Coagulation and ischaemic stroke

Wolfram Doehner, PD, PhD

Center for Stroke Research Berlin

& Department of Cardiology,

Campus Virchow

Charité – Universitätsmedizin Berlin, Germany

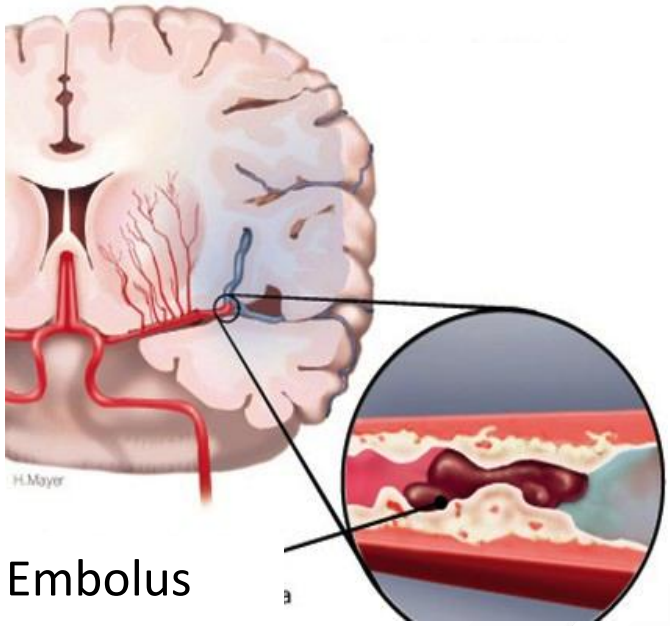
Conflict of Interest

Research support:	EU-FP7, HORIZON-2020, German Ministry of Education and Research, SANOFI, Vifor Pharma,
Consulting	Amgen, Bristol-Myers Squib, Pfizer, Sphingotec, Solartium Dietetics, Stealth Peptides, Boehringer Ingelheim
Speakers Honoraria	Nutricia, SANOFI, Vifor Pharma,

Aetiology of Stroke

85 %

Ischaemic stroke

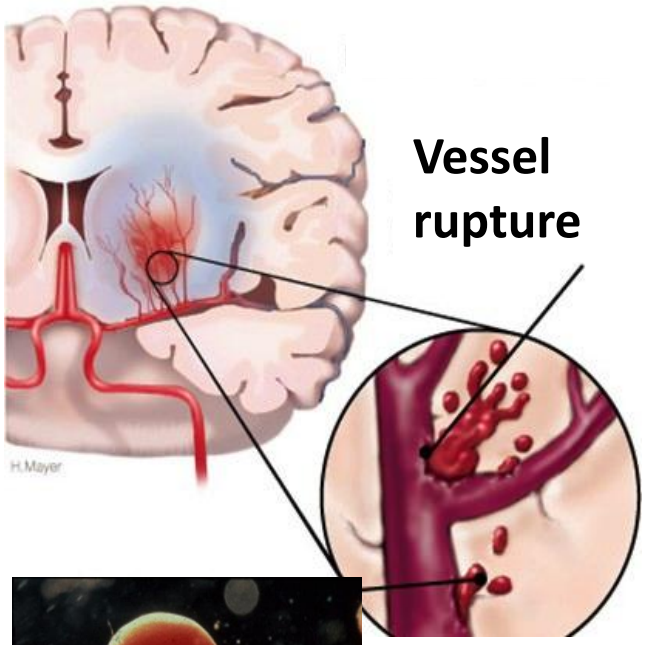


Embolus

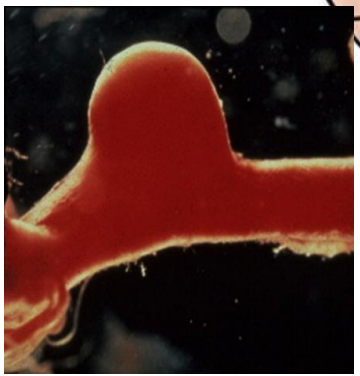
Plaque rupture

15%

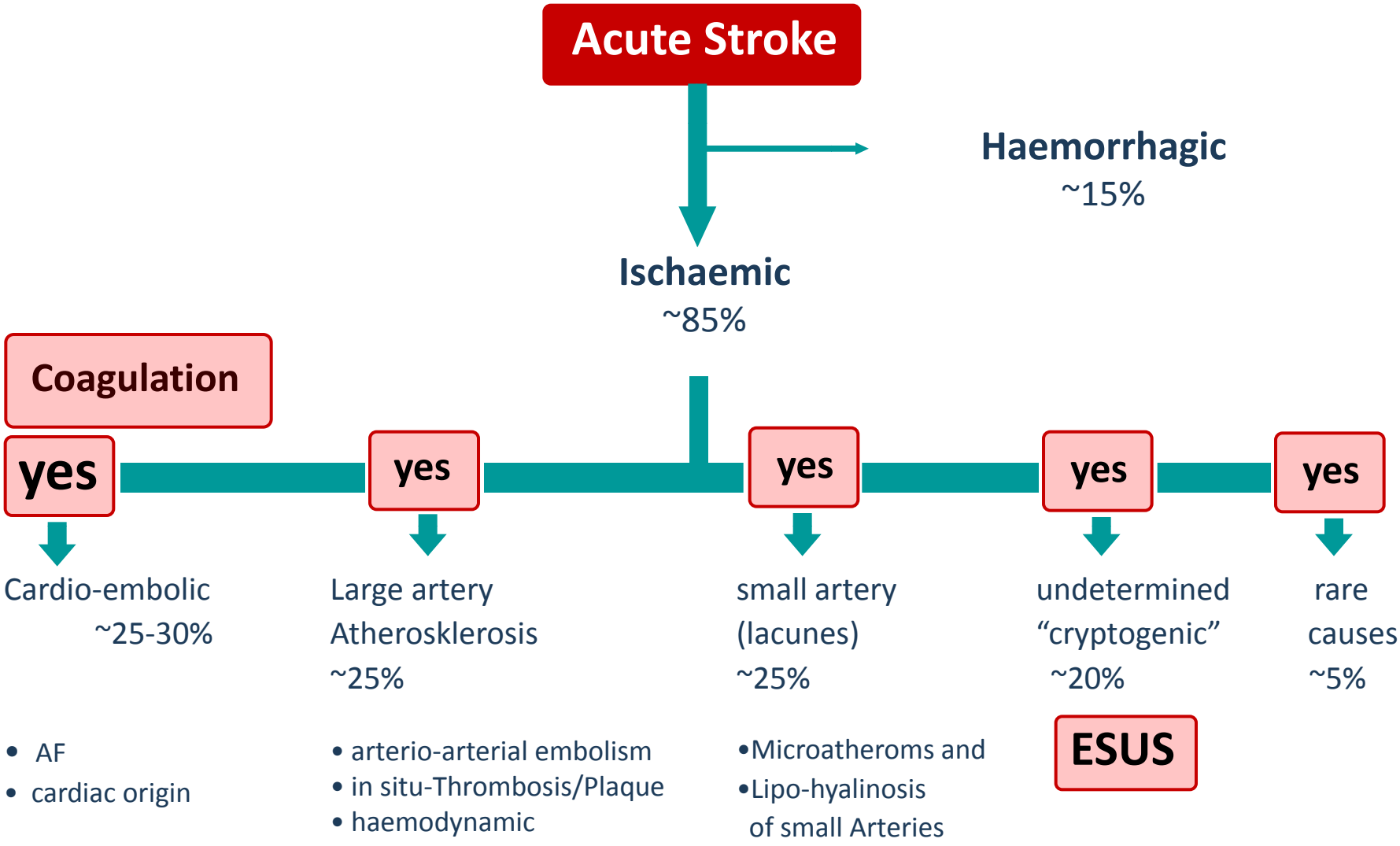
Haemorrhagic stroke



Vessel rupture

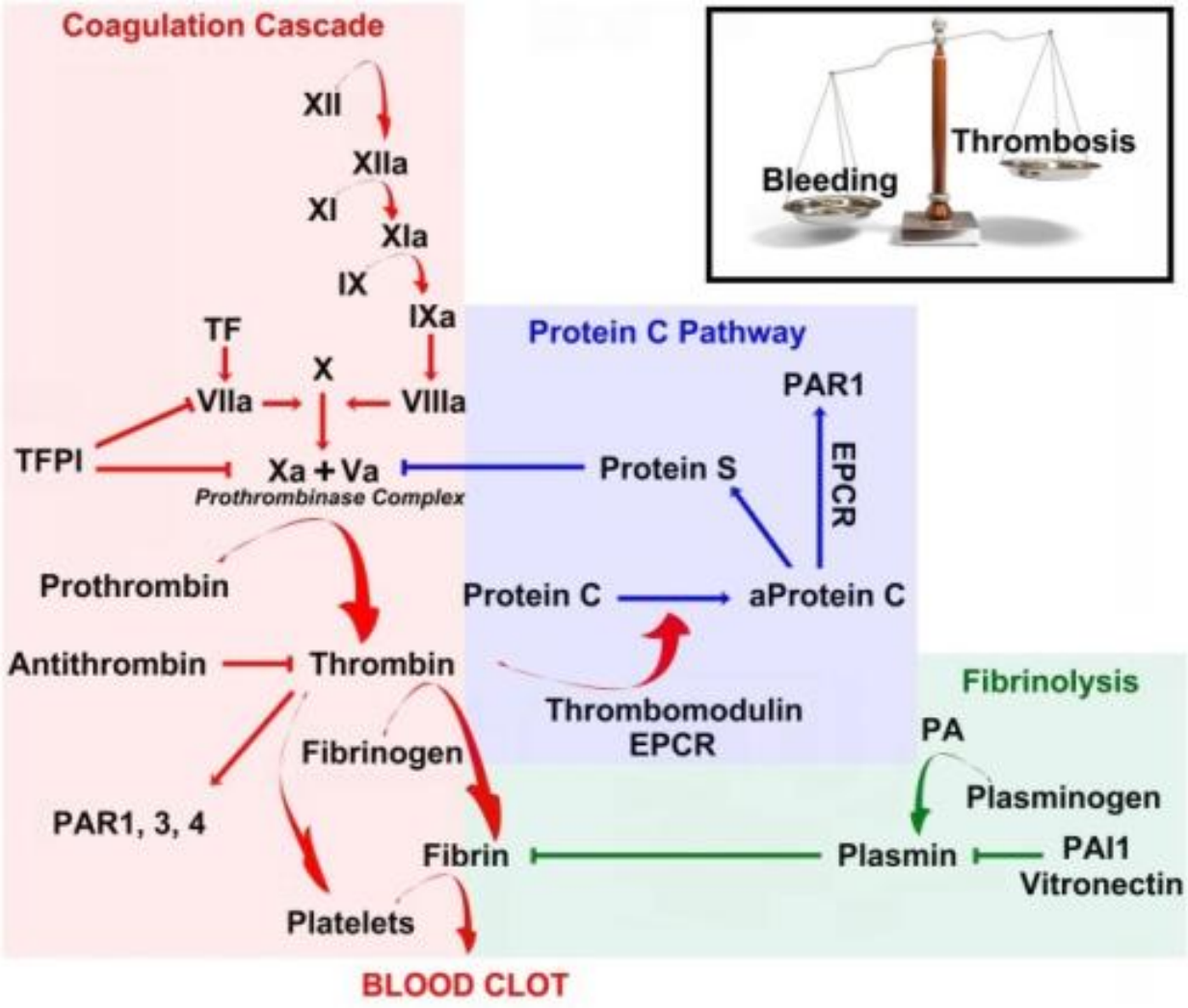


Aetiology of Stroke - TOAST classification

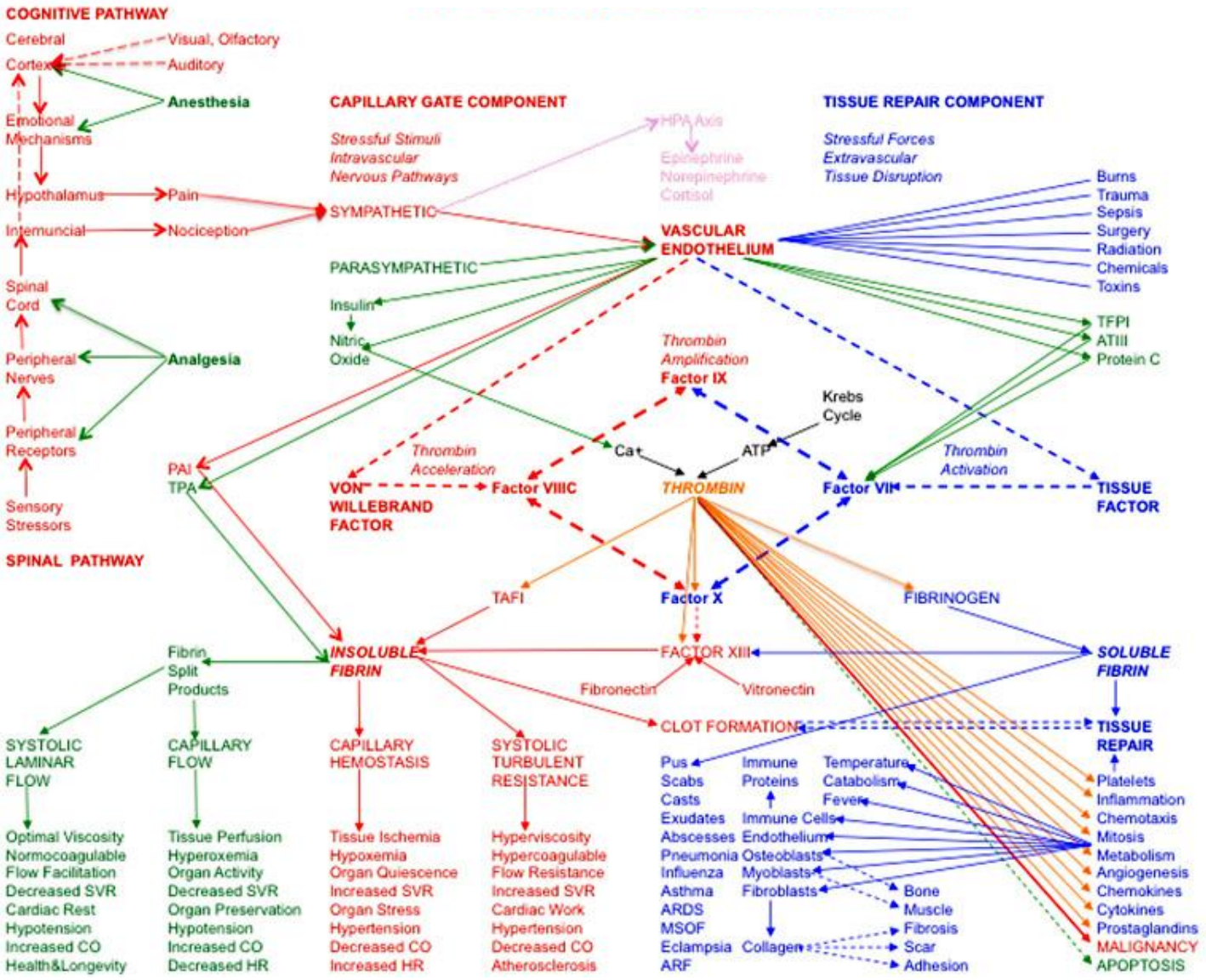


Hart RG *et al.* Lancet Neurol 2014

Physiologic Coagulation Cascade



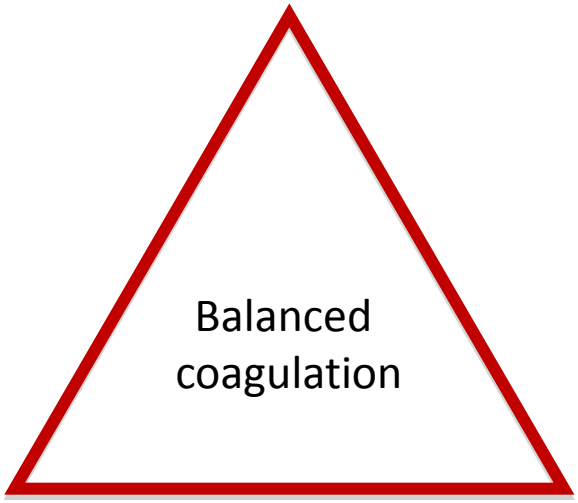
Integrated coagulation repair mechanisms



Basic coagulation principles - Virchow trias

Rudolf Virchow, Berlin, Charite, 1845

Blood flow
Rheology



Vessle Wall
Endothelium function

Blood born factors
Viscosity

Basic coagulation principles

Virchow Trias

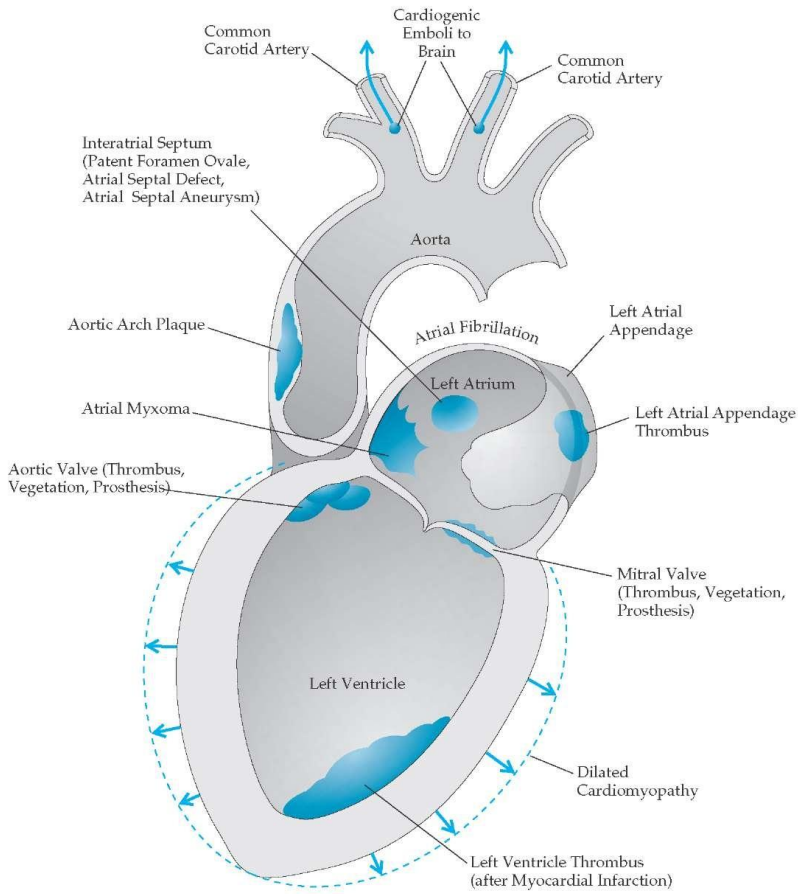
1. Rheology	• Stasis of blood flow • no laminar flow/ turbulences
2. Hypercoagulability	• activated coagulation factors • Activated inflammation • cytokines
3. Endothelial injury	• surface damage • endothelial dysfunction

= Pro-thrombotic state

Rudolf Virchow, Berlin, Charite, 1845

Cardiovascular embolus formation

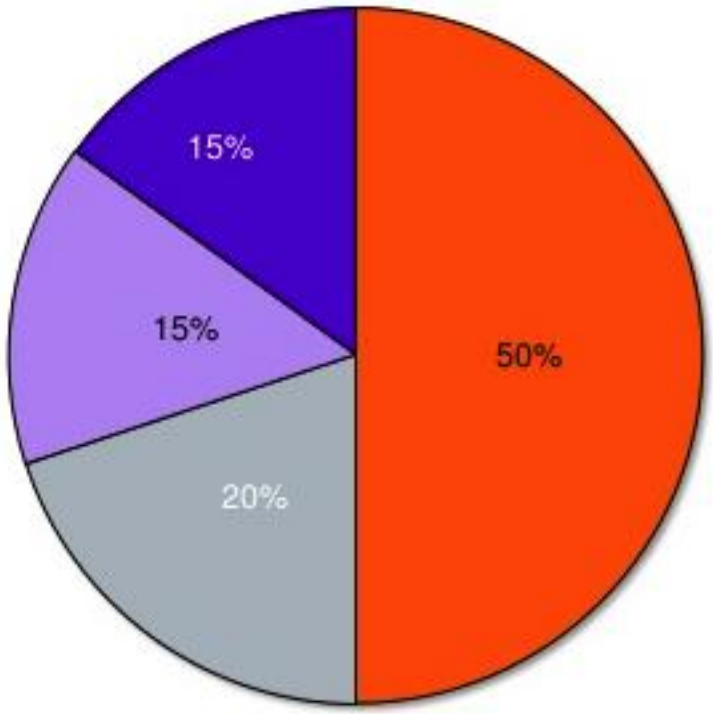
- **Rheology**
- **Hypercoagulability**
- **Endothelial injury**



- **Atrial fibrillation (AF)**
- Reduced LV contractility = CHF
- Recent MI (<4 weeks)
- Regional LV akinesis
- Aneurysm of the LV
- Cardiomyopathy
- Infective Endocarditis
- Rheumatic valve disease
- Heart valve replacement
- overt foramen ovale (permissive)
- Atrial Myxoma

Cardiac causes leading to cardioembolic stroke

AF is the most common cause of cardioembolic stroke



- AF
- Ventricular thrombus
- Valvular heart disease
- Structural heart defects or tumors

Freeman WD, Aguilar MI, Neurol Clin 2008

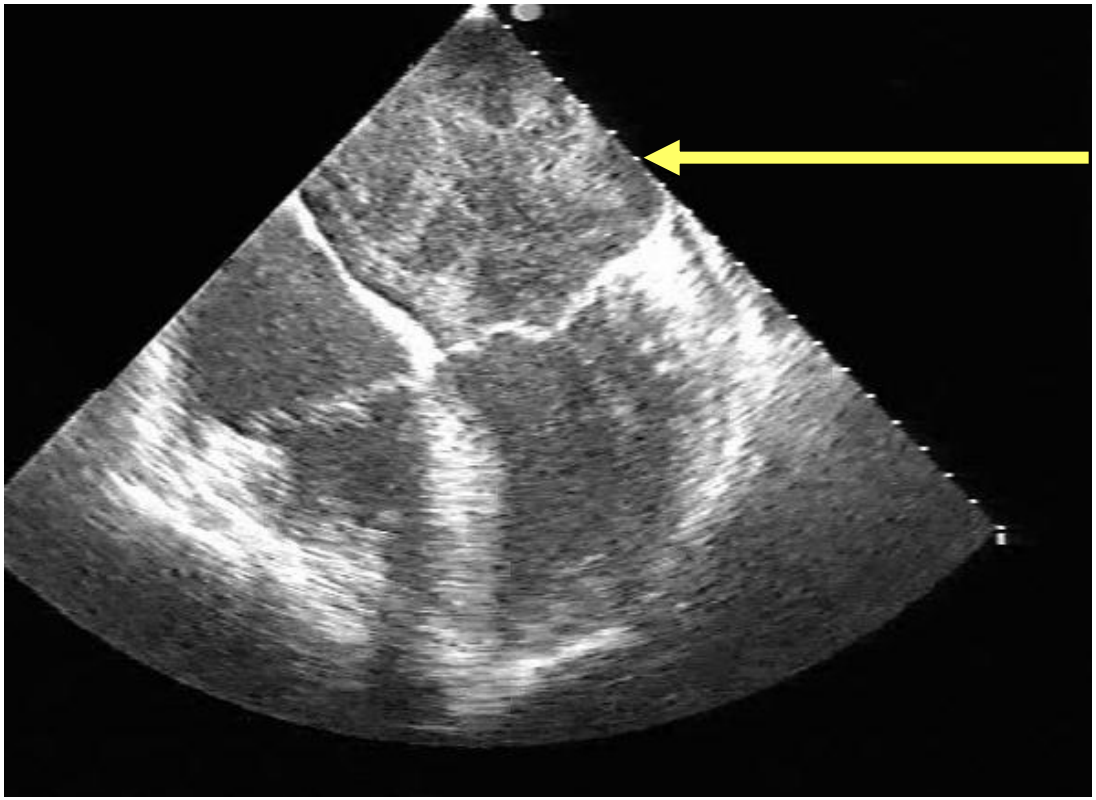
Biomarkers of coagulation - what can we measure ?

	Thrombogenic feature	assessment
Lab	**Coagulation factors**	D-dimer Thrombin-anti-thrombin complex
		Plaminoge activating prot.Fibrine metabolites Plasmin activating inhibitor
		P-selectin ß-Thomboglobulin
	Endothelium dysfunction	V-Willebrand factor Soluble Thrombomodulin E-electin
Echo	**LV dysfunction**	LVEF ↓ Global contractility
		Hypo/Akinesia Aneurysma
ECG	**Atrial fibrillation**	LVEF Thrombocyte aggregation
clinical	**Comorbidities / risk factors**	Scores (CHA_2DS_2 –VASc)

CHF: High risk of cardiac thrombembolism

even in maintained sinus rhythm

CHF = Increase ventricle size + Reduced contractility



Spontaneous echocardio-graphic contrast

- **low blood flow**
- **Hypercoagulability**
- **Endothelial injury**

= Pro-thrombotic state

Rudolf Virchow, Berlin, Charite, 1845

Echo predictors for increased risk of stroke ?

Echocardiographic measurement	validated ?
• Reduced LVEF (<40%)	+++
• enlarged LV size • low LV blood flow (spontaneous contrast) • reduced regional contractility • Aneurysm • enlarged LA size [1] • reduced LAA flow • Tei Index	"Increased risk" but no validated numeric marker

[1] Yaghi S et al. Stroke 2015

Echocardiography – which type for what?

Trans-thoracic echo [TTE]

long distance
lower resolution
no definite exclusion of thrombus

trans-esophageal echo [TEE]

short distance
very high solution
definite exclusion of thrombus

TTE
Left ventricular thrombus
Left ventricular function
Large vegetation
Large tumors
Patent foramen ovale
Atrial septal aneurysm
LVAD associated thrombus

TEE
Left atrial appendage thrombus
Small vegetation (particularly associated with prosthetic valves)
Abscess
Small tumors
Small patent foramen ovale and morphology
Atrial septal aneurysm morphology
Spontaneous echo contrast
Valvular strands
Aortic arch atheroma
LVAD associated thrombus

Nakanishi K and Homma S. *J Cardiol* 2016

Clinical risk factors for embolic stroke

CHA_2DS_2 VASc scores - only in the context of AF related risk

Risk factor	Score
Cardiac failure	1
Hypertension	1
Age >75 years	2
Diabetes mellitus	1
Stroke or TIA	2
Vascular disease	1
Age 65-74	1
Sex category (female)	1

new 2016
No aspirin at all

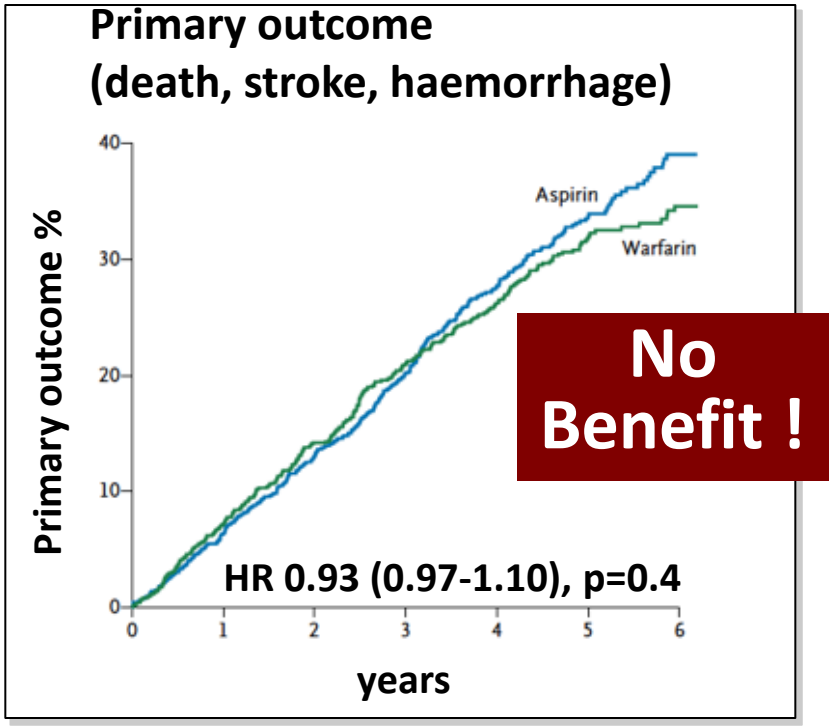
Score:
0 → no anticoagulation
1 → oral anticoagulation should be considered (IIaB)
≥2 → oral anticoagulation (IA)

Warfarin and Aspirin in Patients with Heart Failure and Sinus Rhythm

Shunichi Homma, M.D., John L.P. Thompson, Ph.D., Patrick M. Pullicino, M.D., et al.

The NEW ENGLAND JOURNAL of MEDICINE 2012

- **2002 - 2010**
- **N=2305, systol CHF + sinus rhythm**
- **mean FU 3.5y**



No Benefit !

HFA Consensus statement

- No benefit of warfarin
- No reason to use warfarin routinely in HF with sinus rhythm

Lip G. et al EHJ 2012

Take home - Stroke as a cardiovascular disease

- Coagulation = principle mechanism in all ischaemic strokes
- The trias …
  - **low blood flow**
  - **Hypercoagulability**
  - **Endothelial injury**

  …is involved in **every cardiovascular pathology**
- No good (quantitative) biomarker available. Qualitative: CHA_2DS_2 –VASc
- Anticoagulation is highly effective to prevent ischaemic stroke
- Need for further studies / evidence on anticoagulation strategies
  - novel OAC
  - specific cardiovascular pathologies beyond AF

➔ **Call for cardiologists** to address stroke prevention

ESC COUNCIL Stroke

ESC Council on Stroke: **up-coming agenda**

- **Board elections** June 18
- **Cardiovascular round table** Mar 18
- **Webinars** from Apr 18
- **Joint scientific sessions**
  - ESOC May 18
  - ESC Aug 18
  - EANS Oct 18
- **Next workshop "ESC Heart & Stroke"**
  Jan 2019

THANK YOU

wolfram.doehner@charite.de

Home > Councils > Council on Stroke

Council on Stroke

- Nucleus
- Events
- Membership

ESC COUNCIL ON STROKE

The Council on Stroke

While effective treatment of acute myocardial infarction substantially improved the outcomes of the vast majority of patients during the last 10-15 years, acute stroke remains a major thread with high mortality and/or permanent disability. The incidence of acute stroke is similar to the incidence of acute coronary syndromes, but the outcomes of stroke patients are significantly worse. The rising body of evidence shows, that at least 30-50% (probably even more – this depends on the diagnostic approach) of ischemic strokes are caused by the heart disease (atrial fibrillation,

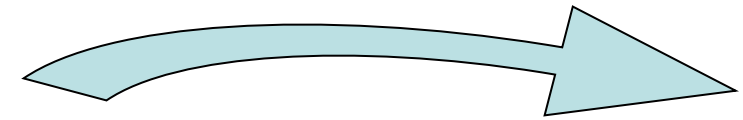
https://www.escardio.org/Councils/Council-on-Stroke

CV involvement in Stroke - the need for joined efforts

CV Risk profile

- **Atrial fibrillation**
- **Hypertension**
- Atherosklerosis
- Myocardial infarction
- Myocarditis
- Endocarditis
- LV Aneurysm
- Chronic heart failure
- Valvular disease
- Valve replacement

- Overt foramen ovale



Post Stroke CV Complication

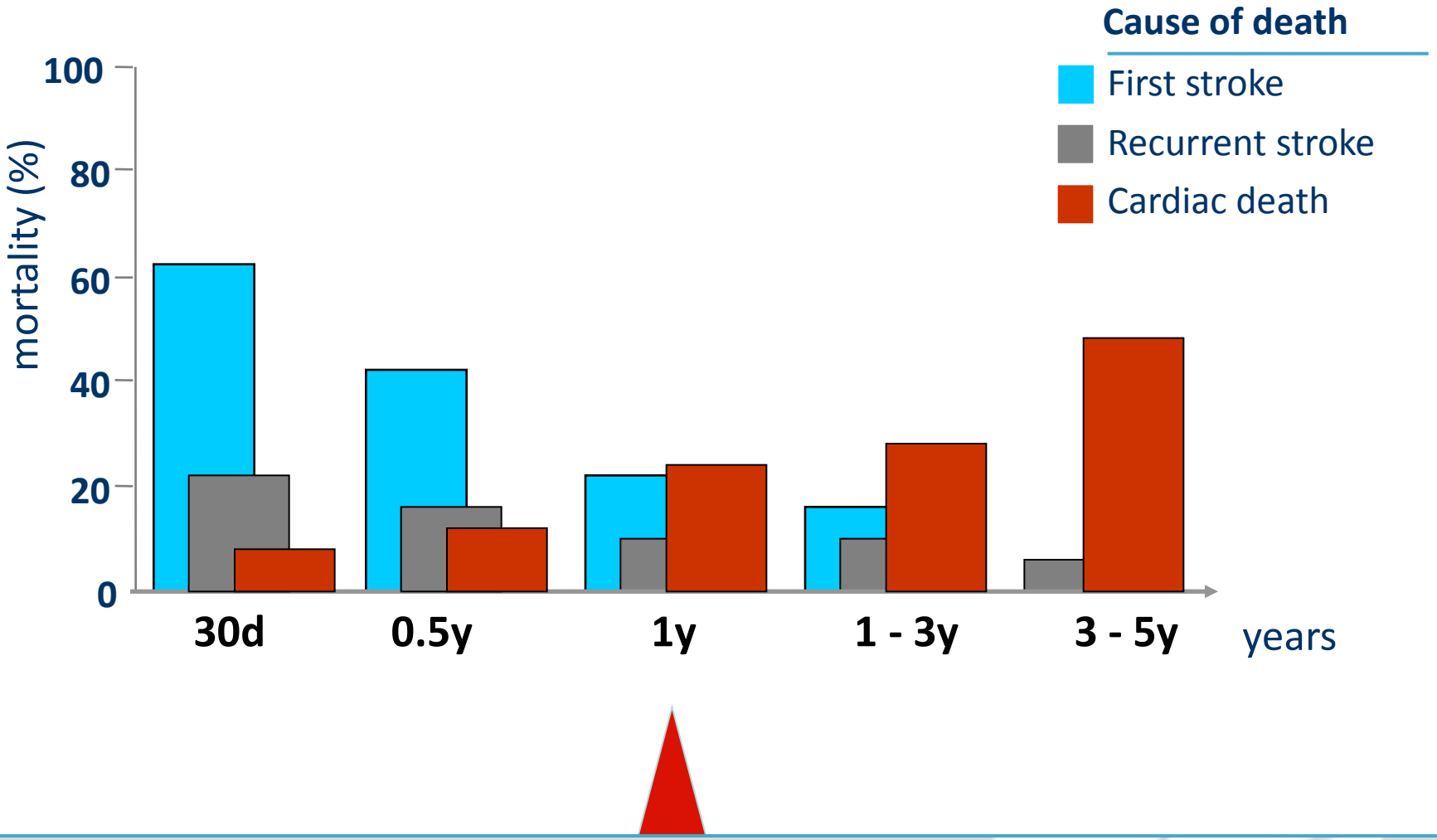
- "All of the above" (secondary prevention)

- Cardiopulm. function
- Arrhythmias
- inadequate RR regulation
- Cardiac / vascular re-embolism
- Myocardial Infarction
- CHF exacerbation
- Thrombosis

Widimsky, *et al.* EHJ 2017

Cardiac cause of death after stroke

Stroke = high risk for subsequent cardiovascular death



Hankey et al Stroke 2000