Secondary stroke prevention and precision medicine

Up to date

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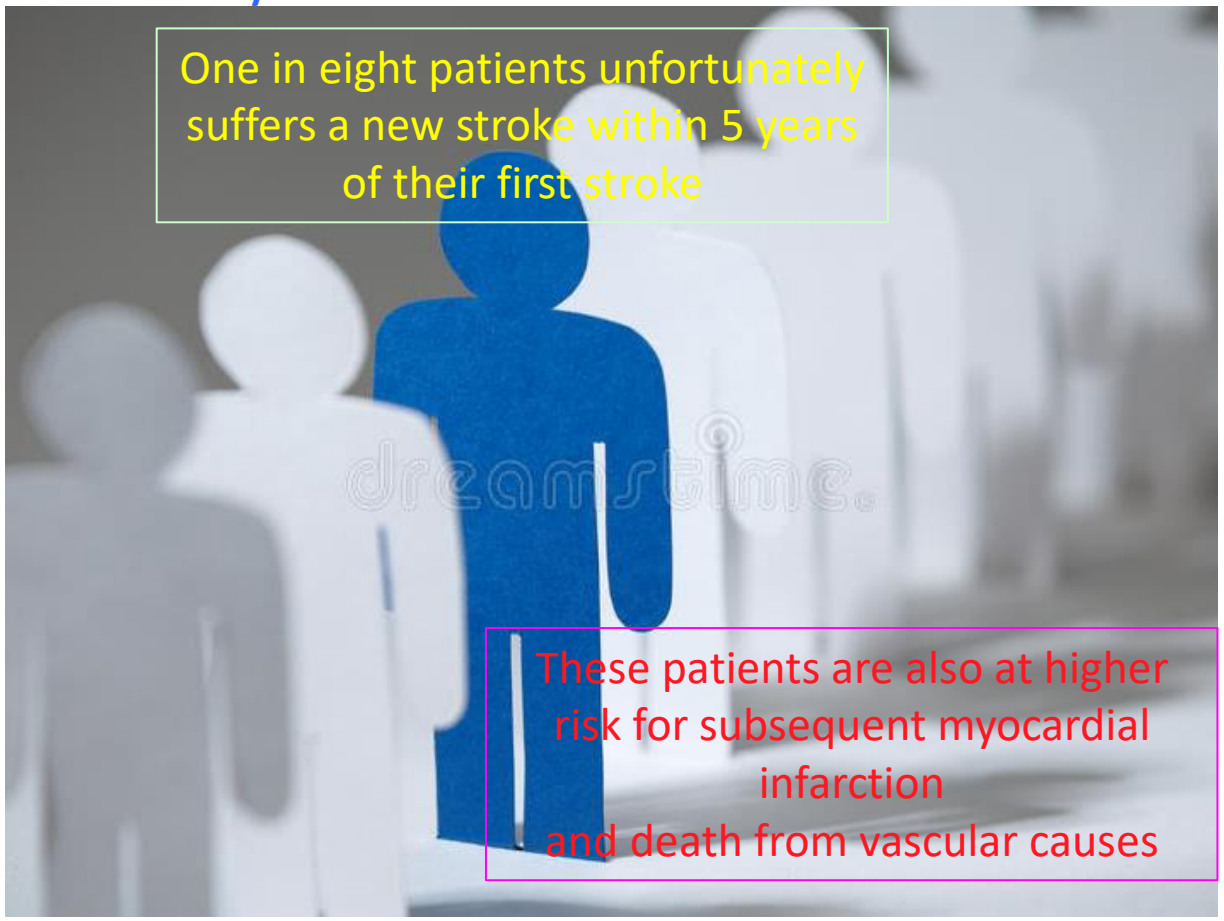
There are 2 main strategies to reduce the global burden of stroke

- Effectively treat patients with acute stroke to minimize death and disability

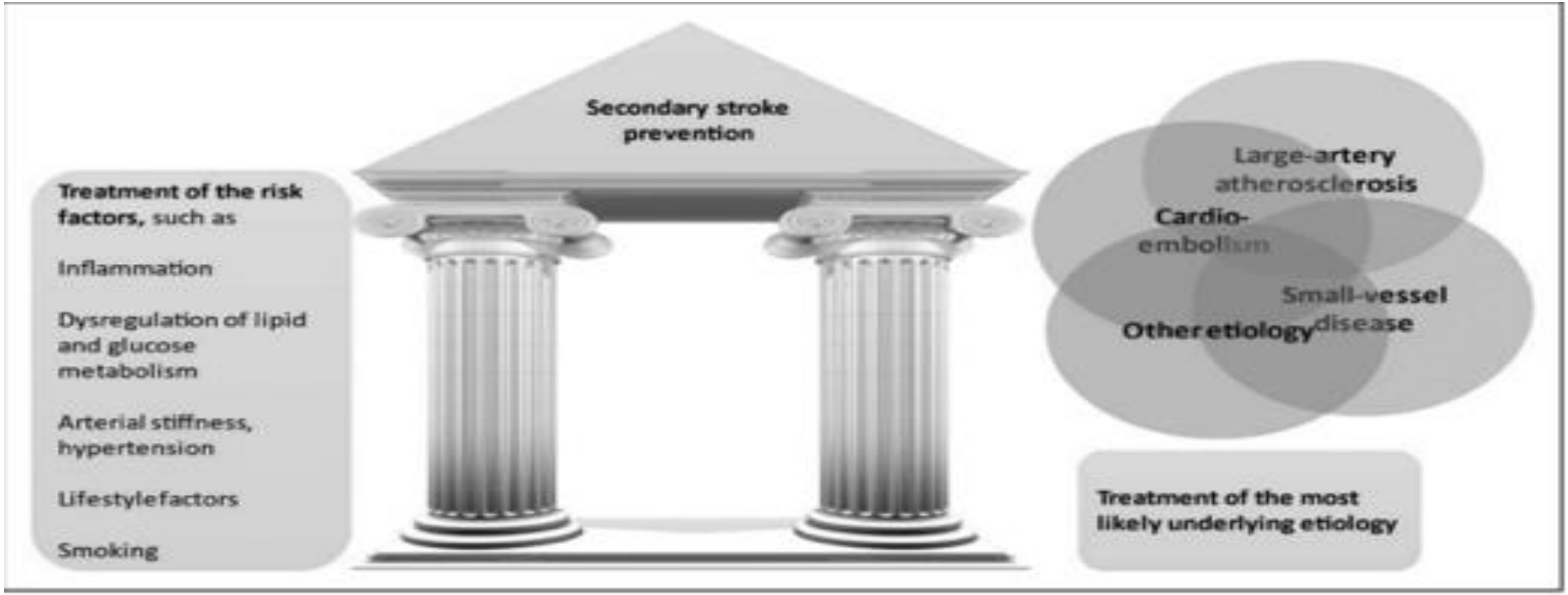
- prevent first-ever stroke and recurrent stroke

People living with stroke in the European Union
is estimated to increase
by one third between 2017 and 2047



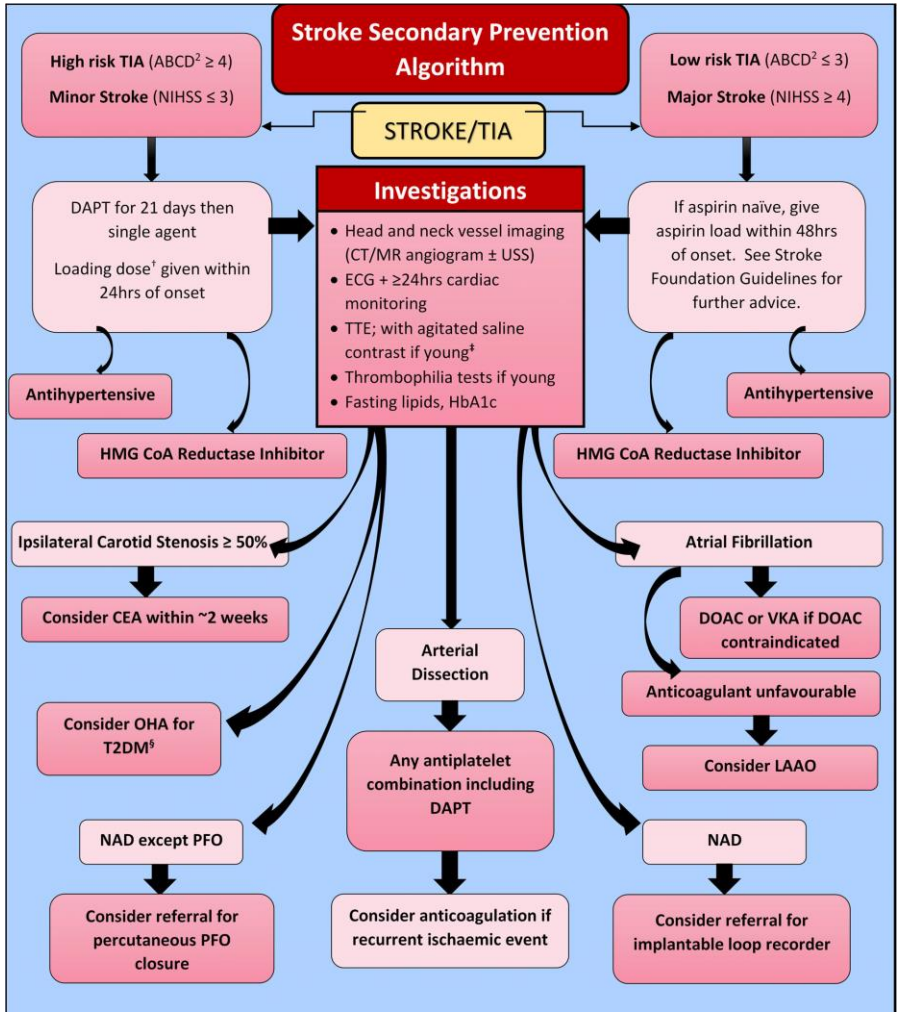
Research in precision medicine could lead to a more individualized treatment allocation, possibly achieving lower recurrence rates of stroke

SECONDARY STROKE PREVENTION



Bicciato G et al., Curr Opin Neurol. 2022

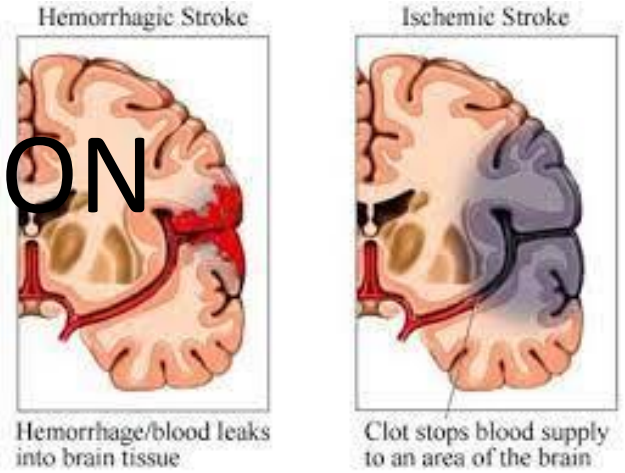
SECONDARY STROKE PREVENTION



- ✓ After ischemic stroke and TIA, the risk of recurrent stroke without treatment is about 10% at 1 week, but it become 25% at 5 years, and 40% at 10 years.
- ✓ Immediate stratification of patients with stroke or TIA is necessary
- ✓ the initiation of secondary prevention treatment depending on the underlying cause will reduce the risk of recurrent stroke by up to 80%

Rothwell PM et al., EXPRESS study: a prospective population-based sequential comparison. Lancet 2007

HYPERTENSION



- Antihypertensive therapy reduces the risk of both ischemic and hemorrhagic stroke.
- All antihypertensive drugs are equally effective in secondary stroke prevention.
- The optimal blood pressure target for secondary stroke prevention is <130/80mmHg
- 120- to 128-mm Hg systolic and 65- to 70-mm Hg diastolic may be target after lacunar stroke.

The lower, is the better?

Meta-analysis: SPS3, PAST-BP, PODCAST, RESPECT

22% Reduction in recurrent stroke risk

SBP <130mmHg is associated with ↓ recurrent stroke risk mainly driven by a ↓ ICH risk

Kitogawa K et al., JAMA Neurol. 2019

SPECIAL POPULATIONS

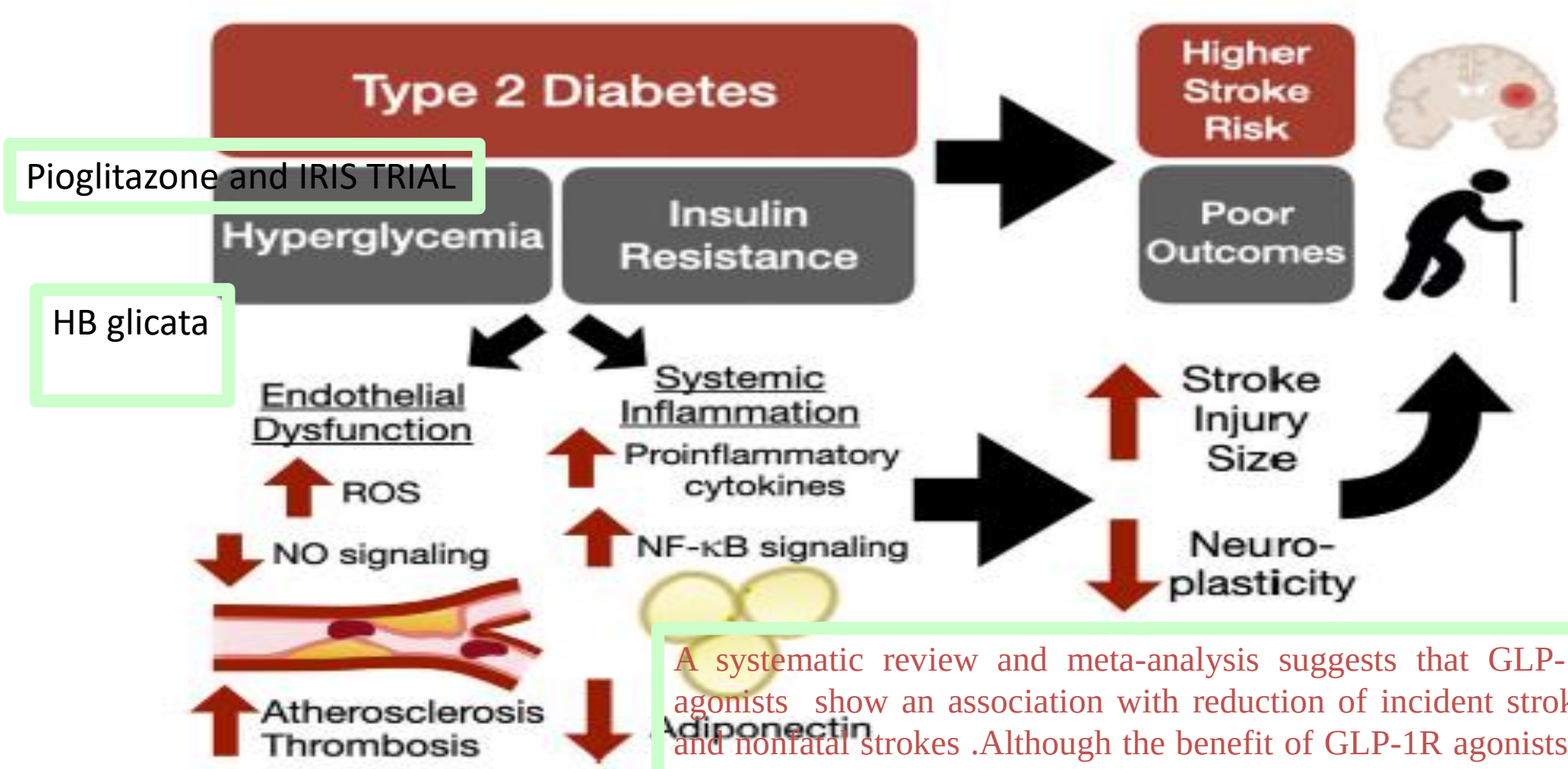
- **Orthostatic hypotension:** Still treat the HTN
- **Significant intracranial stenosis**
- **Bilateral carotid / vertebral stenosis, severe basilar stenosis** (also in view of the circle of Willis anatomy)
- **Frailty**
- **Compelling indications** that can guide treatment targets (e.g. DM, HF)

INTENSIVE TRATMENT MAY AFFECT THE COMPLIANCE!

LIPID DISORDERS

- Meta-analyses of lipid-lowering studies have reported that lipid-lowering therapy was not associated with a statistically significant increased risk of ICH in primary and secondary prevention trials combined.
- The target for the LDL concentration is <1.8 mmol/l (70 mg/dl).
- If the stroke patient not achieve the recommended LDL-C targets despite taking maximally tolerated dose of a HMGCoA reductase inhibitor for at least 6 weeks the addition of ezetimibe is an option to reduce the risk of recurrent major cardiovascular events.

DIABETES: a complex relationship



Pioglitazone and IRIS TRIAL

HB glicata

A systematic review and meta-analysis suggests that GLP-1R agonists show an association with reduction of incident strokes and nonfatal strokes .Although the benefit of GLP-1R agonists in theamelioration of cardiovascular events has been partially attributed to the association of these drugs with cholesterol levels, blood pressure levels, weight loss, and platelet aggregation.

Antiplatelet drugs

- In a pooled analysis of 15,778 patients from 12 trials of aspirin versus control in secondary stroke prevention, aspirin reduced the risk of early recurrent ischemic stroke at 6 weeks by about 60% and disabling or fatal ischemic stroke by about 70%.

Antithrombotic Trialists' Collaboration. BMJ 2002

- Antiplatelet therapy with (predominantly) aspirin reduces the risk of stroke by about 19% in 3 years and the combined endpoint of stroke, MI, and vascular death by about 13%.
- The recommended maintenance dose of aspirin (after a loading dose of 300 mg) is 100.
- avoidance of dual antiplatelet therapy with aspirin and clopidogrel after the first 90 daysg daily and in lacunar infarct.

Antiplatelet drugs are widely recommended for noncardioembolic stroke.

Which drugs? Which combinations?

Aspirin alone	Effective/ Cheap and universally available including OTC	Loading dose and then low dose	If necessary can start without prior brain imaging	IST/CAST UK TIA/ Dutch TIA etc
Aspirin + Dipyridamole	A little more effective than aspirin alone	Similar effect to Clopidogrel alone	Less well tolerated than other regimes	ESPS2 ESPRIT
Clopidogrel alone	A little more effective than aspirin alone	Loading dose and then low dose		CAPRIE
Aspirin + Clopidogrel	More effective than either alone in 1st 3 weeks Not thereafter	Loading dose and then low dose if either new	More bleeding than monotherapy	CHANCE/POINT MATCH/CHARISMA/ SPS3
Aspirin + Ticagrelor	More effective than either alone in 1st 3 weeks	Loading dose and then low dose if either new	More bleeding than monotherapy	THALES

Within 12–24 h of symptom onset
TIA required an ABCD2score ≥4
Minor stroke defined as a NIHSS score ≤3

Trials	Randomization window	Treatment duration	Primary outcome assessment	Included in meta-analysis
Short-duration treatment				
CHANCE[7]	24 h	21 d	90 d	x
POINT[6]	12 h	90 d	90 d	x
Zuo et al[8]	7 d	90 d	90 d	x
He et al[9]	72 h	14 d	14 d	
Wang et al/Hi et al[10,15]	48 h	30 d	30 d	
Long-duration treatment				
MATCH[13]	3 mo	18 mo	18 mo	x
SPS3[12]	6 mo	Mean 3.4 y	Mean 3.4 y	x

DAPT was more effective than SAPT for prevention of secondary ischemic stroke when initiate early after the onset of minor stroke/high-risk transient ischemic attack and treatment duration was **<90 days**, when the treatment duration was longer and initiated later after stroke or transient ischemic attack onset, DAPT was not more effective than SAPT for ischemic stroke prevention and it increased the risk of bleeding.

Brown DL et al.,, Stroke 2021

ANTIPLATELET THERAPY

the first secondary prevention opportunity in ischaemic stroke

- **guidelines recommending aspirin administration within the first 48 h**.
- **CHANCE and POINT** have shown **DAPT** to be superior to aspirin monotherapy in a selected group of patients within 12–24 h of symptom onset in TIA and Minor Stroke.
- …" *We make a strong recommendation based on high quality of evidence for use of 21-days of dual antiplatelet therapy with aspirin and clopidogrel in people with a non-cardioembolic minor ischaemic stroke or high-risk TIA in the past 24 hours*" …

an irregular heart rhythm with the absence of P waves lasting 30 seconds or throughout the entire 10-second 12-lead standard ECG

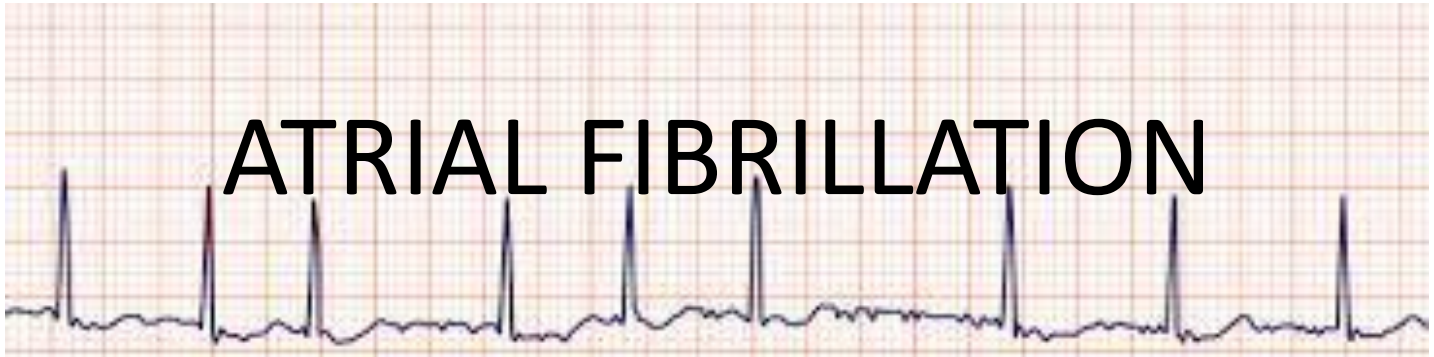
ATRIAL FIBRILLATION

>37.5 million people have AF and 58% of those are aged ≥70 years

Incidence and prevalence of AF are expected to increase in the next three decades due to population growth, ageing, and better survival of patients with AF

AF is associated with a 5-fold increased risk of stroke, and stroke outcomes are more severe in the presence of AF

ATRIAL FIBRILLATION



- …"*In* adult patients with ischaemic stroke or TIA of undetermined origin, we recommend longer duration of cardiac rhythm monitoring of more than 48h and if feasible with loop recorder to increase the detection of subclinical Atrial Fibrillation"

European Stroke Organisation (ESO) guideline on screening for subclinical atrial fibrillation after stroke or transient ischaemic attack of undetermined origin

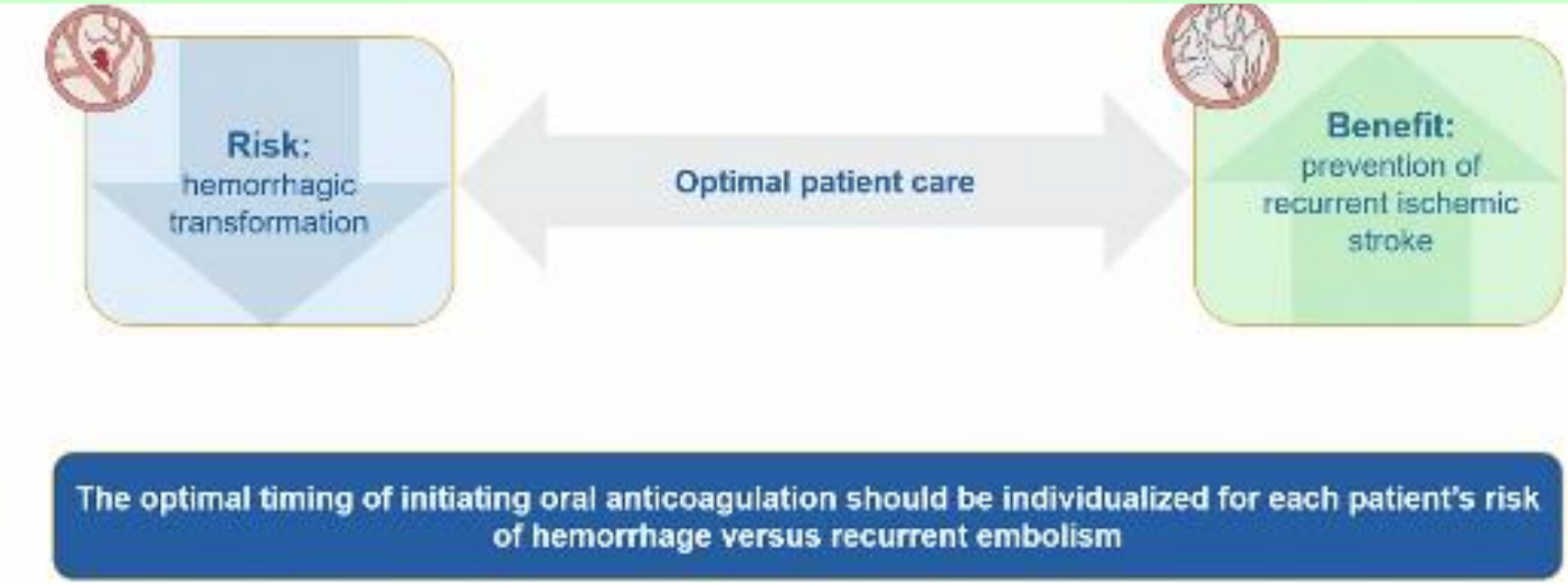
there has been a rapid shift in clinical practice away from using warfarin to using DOACs

A meta-analysis showed a twothird reduction in the risk of stroke with the use of anticoagulation compared with placebo, and 39% reduction compared with aspirin

Stroke Prevention in Atrial Fibrillation II Study.Lancet 1994

SECONDARY STROKE PREVENTION IN ATRIAL FIBRILLATION

apixaban was **compared with aspirin** in the **AVERROES trial**, which randomized patients with nonvalvular AF who are ineligible for warfarin therapy to receive apixaban and this trialwas terminated early due to clear benefit in favor of apixaban for reduction in stroke or systemic embolism without increased risk of major bleeding(including intracranial hemorrhage).



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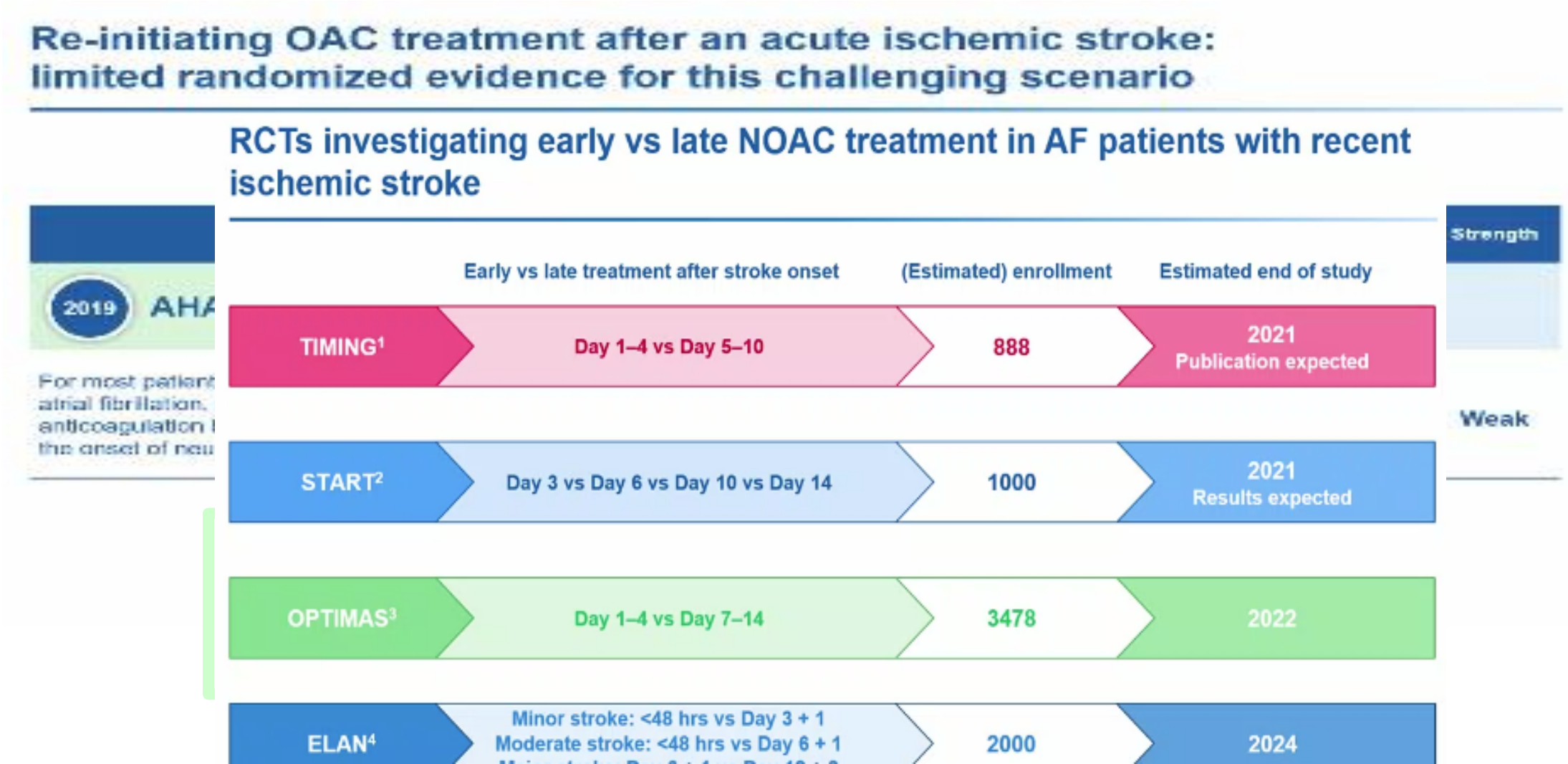
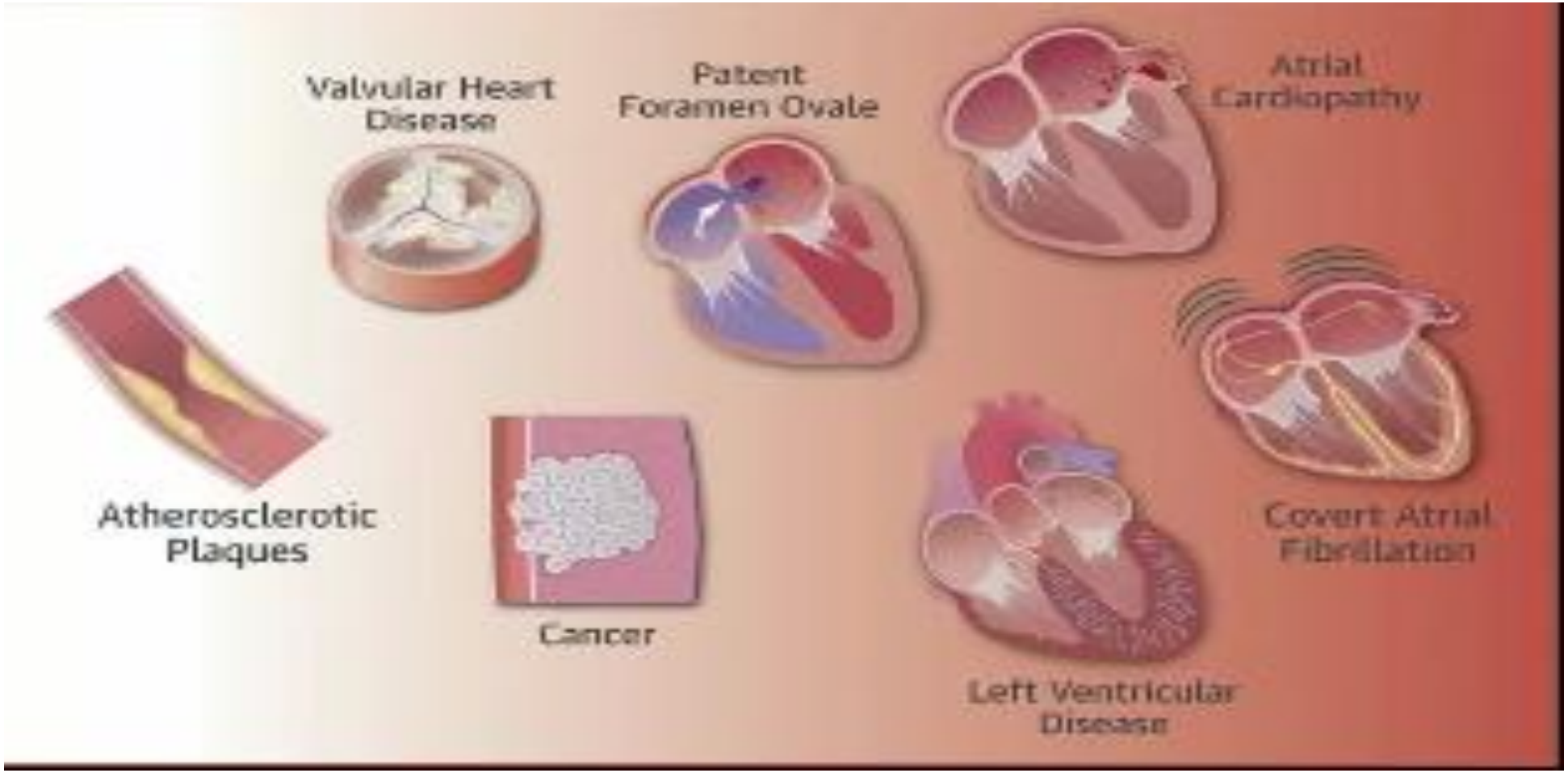


ESUS

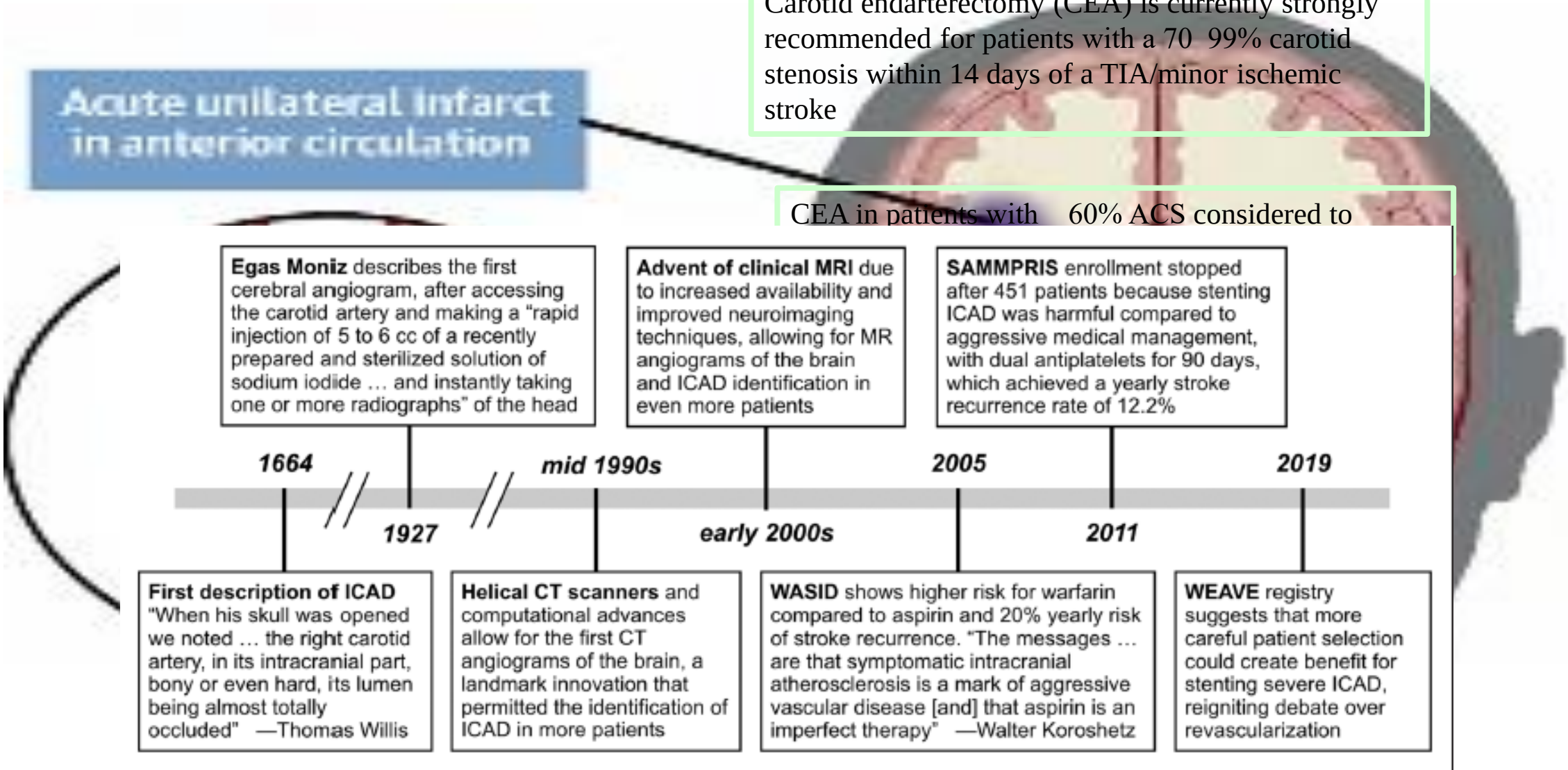
patients with stroke meeting the current definition of ESUS should not routinely be anticoagulated



CAROTID STENOSIS

Carotid endarterectomy (CEA) is currently strongly recommended for patients with a 70 99% carotid stenosis within 14 days of a TIA/minor ischemic stroke

CEA in patients with 60% ACS considered to



SECONDARY PREVENTION and PFO

REDUSE, DEFENSE, CLOSE and RESPECT TRIALS:

closure with antiplatelet therapy (predominantly aspirin)

was more effective than antiplatelet therapy alone

Metaanalysis of 8 randomized trials compared PFO occlusion with drug therapy in 3,313 patients showed 100 ischemic strokes per 1,000 patients with antiplatelet therapy and 13 of 1,000 ischemic strokes after PFO occlusion plus antiplatelet drugs over a period of 5 years.

Tabella 5.2. RoPE Score.

Non storia di ipertensione (+1)
Non storia di diabete (+1)
Non storia di ictus o TIA (+1)
Non fumatore (+1)
Infarto corticale alle neuroimmagini (+1)
Età
18-29 (+5)
30-39 (+4)
40-49 (+3)
50-59 (+2)
60-69 (+1)
>70 (0)
RoPe score totale 0-10

SECONDARY PREVENTION AFTER INTRACRANIAL HAEMORRHAGE

In patients at high risk of ischemic stroke or vascular events and a recent ICH, <u>antiplatelet therapy</u> can be resumed without an significant increased risk of recurrent ICH

RESTART collaboration., lancet 2019

The effects of long-term oral anticoagulant agents for atrial fibrillation (AF) after intracranial haemorrhage (ICH): individual participant data meta-analysis (IPDMA) of randomised controlled trials

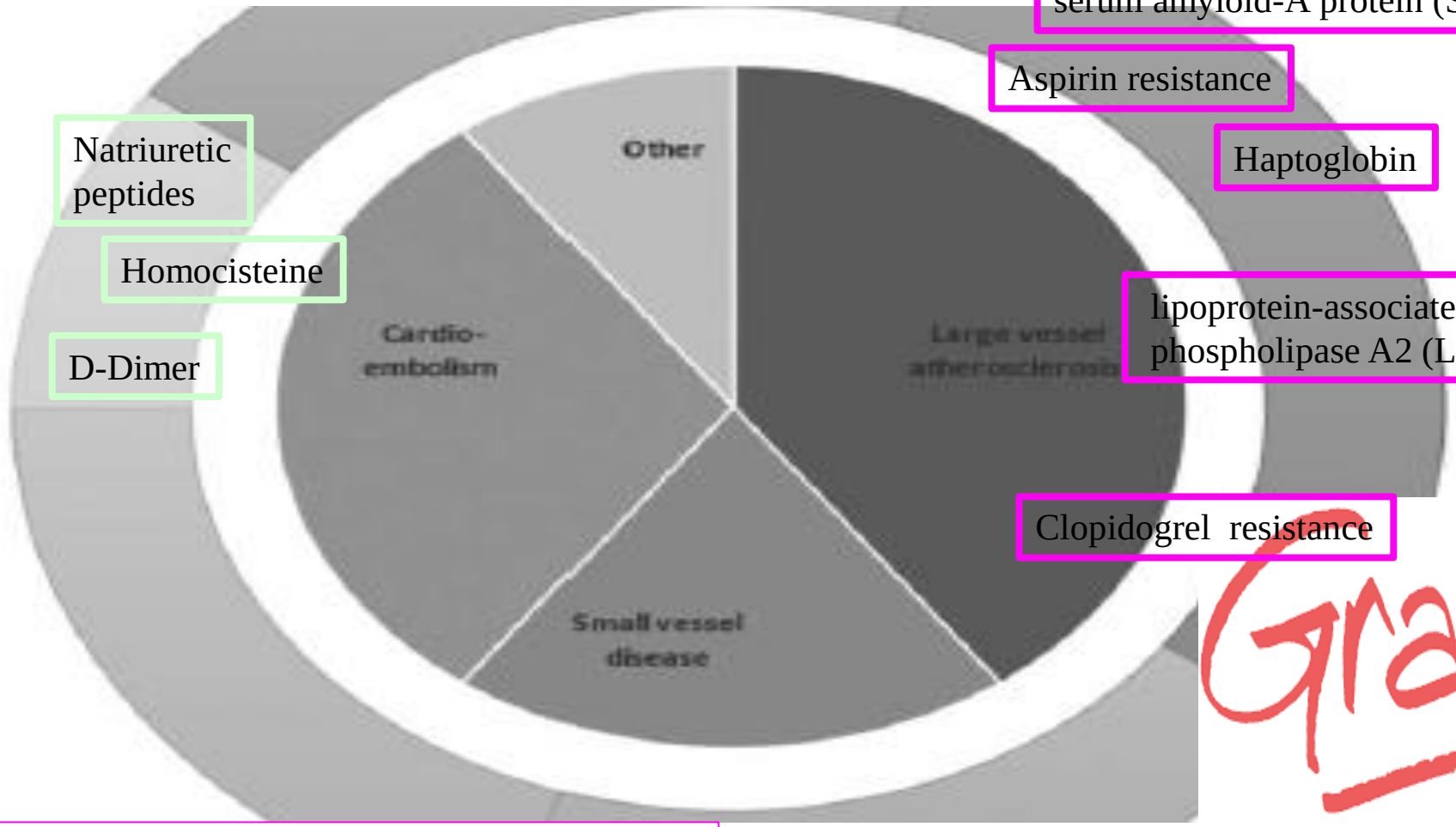
RCT	Stroke	Intervention vs. comparator	Recruited / target	Contact
STATICH	ICH	OAC *vs* no OAC	57 / 250	Rønning/Sandset
A_3ICH	ICH	Apixaban *vs* LAAO *vs* no antithrombotic therapy	60 / 300	Cordonnier
PRESTIGE-AF	ICH	NOAC *vs* no OAC	125 / 654	Veltkamp
ASPIRE	ICH	Apixaban *vs* aspirin	84 / 700	Sheth/Kamel
ENRICH-AF	ICrH	Edoxaban *vs* no OAC	330 / 1,200	Shoamanesh

PRECISION MEDICINE

- *Aim is to identify underlying pathomechanisms with better accuracy and to predict response to different medical treatment in relation to a cluster of a few very similar patients by using their specific 'biomarker pattern'*

PRECISION MEDICINE

- Factor XIa inhibitors in advanced phase 2 clinical stage
- Patients with carotid stenosis>50%:
  - ASS 100mg + Rivaroxaban 2.5mg 1-0-1
- With atherosclerosis associated stroke, target LDL-C are:
  - **<1.8 mmol/l (<70 mg/dl)** (TST Trial, ESO Guidelines[2])
  - **<1.4 mmol/l if CHD /(<55mg/dl)**(EU Guidelines, mostly cardiologic studies)
  - **<1.0 mmol/l (<40mg/dl)** if recurrent event within 2 years



serum amyloid-A protein (SAA)

Aspirin resistance

Haptoglobin

lipoprotein-associated phospholipase A2 (LP-PLA2)

Clopidogrel resistance

Natriuretic peptides

Homocisteine

D-Dimer

Grazie

Bicciato G et al., Curr Opin Neurol. 2022