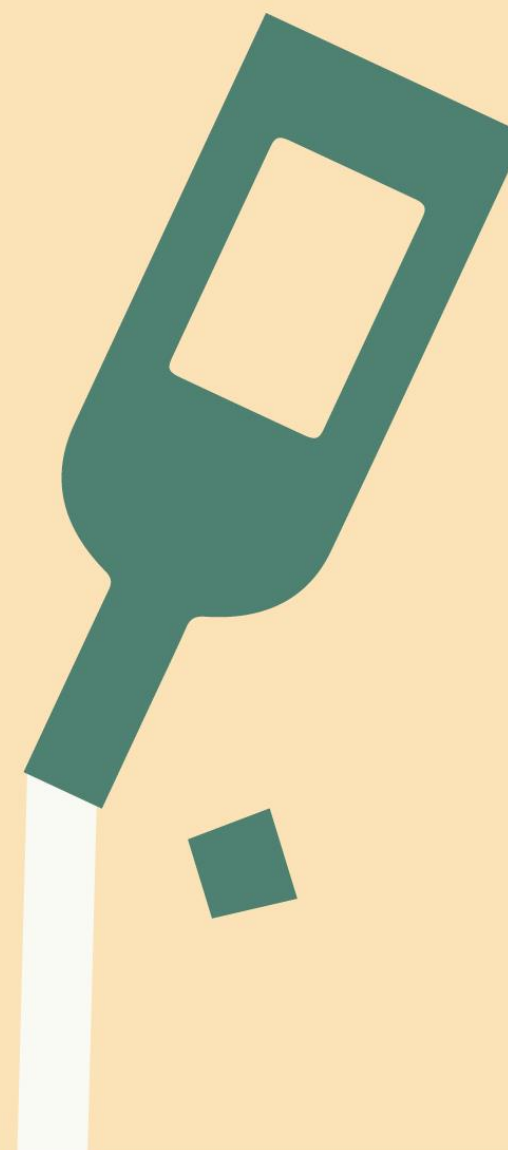
EUROVALVE

& STRUCTURAL CARDIOMYOPATHIES

NH PALERMO



**SAVE
THE DATE**
**OCTOBER
24&25, 2024**



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Flash News on Prosthetic Valve Thrombosis

Cécile OURY, PhD

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Former President of the Belgian Society on Thrombosis and Hemostasis

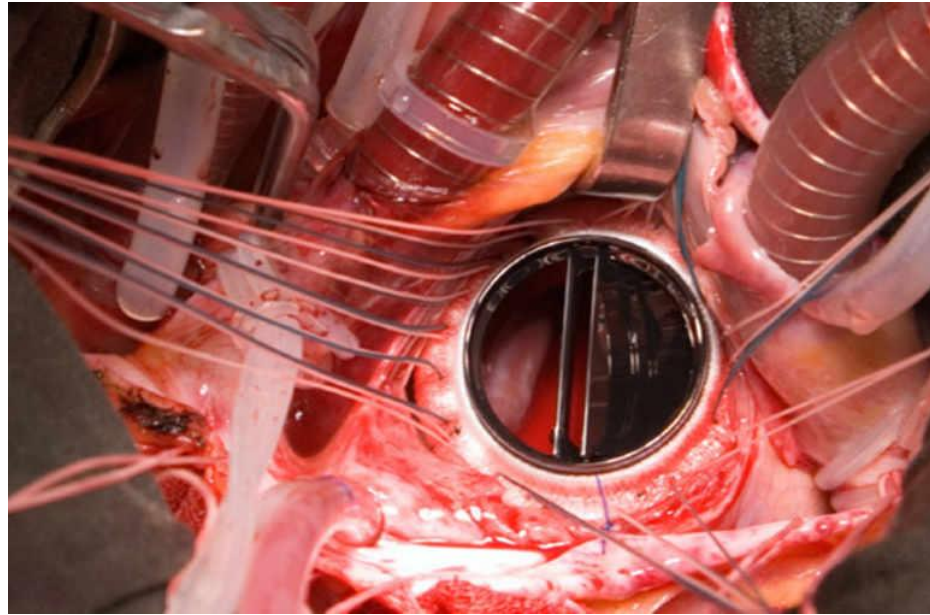
Co-chair of the SSC on Biorheology of the International Society on Thrombosis and Hemostasis



Conflicts of interest

CO is CEO, co-founder and Board Director at CMD-COAT SA

Prosthetic Valve Thrombosis – Mechanical valves



MVT: 0.1% to 5.7% (within 3 months)

- Valve design
- Mitral or tricuspid vs. aortic position
- Likely underestimated (routine imaging of MV is not recommended)

Clinical presentation

Incidental finding in an asymptomatic patient, heart failure, life-threatening embolic events, cardiogenic shock

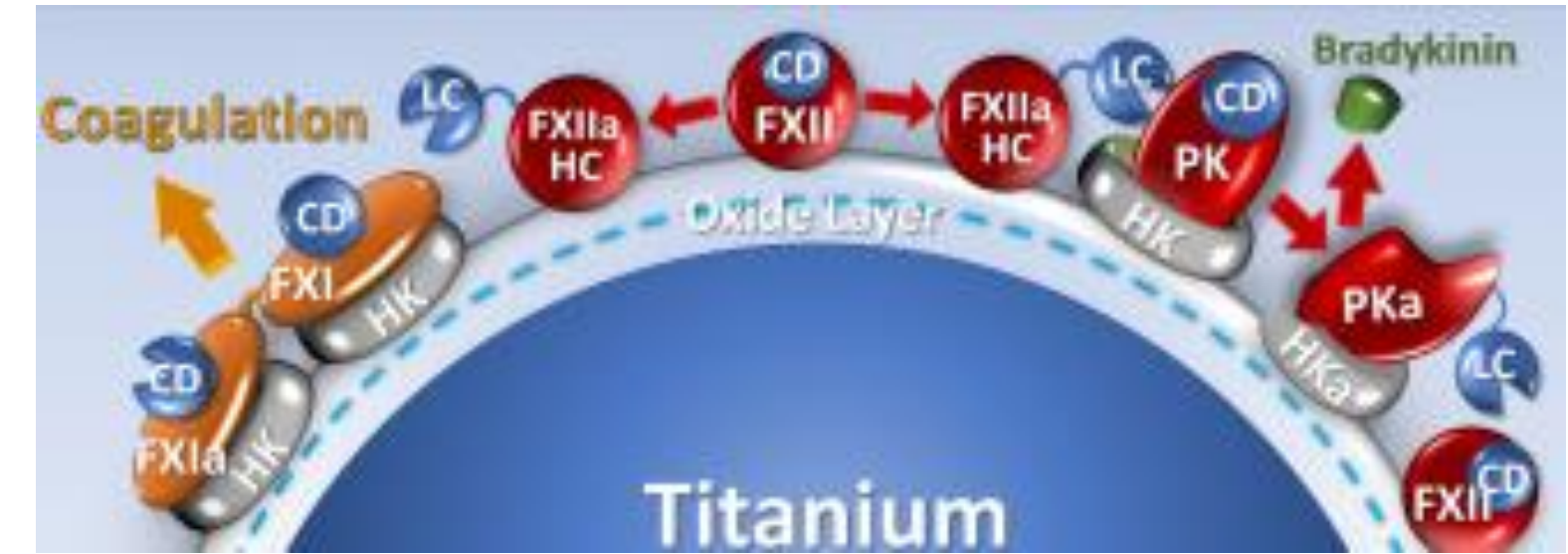
Treatments

- Anticoagulation (warfarin + heparin), thrombolysis, and surgery
- Transcatheter manipulation of immobile leaflets when thrombolytic or surgical risk is prohibitive or as a bridge to surgery
- Important differences between American and European guidelines

Prosthetic Valve Thrombosis – Mechanical valves

Highly thrombogenic materials

- Lifelong VKA anticoagulation but problems persist
- No role for DOACs, so far...



Litvak et al. J Thromb Haemost 2023

RE-ALIGN: dabigatran and warfarin: excess stroke and bleeding with dabigatran

PROACT: the On-X aortic valve can be used with a lower intensity of anticoagulation with warfarin (based on INR)

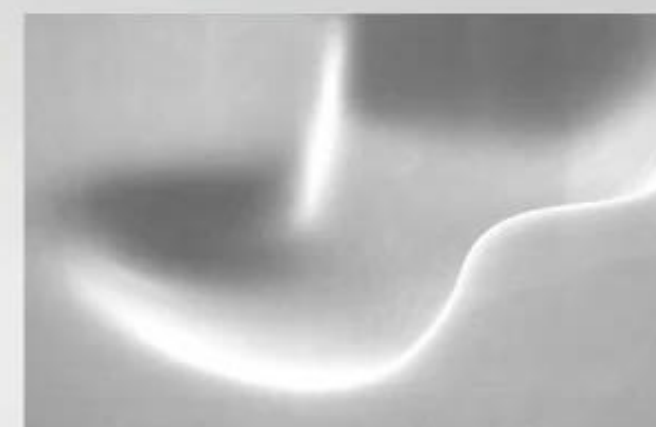
PROACT Xa: apixaban less effective than warfarin for the prevention of aortic valve thrombosis or thromboembolism

Although promising in an heterotypic swine model !



Smoother Surface

On-X Heart Valves have a smoother surface⁶ on the entire body and leaflets to reduce thrombogenicity.⁷



Smooth Pivot⁷



Pure Pyrolytic Carbon⁷

6. More RB and Haubold A.D. Surface Chemistry & Surface Roughness of Chemical Polycarbons. Cells & Materials Vol 6; No 4; 1996:273-276
7. LaGrange L et al. Compatibility of carbon and blood. Hegyeli RJ, Editor, Artificial Heart Program Conference, Washington, DC, June 9-13, 1969, 47-58.

Prosthetic Valve Thrombosis – Biological valves

Less thrombogenic than mechanical valves

Clinical valve thrombosis is rare (1.2%)

Subclinical thrombosis (SLT) – HALT/RLM on MDCT is common

12-38% after TAVR

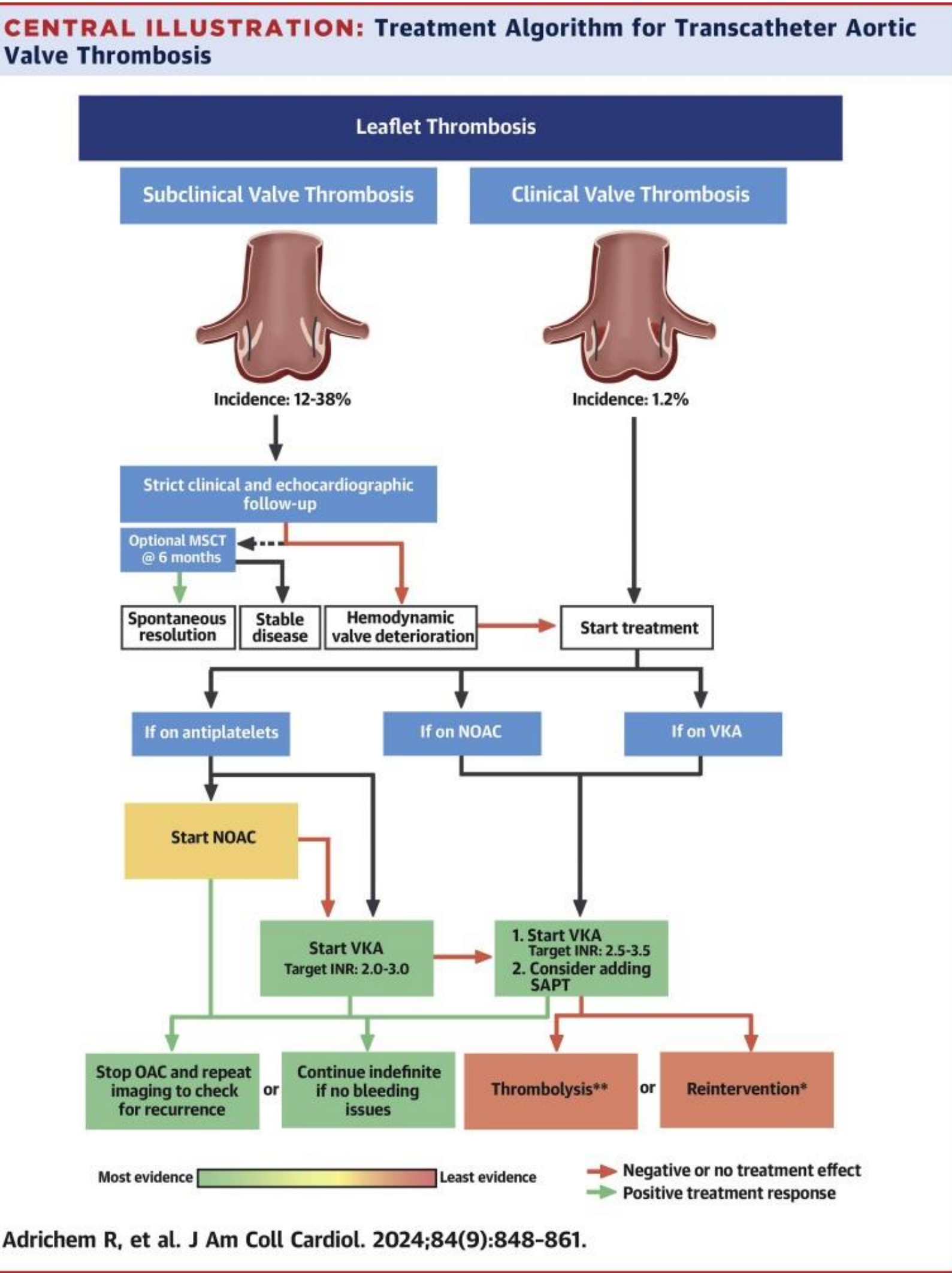
Less after SAVR (5-15%)

Most cases of SLT are incidental

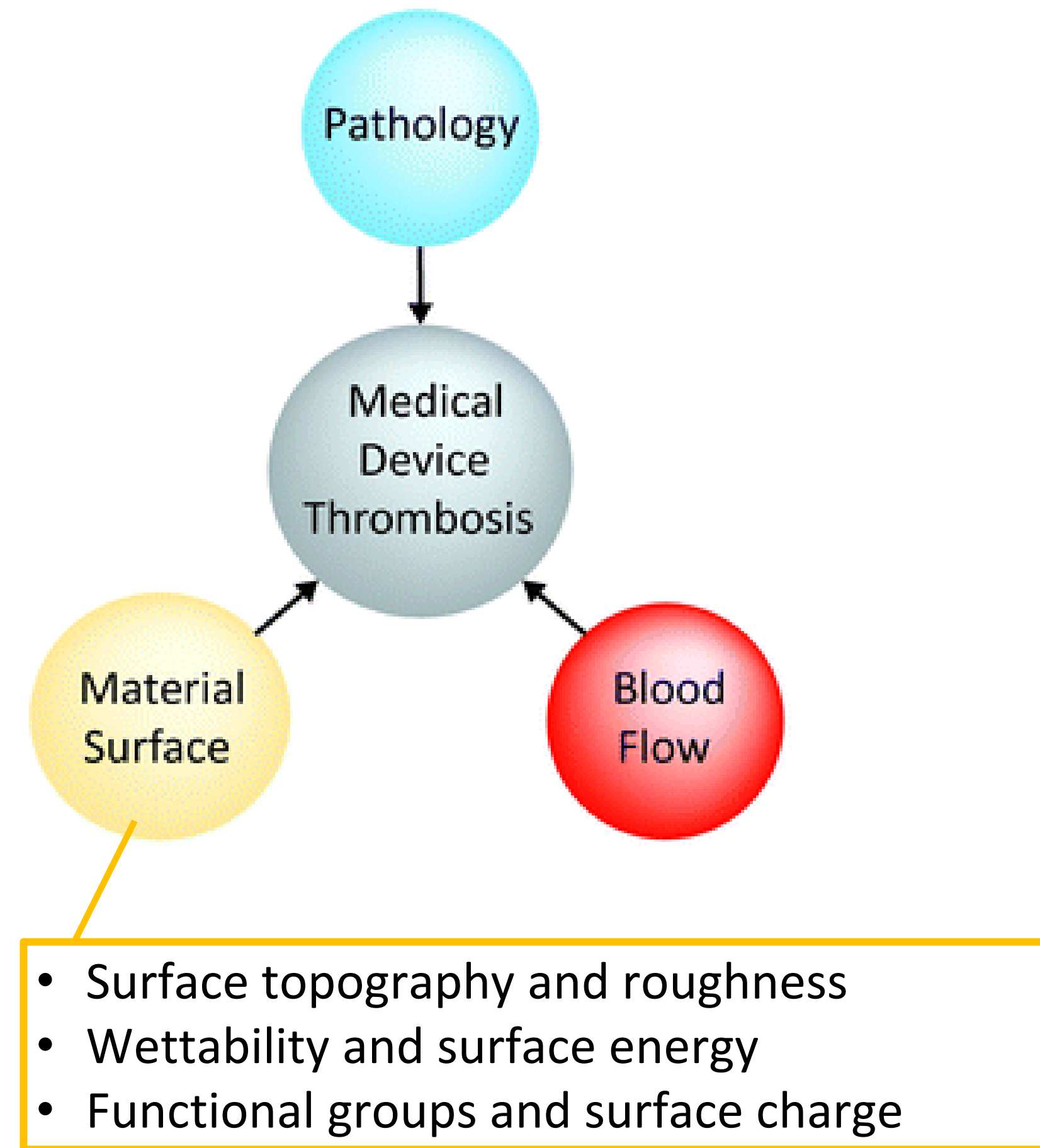
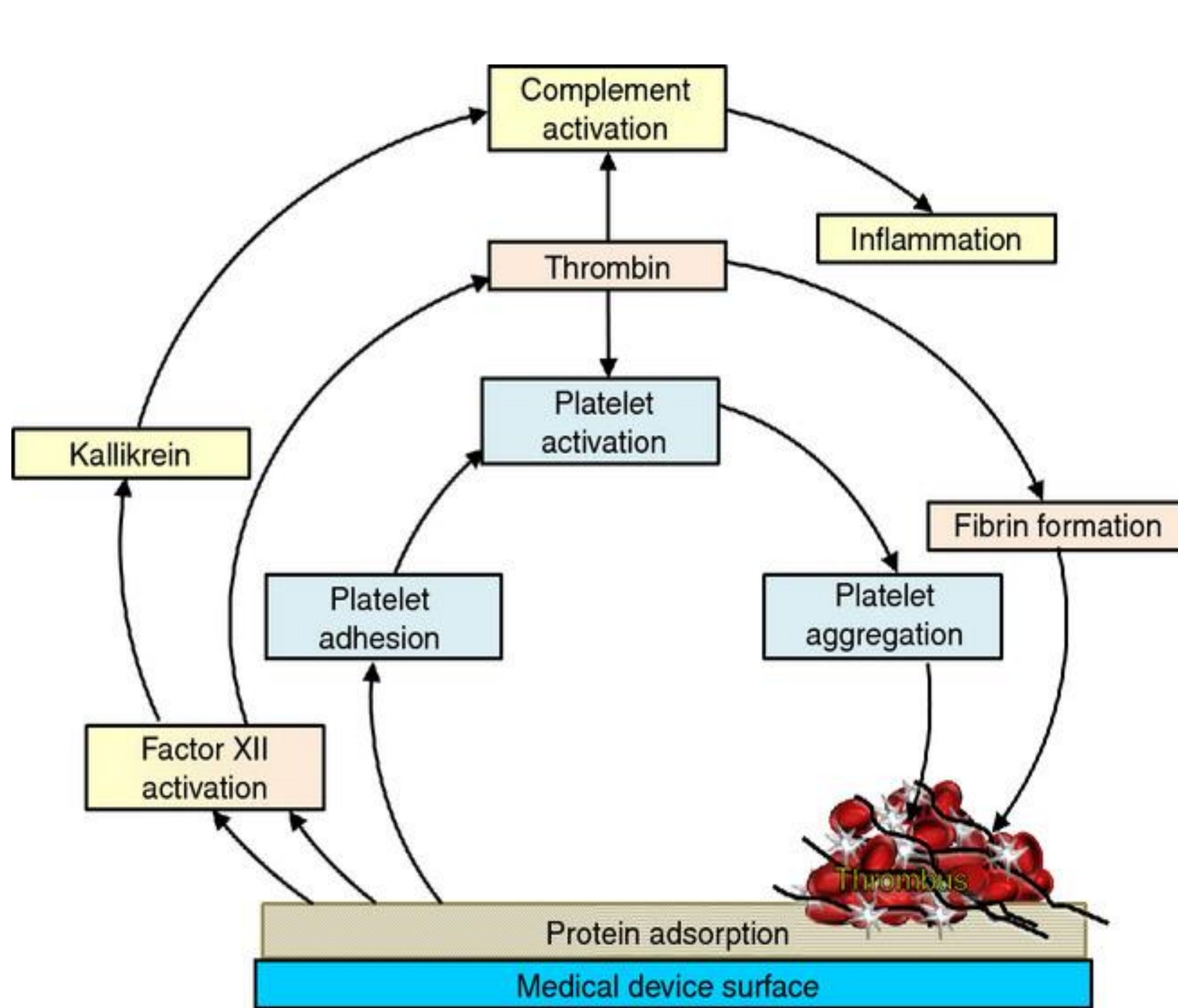
No association of SLT with cerebral thromboembolism, neurologic or neurocognitive dysfunction or other adverse clinical outcomes

Maybe with valve deterioration or longer-term outcomes

To be determined



Medical device thrombosis: what causes it?



Medical device thrombosis: major limitations of test methods

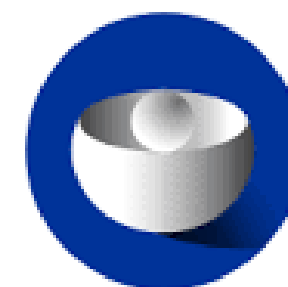
Hemocompatibility/thrombogenicity testing of blood-contacting MDs

« Hemocompatibility is a measure of the thrombotic response induced by a material or device in contact with blood, including platelet response, complement activation, and coagulation cascade initiation. »

- Available guidelines do not specify flow system to be used for *in vitro* testing

Even if ISO 10993-4 recognizes that « materials/devices in a high blood flow environment interact with blood differently in a low blood flow environment »

- Lack of standardization
- Animal blood is not human blood: lack of validated preclinical models
- Clinical relevance of the assays remains unclear
- Lack of awareness from regulatory agencies



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Medical device thrombosis: major limitations of test methods

Hemocompatibility testing recommendations and criteria need to be revisited to take into account MD materials and flow conditions



MD classification must be refined based on flow type (in addition to its intended use and duration of contact as defined in ISO 10993-1)



Bark DL, Vital E, Oury C, Lam WA, Gardiner EE. Recommendations for defining disturbed flow as laminar, transitional, or turbulent in assays of hemostasis and thrombosis: Communication from the ISTH SSC Subcommittee on Biorheology. J Thromb Haemost. 2024 Oct 10

→ Recommendation document on flow-based hemocompatibility assays in preparation

Anna Waterhouse, PhD, The University of Sydney, AU
Cécile Oury, PhD, University of Liège, BE

An urgent need for innovation

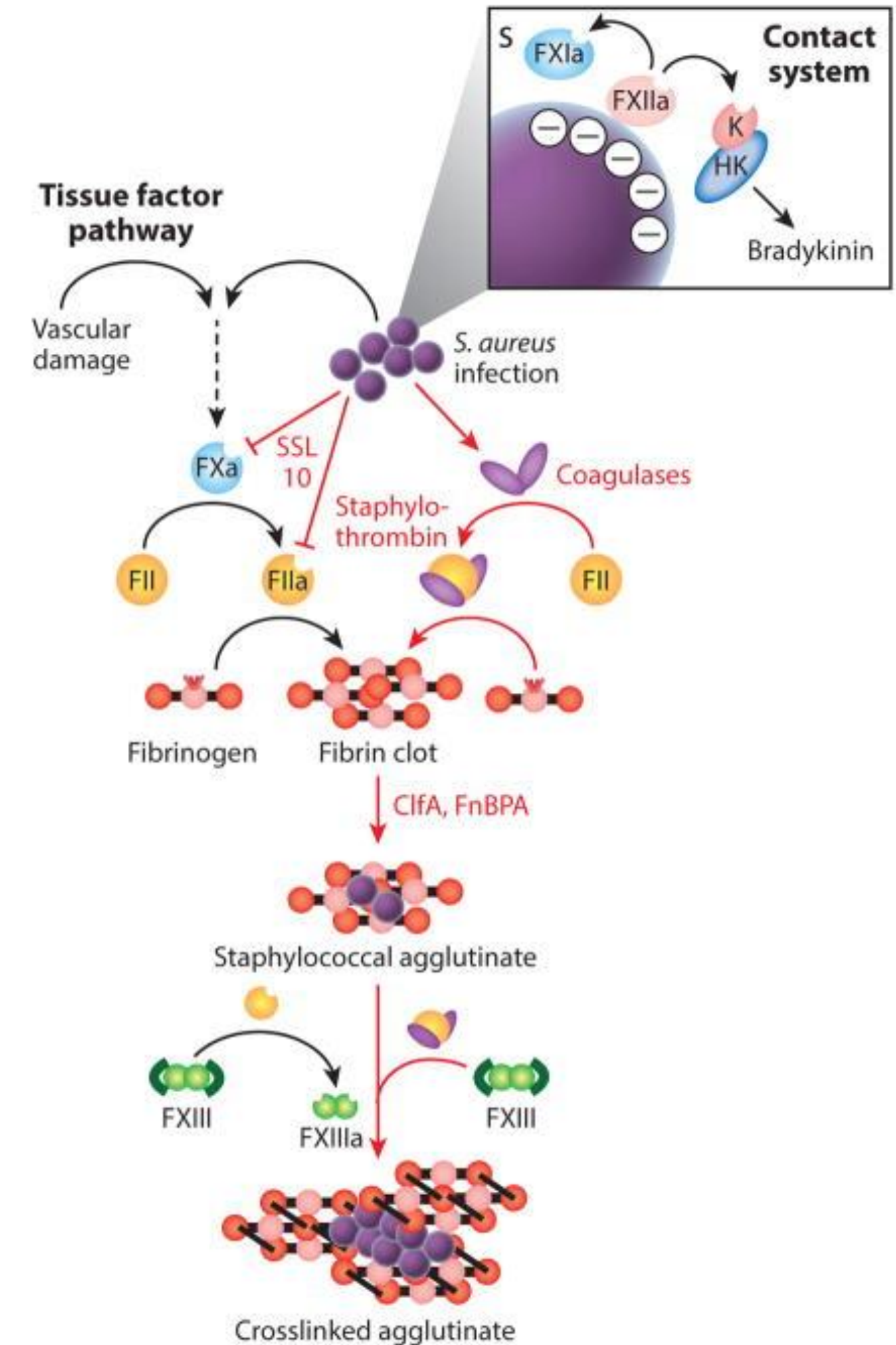
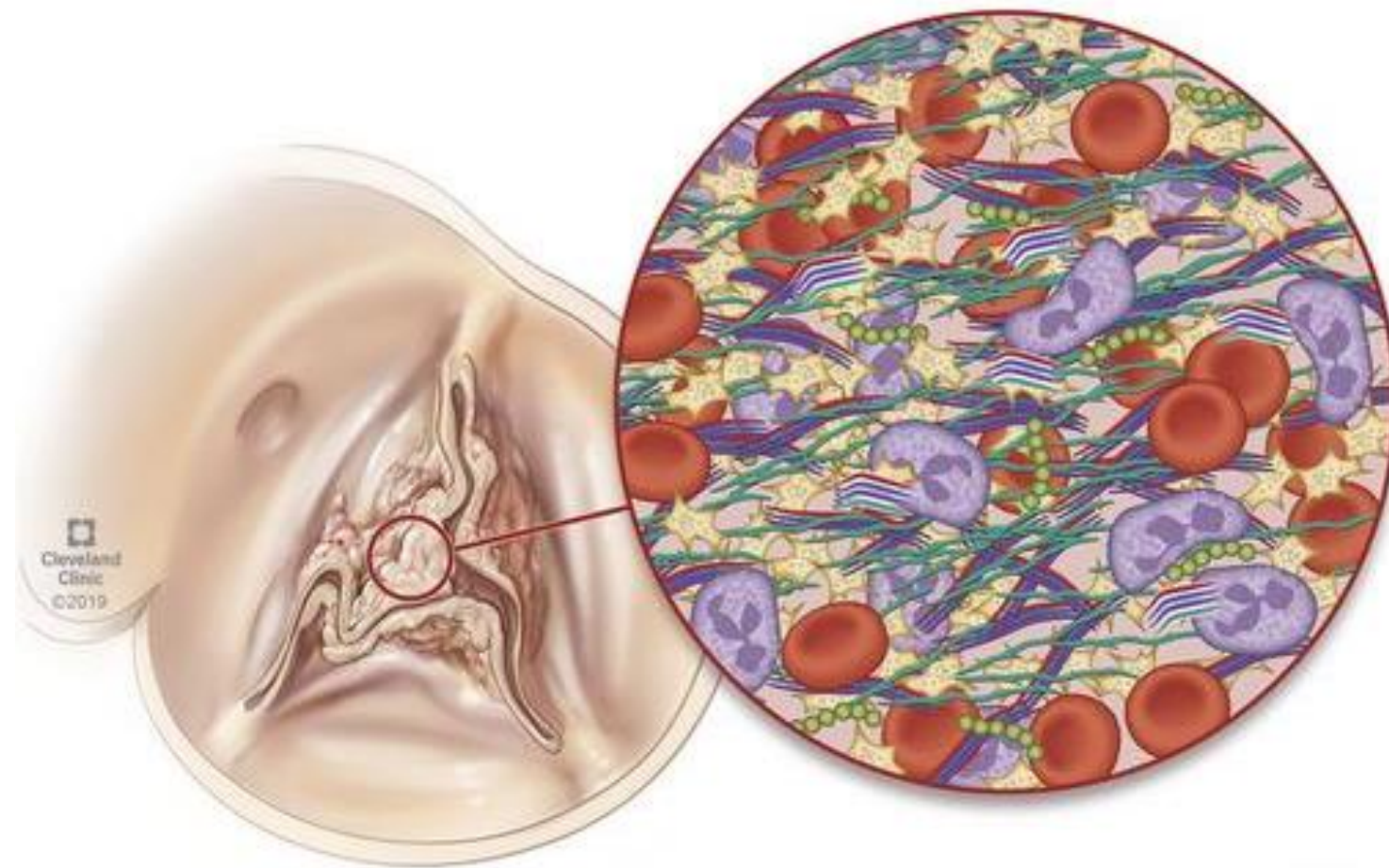
- The use of prosthetic valves is increasing
- Prosthesis hemocompatibility remains an issue and/or is not perfectly evaluated in preclinical testing
- The choice of anti-thrombotic regimens is challenging (role for FXI/FXIa inhibitors?)
Reflexions from the ESC 2024 Jeffrey I. Weitz
- Treatment options are limited/not efficient/not clearly defined, device withdrawal

→ **Preventive measures are preferable**

→ **Thrombosis prevention will also decrease infection rate**

Prosthetic valve infections

S. aureus promotes thrombosis
and thrombosis increases infection risk



The solution is a prosthetic valve surface with anti-thrombotic and antimicrobial properties

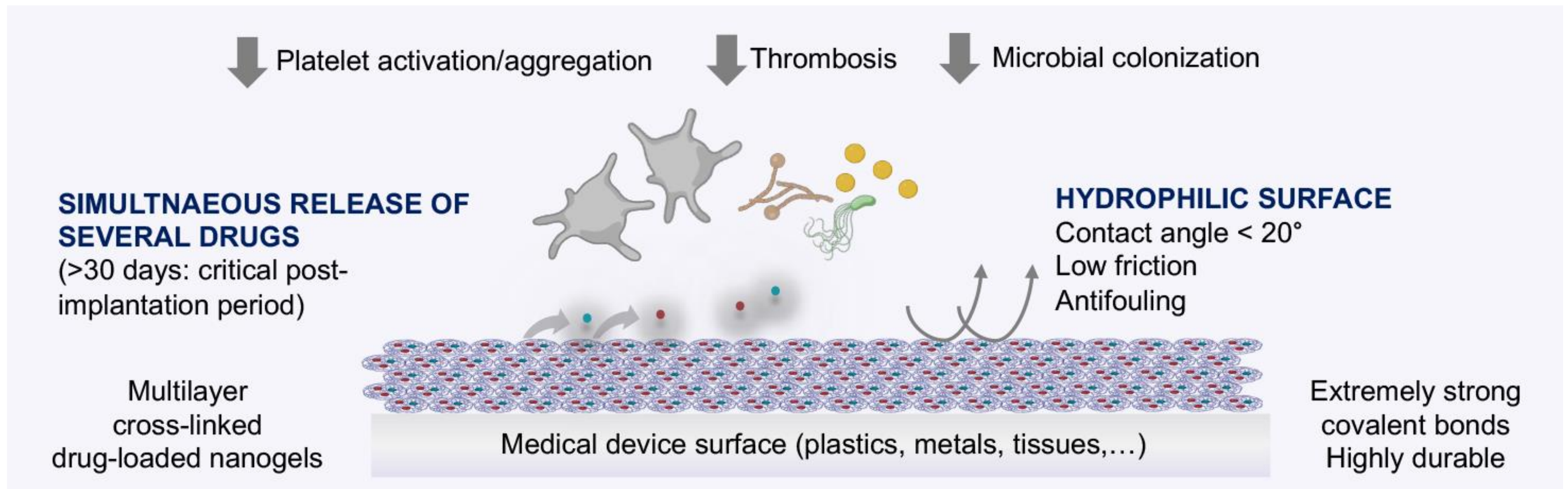
To reduce the need for systemic anticoagulation/antibiotics

↓ Risk of thrombosis/bleeding

↓ Antimicrobial resistance

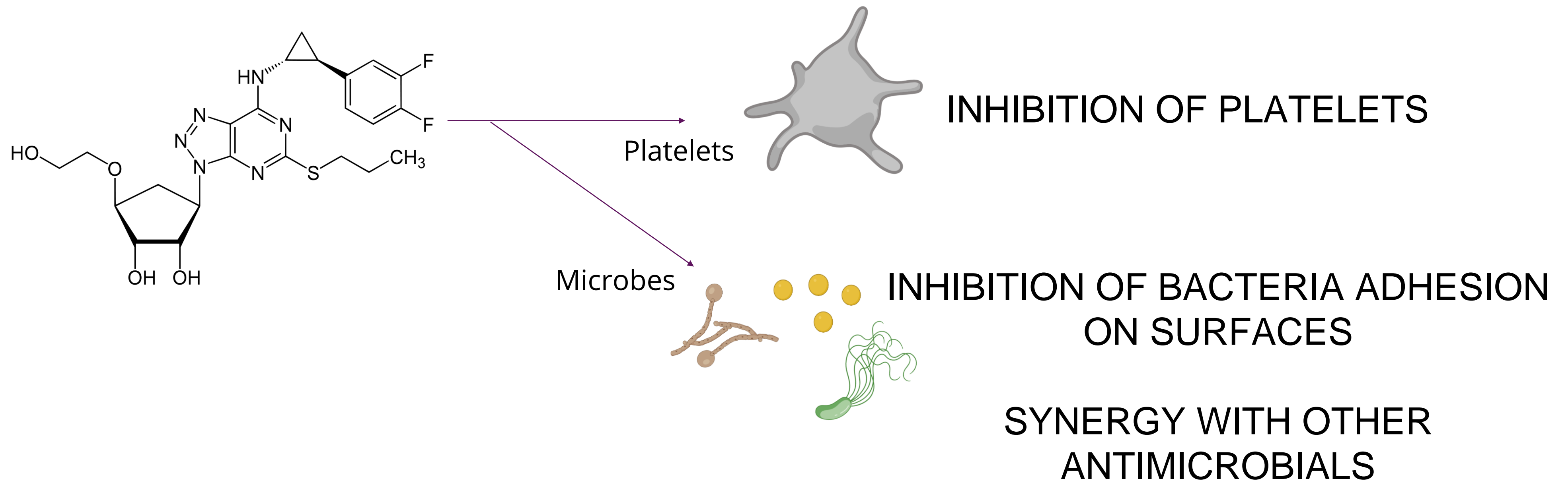
Nanoreservoir Coating

Combining surface modification and drug release for simultaneous antithrombotic and antimicrobial effects



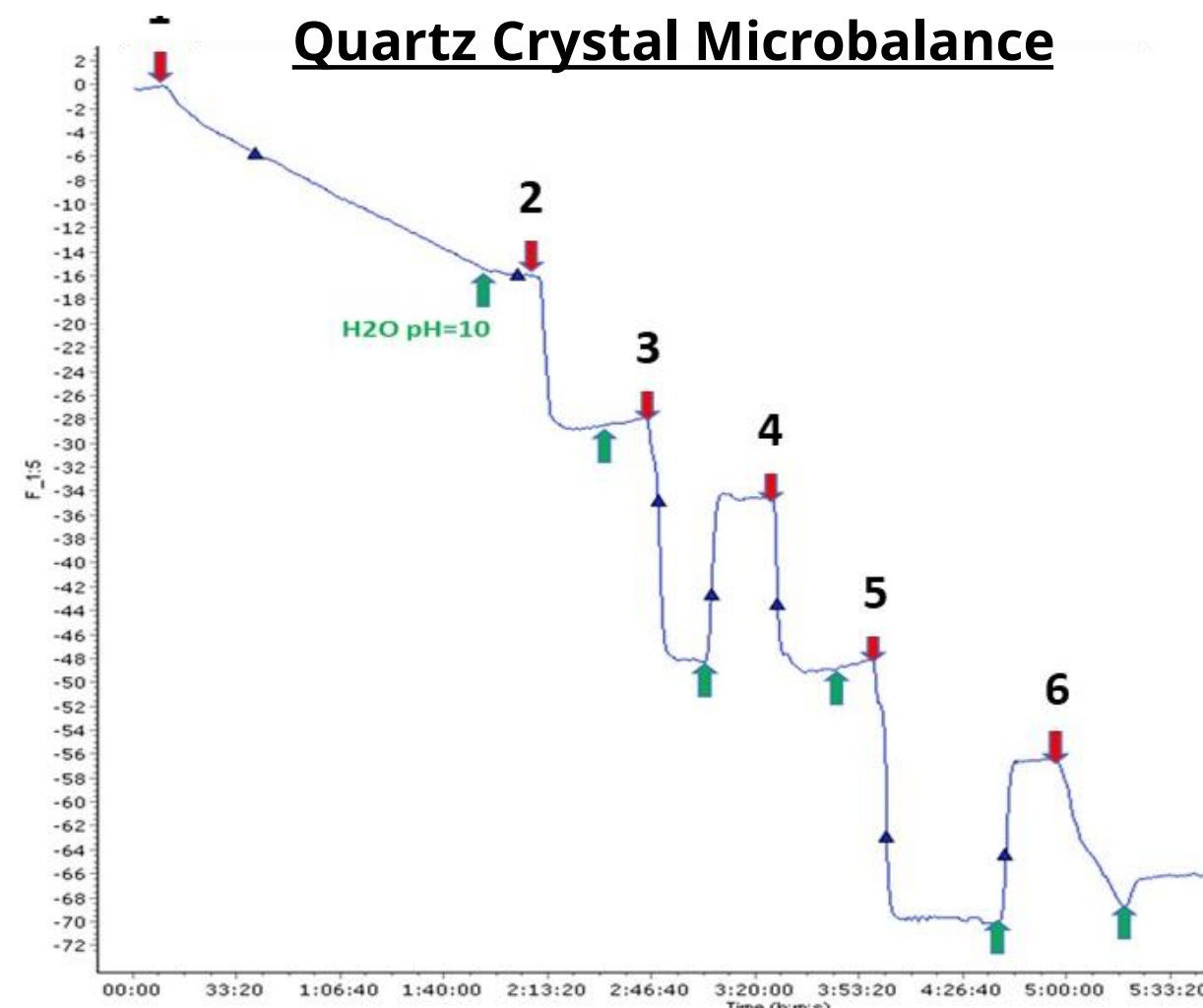
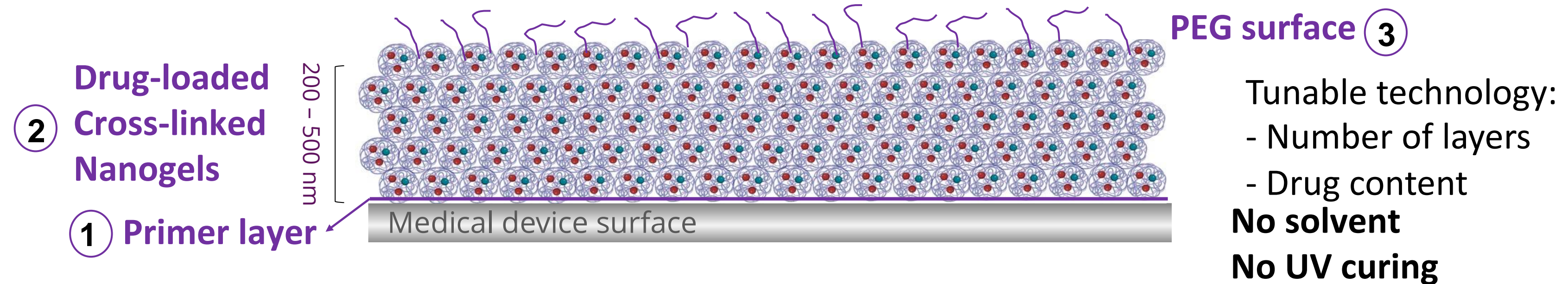
Nanoreservoir Coating

Exploiting the dual antiplatelet and antimicrobial activity of ticagrelor



Nanoreservoir Coating

Building-up the nanoreservoir coating: layer-by-layer deposition



Highly hydrophilic surface

	Before coating	After coating
Contact angle (30 s) °C	61.17 ± 1.04	18.25 ± 1.54

Nanoreservoir Coating



➤ Mechanical heart valve (Ti+Pyrolytic carbon/Dacron™)



➤ Biological heart valves

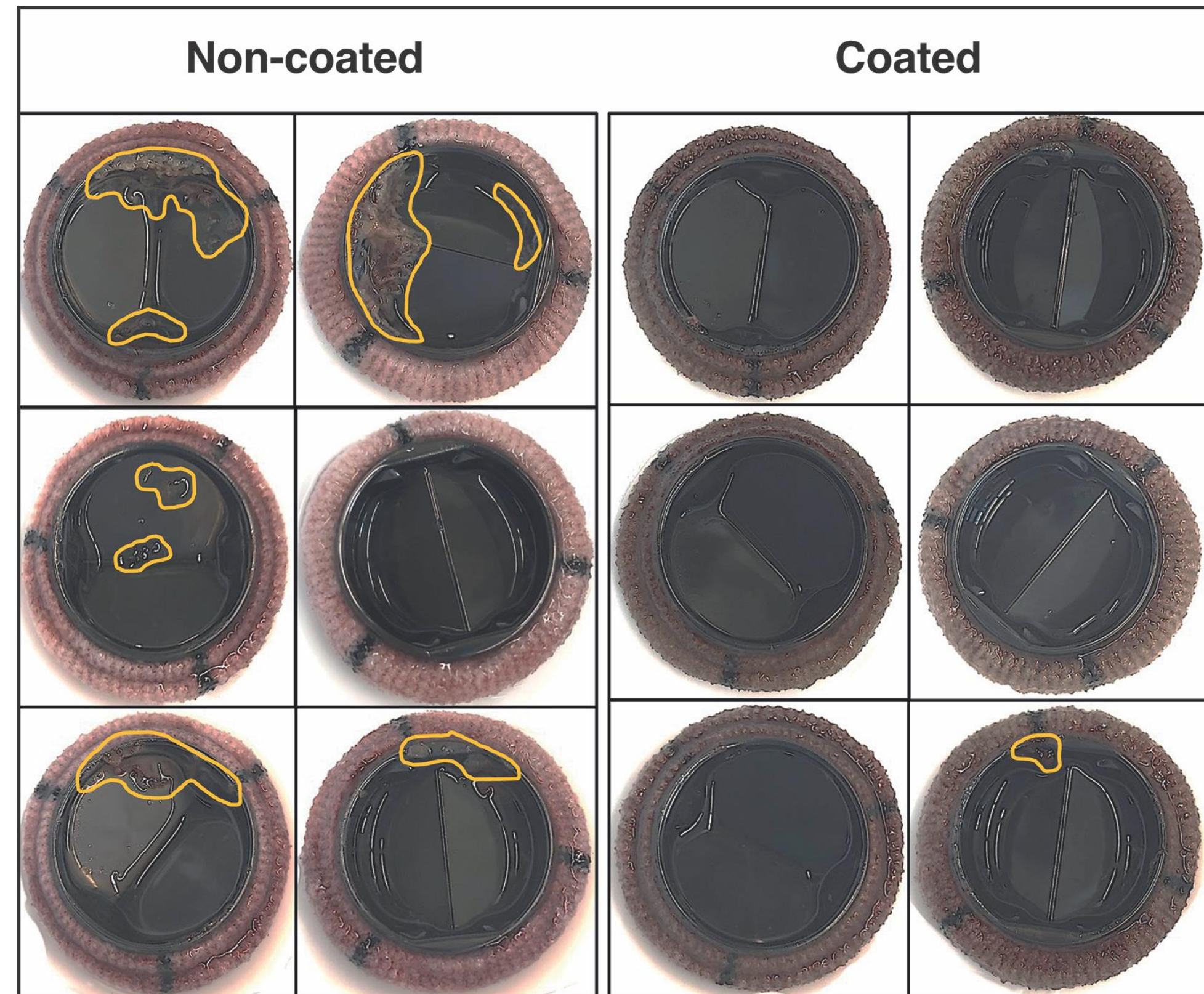
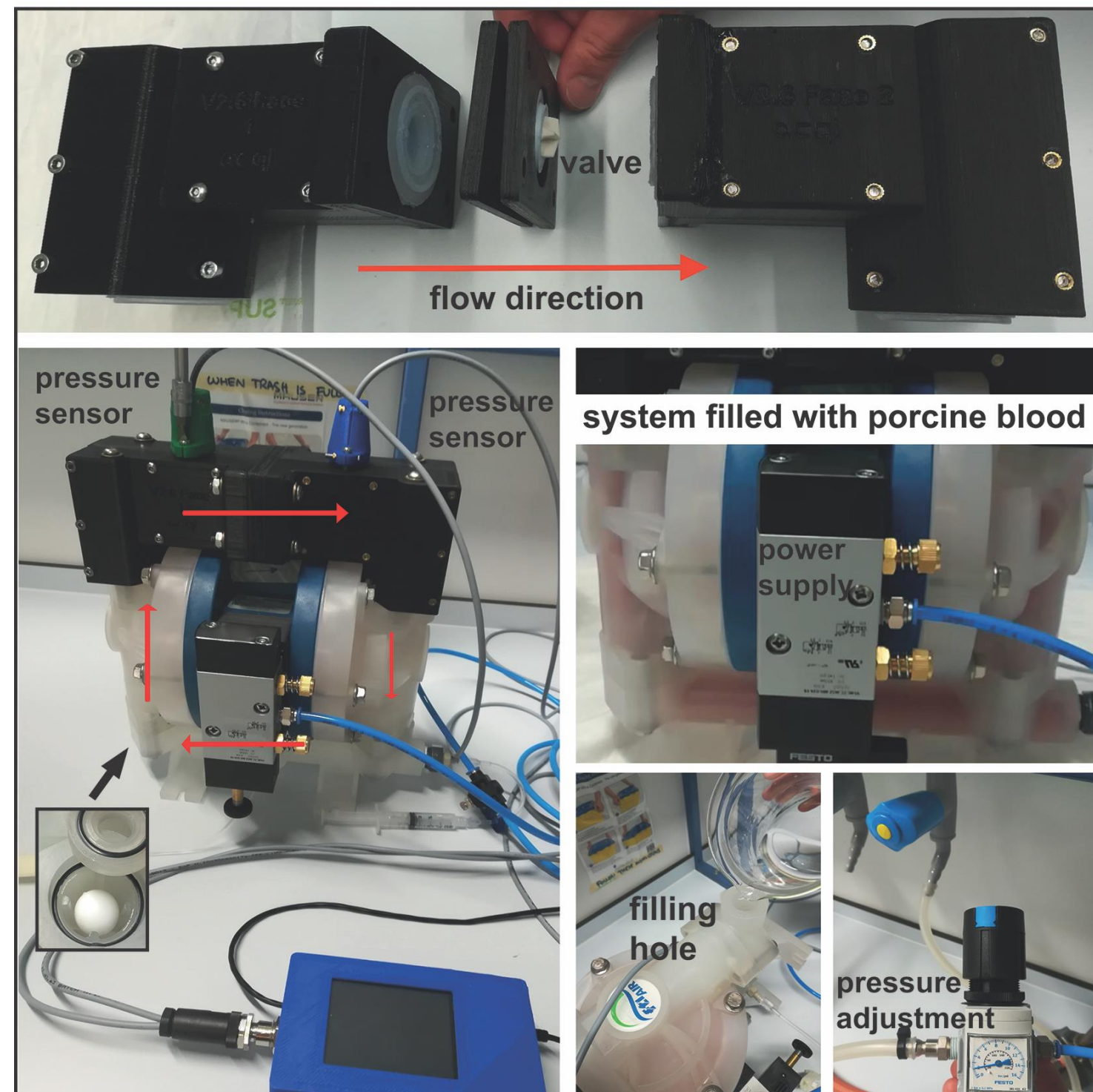
Nanoreservoir Coating

Anti-thrombotic performance



19-mm Open Pivot™ standard aortic heart valve

Pulsatile flow 5 hours - Heparinized arterial blood



Lancellotti et al. JTH 2023



Nanoreservoir Coating

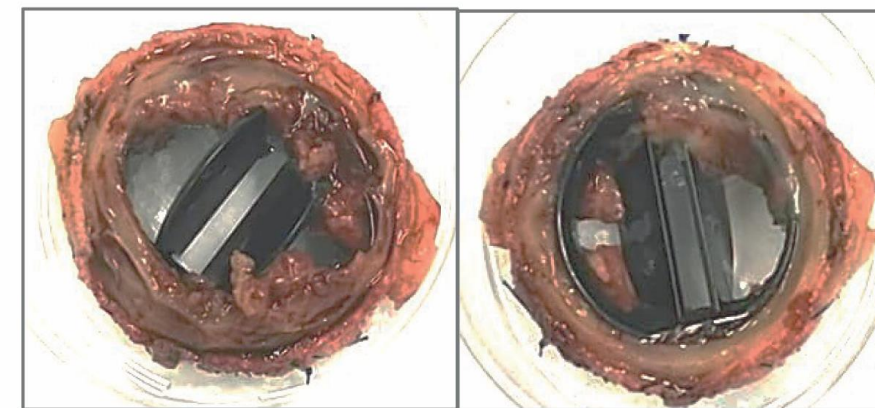
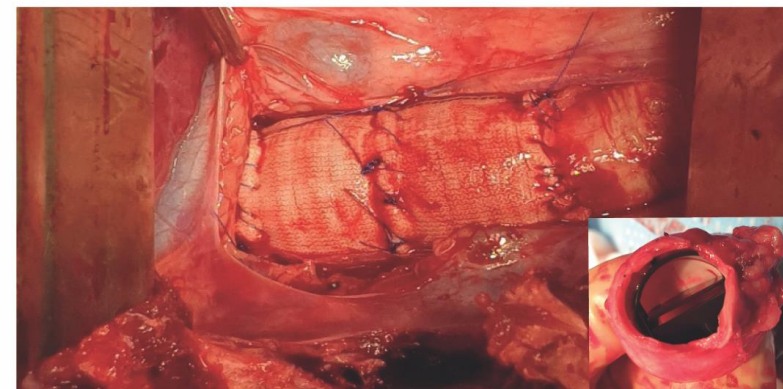
Anti-thrombotic performance

In vivo POC on mechanical prosthetic heart valves

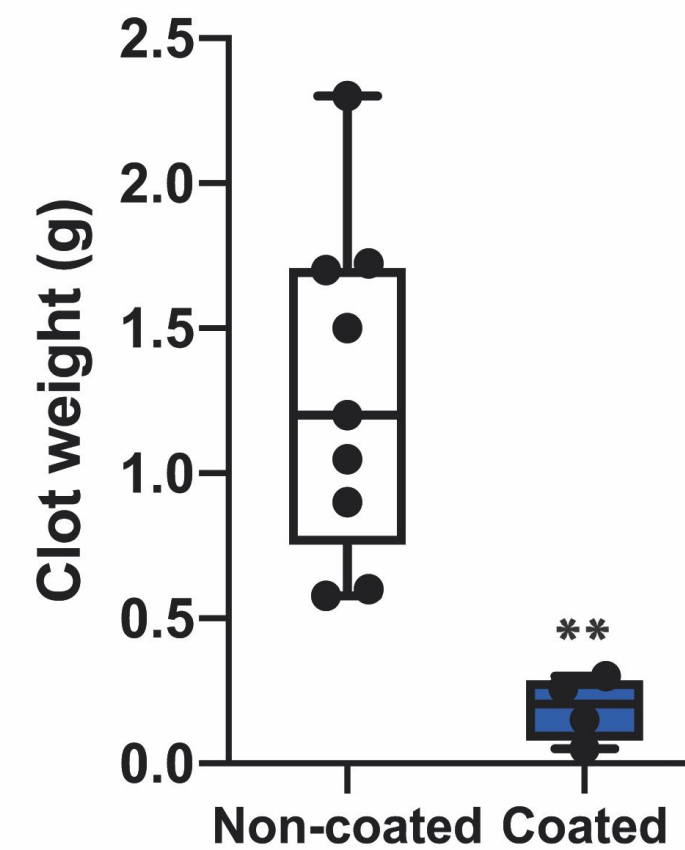
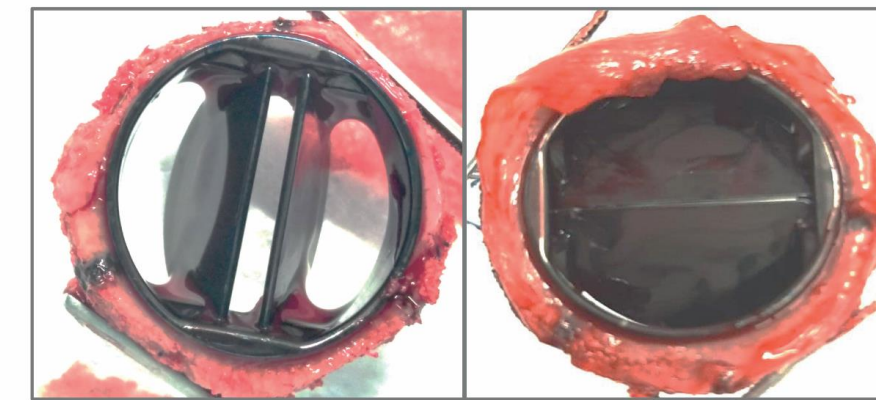
Implantation of coated and non-coated mechanical valves in pig thoracic aorta for 1 month
No anticoagulation



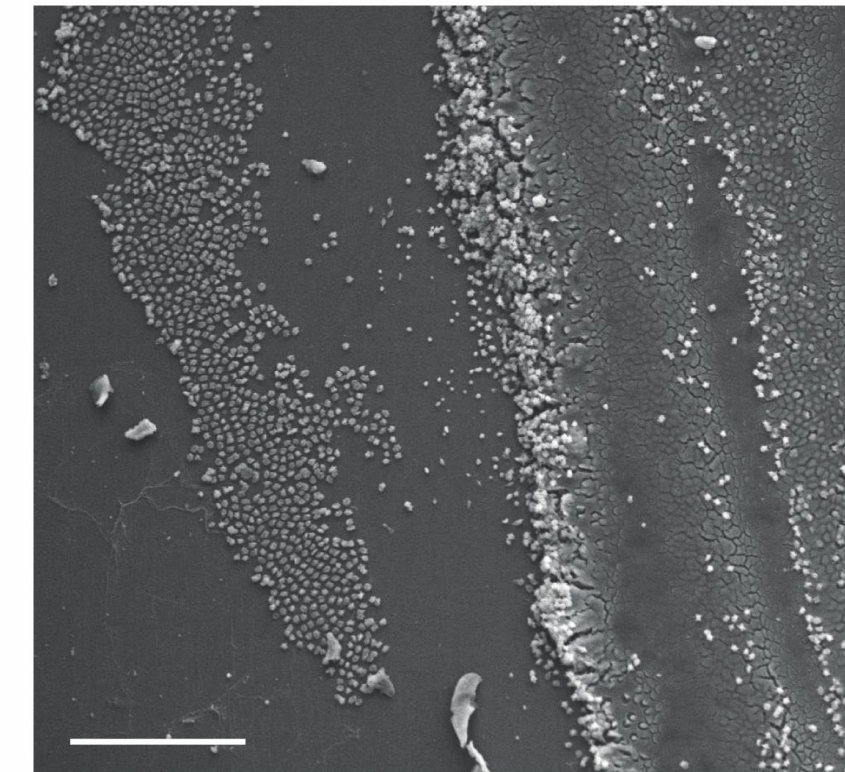
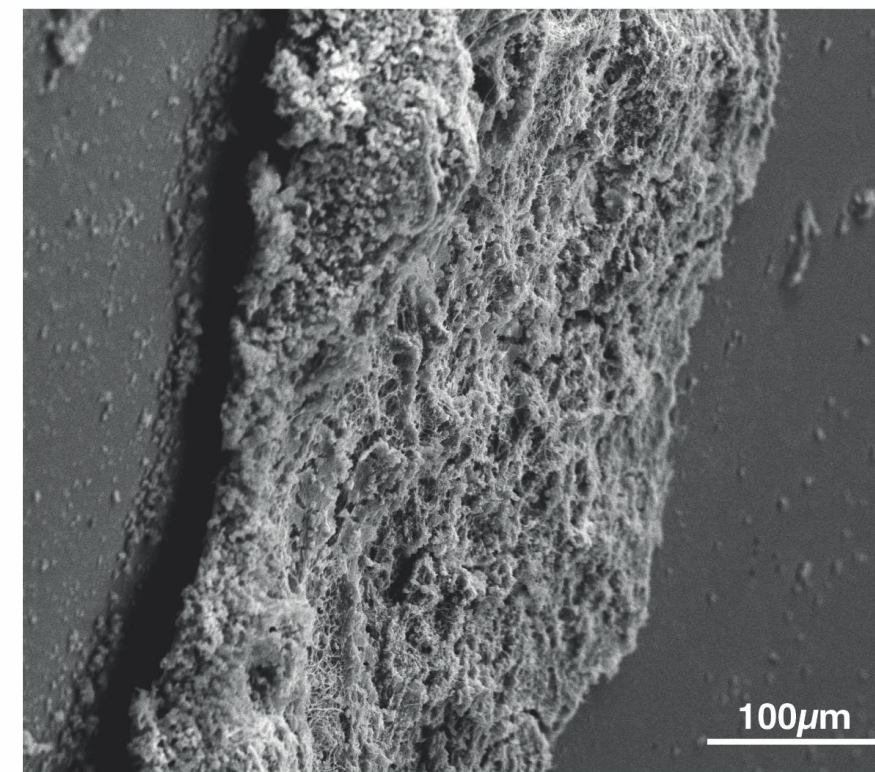
Non-coated



Coated



d



Nanoreservoir Coating

Biological valves

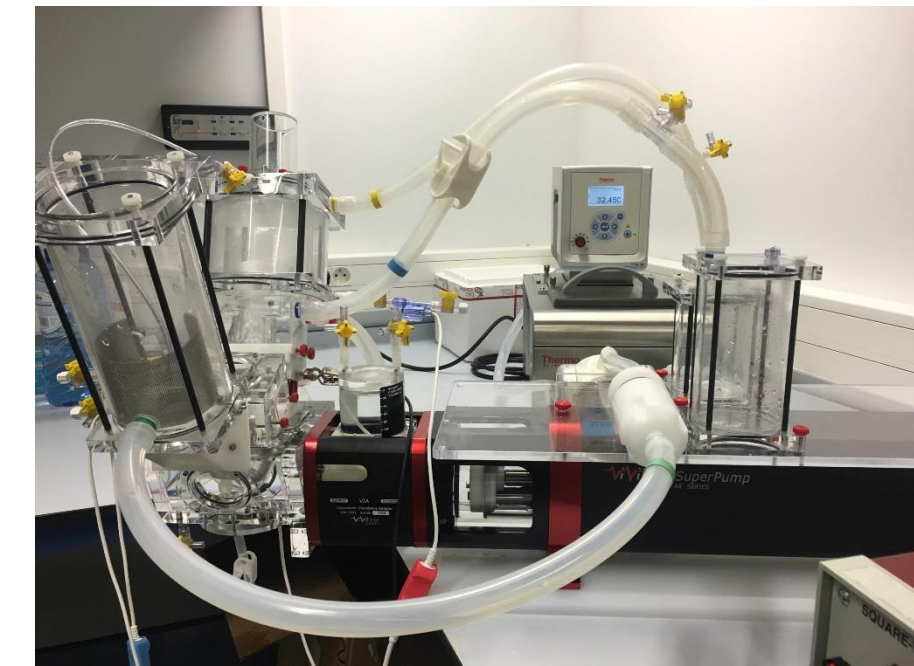


Non-coated

Coated

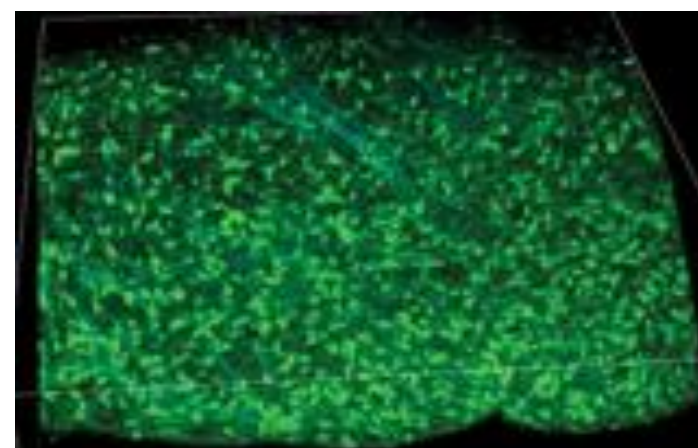
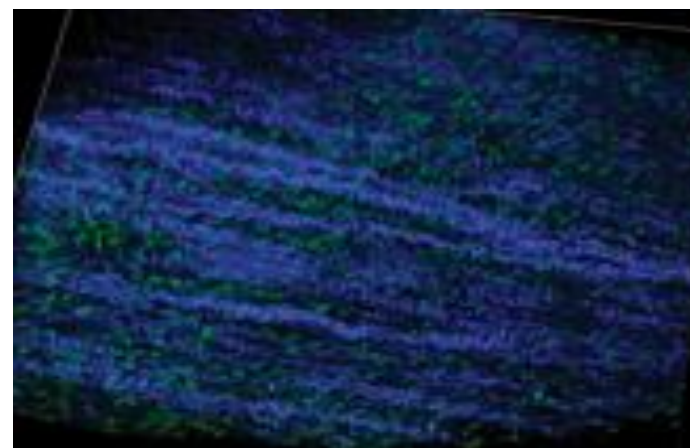


Non-coated



Pulse duplicator

Coated



Multiphoton microscopy

Coating durability

Resist to 200 million cycles in a valve durability tester (= 6yrs of life)

Nanoreservoir Coating

Biological valves



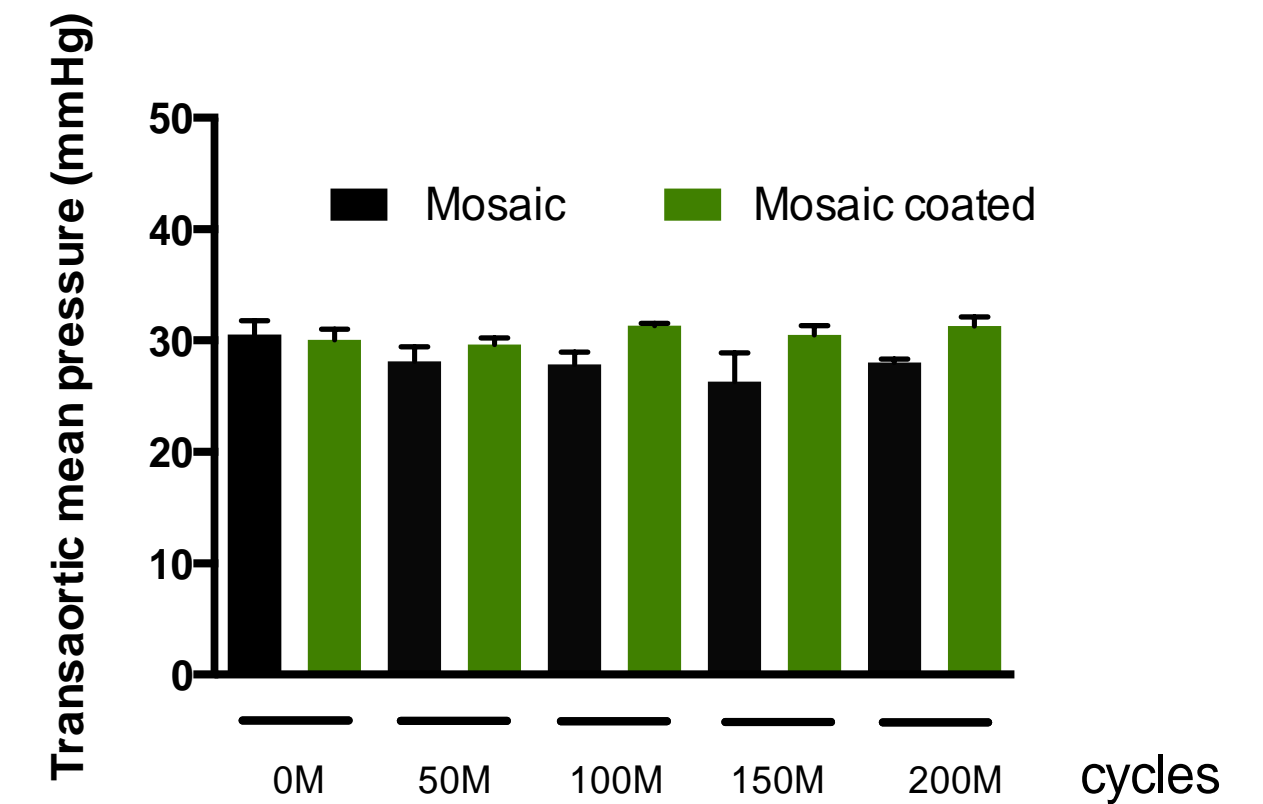
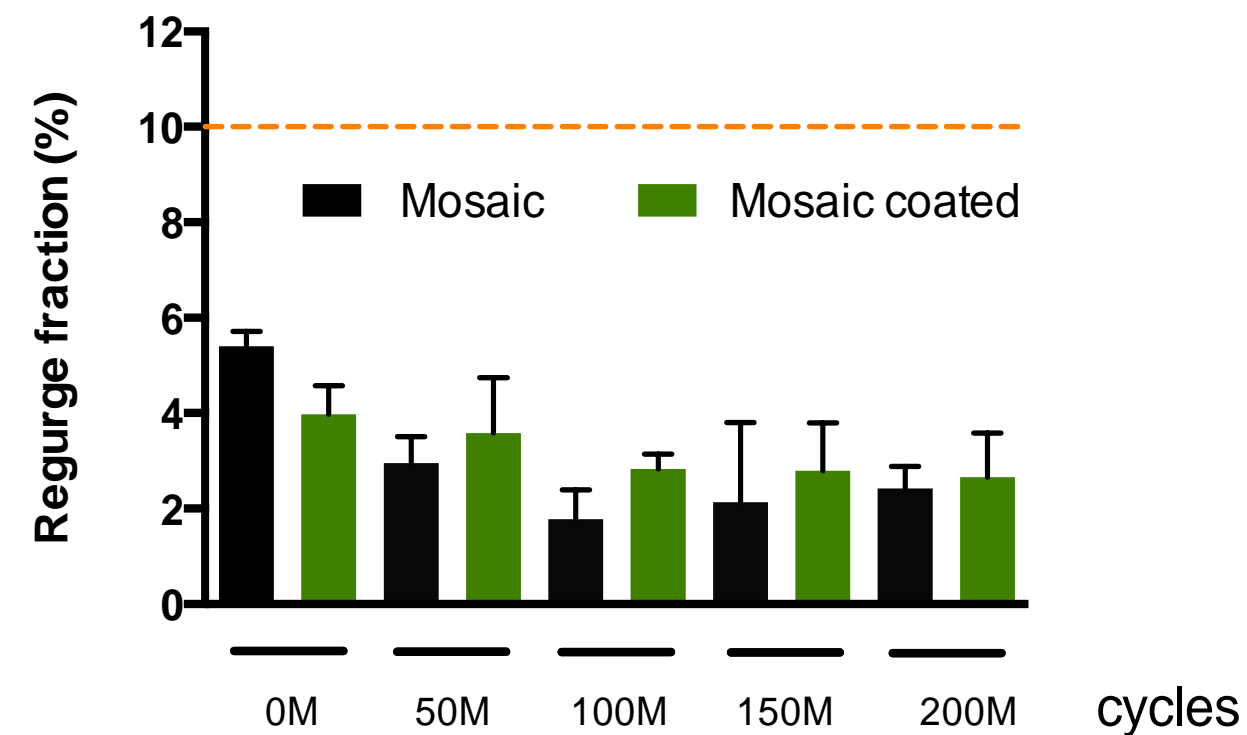
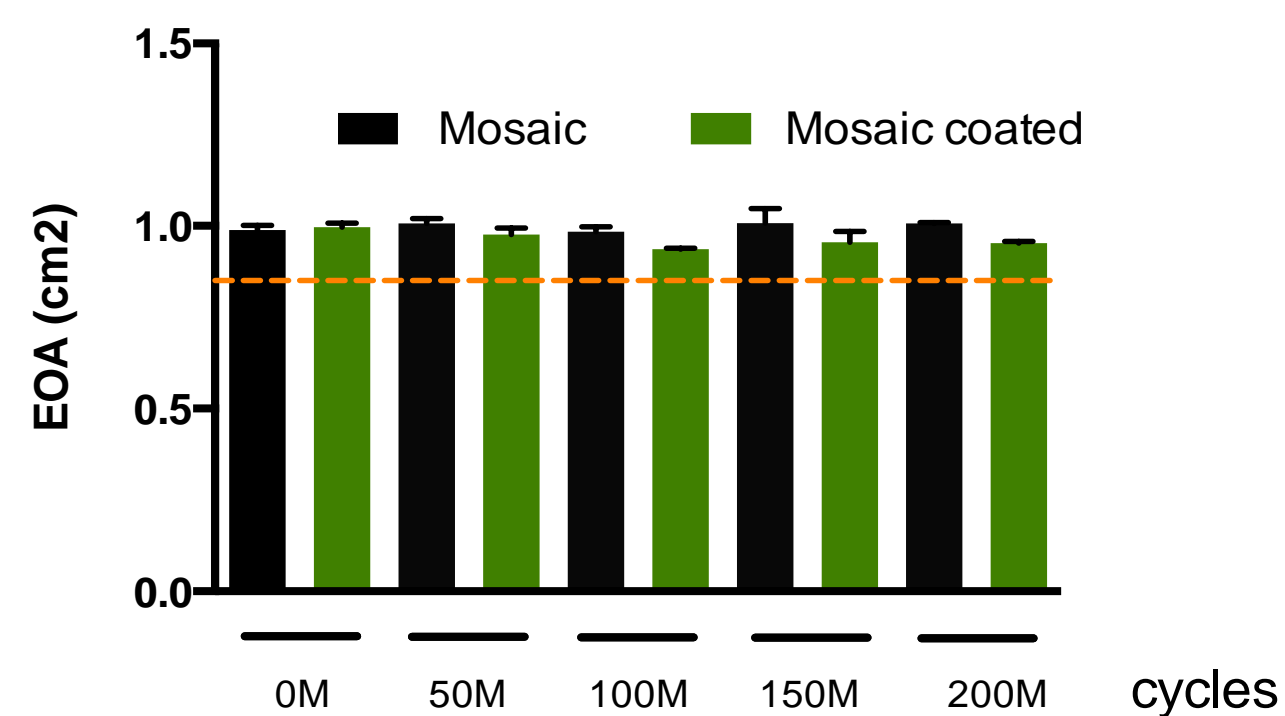
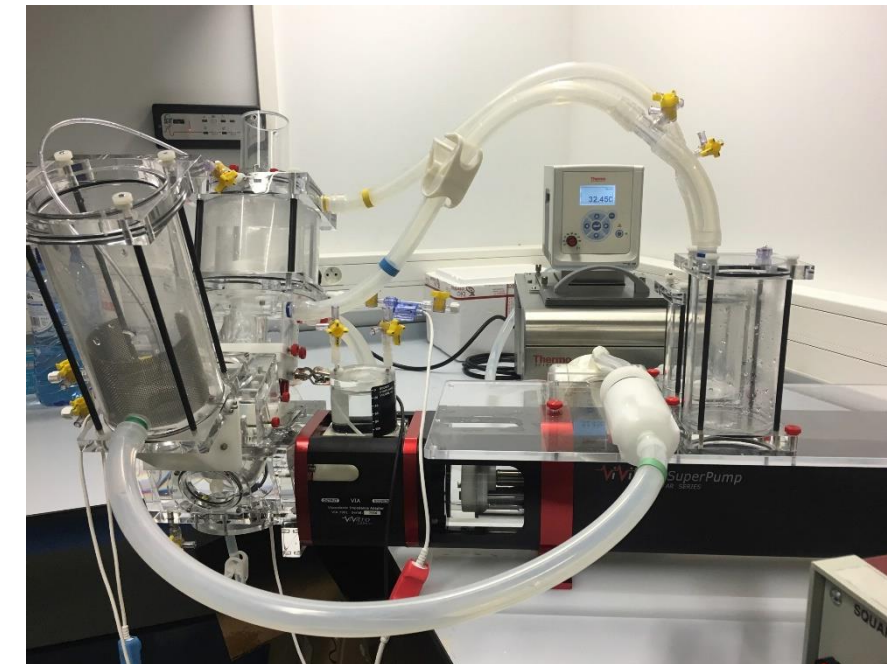
Non-coated



Coated



Pulse duplicator



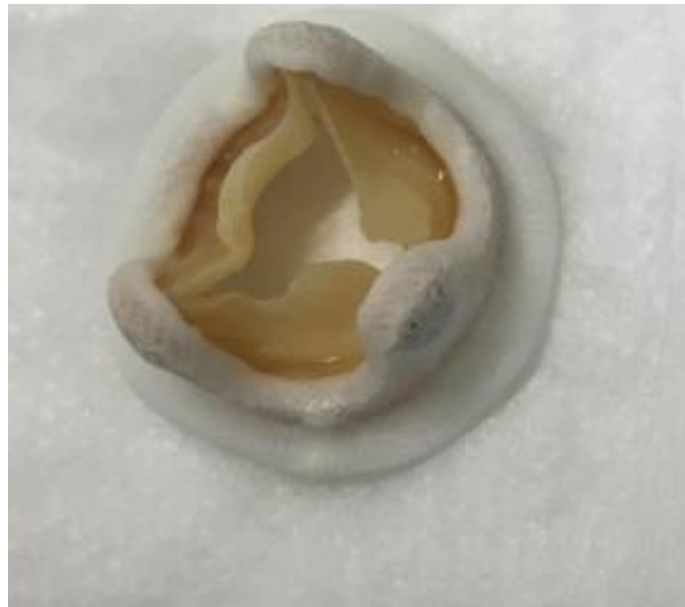
Nanoreservoir Coating

Antibacterial performance



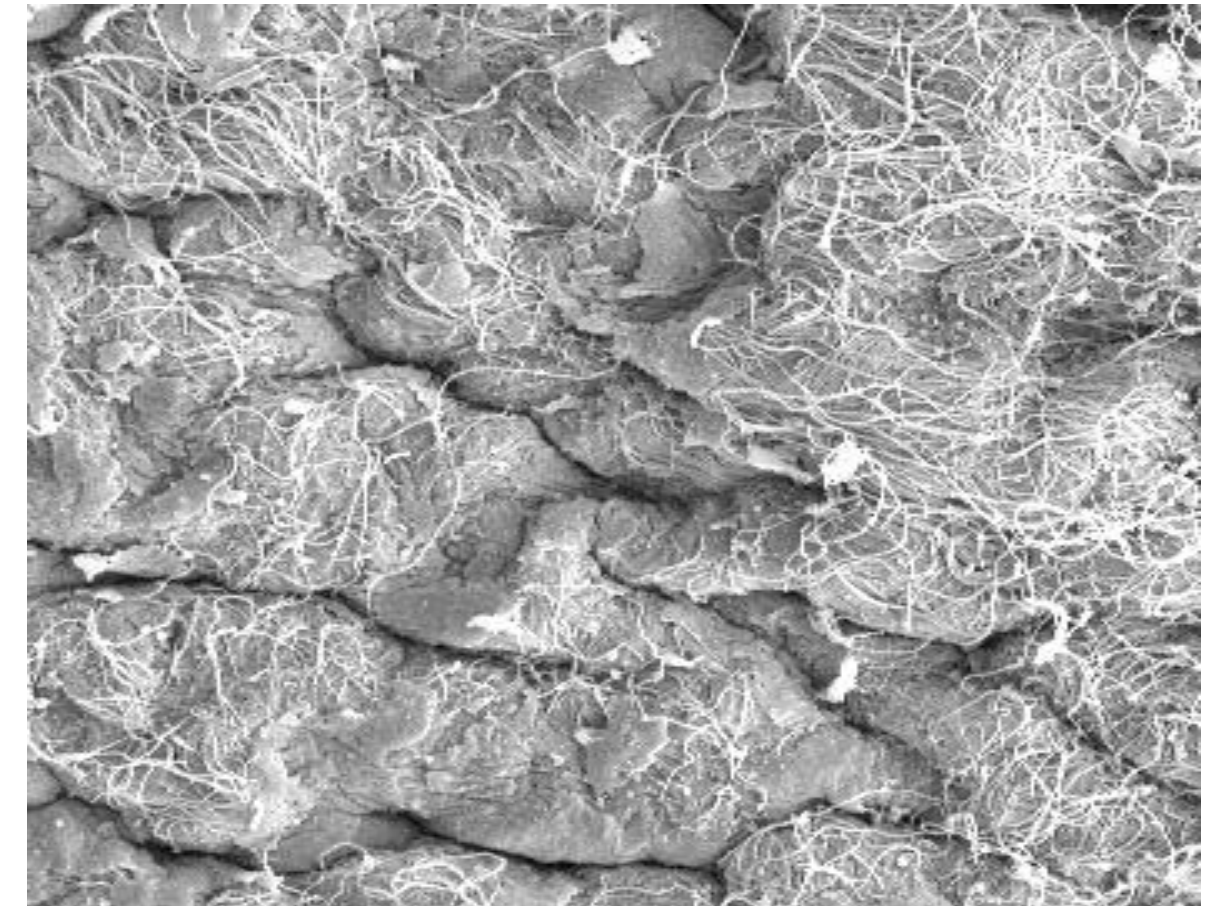
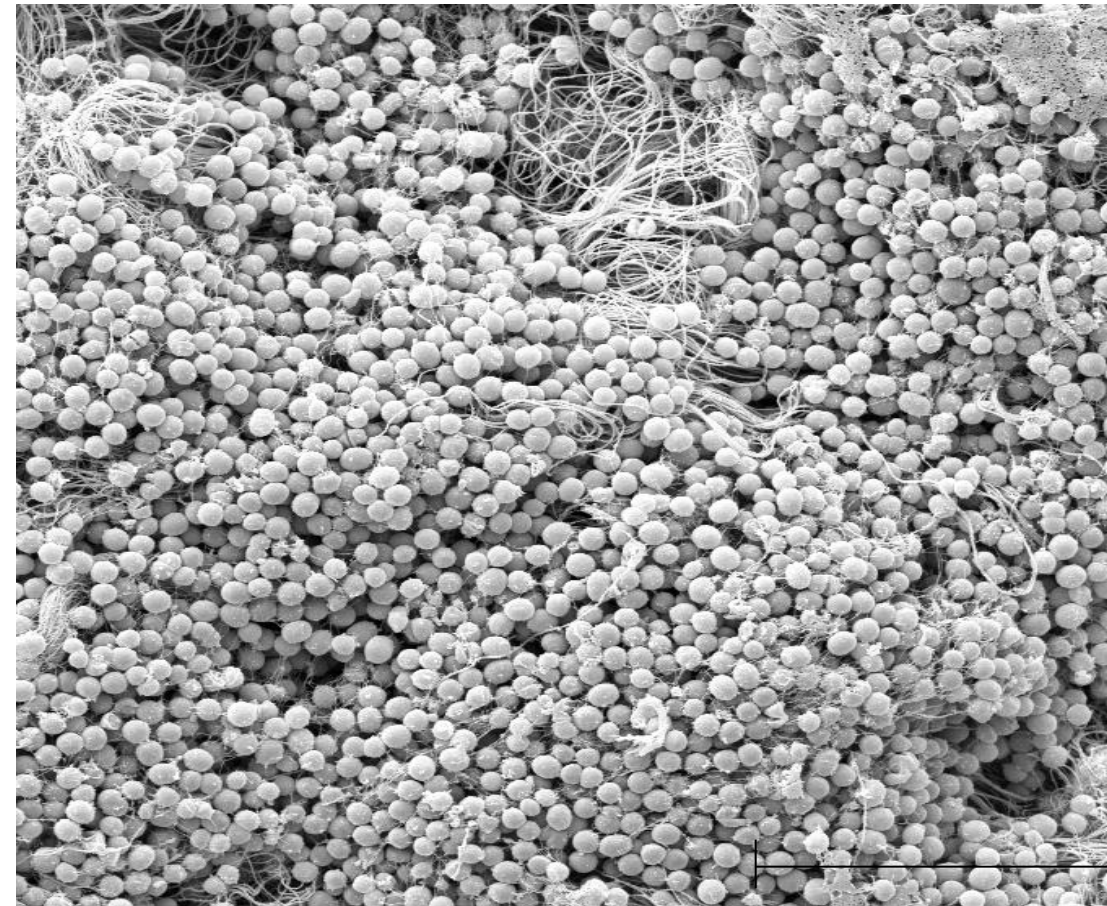
Non-coated

Coated



Non-coated

Coated



**Anti-staphylococcal
activity**

Scanning electron microscopy

Conclusions

- Medical need for new approaches to prevent prosthetic valve thrombosis
- High potential for innovative coating strategies with simultaneous antithrombotic and antimicrobial activities
- Need to review and standardise hemocompatibility test methods according to defined prosthesis flow conditions to improve clinical relevance of data

Acknowledgements

Laboratory of Cardiology GIGA-Metabolism and Cardiovascular Biology

Cécile Oury, PhD
Patrizio Lancellotti, MD, PhD
Alain Nchimi, MD, PhD
Kirsten Leeten
Céline D'Emal
Margaux Debuissou
Sofia Melo



Surgical Research Center GIGA-Cardiovascular Sciences

Natzi Sakalihasan, MD, PhD
Lucia Musumeci, PhD
Jean-Paul Cheramy-Bien



Dept clinical sciences, Faculty of Veterinary Medicine

Charlotte Sandersen, DVM, PhD
Alexandra Gougnard, DVM



Center for research on macromolecules, Dept of chemistry, CESAM

Christine Jérôme, PhD
Christophe Detrembleur



CMD-COAT SA

Abdelhafid Aqil, PhD
Bartosz Ditkowski, PhD
Céline Delierneux, PhD
Robin Scalbert
Maurine Devillé
Sébastien Cajot



Center for interdisciplinary research on Medicines

Bernard Pirotte, PharmD, PhD
Eric Goffin, PharmD





Thank you for your attention