Proposition for a general antiplatelet prophylaxis strategy

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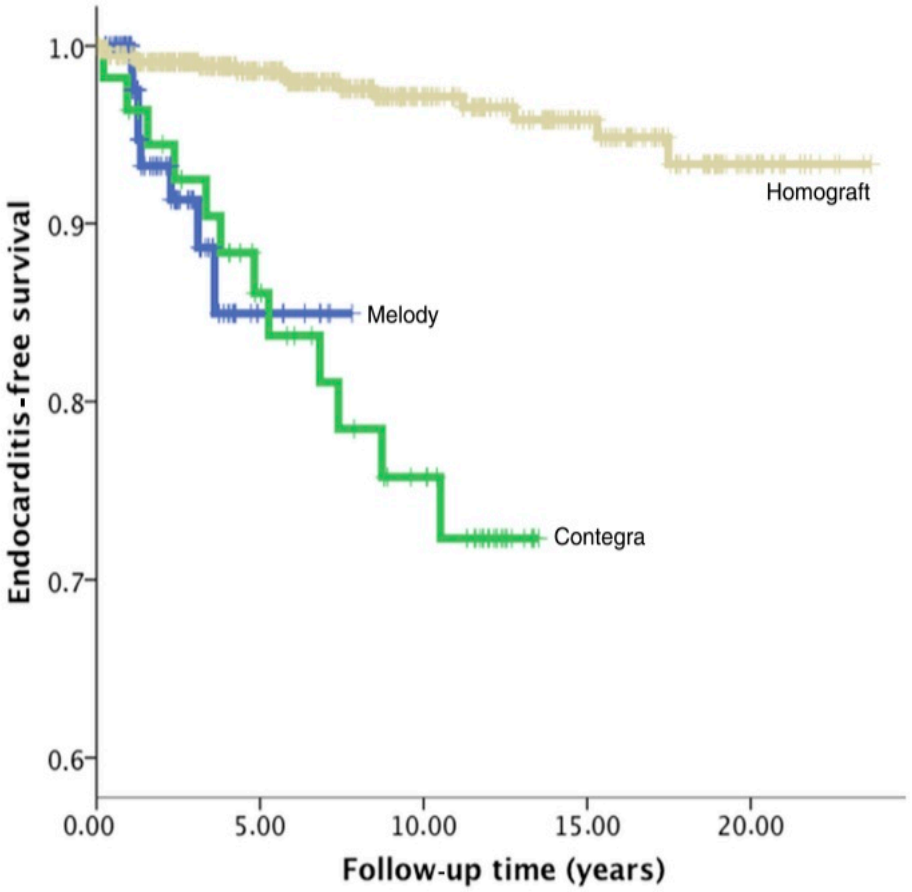
IE: Societal challenges

Risk of IE



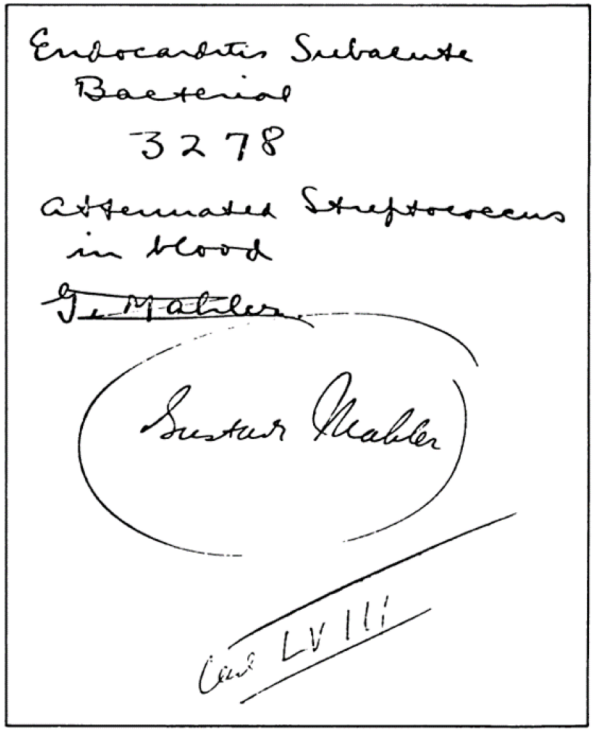
van Dijk *et al* 2015, Heart

Factors increasing risk of IE

- invasive medical treatment
  - ↑ *S. aureus* IE
- antibiotic resistance
- age of population and patients

- limited effect of prophylaxis

Gustav Mahler, 1911


Endocarditis Subacute
Bacterial
3278
Attenuated Streptococcus
in blood
G. Mahler.
Gustav Mahler
Cas LVIII

Front page of George Baehr and Emanuel Libman's bacteriological report on Mahler's blood culture.

Mahler received an experimental serum therapy and was symptomatically treated with aspirin, which could be synthesized since 1897.

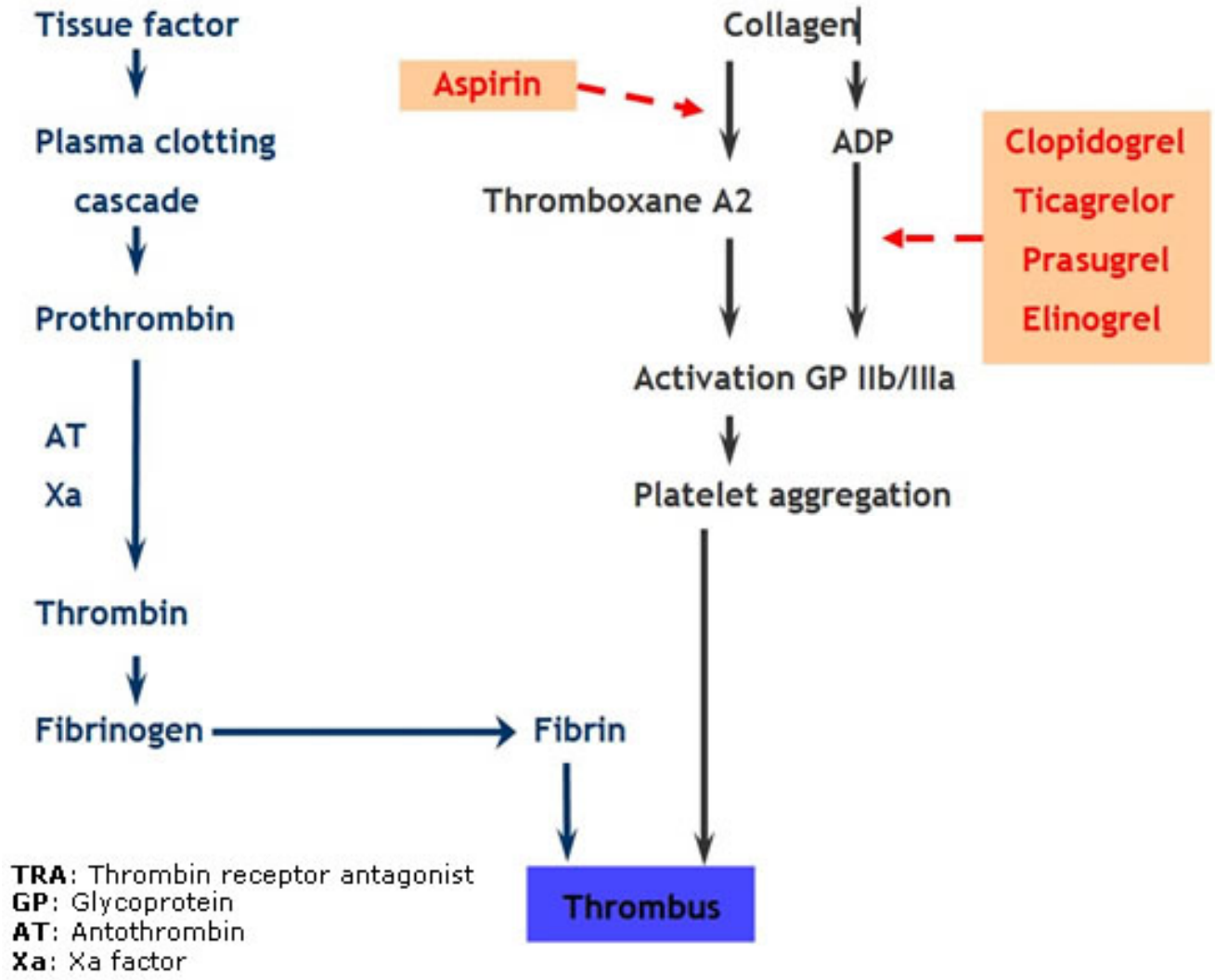
Diagnostik gestützt wird. Der Kardiologe Libman hat sich über ein Jahrzehnt lang mit der neuen Technik der Blutkultur befasst und etwa 3 000 Kulturen untersucht (17). Doch es soll noch eine ganze Zeit dauern, bis eine wirksame Therapie verfügbar ist. Mahler wird mit einer experimentellen Serumtherapie und symptomatisch mit Acetylsalicylsäure, die gerade erst seit 1897 in reiner Form synthetisiert werden kann, behandelt. Eine Heilung ist damit natürlich nicht möglich. 1909 entwickelten Paul Ehrlich und Sahachiro Hata das Salvarsan und 1932 von Mietch und Klarer ein Sulfonamid, das unter dem Namen Prontosil bekanntwurde. Dessen antibakterielle

Franzen C, Dtsch Arztebl 2011; 108(19): A 1056–8

Role of antiplatelet agents in IE prevention?

Mechanisms anti-aggregant therapy

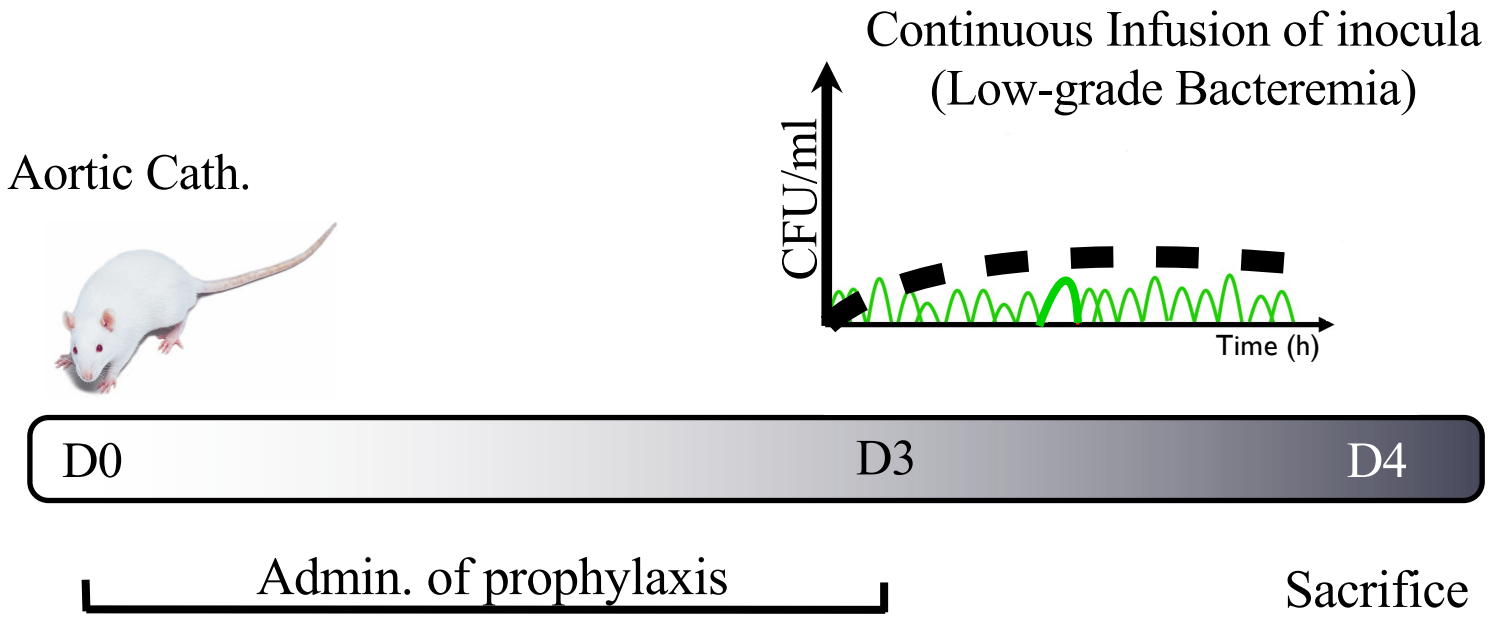
- **ASA**: irreversible inhibition of cyclo-oxygenases (COX)
  - ↓ prostaglandine
  - ↓ thromboxane A2
- **Clopidogrel, Ticagrelor**:
- inhibition of platelet adenosindiphosphate (ADP) receptor



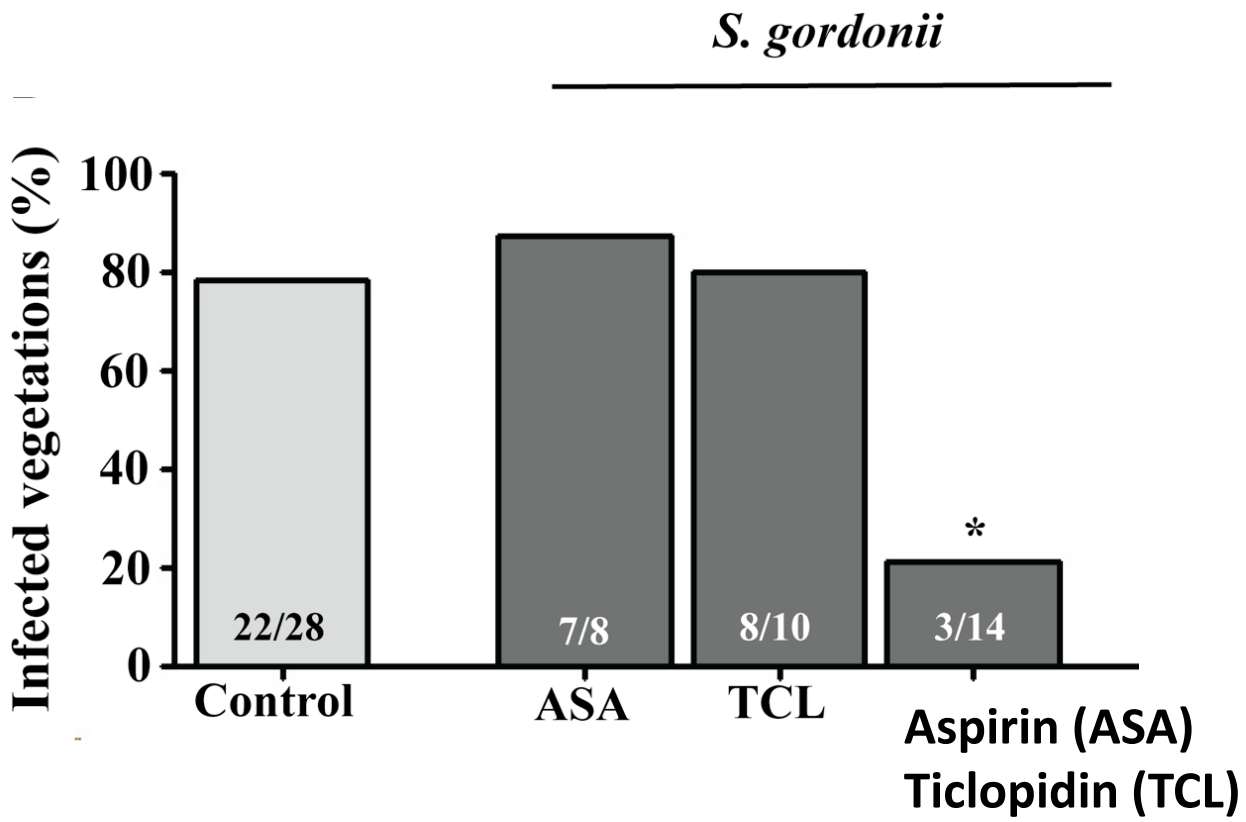
IE Prophylaxe?

Prophylaxis of Experimental Endocarditis With Antiplatelet and Antithrombin Agents: A Role for Long-term Prevention of IE in Humans?

Veloso TR et al, J Infect Dis 2015, 211(1); 72-79



Anti-platelet agents prophylactic efficacy



* *P < 0.05 compared to control*

Veloso TR et al, J Infect Dis 2015, 211(1); 72-79

Low-Dose Acetylsalicylic Acid Treatment and Impact on Short-Term Mortality in *Staphylococcus aureus* Bloodstream Infection: A Propensity Score–Matched Cohort Study

Michael Osthoff, MD[1]; Jan A. Sidler, MD[1]; Botond Lakatos, MD[1]; Reno Frei, MD[2]; Marc Dangel, MPH[1]; Maja Weisser, MD[1]; Manuel Battegay, MD[1]; Andreas F. Widmer, MD, MS[1]

- retrospective study of 839 *S. aureus* and 602 *E. coli* bloodstream infection episodes
- matching of low dose ASA users and non-users

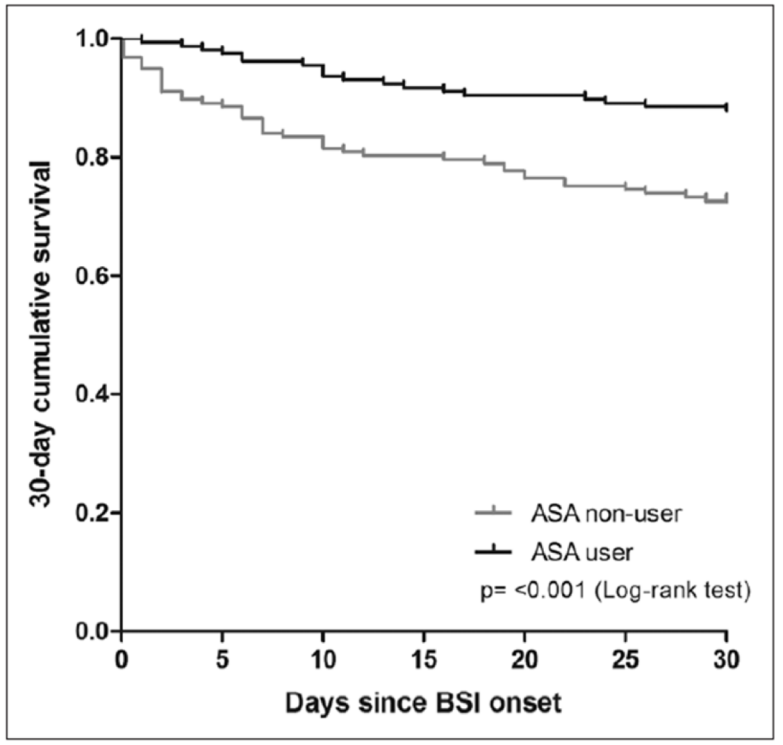
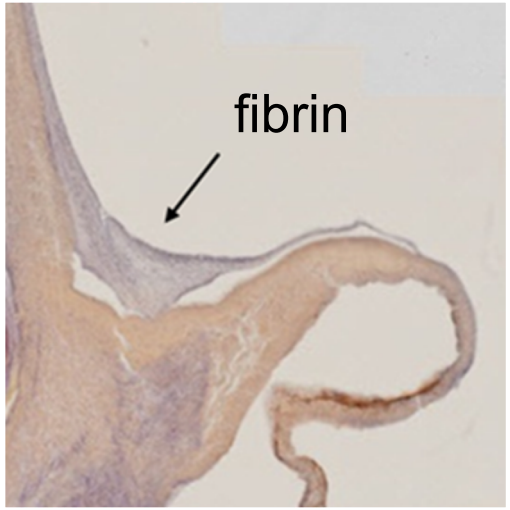


Figure 2. Survival curves in propensity score–matched low-dose acetylsalicylic acid (ASA) users and nonusers with *Staphylococcus aureus* bloodstream infection; Kaplan-Meier estimates. BSI = bloodstream infection.

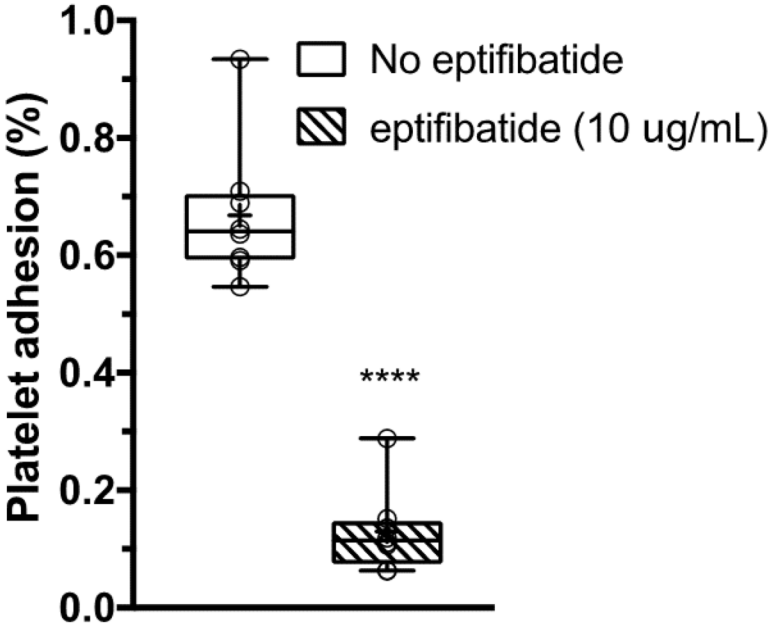
Osthoff et al, Crit Care Med 2016, 44(4); 773-781

Role of fibrin and platelets



Fibrin deposition in the valvular sinus
(Brown Hopps staining)

Platelet adhesion to RVOT tissues



- predisposition for bacterial and platelet adhesion?

Jewgenow et al., Int J Cardiol 281: 113-118; 2019

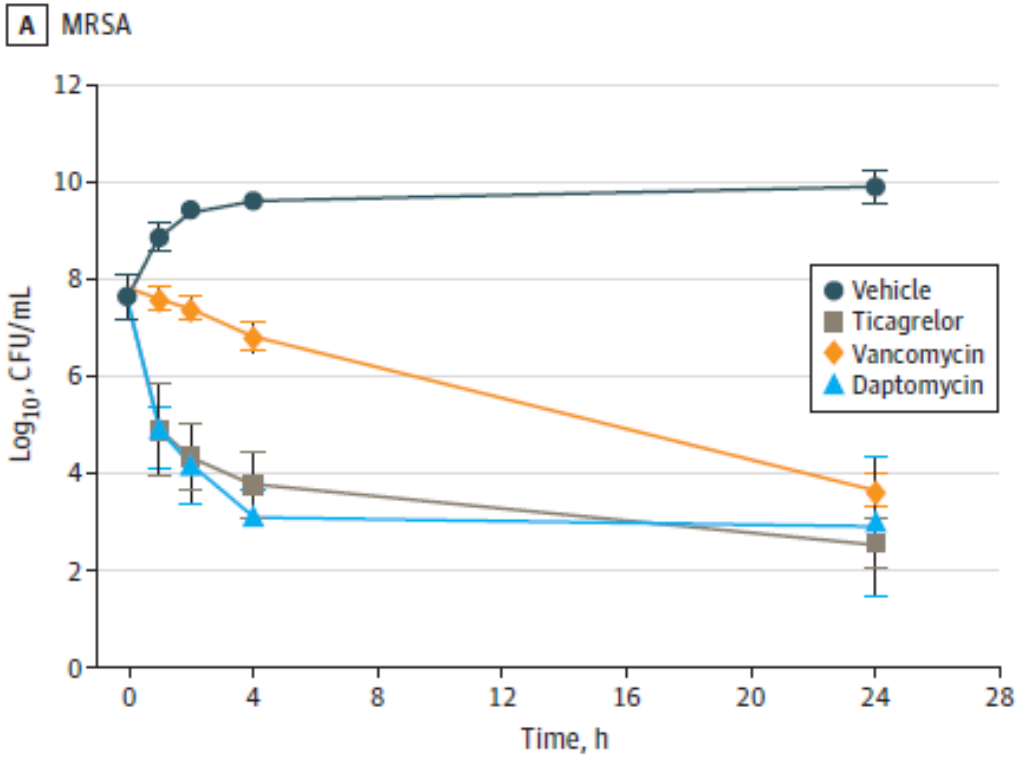
(Ditkowski et al, unpublished data)

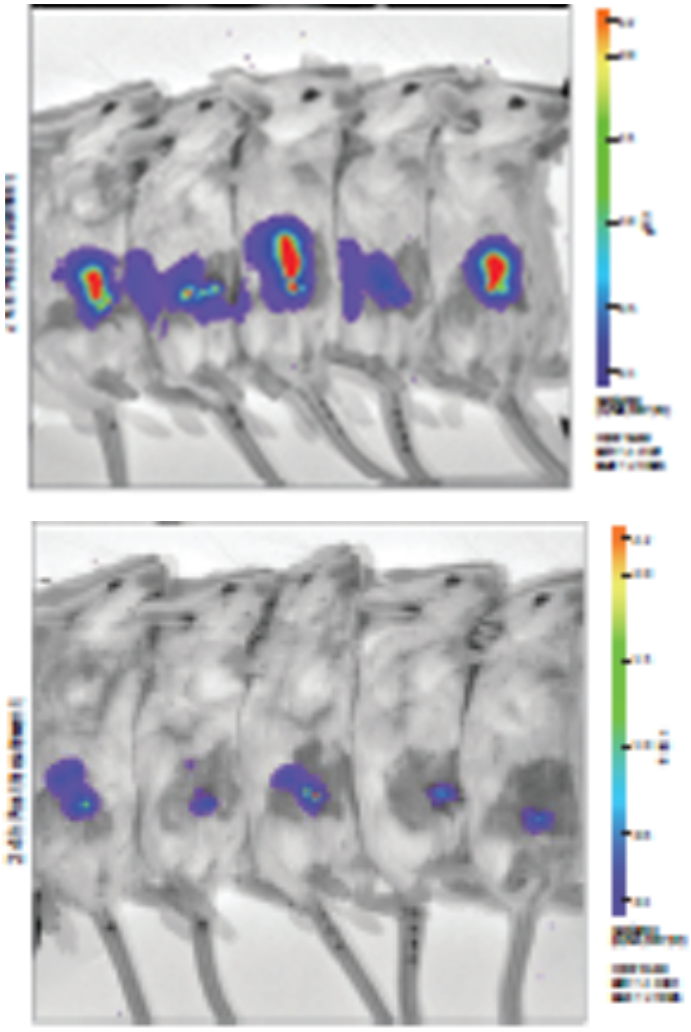
JAMA Cardiol. 2019 May 8. doi: 10.1001/jamacardio.2019.1189. [Epub ahead of print]

Antibacterial Activity of Ticagrelor in Conventional Antiplatelet Dosages Against Antibiotic-Resistant Gram-Positive Bacteria.

Lancellotti P[1,2], Musumeci L[1], Jacques N[1], Servais L[1], Goffin E[1,3], Pirotte B[3], Oury C[1].

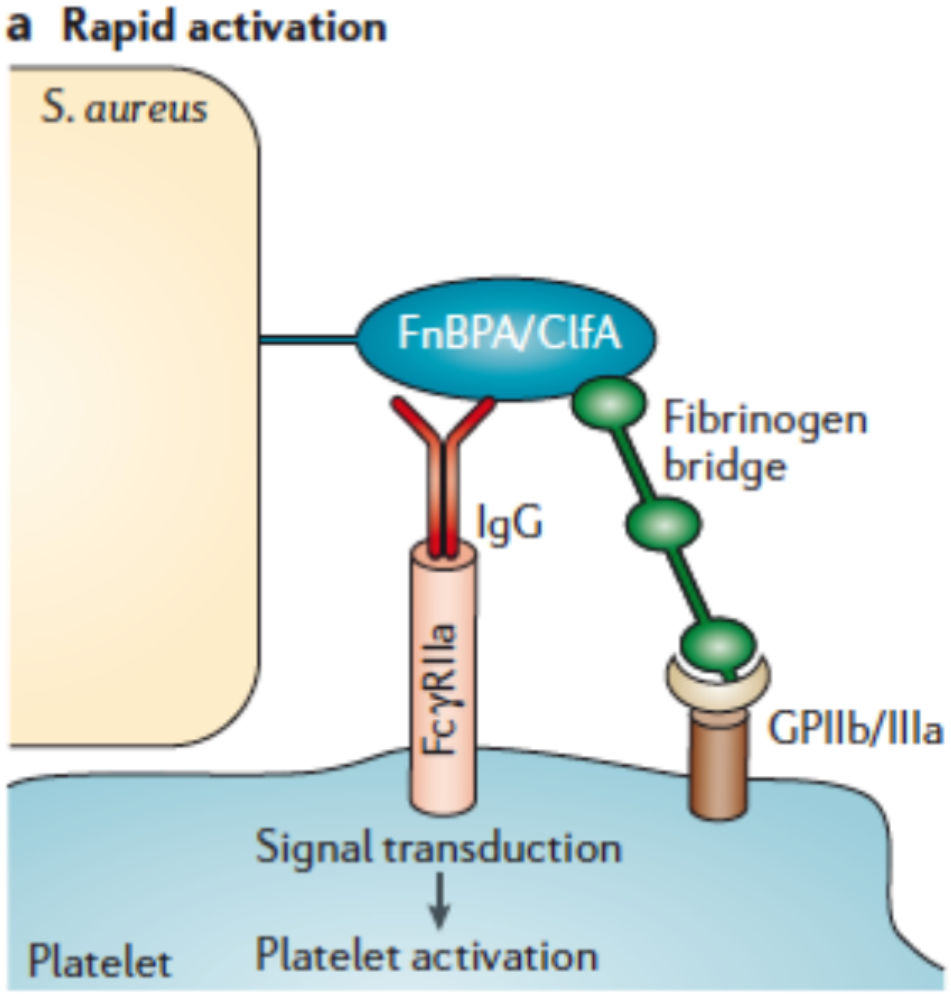
Figure 1. In vitro Characterization of Bactericidal and Anti-Biofilm Activity





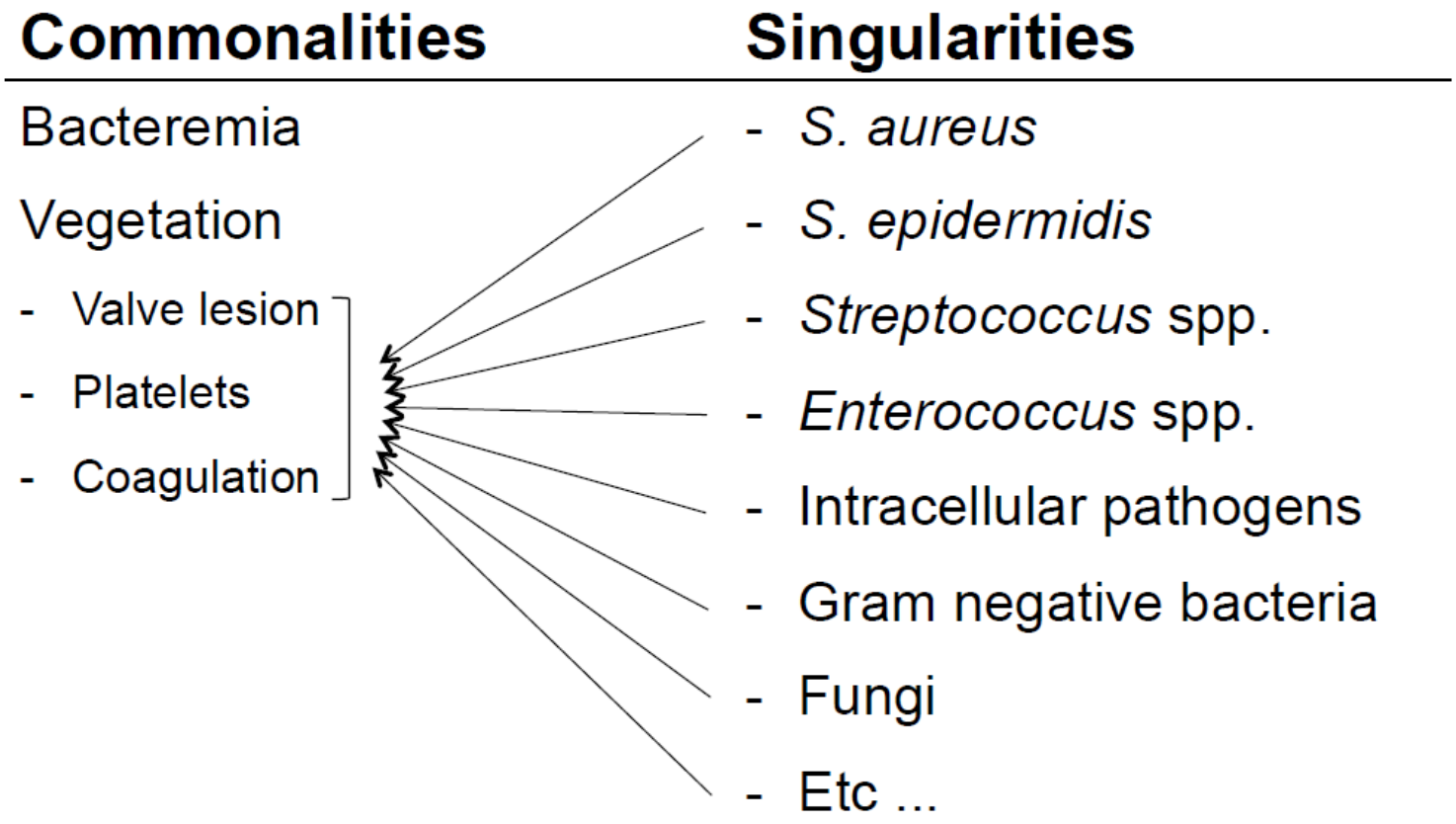
Bioluminescent signals of *in vivo* bactericidal activity

S. aureus and platelets



Fitzgerald et al. *Nature Rev Microbiol* 2005; 4:445-57

Its just common sense



Courtsey from P. Moreillon

In-vivo anti-platelet therapy

Hypothesis

Aspirin and platelet ADP receptor antagonists could diminish bacterial-platelet interaction with valvular tissue and thus be beneficial in IE prevention.

Planned analysis

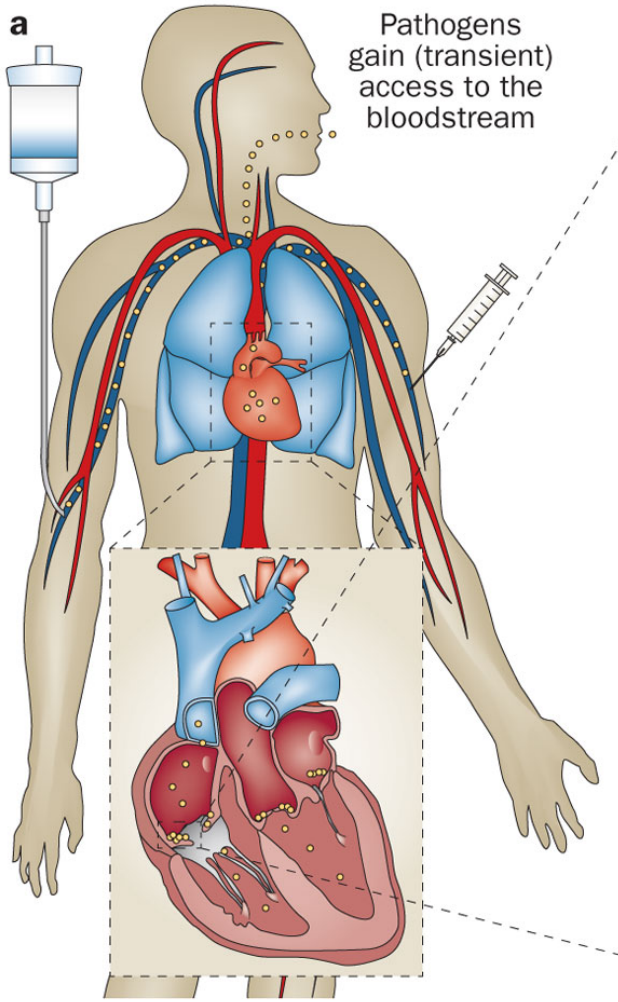
IE databank UZ Leuven

- W. Oosterlinck, Cardiac Surgery
- M.C. Herregods, Cardiology
- W. Peetermans, Infectious Diseases

> 740 adult patients, 2000 – 2019

- modified Duke criteria
- treatment conform to ESC guidelines

Cooperation with P. Moreillon and
J. Entenza, Exp. Microbiology, Lausanne



Planned analysis

Retrospective and prospective case control study

Patients

bioprosthetic aortic valve with native aortic valve

→ IE vs. non IE

→ ASA vs. no ASA

(odds-ratio and chi-square test)

250 patients in each group (power of 80 % of the analysis)

- risk of IE 0.7 % / patient year after bio-prosthetic valve
- 10 % of patients under ASA
- estimated decrease of IE risk under ASA 50 %

Discussion

- Feasibility of multi-center study

? participation of other centers

? patient cohort

? expansion to other anti-coagulant agents

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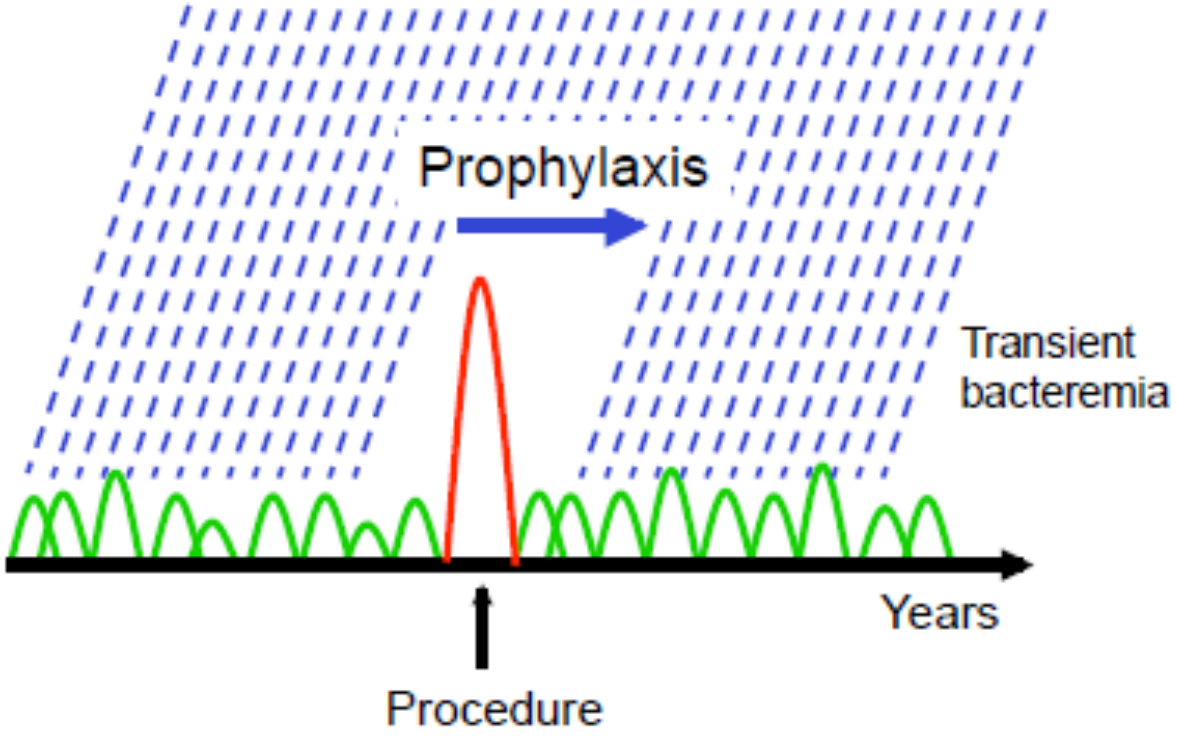
Limited Effect of Antibiotic Prophylaxis



van der Meer 1992. *Lancet*; 339:135-9

Wilson et al. *Circulation* 2007 Oct 9;116(15):e376-7.

courtsey from P. Moreillon, Lausanne