Anti-Thrombotic Therapy – Update 2017

Sophia-Antipolis (France), February 23-25 2017

European Heart House

SESSION 1: PATHOPHYSIOLOGY AND METHODOLOGY

Understanding Thrombosis in...

February 23 2017

14:10-15:45

Atrial fibrillation

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"G. Monasterio" Foundation – Pisa, Italy

February 23, 2017 – 14:50-15:05 – 15 min. + 5 disc.

Prof. Raffaele De Caterina
Conflicts of Interest

- Co-author ESC Guidelines on Atrial Fibrillation 2010-2012
- Steering Committee member, National Coordinator for Italy, and Co-author of APPRAISE-2, ARISTOTLE, AVERROES, ENGAGE-AF, Re-DUAL PCI
- Fees, honoraria and research funding from Sanofi-Aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Novartis, Merck

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)	
Risk factor	**Score**
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

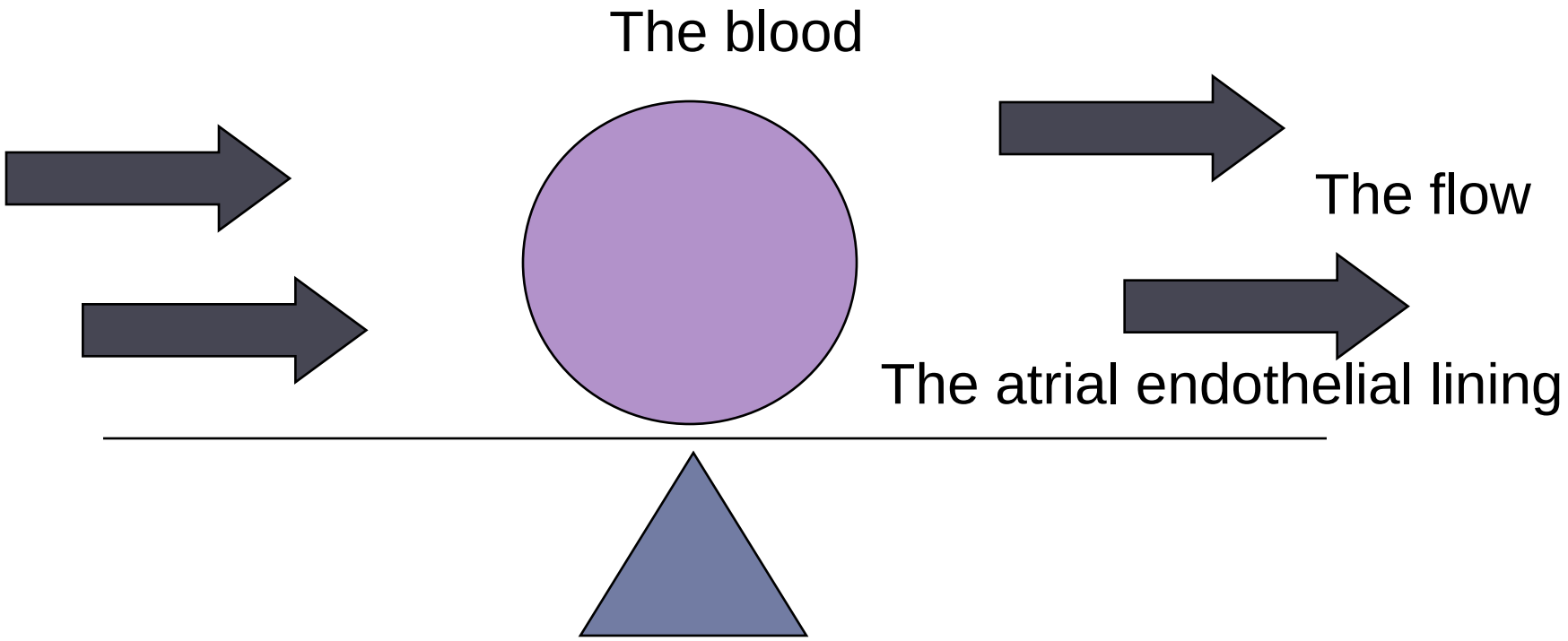
CHA_2DS_2-VASc score	Patients (n = 73538)	Stroke and thromboembolism event rate at 1 year follow-up (%)
0	6369	0.78
1	8203	2.01
2	12771	3.71
3	17371	5.92
4	13887	9.27
5	8942	15.26
6	4244	19.74
7	1420	21.50
8	285	22.38
9	46	23.64

Adapted from Olesen JB, et al., *Br Med J* 2011;**342**:doi: 10.1136/bmj.d124

Therefore:

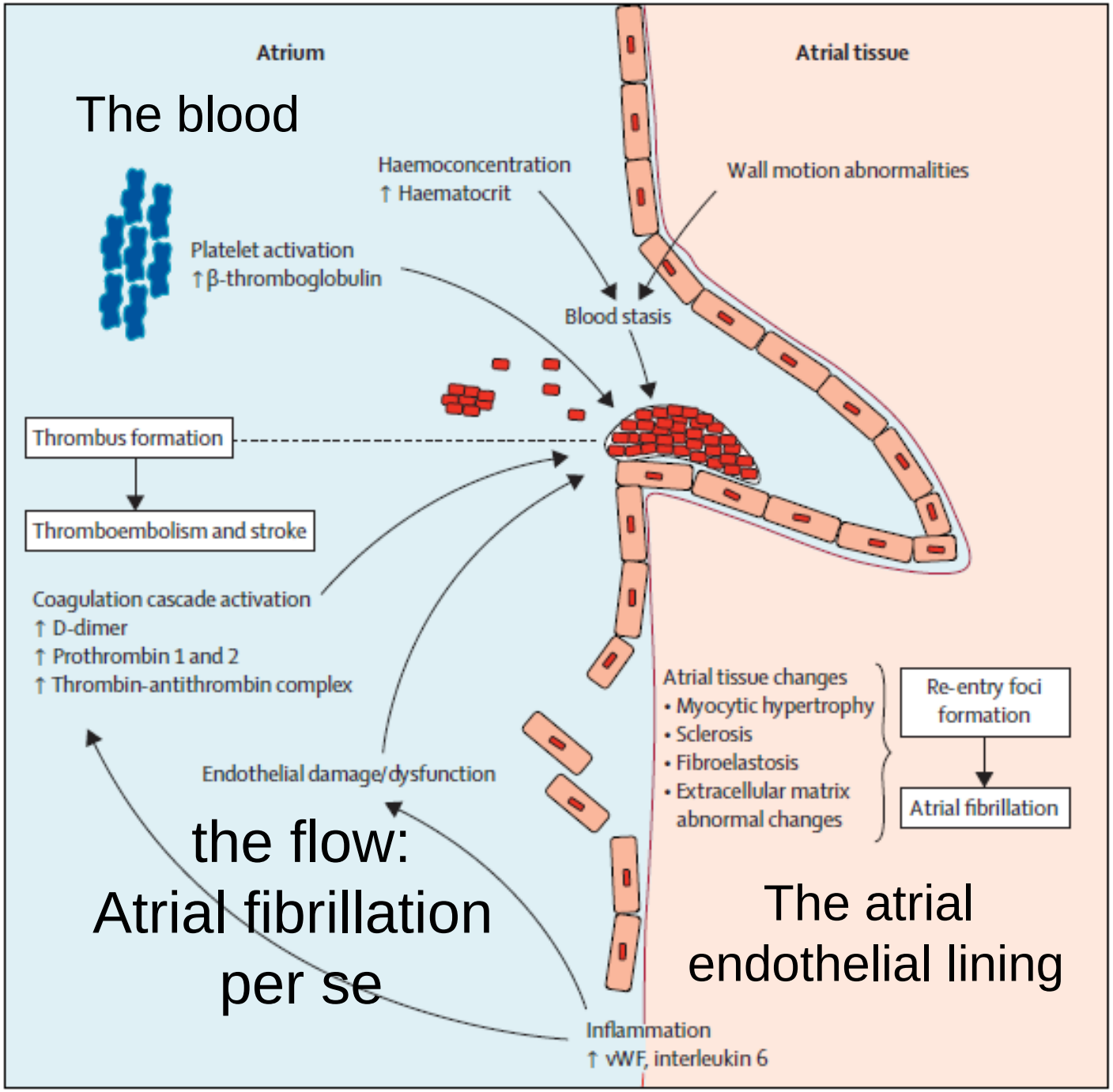
- One single condition, non-valvular AF, associated with extremely variable risk of stroke, from <1%/year to >6%/year
- Lone AF has a risk of stroke similar to that of the normal population (<1%/year)
- The presence of AF alone is not sufficient to increase the risk of stroke
- The presence of risk factors largely determines the prothrombotic state in AF

Left atrial/Left atrial appendage thrombosis – Virchow revisited



Localizing factor

- Atrial fibrillation per se



Components of Virchow's triad for thrombogenesis in atrial fibrillation

Watson T, et al, *Lancet 2009; 373: 155–66*

Flow abnormalities

- Blood stasis in the atria an obvious common denominator in AF, greater with mitral stenosis, less severe with associated mitral regurgitation
- Blood stasis increases with LA size
- Exacerbated by the occurrence of ventricular tachycardia, reducing the diastolic filling time and the atrial contribution to ventricular filling
- Documentable as spontaneous echo-contrast at TEE and as reduced Doppler flow velocities in the LAA
- … but blood flow stasis is present also in lone AF, where the thromboembolic risk is similar to that of the general population, therefore stasis alone CANNOT explain the increased risk of stroke in AF

Black IW, et al. J Am Coll Cardiol 1993;21:451-457
Goldman ME, et al. - [SPAF-III] study. J Am Soc Echocardiogr 1999;12:1080-1087.

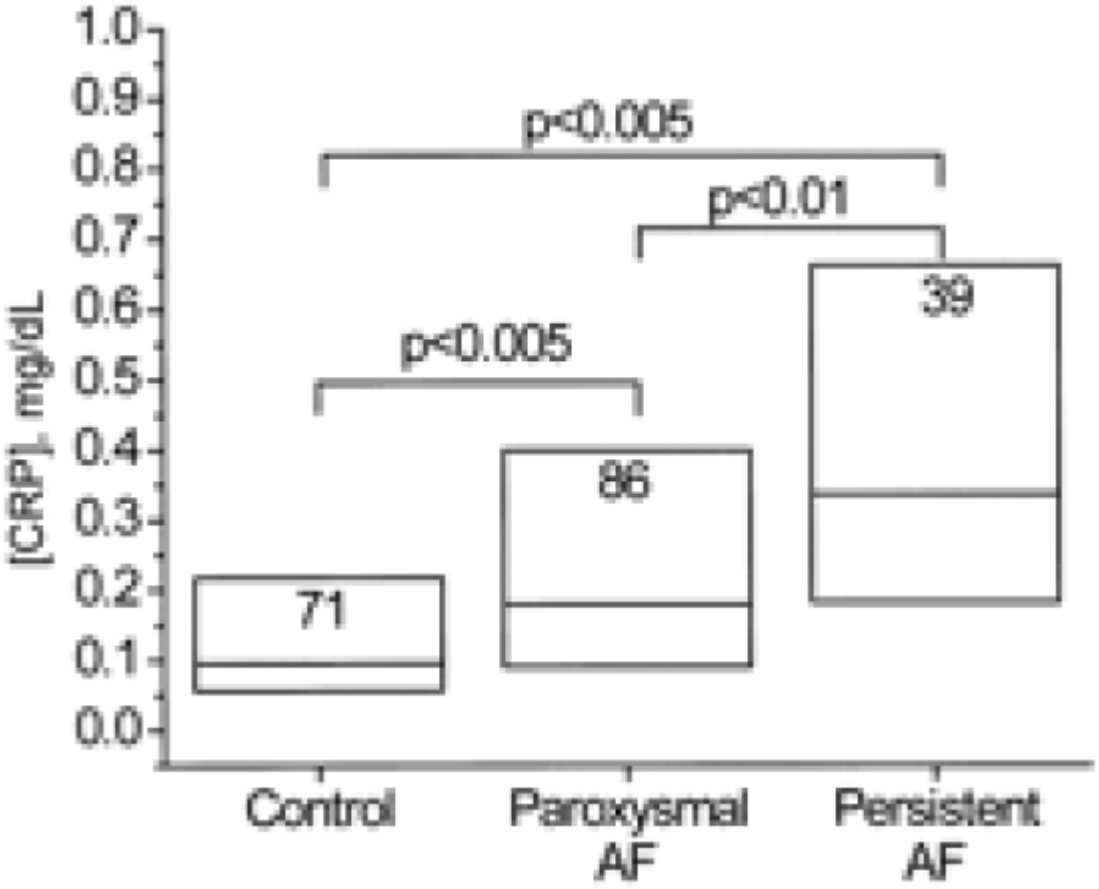
Atrial endocardial damage

- Electron-microscopy aspects of atrial endocardial damage[1] and of a “rough” endothelium[2]
- Aspects of LAA endocardial fibroelastosis[3]
- Systemic and vascular inflammation described in AF, as documented by elevated CRP levels[4]
- Increased fibrosis and levels of MMPs/TIMP in the atria correlating with risk factors[5]
- Increased atrial endothelial expression of tissue factor, again as a correlate of risk factors

1. Goldsmith I, et al. Am Heart J 2000;140:777-784.
2. Masawa N, et al. Virchows Arch Pathol Anat Histopathol 1993;422:67-71.
3. Shirani J, et al. Cardiovasc Pathol 2000;9:95-101.
4. Aviles RJ, et al. Circulation. 2003;108:3006.
5. Marin F, et al. Stroke 2003;34:1181-1186.
6. Nakamura Y, et al. Thromb Res 2003;111:137-142

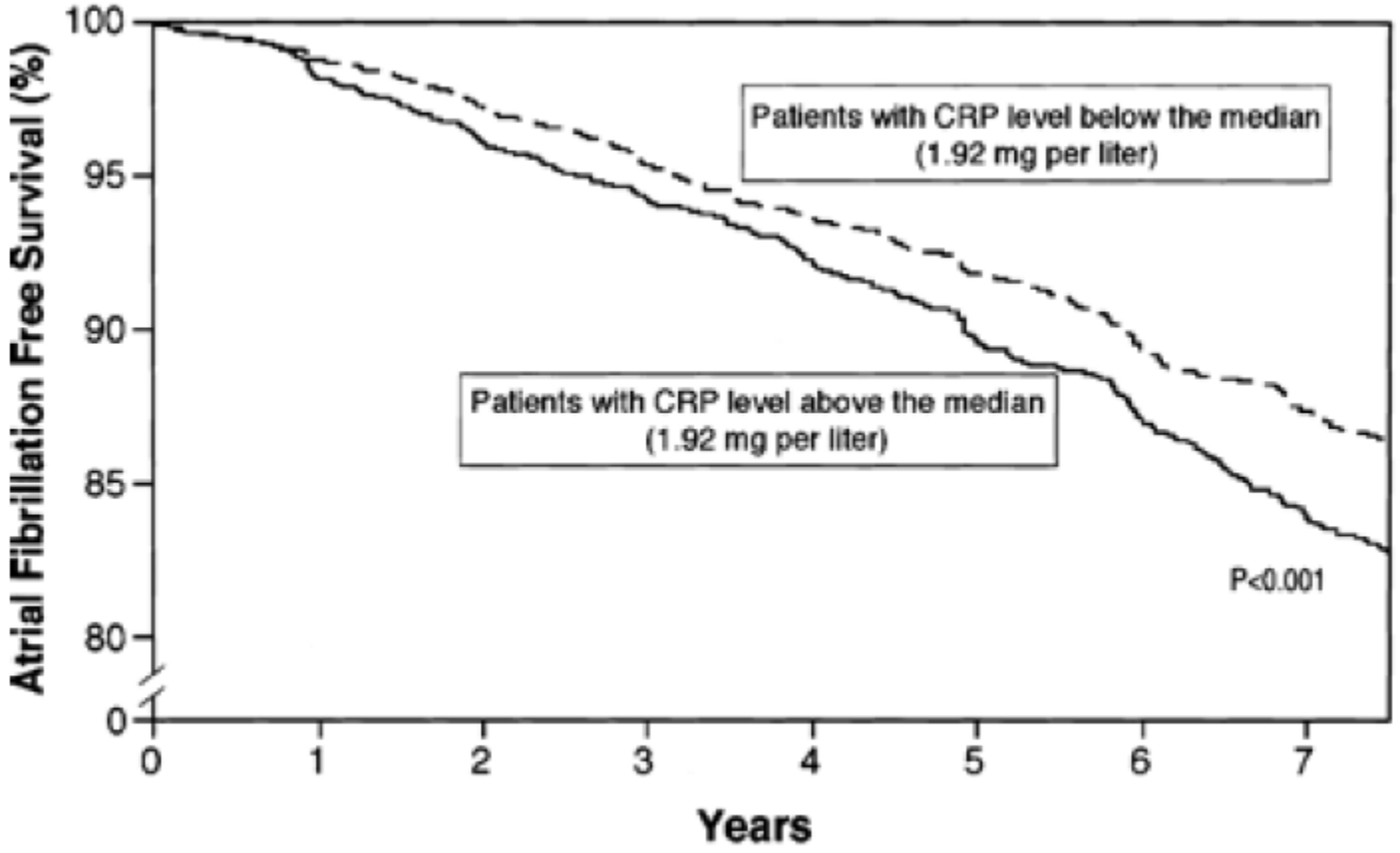
Inflammation and AF burden

Step-wise elevation of CRP with increasing burden of AF



Chung MK, et al. Circulation 2001;104:2886

Probability of new-onset AF as a function of higher-than median or lower-than median baseline CRP



Aviles RJ, et al. Circulation. 2003;108:3006.

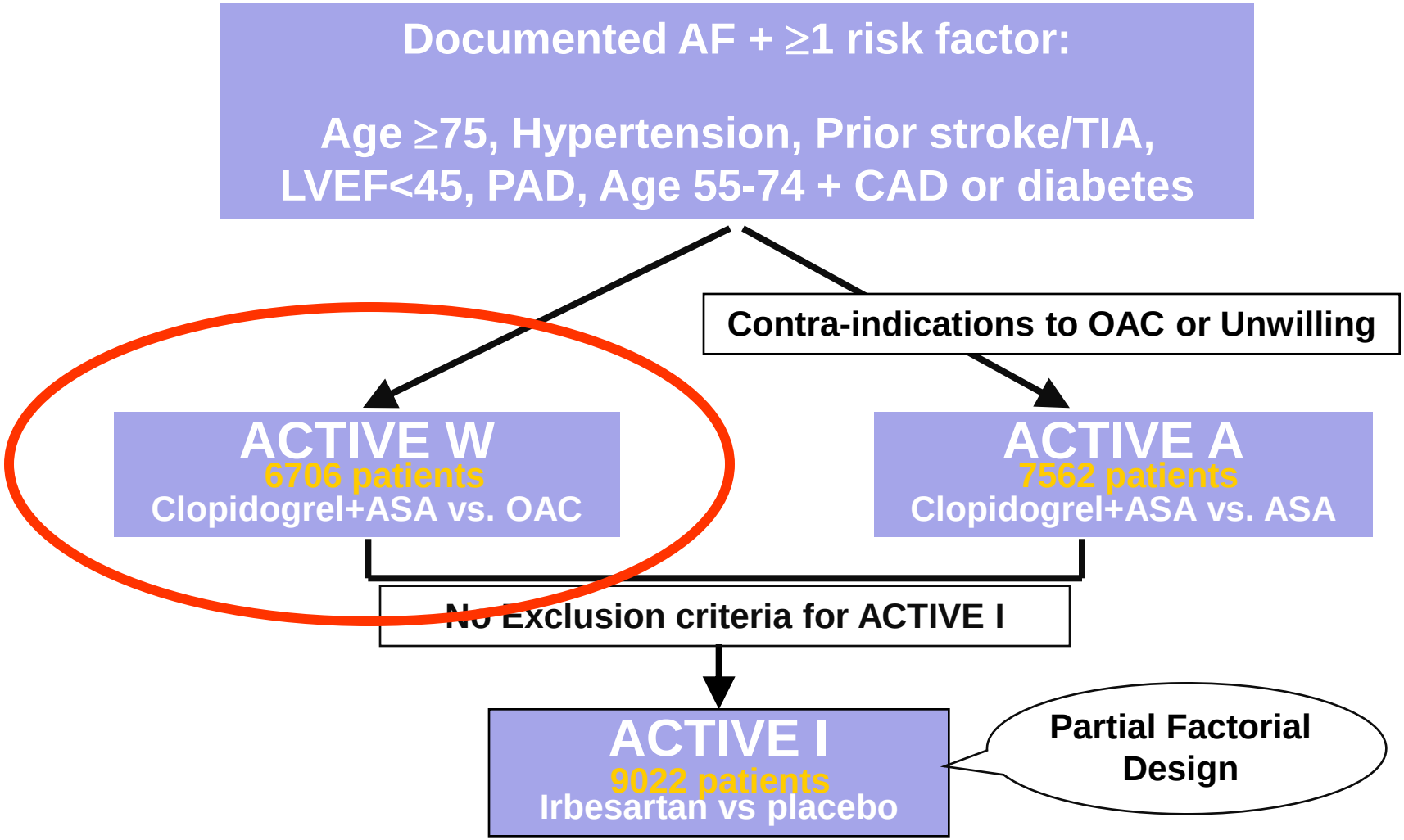
Abnormalities of blood constituents

- Platelets
- Coagulation

Platelet abnormalities in AF

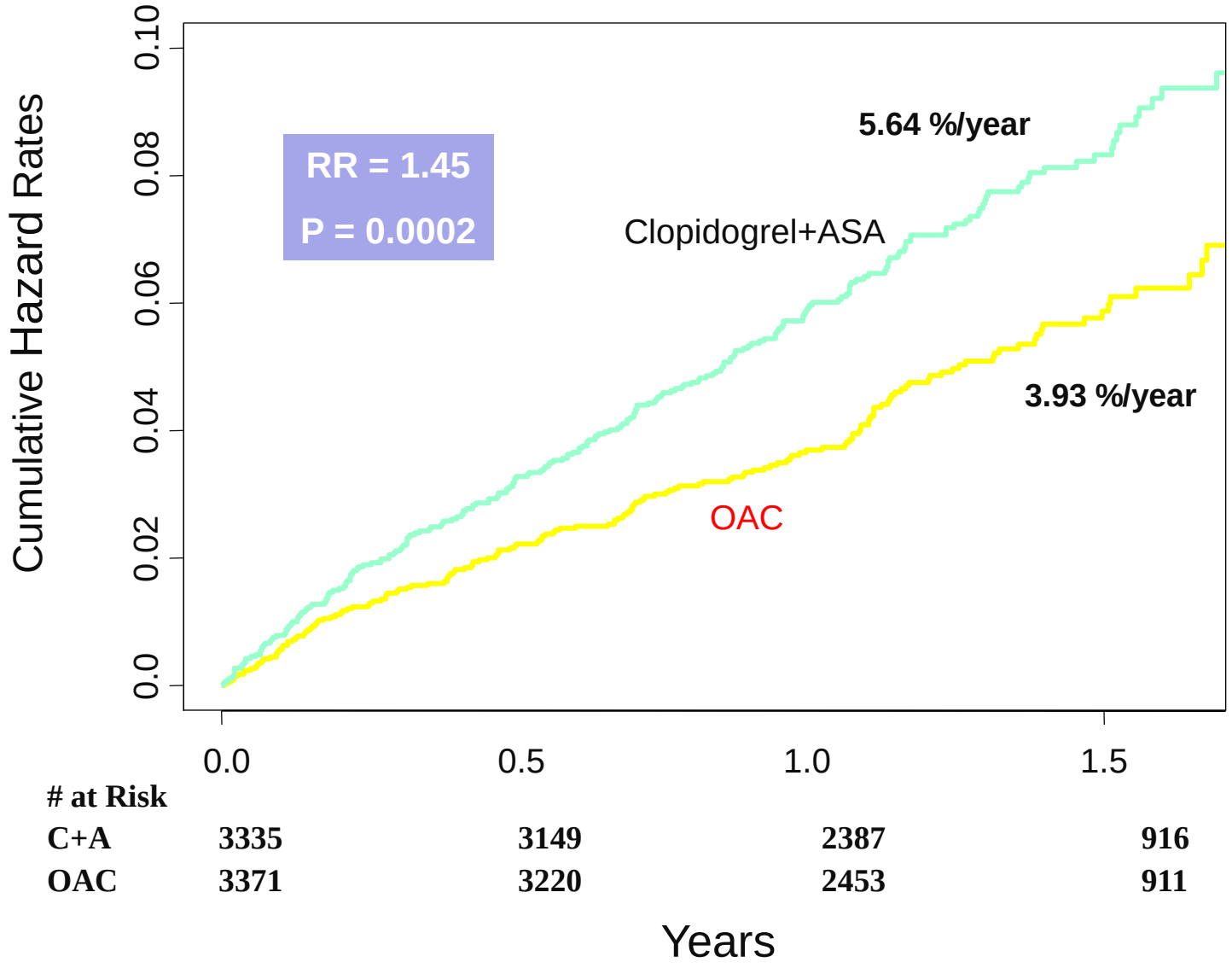
- Increased systemic levels of beta-thromboglobulin and platelet factor 4 (less consistent data) (Lip GY, *et al*. Circulation 1996;94:425. Sohara H, *et al*. J Am Coll Cardiol 1997;29:106)
- However plasma levels of P-selectin were unrelated to estimated stroke risk among patients in the SPAF III trial despite associations between soluble P-selectin levels and atherothrombotic risk factors, such as smoking and peripheral vascular disease (Conway DSG, et al. Circulation 2002;106:19627)

The ACTIVE Program



ACTIVE-W: Primary Endpoint

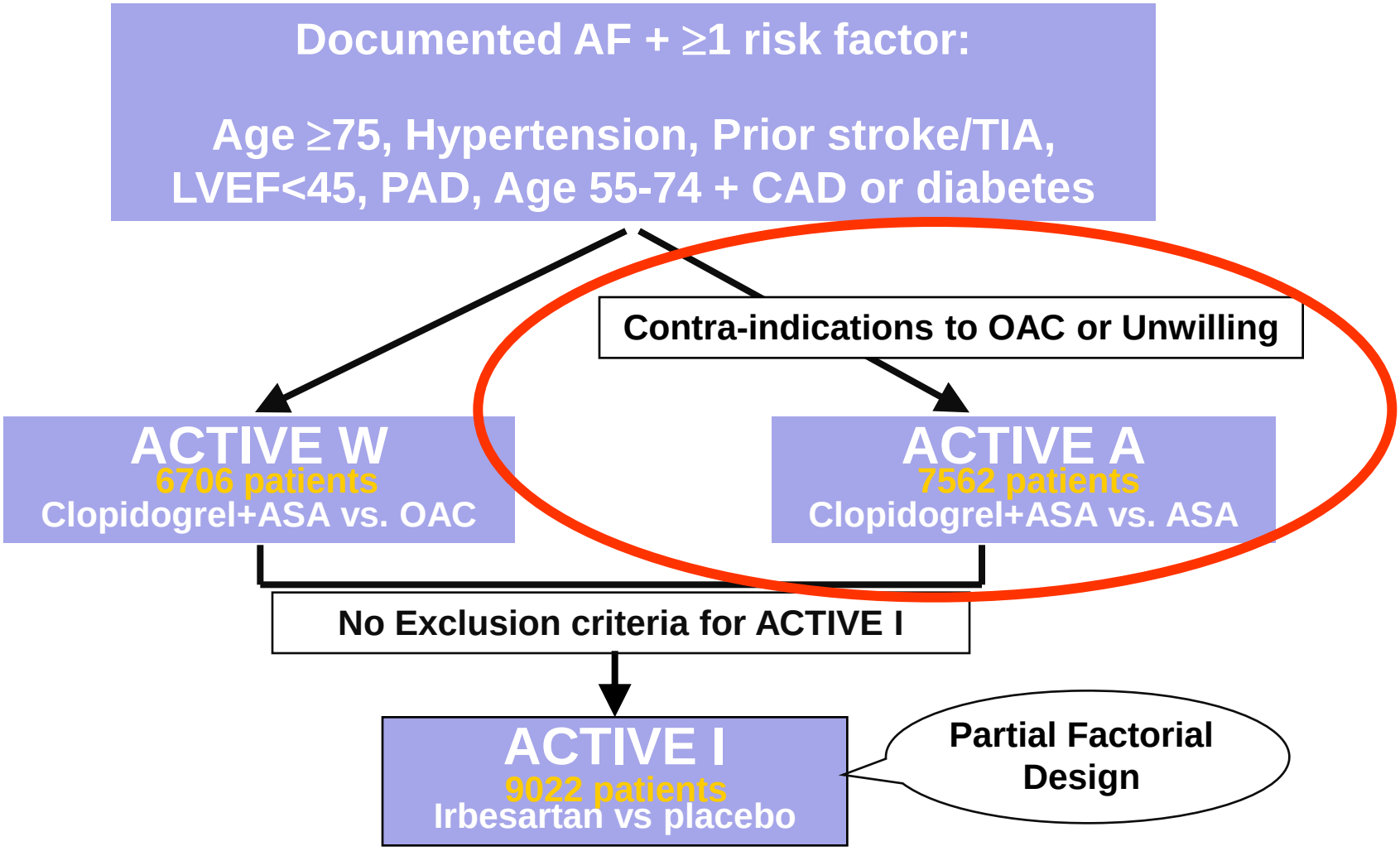
Stroke, Non-CNS Systemic Embolism, MI & Vascular Death



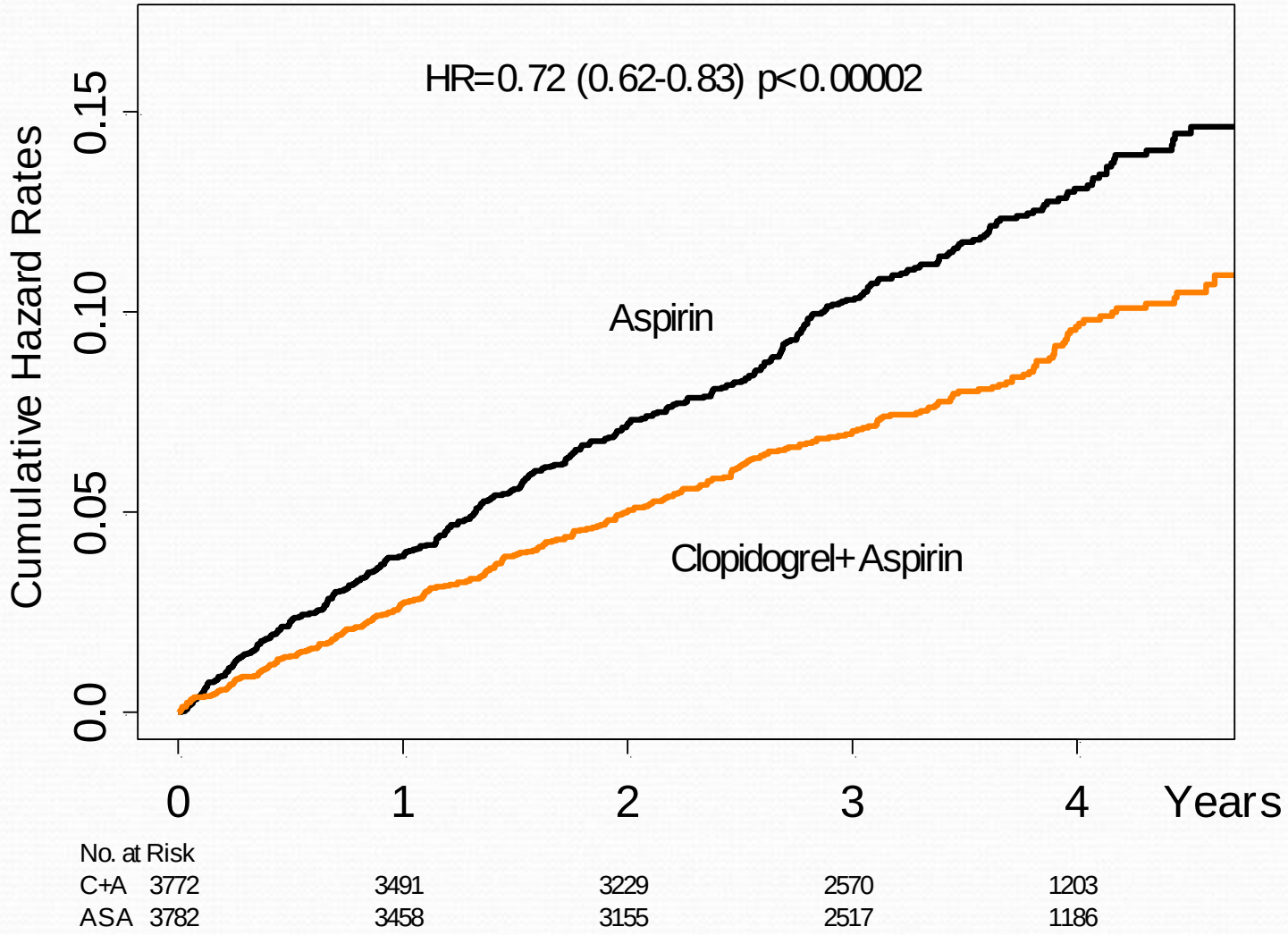
# at Risk				
C+A	3335	3149	2387	916
OAC	3371	3220	2453	911

ACTIVE Writing Group, Lancet 2006;367:1903

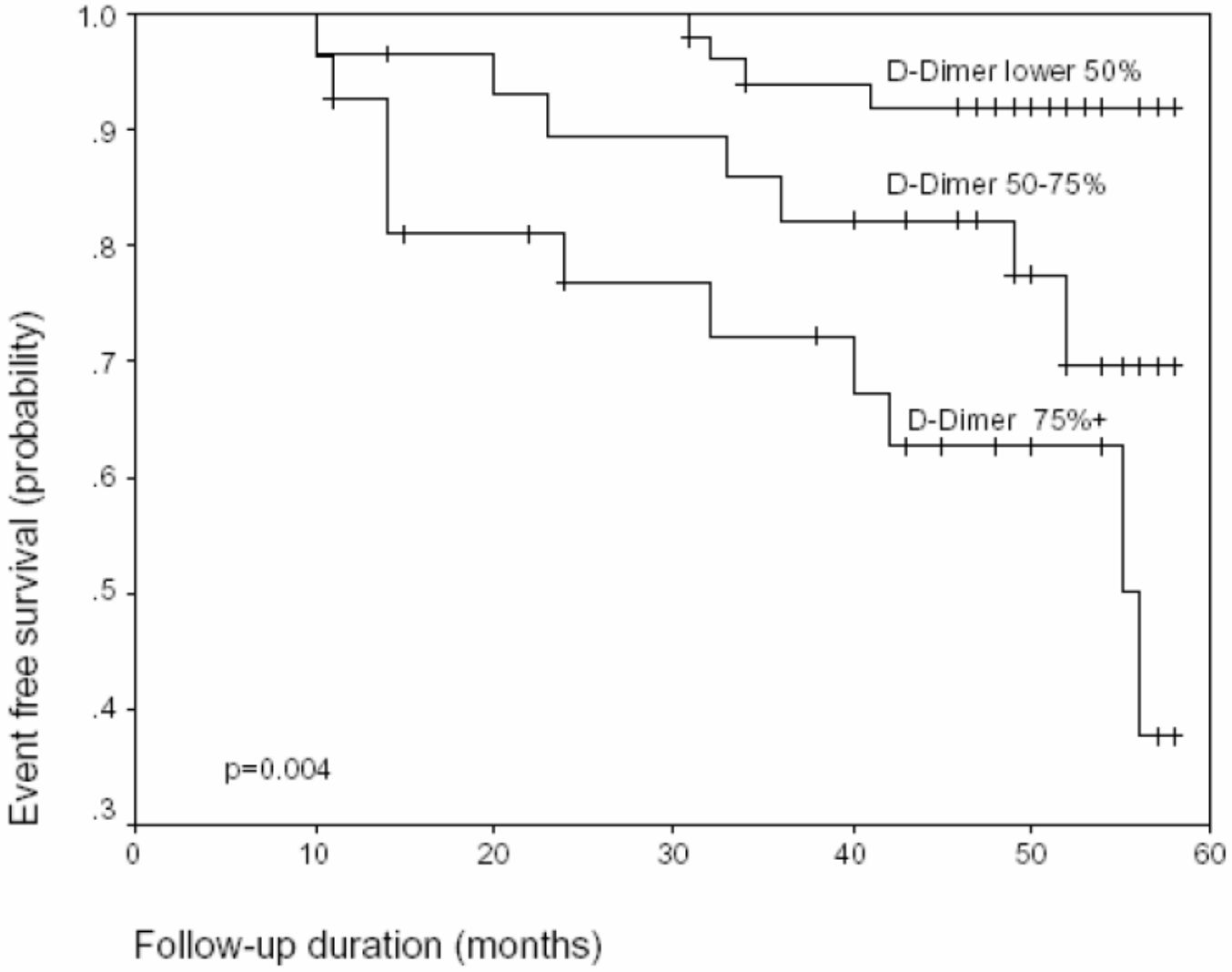
The ACTIVE Program



ACTIVE-A outcomes - Stroke



Event-free survival as a function of D-dimer levels under VKA in atrial fibrillation



Vene N, et al. Thromb Haemost. 2003;90:1163-1172.

Therefore

- Platelet abnormalities play some role in thrombogenesis in AF
- This may occur because of the cross talk between primary and secondary hemostasis
- But in any case the contribution of coagulation is probably higher

Reversing coagulation abnormalities in AF

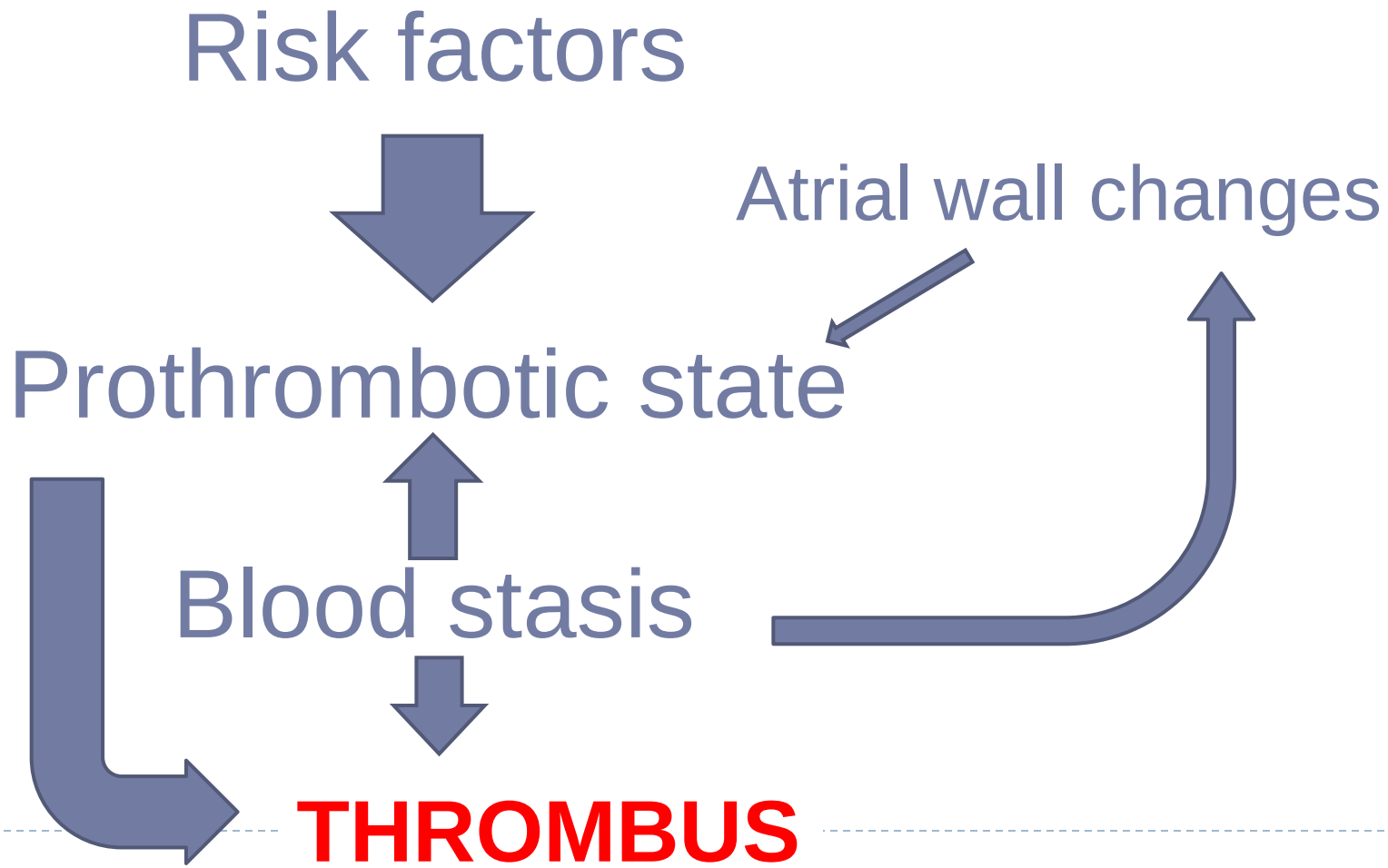
- An AFASAK-2 substudy [1] reported that only dose-adjusted warfarin (INR 2–3) had an effect on the amounts of prothrombin fragments 1 and 2 after 3 months' treatment.
- Fixed low-dose warfarin, combined low-dose warfarin and aspirin, or aspirin alone had little effect on prothrombin fragments.
- Similarly, fixed low-dose warfarin or aspirin-warfarin combination treatment did not substantially reduce other markers of thrombogenesis in AF, whereas dose-adjusted warfarin did. [2]

1. Koefoed BG, et al. *Thromb Haemost 1997;* ***77: 845–48.***
2. Li-Saw-Hee FL, et al. *Stroke 2000;* ***31: 828–33.***

What drives the prothrombotic state in atrial fibrillation?

- Inflammation 
- Growth factors
- Excessive extracellular matrix turnover
- Decreased NO
- Activation of the renin-angiotensin-aldosterone system

Interactions of the elements in Virchow's triad in determining thrombus formation in AF

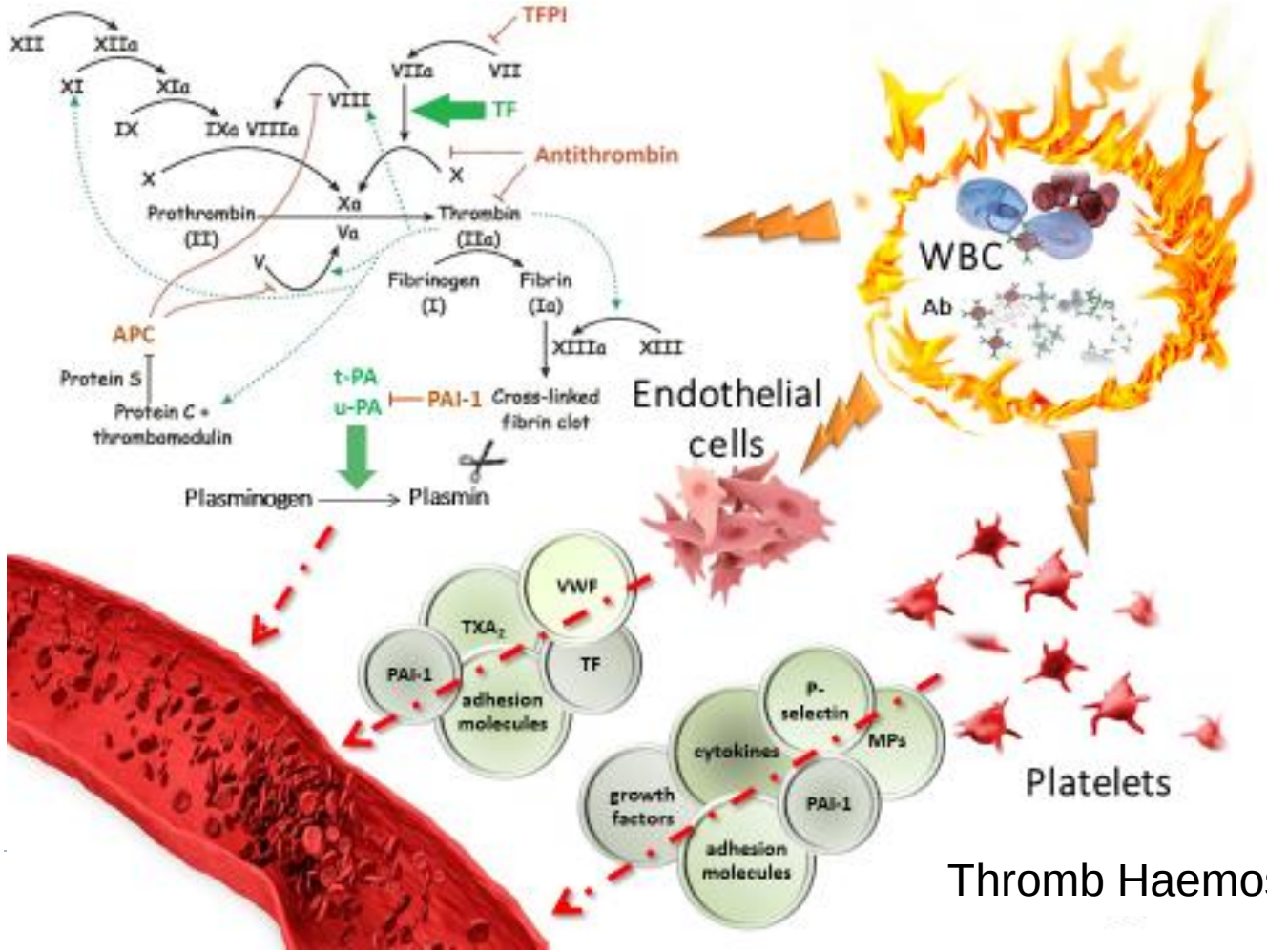


Thus, knowledge and understanding of the mechanisms by which risk factors prompt a thrombogenic state may help in risk stratifying and in guiding new therapies in atrial fibrillation

Inflammation and thrombosis – testing the hypothesis with anti-inflammatory drug trials

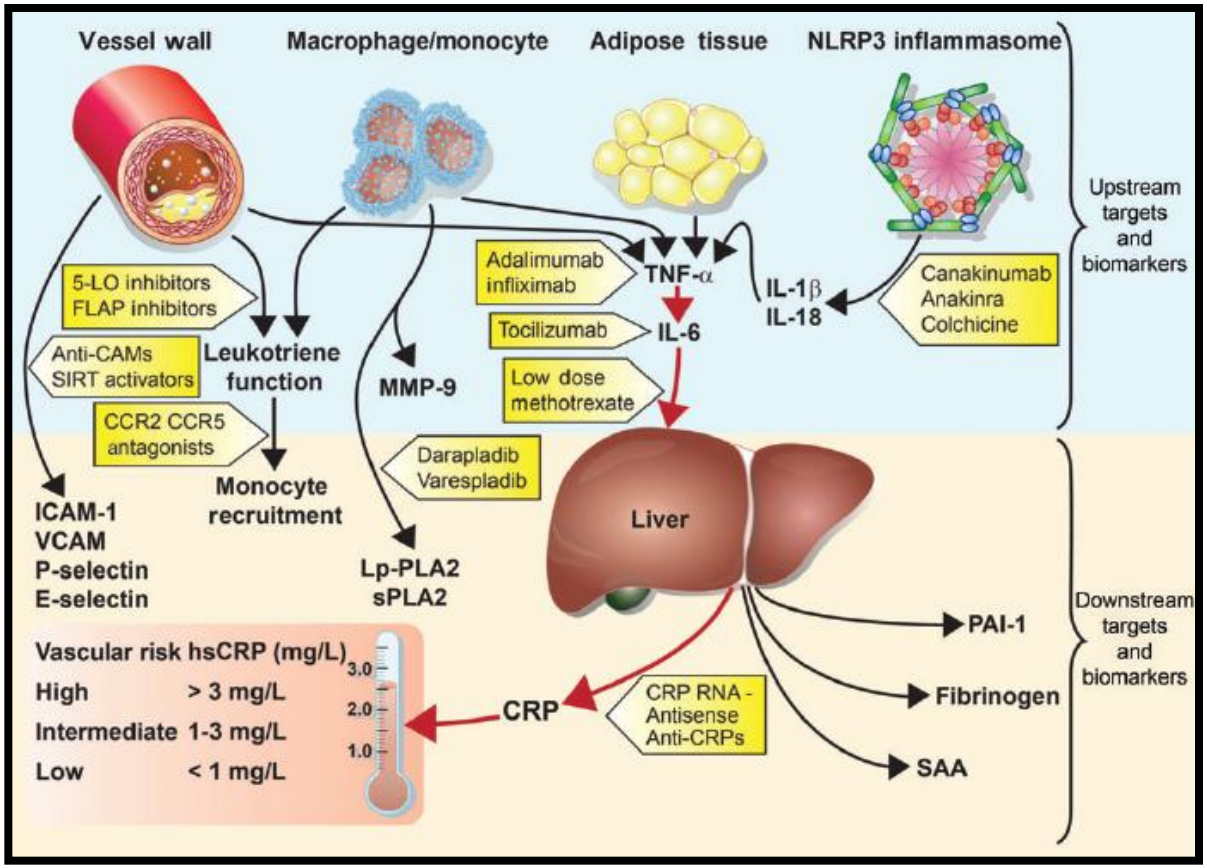
Raffaele De Caterina[1]; Emilia D'Ugo[1]; Peter Libby[2]

[1]"G. d'Annunzio" University and Center of Excellence on Aging, Chieti, Italy; [2]Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA



Thromb Haemost 2016; 116

INFLAMMATORY PATHWAYS AS POTENTIAL TARGETS FOR ATHEROSCLEROTIC THERAPIES

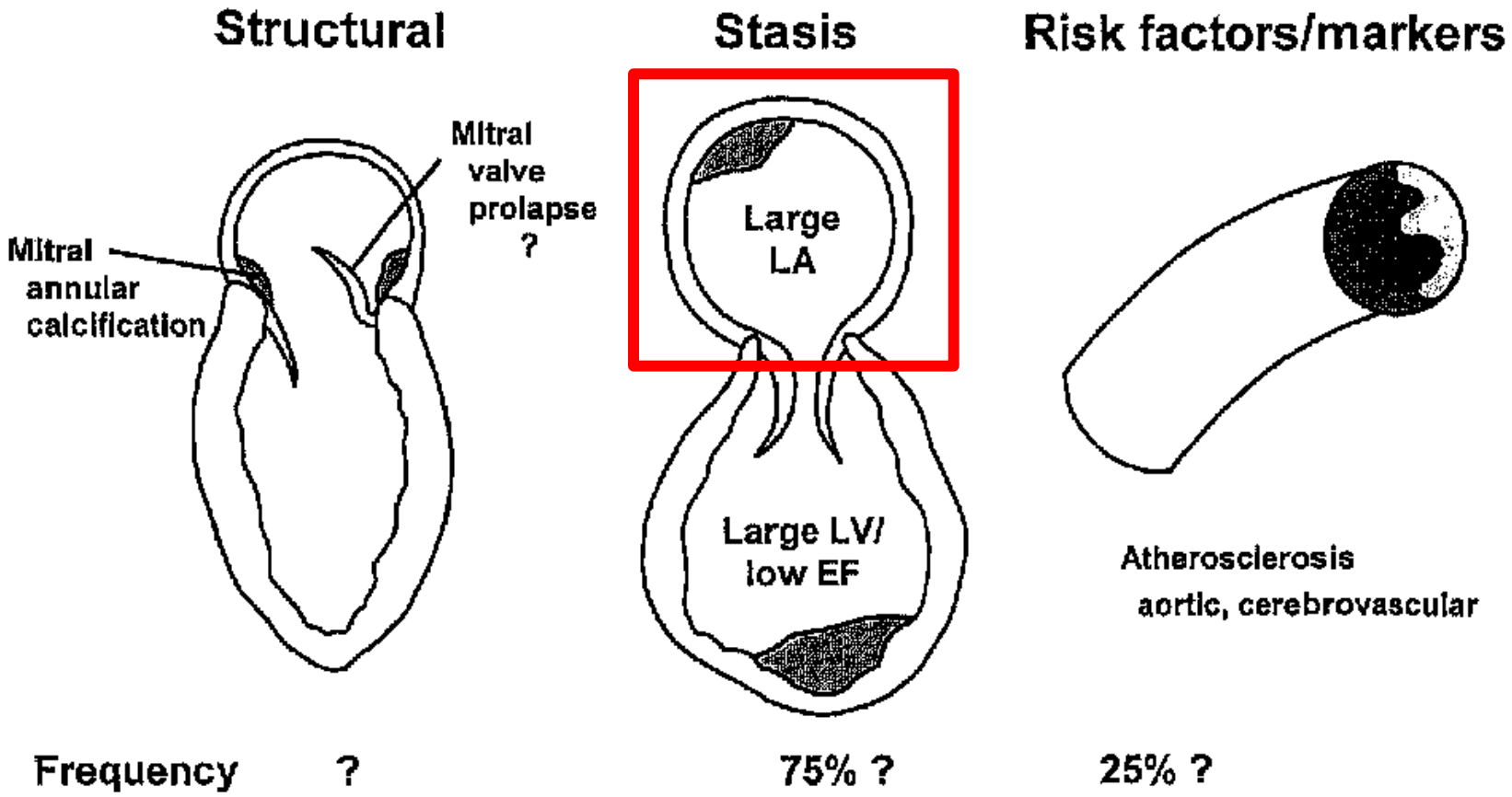


Ongoing large randomized controlled trials designed to evaluate the effect of anti-inflammatory drugs on atheriosclerosis, including CANTOS and CIRT, also assess the impact of antiinfiammatory therapy on incident VTE, will shed light on the hypothesis of inflammation-mediated thrombosis

Ridker et al. Anti-inflammatory therapies for cardiovascular disease. European Heart Journal (2014) 35, 1782–1791

…but let’s not forget that not all strokes in atrial fibrillation are thromboembolic…

The multi-factorial etiology of stroke in AF



Gersh et al, 1995

Thank you!