



ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ

Εθνικόν και Καποδιστριακόν
Πανεπιστήμιον Αθηνών

— ΙΔΡΥΘΕΝ ΤΟ 1837 —

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ «ΚΑΡΔΙΟΜΕΤΑΒΟΛΙΚΗ ΙΑΤΡΙΚΗ»

Πρωτογενής Πρόληψη ΑΕΕ
Δευτερογενής πρόληψη (αντιθρομβωτική αγωγή)

Κακαλέτσης Νικόλαος

Παθολόγος

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Stroke Research Fellow, HUS Helsinki University Hospital and University of Helsinki, Finland

6 Μαρτίου 2025

Leading causes of death globally

○ 2000 ● 2019

1. Ischaemic heart disease

2. Stroke

3. Chronic obstructive pulmonary disease

4. Lower respiratory infections

5. Neonatal conditions

6. Trachea, bronchus, lung cancers

7. Alzheimer's disease and other dementias

8. Diarrhoeal diseases

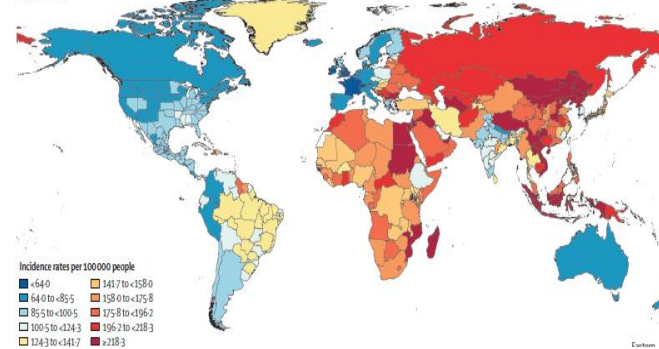
9. Diabetes mellitus

10. Kidney diseases

Number of deaths (in millions)

● Noncommunicable ● Communicable ● Injuries

A All strokes



Top 10 global causes of disability-adjusted life years (DALYs) in 2019

1. Neonatal conditions

2. Ischaemic heart disease

3. Stroke

4. Lower respiratory infections

5. Diarrhoeal diseases

6. Road injury

7. Chronic obstructive pulmonary disease

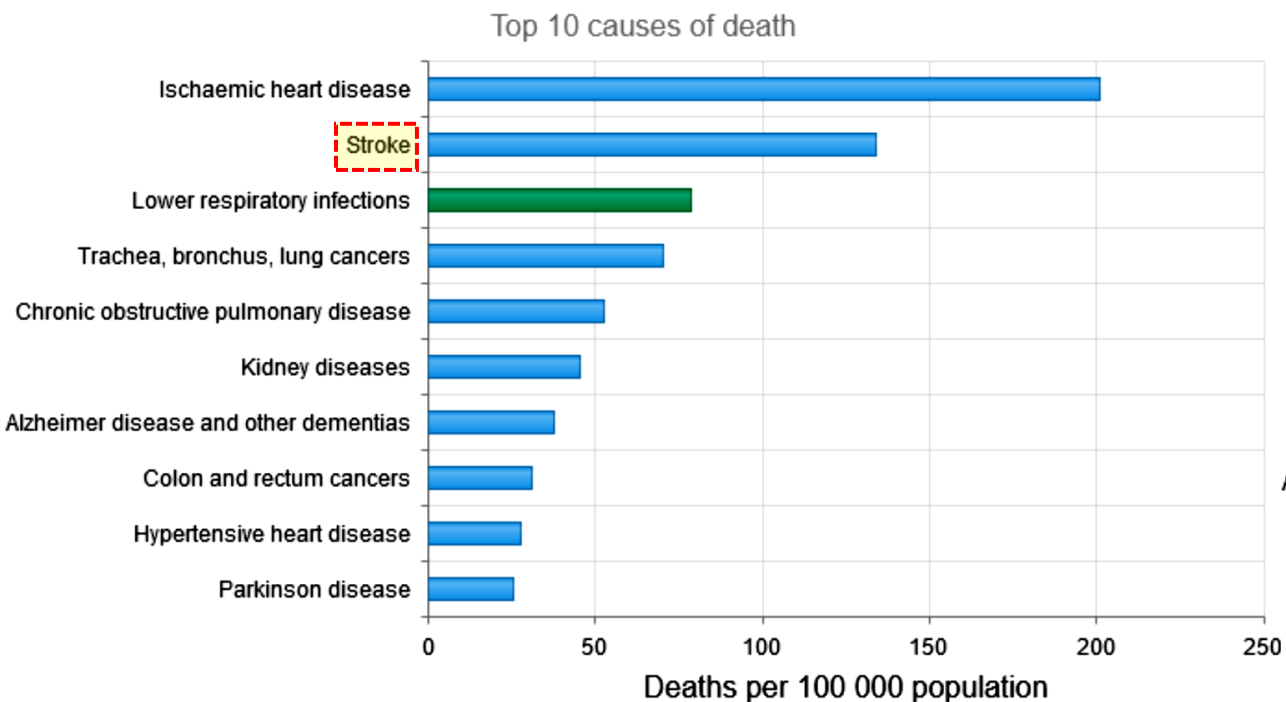
8. Diabetes mellitus

9. Tuberculosis

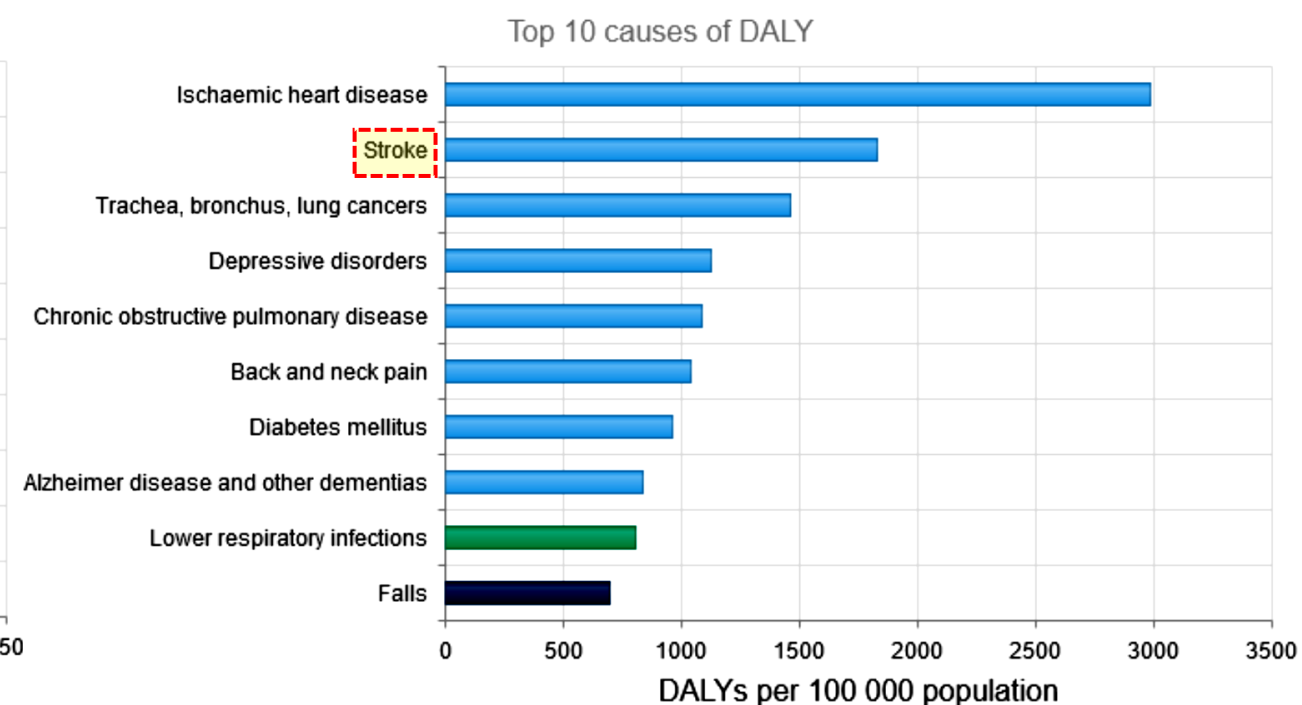
10. Congenital anomalies



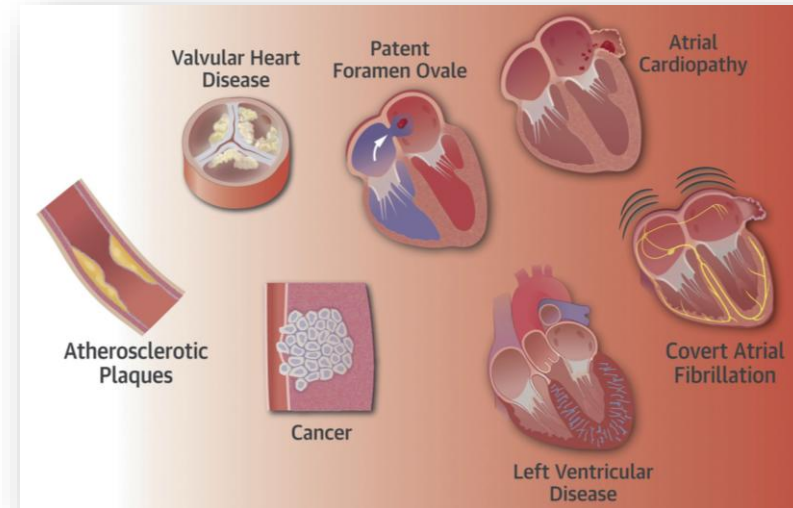
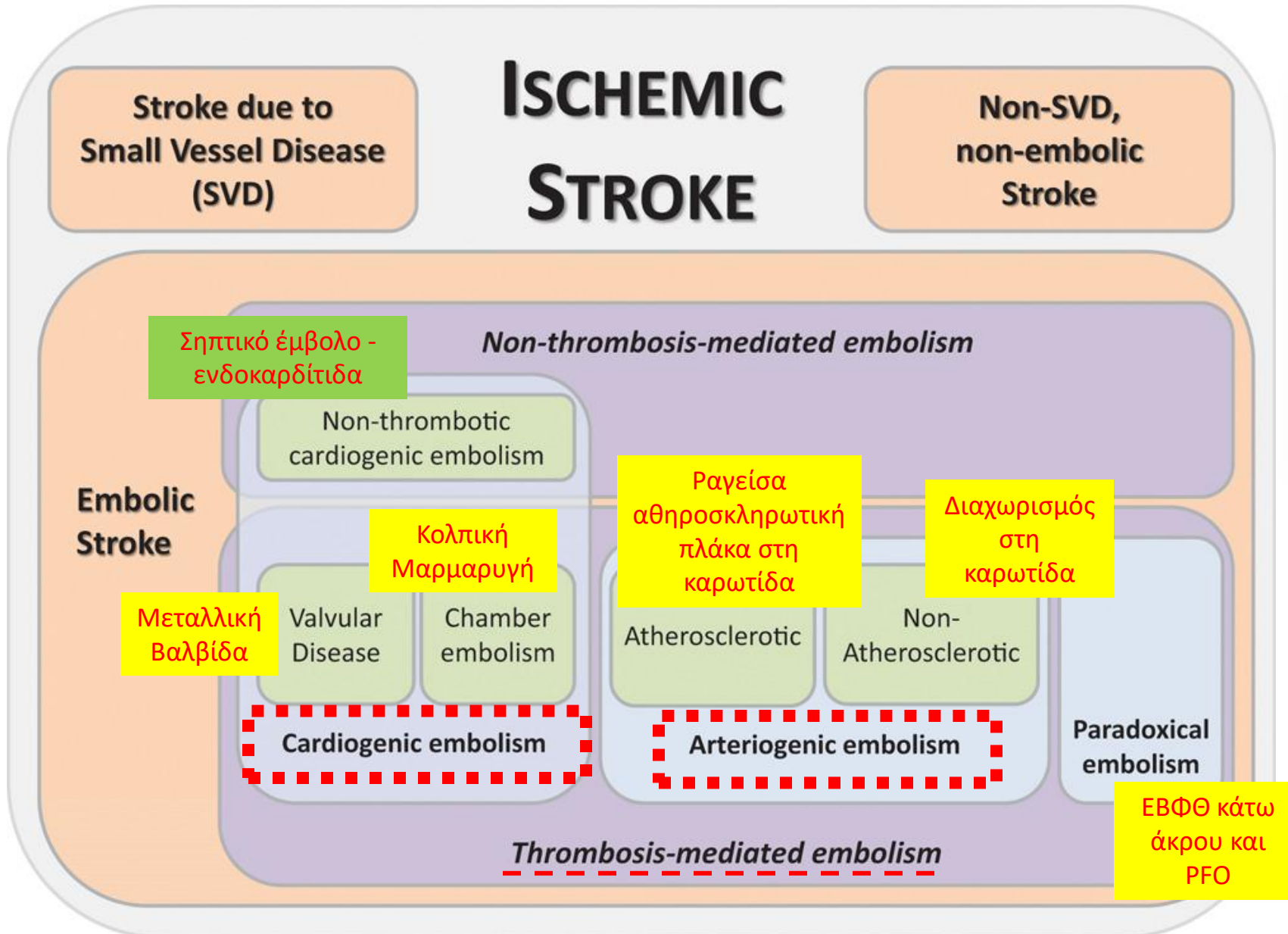
Top 10 causes of death in Greece for both sexes aged all ages (2019)



Top 10 causes of DALY in Greece for both sexes aged all ages (2019)



Ischemic stroke is an etiologically heterogeneous syndrome

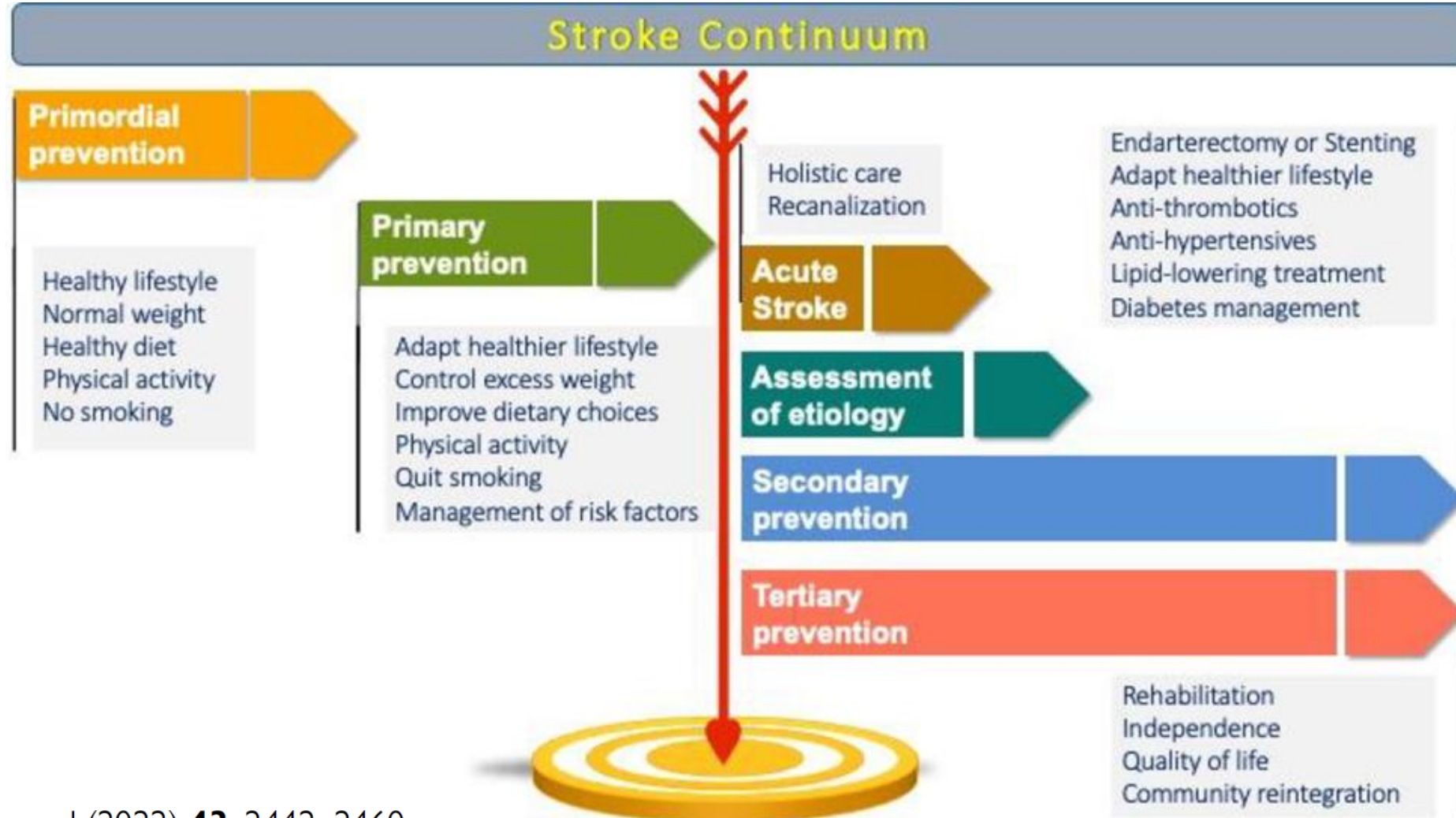


Ntaios G. Embolic Stroke of Undetermined Source: JACC Review Topic of the Week. J Am Coll Cardiol. 2020 Jan 28;75(3):333-340.

In order to optimize the **secondary prevention strategy** in a patient with ischemic stroke, it is rational to identify the underlying etiologic pathology.

Integrated care for optimizing the management of stroke and associated heart disease: a position paper of the European Society of Cardiology Council on Stroke

Gregory Y. H. Lip ^{1,2,3,4,*†}, Deirdre A. Lane^{1,2}, Radosław Lenarczyk³, Giuseppe Boriani ⁵, Wolfram Doehner ⁶, Laura A. Benjamin⁷, Marc Fisher⁸, Deborah Lowe⁹, Ralph L. Sacco¹⁰, Renate Schnabel¹¹, Caroline Watkins¹², George Ntaios ¹³, and Tatjana Potpara ^{4,14†}



Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study

INTERSTROKE

- 26,919 participants were recruited (1/2007 – 8/2015)
- from 32 countries (Asia, America, Europe, Australia, Middle East, Africa)
- 13,447 cases (10,388 AIS & 3,059 ICH) and 13,472 controls

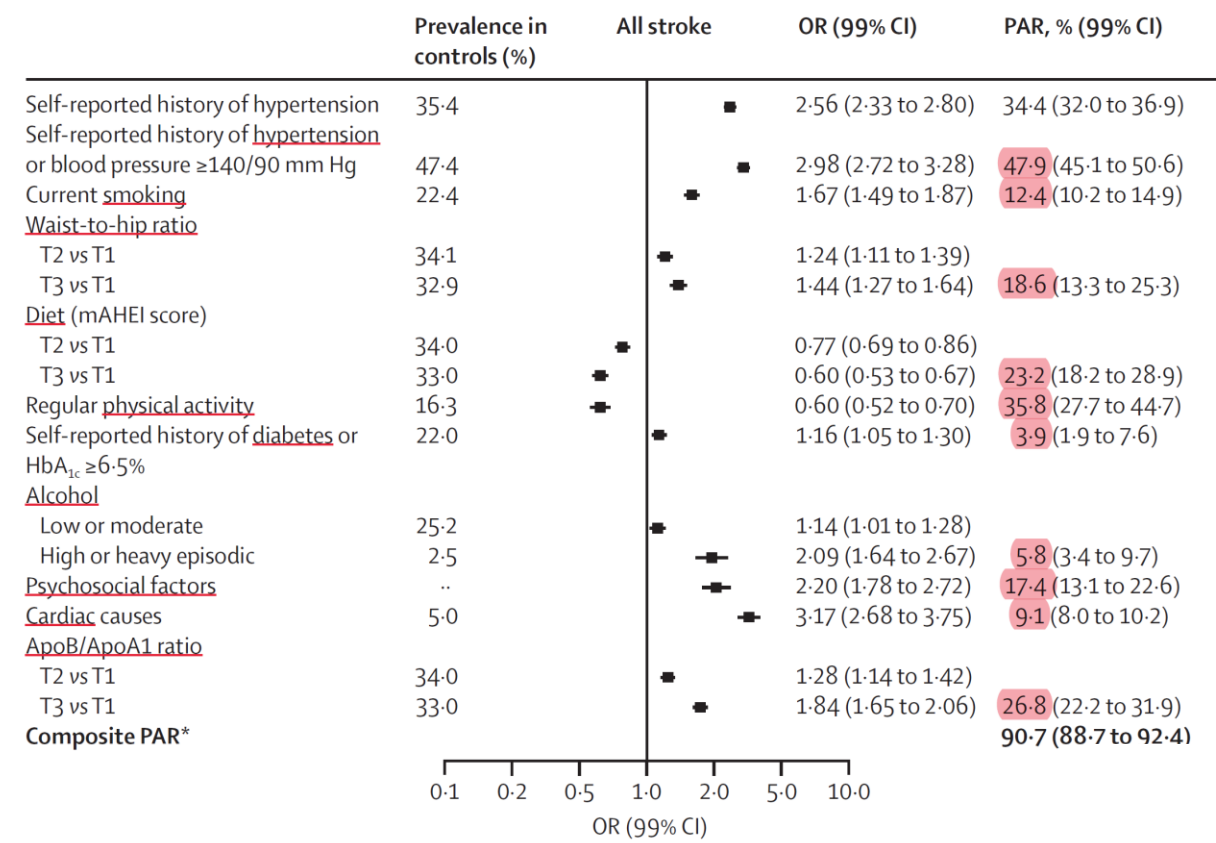


TABLE 1. TEN MODIFIABLE RISK FACTORS CONTRIBUTING TO 90% OF STROKES WORLDWIDE	
Risk factor	Percent*
1. Hypertension	47.9%
2. Physical activity	35.8%
3. Apo/ApoA1 ratio	26.8%
4. Diet	23.2%
5. Waist-to-hip ratio	18.6%
6. Psychosocial factors	17.4%
7. Current smoker	12.4%
8. Cardiac causes	9.1%
9. Alcohol consumption	5.8%
10. Diabetes mellitus	3.9%
* Population attributable risk percent is the percent of the incidence of a disease in the population that is due to exposure. For example, 47.9% of all strokes in the world can be attributed to hypertension.	

Stroke Risk Factors, Genetics, and Prevention

	Nonmodifiable Risk Factors	Modifiable Risk Factors
Ischemic stroke	Age	Hypertension
	Sex	Current smoking
	Race/ethnicity	Waist-to-hip ratio
		Diet
		Physical inactivity
		Hyperlipidemia
		Diabetes mellitus
		Alcohol consumption
		Cardiac causes
		Apolipoprotein B to A1
	Genetics*	

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		Diabetes mellitus
		Alcohol consumption
		Cardiac causes
		Apolipoprotein B to A1
	Genetics*	

Primary and Secondary Prevention of Ischemic Stroke and Cerebral Hemorrhage

JACC Focus Seminar

Lifestyle modifications including:

- healthy diet
- weight loss
- termination of smoking
- regular physical activity

are recommended.



ONTARGET TRANSCEND

Relationship Between **Healthy Diet** and Risk of Cardiovascular Disease Among Patients on Drug Therapies for Secondary Prevention

A Prospective Cohort Study of 31 546 High-Risk Individuals From 40 Countries

mAHEI, modified Alternative Healthy Eating Index

Table 3. HRs and 95% CIs of the Composite Outcome for Individuals With Risk Factors or History of Diseases and According to Quintiles of the Modified Alternative Healthy Eating Index (Quintile 5 Versus 1, Healthiest Versus Unhealthiest)

	mAHEI				P for Trend
	Q2 vs Q1	Q3 vs Q1	Q4 vs Q1	Q5 vs Q1	
Hypertensive (n=26 307)	0.99 (0.91–1.08)	0.91 (0.83–1.01)	0.85 (0.77–0.95)	0.83 (0.74–0.92)	<0.0001
Normotensive (n=5239)	0.74 (0.58–0.95)	0.69 (0.53–0.88)	0.61 (0.47–0.78)	0.56 (0.42–0.74)	<0.0001
Diabetes mellitus, FPG ≥7 mg/dL (n=12 869)	0.96 (0.85–1.09)	0.91 (0.80–1.04)	0.86 (0.75–0.99)	0.75 (0.65–0.87)	<0.0001
No diabetes mellitus, FPG <7 mg/dL (n=18 676)	0.95 (0.84–1.07)	0.85 (0.74–0.96)	0.78 (0.69–0.90)	0.81 (0.71–0.92)	<0.0001
LDL median ≥2.80 mg/dL (n=15 254)	0.97 (0.87–1.09)	0.89 (0.79–1.00)	0.83 (0.73–0.95)	0.82 (0.72–0.94)	<0.001
LDL median <2.80 mg/dL (n=15 218)	0.94 (0.82–1.07)	0.87 (0.76–1.01)	0.82 (0.71–0.95)	0.76 (0.66–0.87)	<0.0001
With stroke/transient ischemic attack (n=6644)	0.94 (0.80–1.12)	0.82 (0.69–0.97)	0.79 (0.65–0.95)	0.78 (0.66–0.93)	<0.0001
Without stroke/transient ischemic attack (n=24 892)	0.96 (0.86–1.05)	0.90 (0.81–1.00)	0.83 (0.74–0.94)	0.78 (0.69–0.89)	<0.0001
With CAD (n=23 520)	0.97 (0.88–1.07)	0.85 (0.76–0.95)	0.83 (0.73–0.93)	0.78 (0.69–0.88)	<0.001
Without CAD (n=8026)	0.93 (0.77–1.12)	0.98 (0.83–1.16)	0.83 (0.69–0.99)	0.82 (0.69–0.98)	0.01
With PAD (n=4140)	0.92 (0.76–1.11)	1.02 (0.83–1.23)	0.77 (0.62–0.94)	0.92 (0.73–1.14)	0.1
Without PAD (n=27 406)	0.96 (0.88–1.06)	0.85 (0.77–0.95)	0.83 (0.74–0.93)	0.77 (0.68–0.86)	<0.0001

Patients in the healthier quintiles of mAHEI scores had a significantly *lower risk of CVD* (HR: **0.78**, 95%CI: 0.71-0.87).

The reductions in risk for CV death, myocardial infarction, and **stroke** were 35%, 14%, and **19%**, respectively. The protective association was *consistent regardless of whether patients were receiving proven drugs*.

Conclusions

A **higher-quality diet** was associated with a **lower risk of recurrent CVD** events among **people ≥55** years of age with CVD or diabetes mellitus.

Highlighting the importance of healthy eating by health professionals would substantially reduce CVD recurrence and save lives globally.

Circulation. 2012;126:2705-2712

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts

PREDIMED



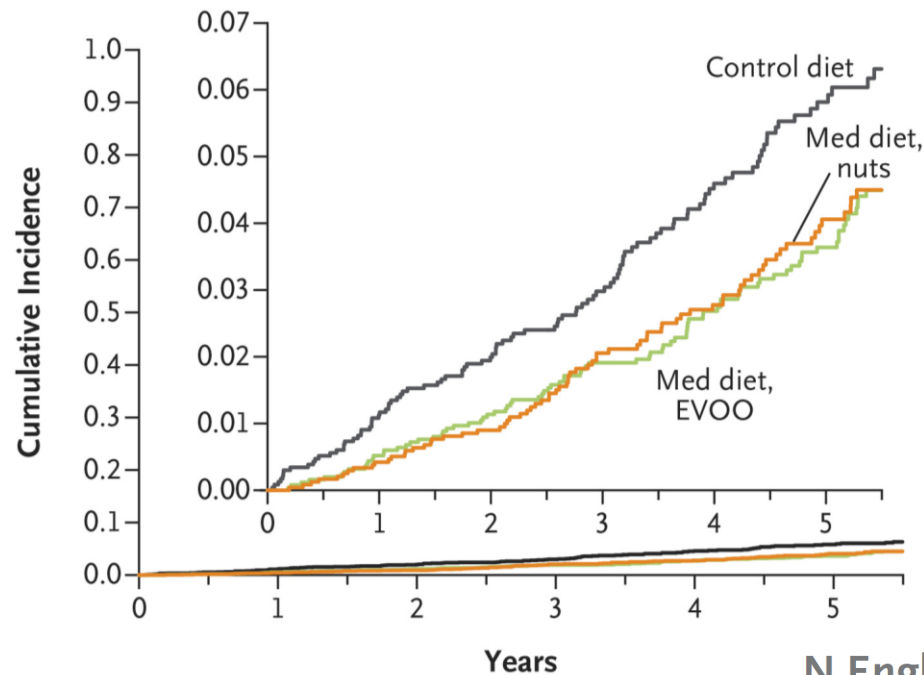
MeDiet + EVOO
N = 2543

MeDiet + Nuts
N = 2454

Control Diet
N = 2450

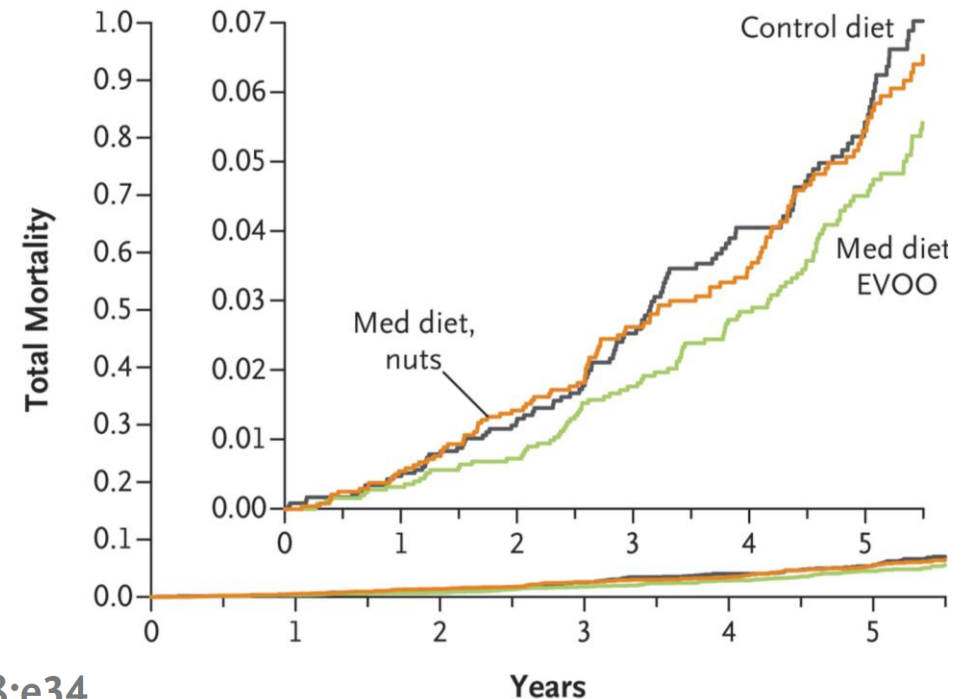
A Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)

Med diet, EVOO: hazard ratio, 0.69 (95% CI, 0.53–0.91)
Med diet, nuts: hazard ratio, 0.72 (95% CI, 0.54–0.95)



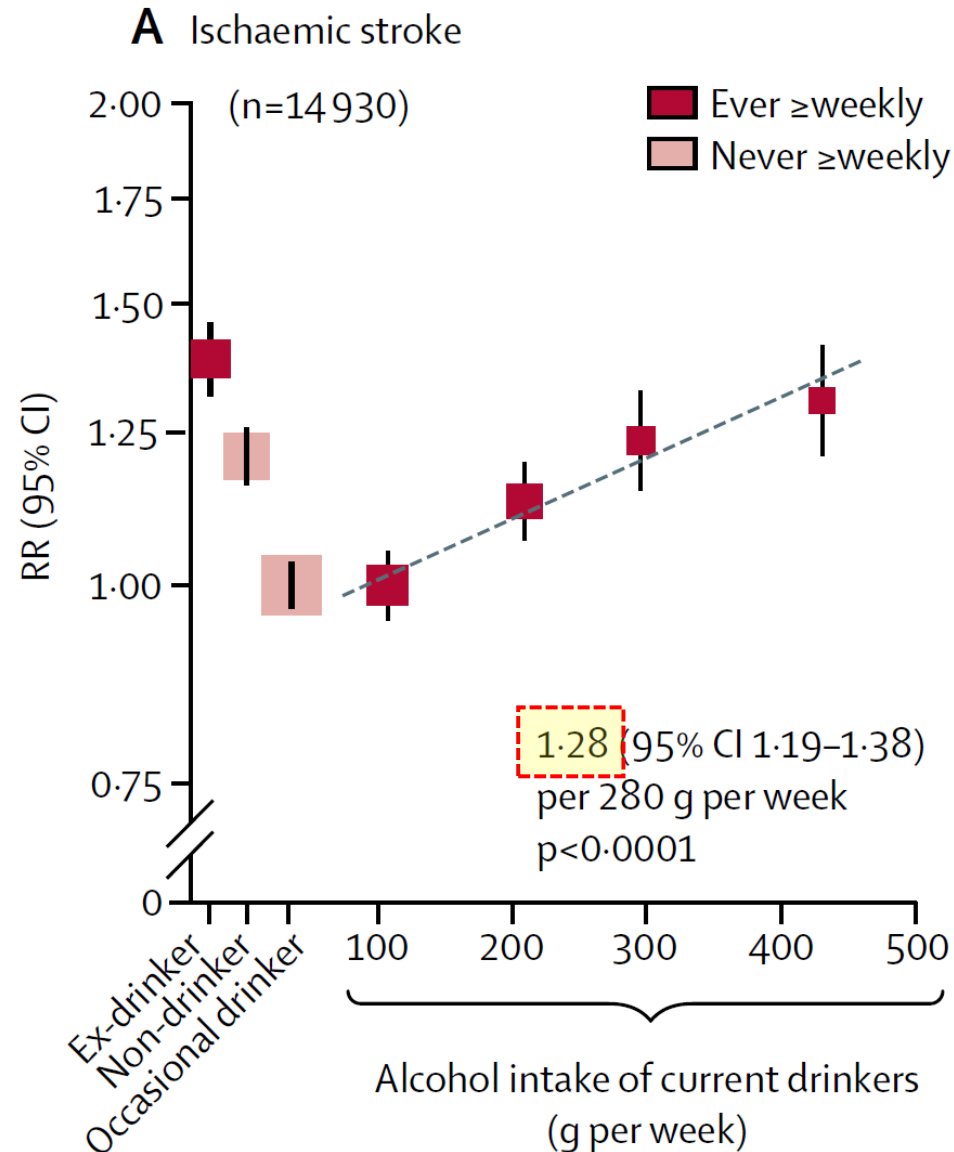
B Total Mortality

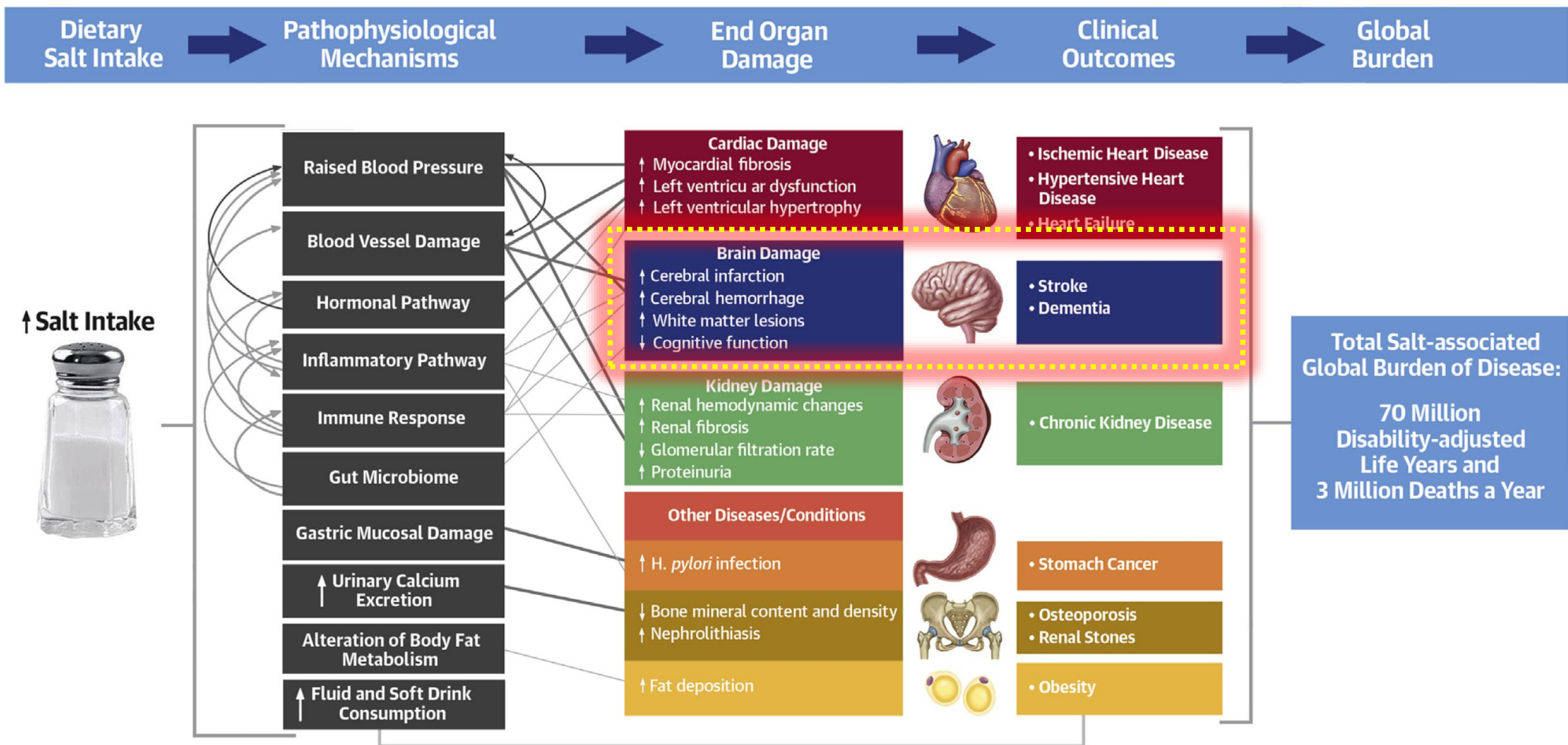
Med diet, EVOO: hazard ratio, 0.90 (95% CI, 0.69–1.18)
Med diet, nuts: hazard ratio, 1.12 (95% CI, 0.86–1.47)



Conventional and genetic evidence on **alcohol** and vascular disease aetiology: a prospective study of 500 000 men and women in China

*prospective China Kadoorie Biobank
enrolled 512,715 adults*





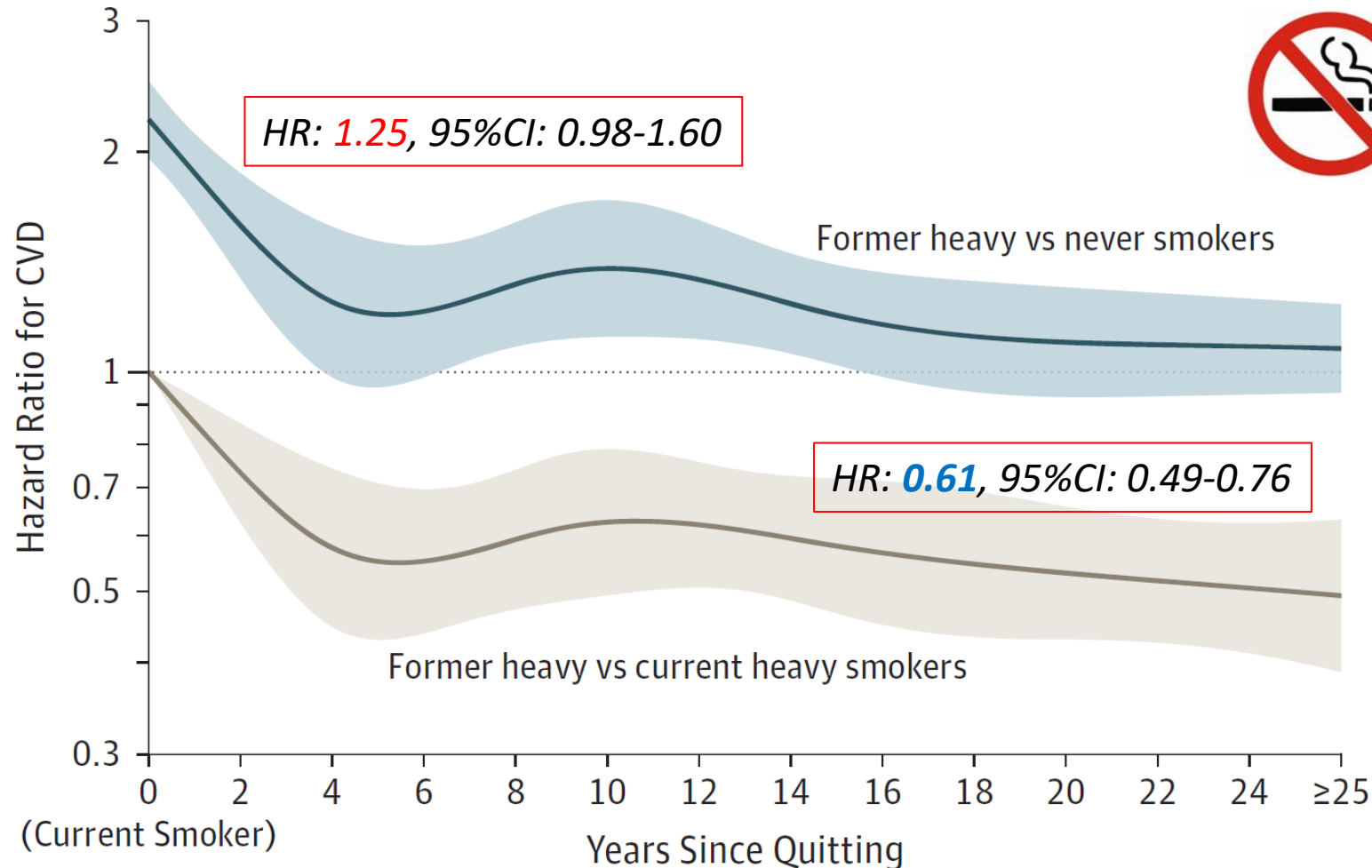
How Far Should **Salt** Intake Be Reduced?

TABLE 2. Predicted Reductions in Stroke and IHD Deaths With Reductions in Salt Intake

 Measure	Reduction in Salt Intake					
	3 g/d (50 mmol/d)		6 g/d (100 mmol/d)		9 g/d (150 mmol/d)	
	SBP	DBP	SBP	DBP	SBP	DBP
Fall in BP in all participants, mm Hg (from the meta-analysis)	2.5	1.4	5	2.8	7.5	4.2
Reduction in stroke death, %	12	14	23	25	32	36
Stroke deaths prevented in UK, n/y	7300	8300	13,700	15,500	19,300	21,600
Reduction in IHD death, %	9	10	16	19	23	27
IHD deaths prevented in UK, n/y	10,600	12,400	20,300	23,600	29,100	33,700

Association of **Smoking** Cessation With Subsequent Risk of Cardiovascular Disease

A Risk of CVD among former vs never smokers including current smokers



8,770 individuals from
Framingham Heart Study participants
without baseline CVD,
mean age of 42.2 years and
45% male

CONCLUSIONS & RELEVANCE

Among heavy smokers, **smoking cessation** was associated with significantly **lower risk of CVD** within 5 years relative to current smokers. However, relative to never smokers, former smokers' CVD risk remained significantly elevated beyond 5 years after smoking cessation.

Physical activity and risk of ischemic stroke in the Northern Manhattan Study



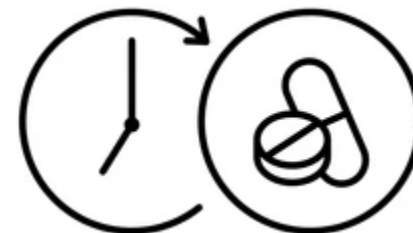
Table 3 Risk of ischemic stroke associated with physical activity in the Northern Manhattan Study

Physical activity intensity	Unadjusted HR	95% CI	Partially adjusted HR*	95% CI	Fully adjusted HR†	95% CI
Any vs none	0.86	0.66-1.12	0.80	0.61-1.04	0.86	0.66-1.13
Light vs none	0.97	0.74-1.28	0.90	0.68-1.19	0.94	0.71-1.25
Moderate to heavy vs none	0.65	0.44-0.95	0.57	0.38-0.85	0.65	0.43-0.98
Moderate to heavy vs light to none combined	0.66	0.46-0.94	0.60	0.41-0.88	0.68	0.46-0.99



The initial non-pharmacological approach is very important in patients at very high risk of future CV events, such as stroke or TIA patients:

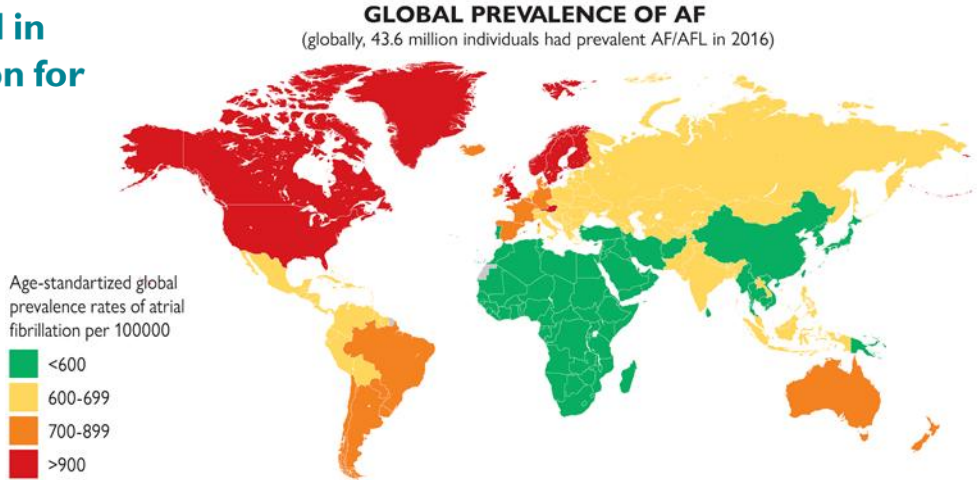
- *increasing the potential of a better physician-to-patient interaction,*
- &
- *adherence to treatment.*



Stroke Risk Factors, Genetics, and Prevention

	Nonmodifiable Risk Factors	Modifiable Risk Factors
Ischemic stroke	Age	Hypertension
	Sex	Current smoking
	Race/ethnicity	Waist-to-hip ratio
		Diet
		Physical inactivity
		Hyperlipidemia
		Diabetes mellitus
		Alcohol consumption
		Cardiac causes
		Apolipoprotein B to A1
	Genetics*	

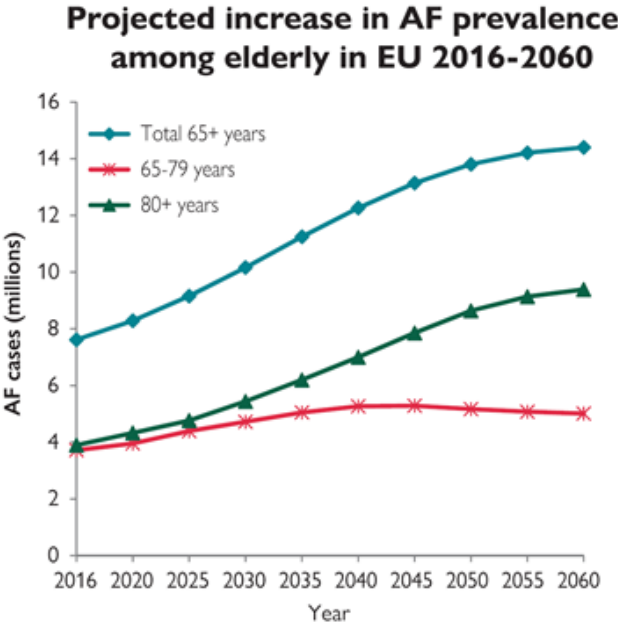
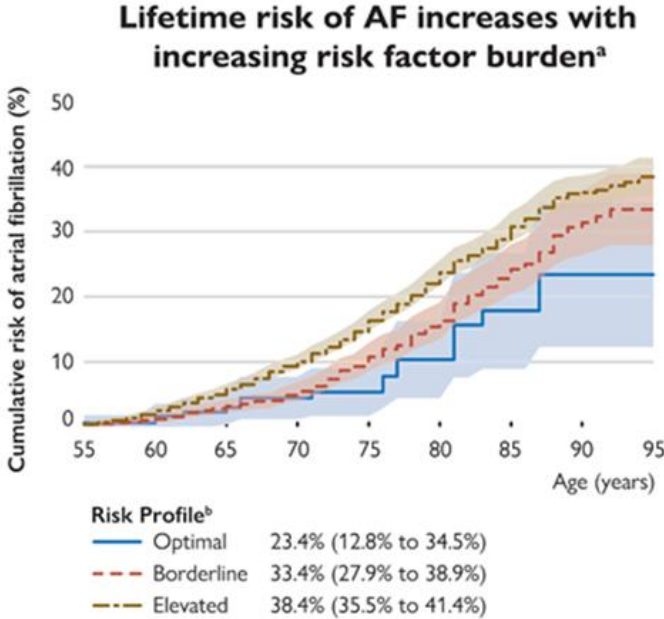
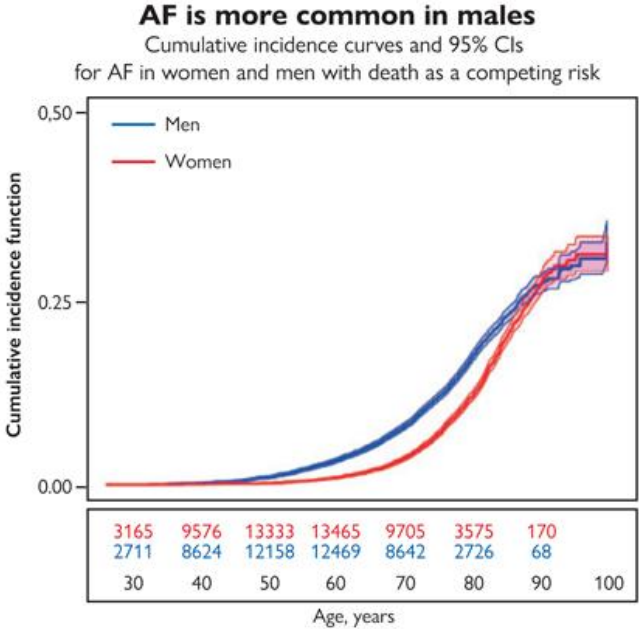
2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)



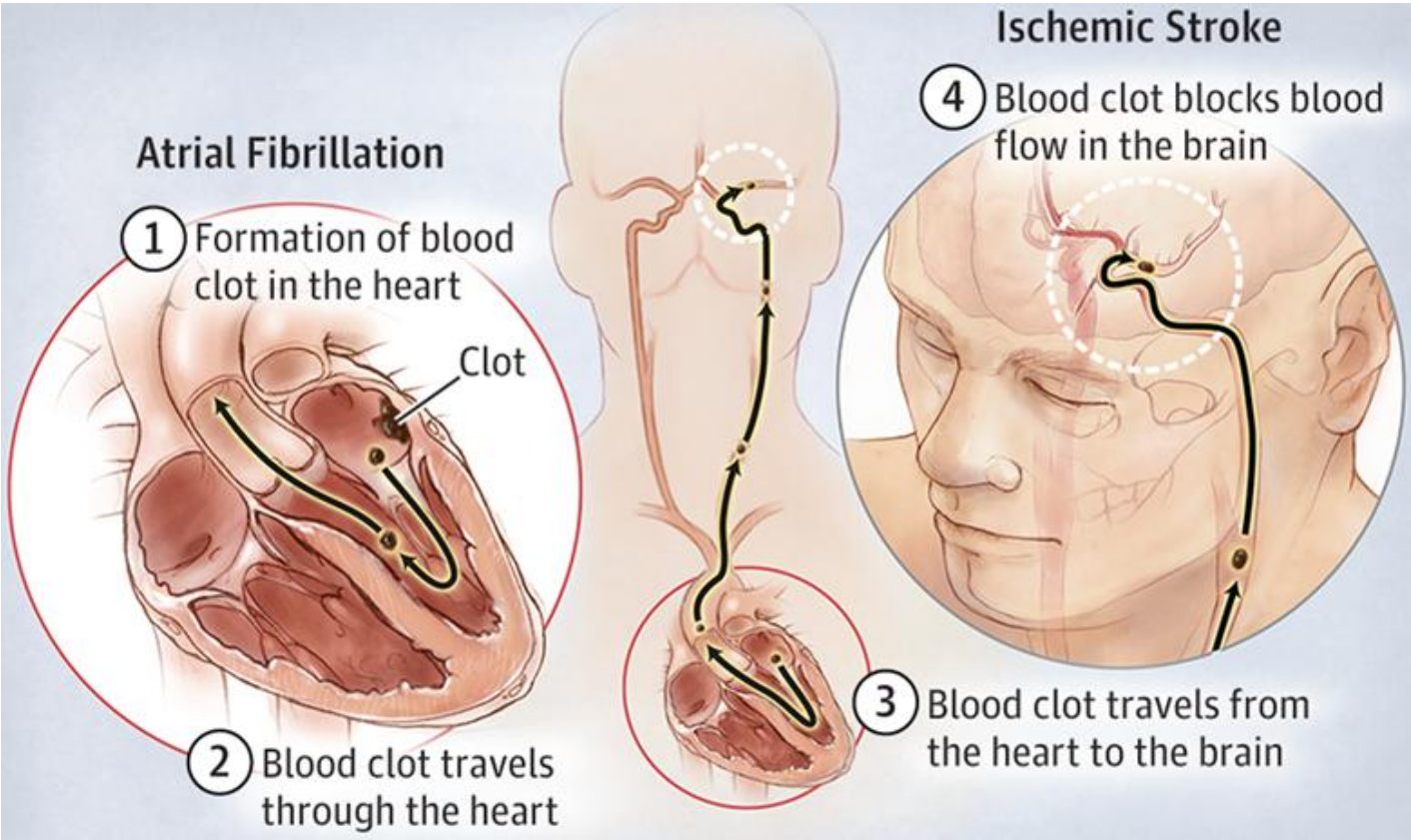
LIFETIME RISK for AF
1 in 3 individuals



of European ancestry
at index age of 55 years
37.0% (34.3% to 39.6%)



2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)



CHA ₂ DS ₂ -VASc score		Points awarded
Risk factors and definitions		
C	Congestive heart failure Clinical HF, or objective evidence of moderate to severe LV dysfunction, or HCM	1
H	Hypertension or on antihypertensive therapy	1
A	Age 75 years or older	2
D	Diabetes mellitus Treatment with oral hypoglycaemic drugs and/or insulin or fasting blood glucose >125 mg/dL (7 mmol/L)	1
S	Stroke Previous stroke, TIA, or thromboembolism	2
V	Vascular disease Angiographically significant CAD, previous myocardial infarction, PAD, or aortic plaque	1
A	Age 65 – 74 years	1
Sc	Sex category (female)	1
Maximum score		9

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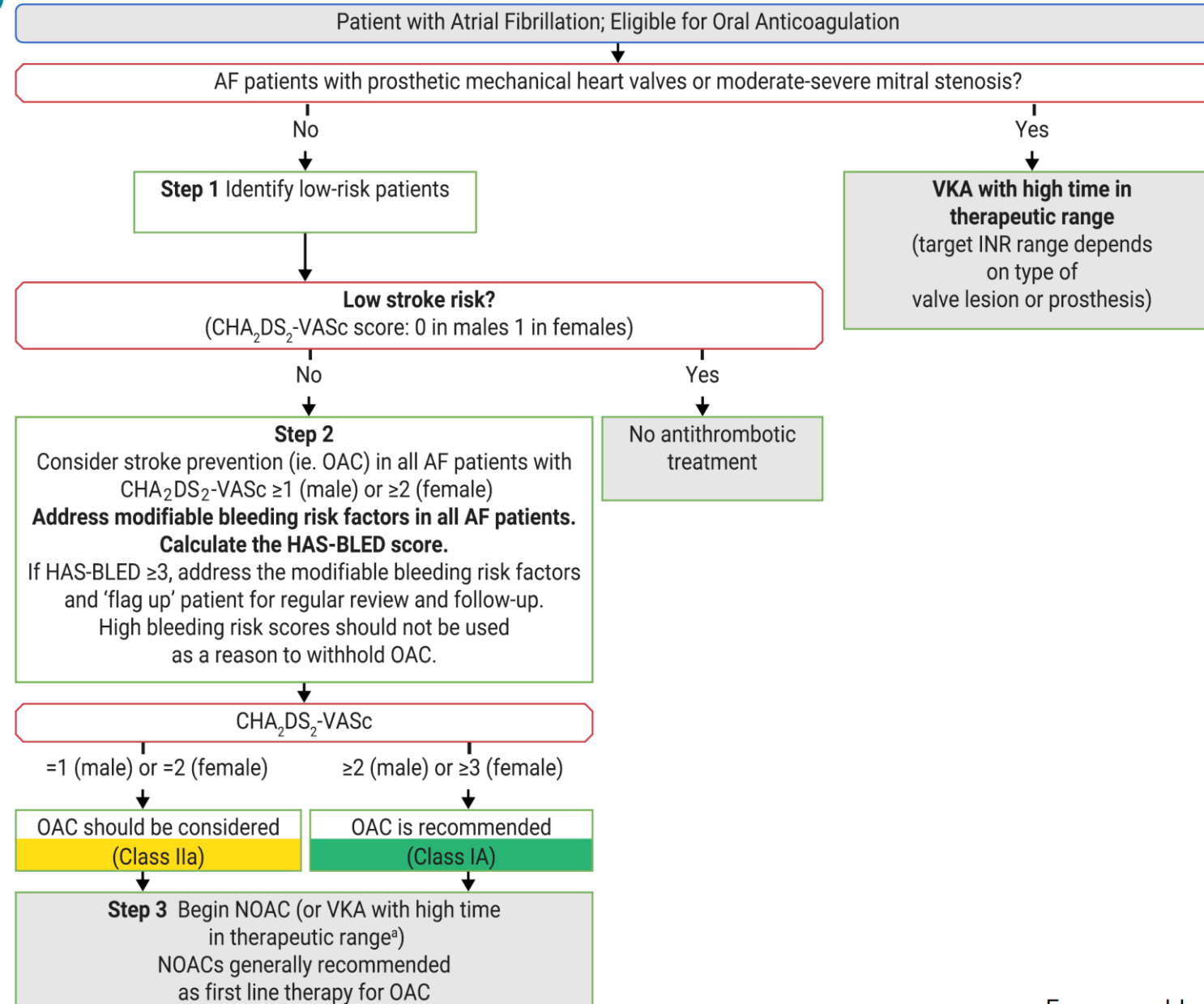
Refining Clinical Risk Stratification for Predicting Stroke and Thromboembolism in Atrial Fibrillation Using a Novel Risk Factor-Based Approach

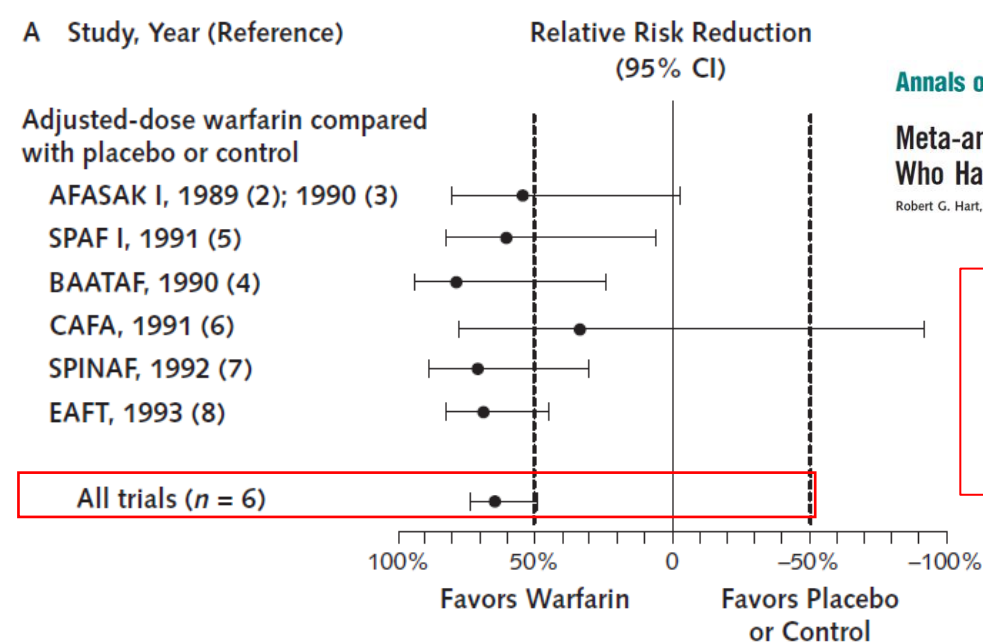
The Euro Heart Survey on Atrial Fibrillation

Table 6—Stroke or Other TE at 1 Year Based on the 2009 Birmingham (CHA₂DS₂-VASc) Scoring System

CHA ₂ DS ₂ -VASc Score	No.	Number of TE Events	TE Rate During 1 y (95% CI)	TE Rate During 1 y, Adjusted for Aspirin Prescription, ^a %
0	103	0	0% (0-0)	0
1	162	1	0.6% (0.0-3.4)	0.7
2	184	3	1.6% (0.3-4.7)	1.9
3	203	8	3.9% (1.7-7.6)	4.7
4	208	4	1.9% (0.5-4.9)	2.3
5	95	3	3.2% (0.7-9.0)	3.9
6	57	2	3.6% (0.4-12.3)	4.5
7	25	2	8.0% (1.0-26.0)	10.1
8	9	1	11.1% (0.3-48.3)	14.2
9	1	1	100% (2.5-100)	100
Total	1,084	25	P Value for trend 0.003	

CHEST 2010; 137(2):263–272





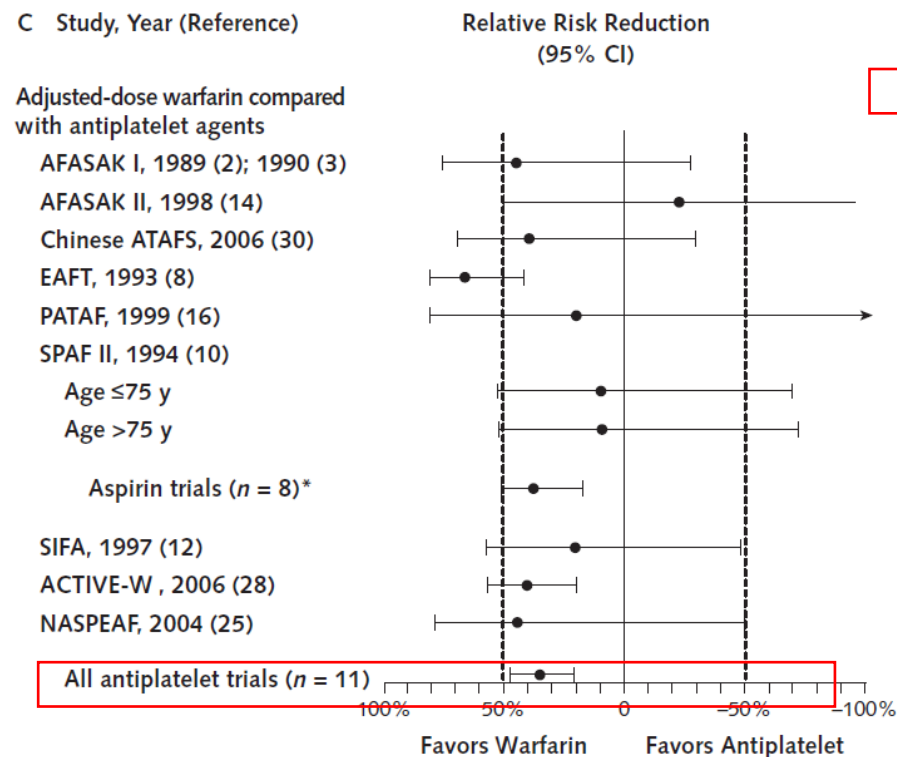
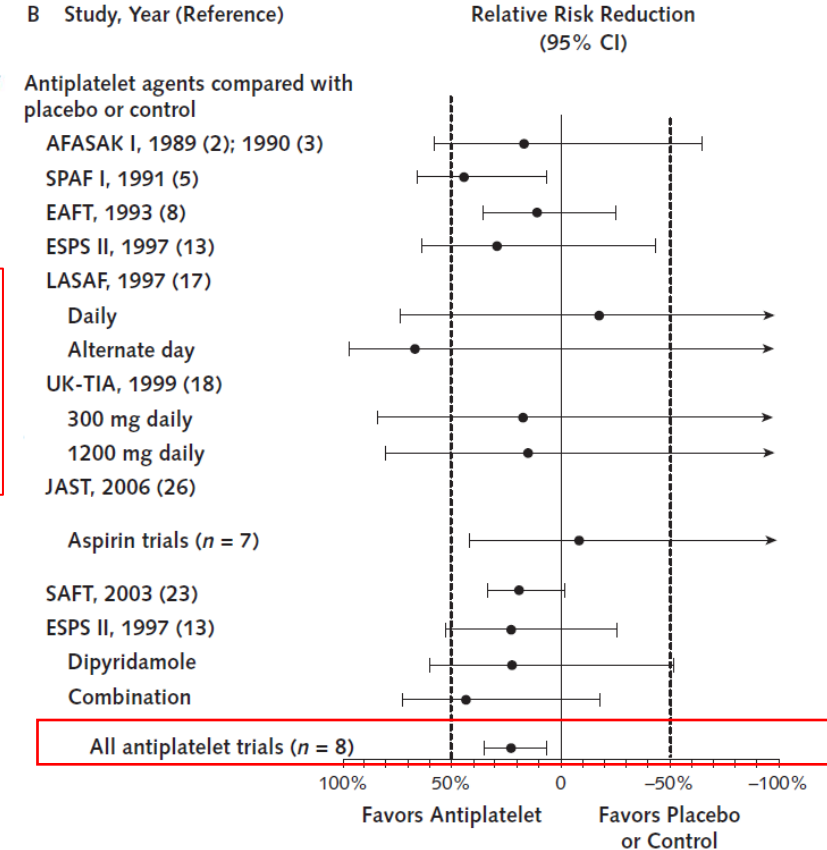
Annals of Internal Medicine

Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation

Robert G. Hart, MD; Lesly A. Pearce, MS; and Maria I. Aguilar, MD

Adjusted-dose **warfarin** and **antiplatelet** agents reduce stroke by approximately **60%** and by approximately **20%**, respectively, in patients who have AF.

REVIEW



Warfarin is substantially more efficacious (by approximately **40%**) than **antiplatelet** therapy.

ROCKET AF

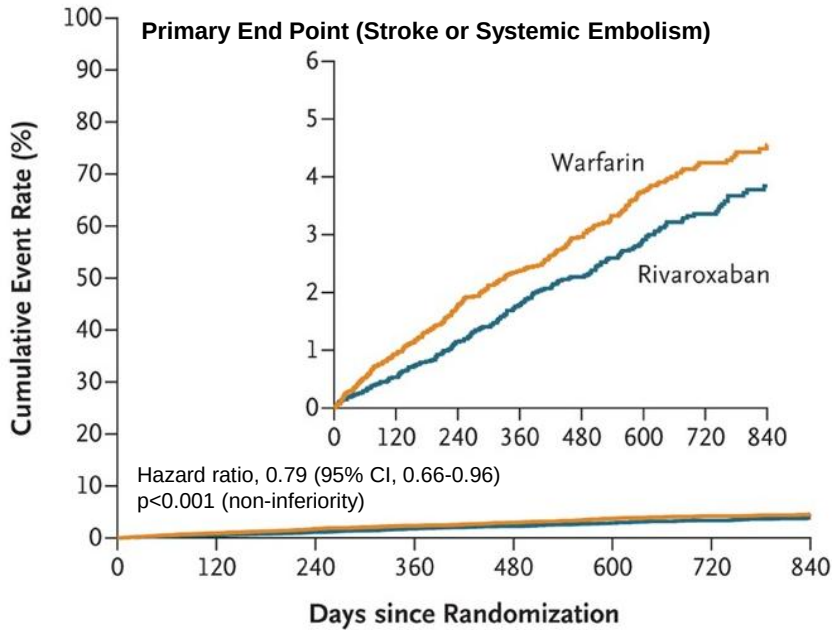
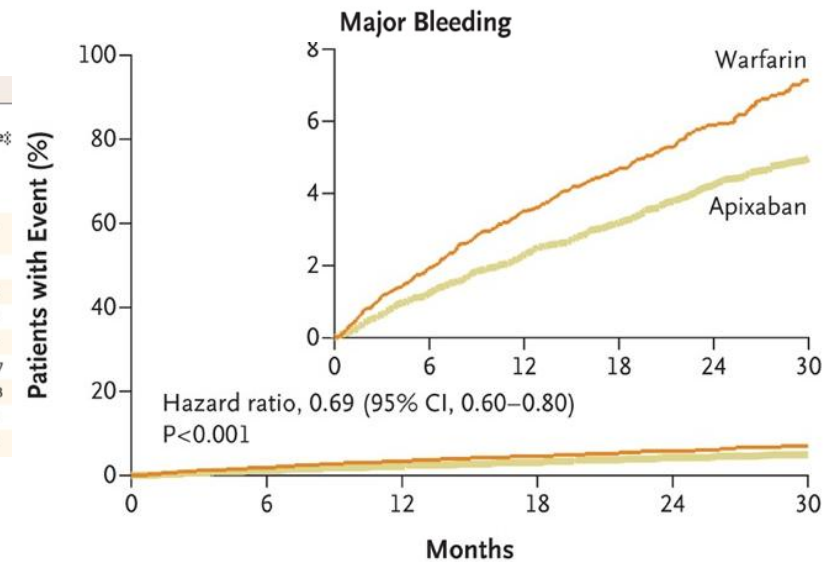
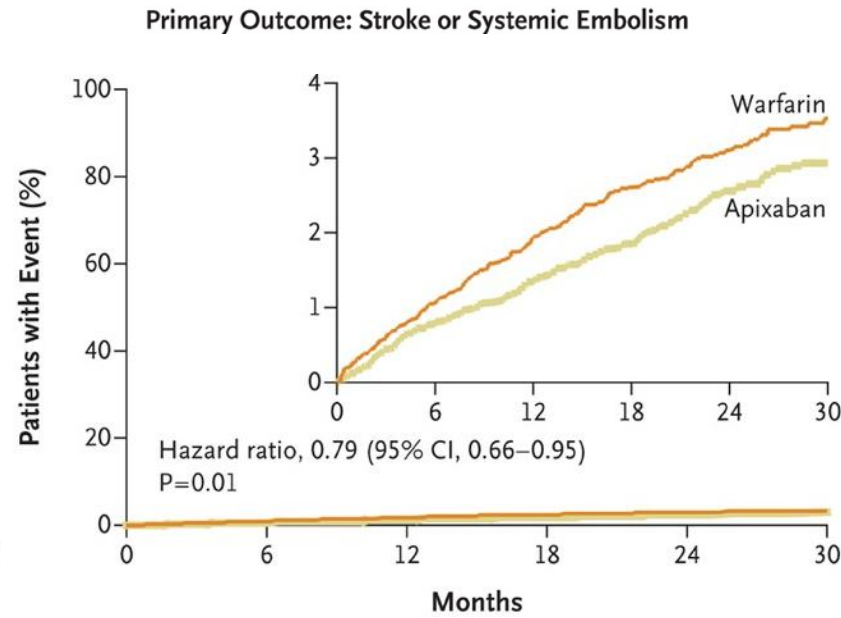


Table 3. Rates of Bleeding Events.^a

Variable	Rivaroxaban (N=7111)		Warfarin (N=7125)		Hazard Ratio (95% CI) [†]	P Value [‡]
	Events no. (%)	Event Rate no./100 patient-yr	Events no. (%)	Event Rate no./100 patient-yr		
Principal safety end point: major and nonmajor clinically relevant bleeding [§]	1475 (20.7)	14.9	1449 (20.3)	14.5	1.03 (0.96–1.11)	0.44
Major bleeding						
Any	395 (5.6)	3.6	386 (5.4)	3.4	1.04 (0.90–1.20)	0.58
Decrease in hemoglobin ≥ 2 g/dl	305 (4.3)	2.8	254 (3.6)	2.3	1.22 (1.03–1.44)	0.02
Transfusion	183 (2.6)	1.6	149 (2.1)	1.3	1.25 (1.01–1.55)	0.04
Critical bleeding [¶]	91 (1.3)	0.8	133 (1.9)	1.2	0.69 (0.53–0.91)	0.007
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5	0.50 (0.31–0.79)	0.003
Intracranial hemorrhage	55 (0.8)	0.5	84 (1.2)	0.7	0.67 (0.47–0.93)	0.02
Nonmajor clinically relevant bleeding	1185 (16.7)	11.8	1151 (16.2)	11.4	1.04 (0.96–1.13)	0.35

ARISTOTLE



N Engl J Med 2011;365:981-92

RE-LY

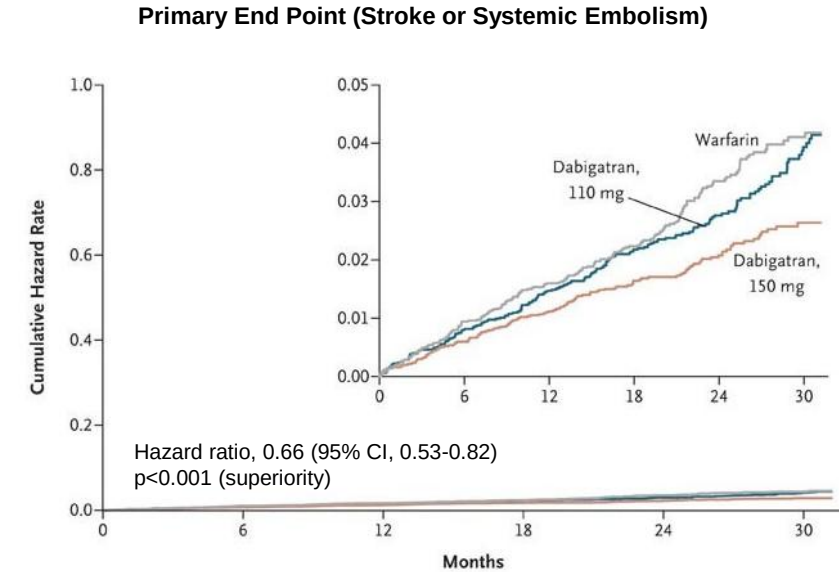


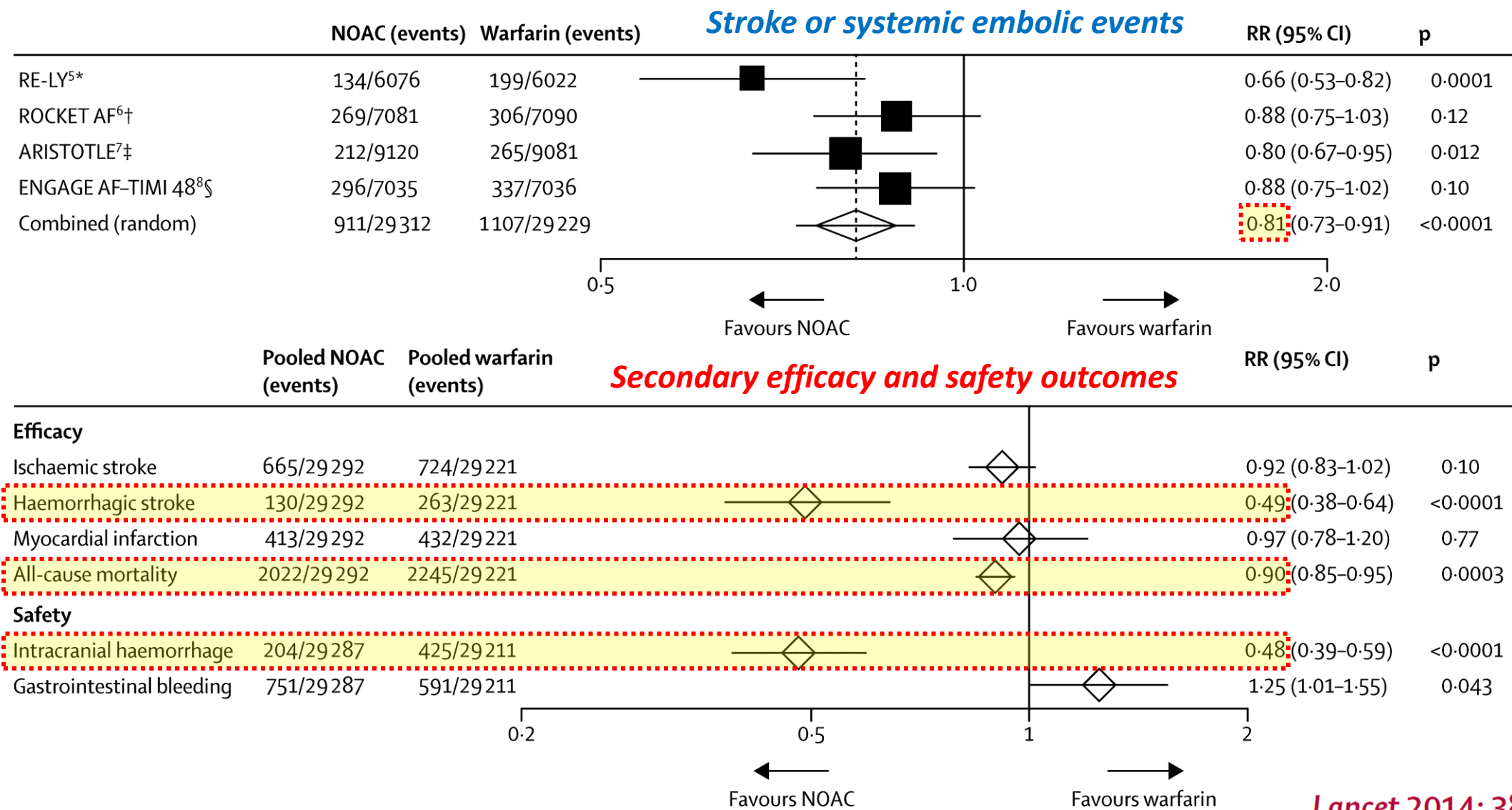
Table 3. Safety Outcomes, According to Treatment Group.^a

Event	Dabigatran, 110 mg		Dabigatran, 150 mg		Warfarin		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin	
	no. of patients	%/yr	no. of patients	%/yr	no. of patients	%/yr	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Major bleeding	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003	0.93 (0.81–1.07)	0.31
Life-threatening	145	1.22	175	1.45	212	1.80	0.68 (0.55–0.83)	<0.001	0.81 (0.66–0.99)	0.04
Non-life threatening	198	1.66	226	1.88	208	1.76	0.94 (0.78–1.15)	0.56	1.07 (0.89–1.29)	0.47
Gastrointestinal [†]	133	1.12	182	1.51	120	1.02	1.10 (0.86–1.41)	0.43	1.50 (1.19–1.89)	<0.001
Minor bleeding	1566	13.16	1787	14.84	1931	16.37	0.79 (0.74–0.84)	<0.001	0.91 (0.85–0.97)	0.005
Major or minor bleeding	1740	14.62	1977	16.42	2142	18.15	0.78 (0.74–0.83)	<0.001	0.91 (0.86–0.97)	0.002
Intracranial bleeding	27	0.23	36	0.30	87	0.74	0.31 (0.20–0.47)	<0.001	0.40 (0.27–0.60)	<0.001
Extracranial bleeding	299	2.51	342	2.84	315	2.67	0.94 (0.80–1.10)	0.45	1.07 (0.92–1.25)	0.38
Net clinical benefit outcome [‡]	844	7.09	832	6.91	901	7.64	0.92 (0.84–1.02)	0.10	0.91 (0.82–1.00)	0.04

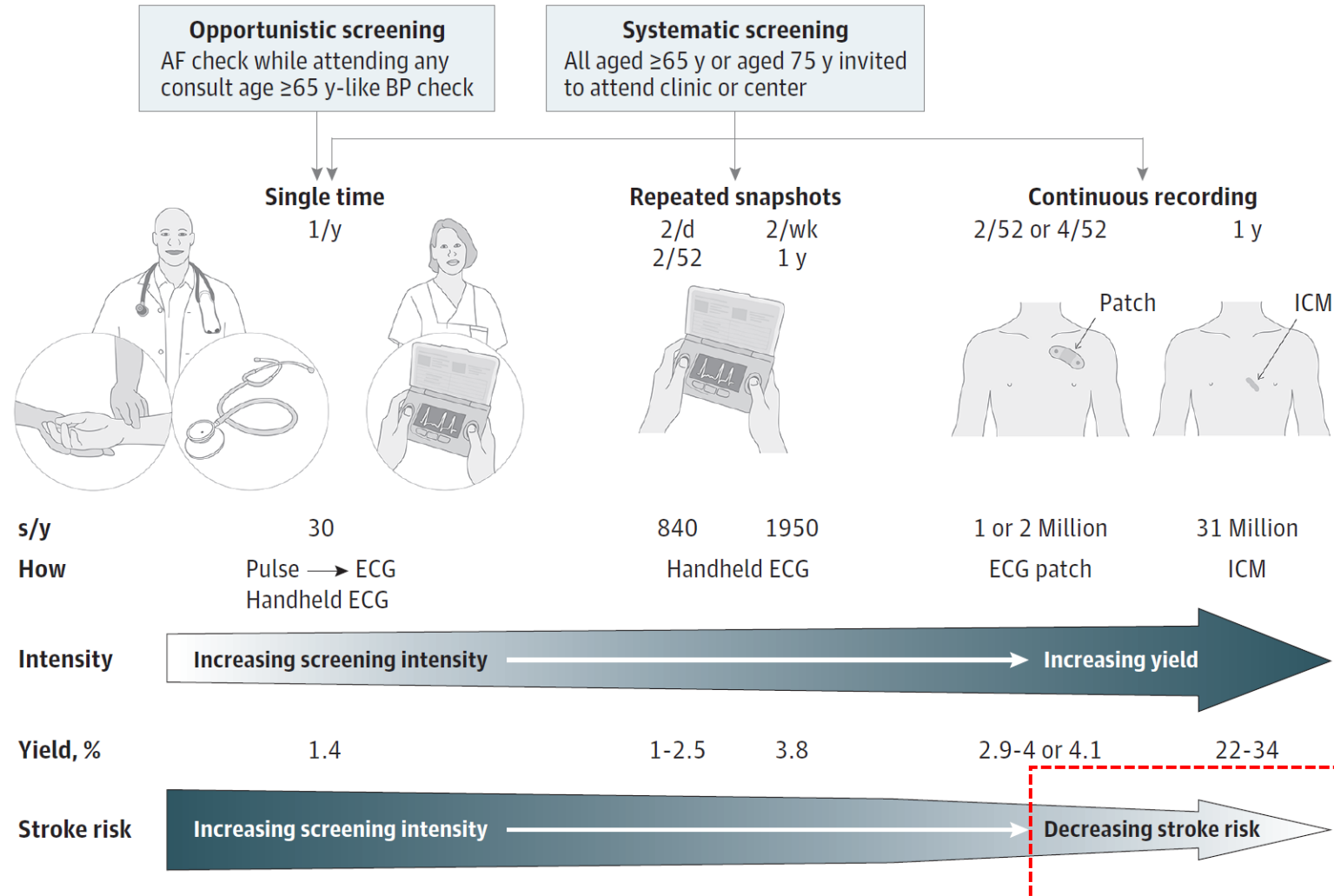
N Engl J Med 2009;361:1139-51

N Engl J Med 2011;365:883-91

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials



Opportunistic Electrocardiogram Screening for Atrial Fibrillation to Prevent Stroke



2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)

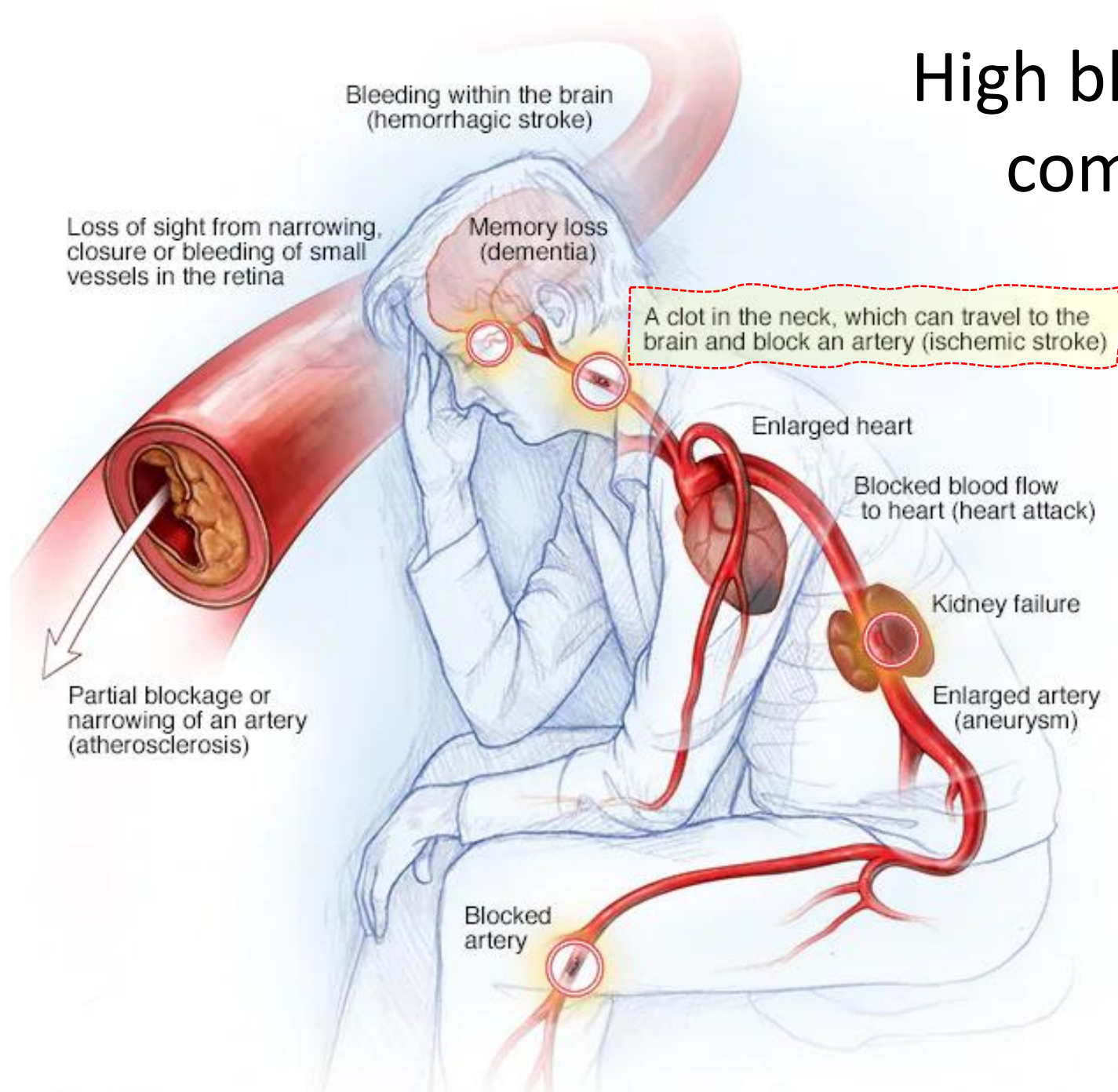
Recommendations	Class ^a	Level ^b
For stroke prevention in AF patients who are eligible for OAC, NOACs are recommended in preference to VKAs (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis). ^{423,424}	I	A
For stroke risk assessment, a risk-factor-based approach is recommended, using the CHA ₂ DS ₂ -VASc clinical stroke risk score to initially identify patients at ‘low stroke risk’ (CHA ₂ DS ₂ -VASc score = 0 in men, or 1 in women) who should not be offered antithrombotic therapy. ^{334,388}	I	A
OAC is recommended for stroke prevention in AF patients with CHA ₂ DS ₂ -VASc score ≥2 in men or ≥3 in women. ⁴¹²	I	A
OAC should be considered for stroke prevention in AF patients with a CHA ₂ DS ₂ -VASc score of 1 in men or 2 in women. Treatment should be individualized based on net clinical benefit and consideration of patient values and preferences. ^{338,378,380}	IIa	B
For bleeding risk assessment, a formal structured risk-score-based bleeding risk assessment is recommended to help identify non-modifiable and address modifiable bleeding risk factors in all AF patients, and to identify patients potentially at high risk of bleeding who should be scheduled for early and more frequent clinical review and follow-up. ^{388,395,404,406}	I	B

For a formal risk-score-based assessment of bleeding risk, the HAS-BLED score should be considered to help address modifiable bleeding risk factors, and to identify patients at high risk of bleeding (HAS-BLED score ≥ 3) for early and more frequent clinical review and follow-up. ^{388,395,404,406}	IIa	B
Stroke and bleeding risk reassessment at periodic intervals is recommended to inform treatment decisions (e.g. initiation of OAC in patients no longer at low risk of stroke) and address potentially modifiable bleeding risk factors. ^{c389,478,479}	I	B
In patients with AF initially at low risk of stroke, first reassessment of stroke risk should be made at 4 - 6 months after the index evaluation. ^{385–387}	IIa	B
If a VKA is used, a target INR of 2.0 - 3.0 is recommended, with individual TTR $\geq 70\%$. ⁴¹⁴	I	B
In patients on VKAs with low time in INR therapeutic range (e.g. TTR $<70\%$), recommended options are:	I	B
● Switching to a NOAC but ensuring good adherence and persistence with therapy ^{415,416} ; or		
● Efforts to improve TTR (e.g. education/counselling and more frequent INR checks). ⁴⁸⁰	IIa	B
Antiplatelet therapy alone (monotherapy or aspirin in combination with clopidogrel) is not recommended for stroke prevention in AF. ^{440,441,480,481}	III	A
Estimated bleeding risk, in the absence of absolute contraindications to OAC, should not in itself guide treatment decisions to use OAC for stroke prevention.	III	A
Clinical pattern of AF (i.e. first detected, paroxysmal, persistent, long-standing persistent, permanent) should not condition the indication to thromboprophylaxis. ¹⁶⁰	III	B
Recommendations for occlusion or exclusion of the LAA		
LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (e.g. intracranial bleeding without a reversible cause). ^{448,449,481,482}	IIb	B
Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery. ^{459,483}	IIb	C

Stroke Risk Factors, Genetics, and Prevention

	Nonmodifiable Risk Factors	Modifiable Risk Factors
Ischemic stroke	Age	Hypertension
	Sex	Current smoking
	Race/ethnicity	Waist-to-hip ratio
		Diet
		Physical inactivity
		Hyperlipidemia
		Diabetes mellitus
		Alcohol consumption
		Cardiac causes
		Apolipoprotein B to A1
	Genetics*	

High blood pressure complications

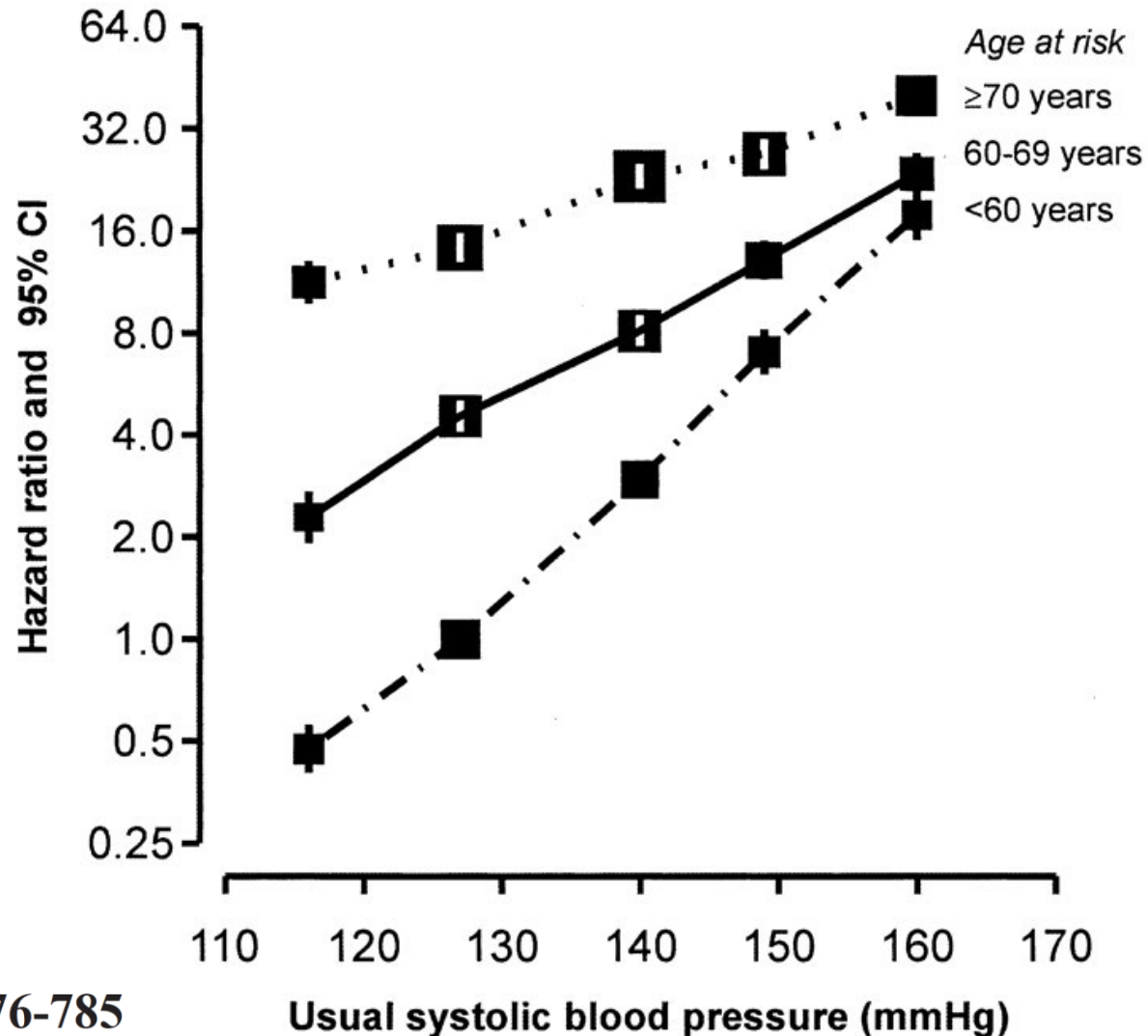


Blood Pressure and Stroke

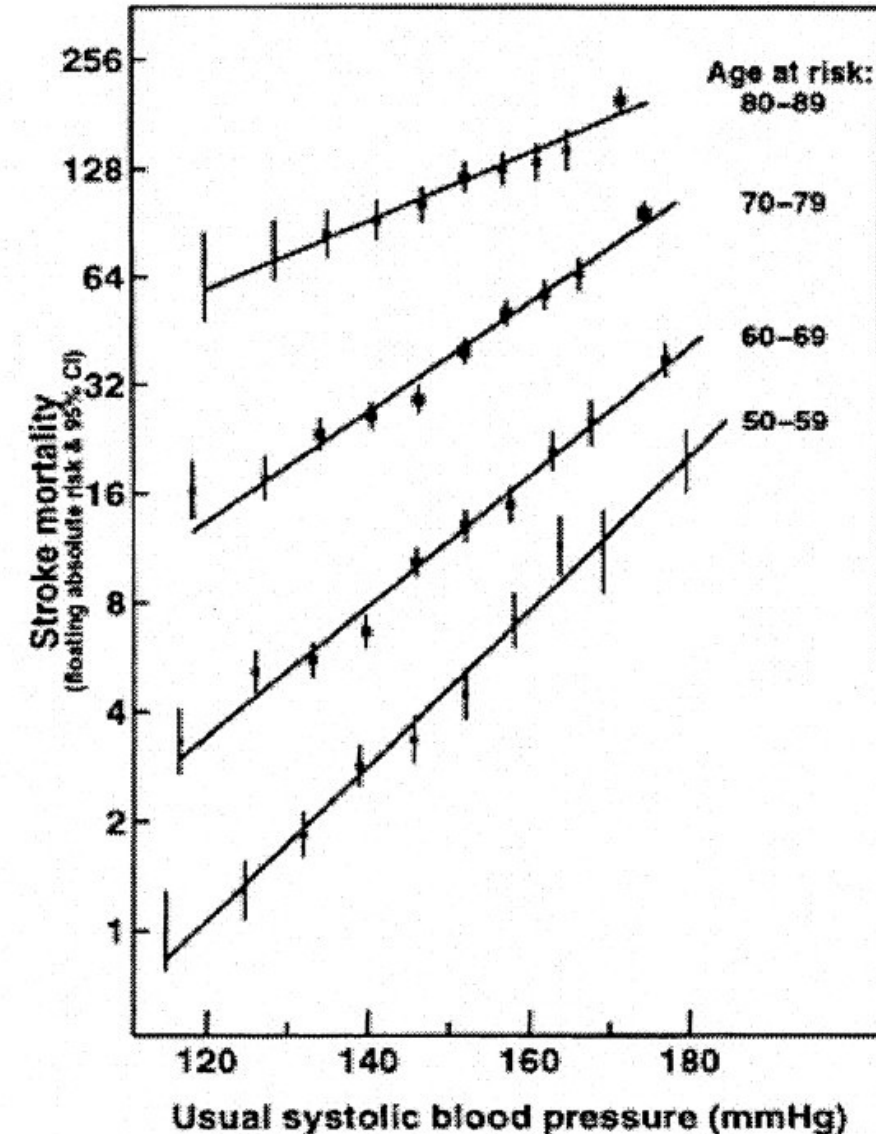
An Overview of Published Reviews

Usual SBP and **risk of stroke** by age, with data from **prospective** cohort study overviews.

Asia Pacific Cohort Studies Collaboration



Prospective Studies Collaboration



Blood Pressure and Stroke

An Overview of Published Reviews

**Blood pressure
lowering trials**

**Net difference
in SBP/DBP**

**Relative risk reduction
of stroke (95% CI)**

Mean age at entry

< 60 years

12 / 4



40% (26 – 52%)

60-69 years

6 / 3



28% (23 – 35%)

70+ years

13 / 6



28% (21 – 35%)

Mean baseline SBP

< 140mmHg

3 / 1



30% (15 – 42%)

140-160mmHg

10 / 4



26% (17 – 34%)

> 160mmHg

13 / 6



32% (25 – 38%)

History of stroke/TIA

Few/no participants

11 / 5



35% (28 – 41%)

Most/all participants

9 / 4



22% (12 – 31%)

History of vascular disease

Few/no participants

13 / 6



38% (30 – 45%)

Most/all participants

6 / 3

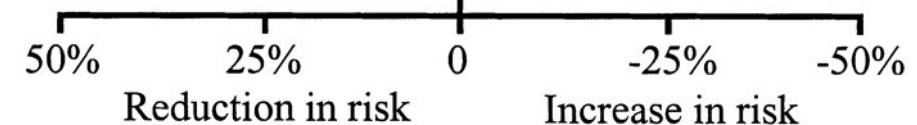


24% (16 – 31%)

Overall



30% (26 – 32%)

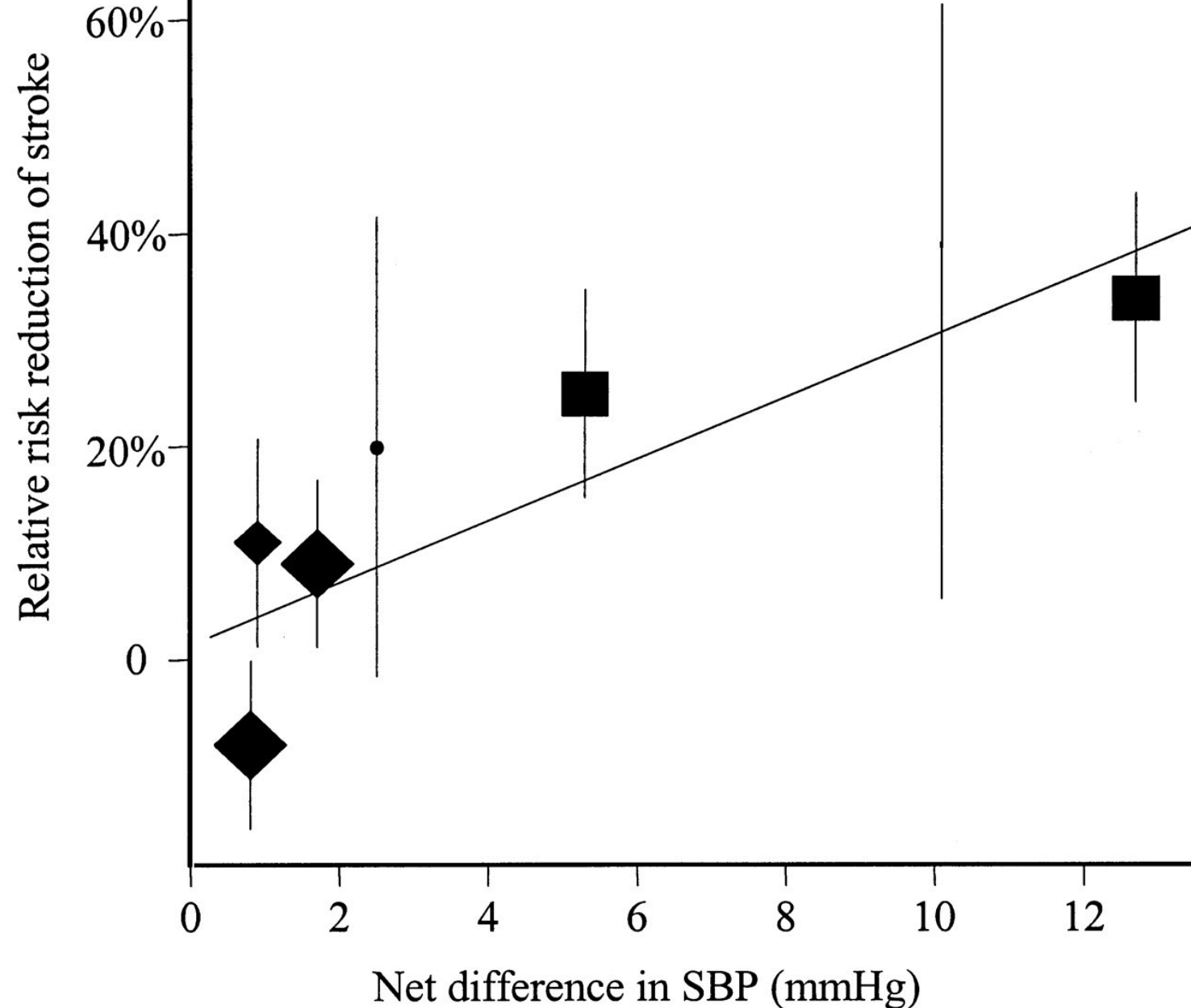


RCTs comparing
antihypertensive drugs
with a placebo (or no
treatment) by subgroup

Blood Pressure and Stroke

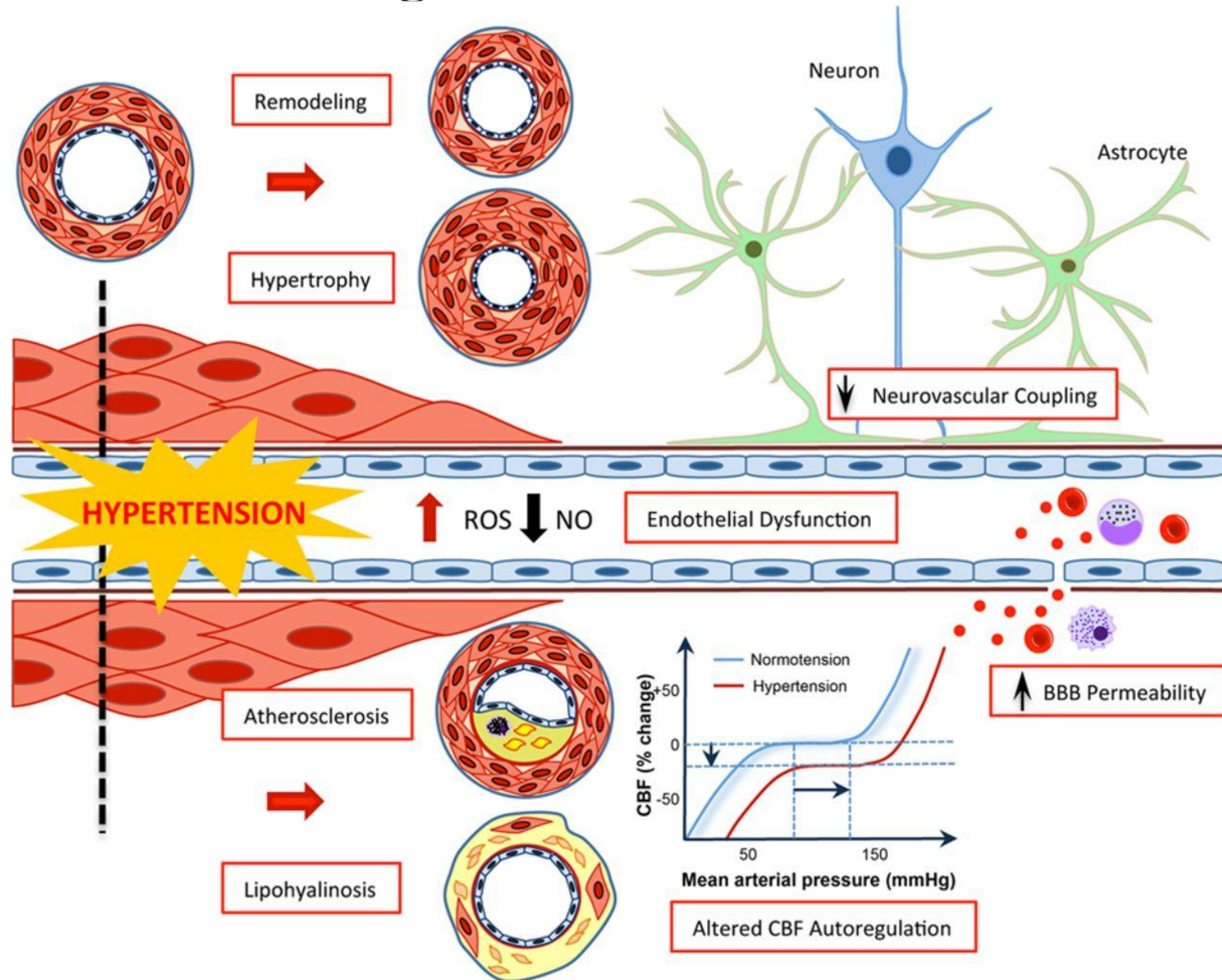
An Overview of Published Reviews

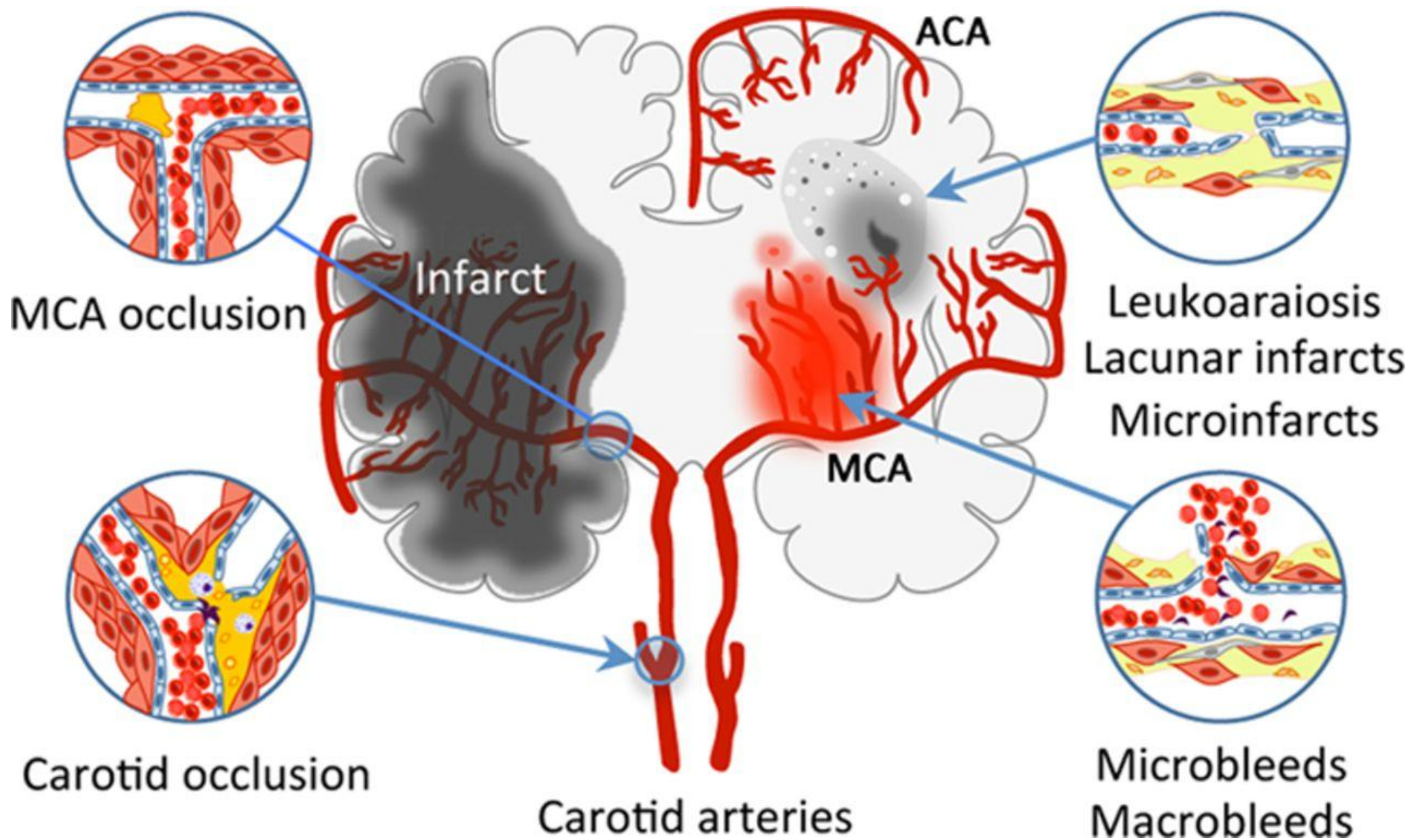
Net **reduction in SBP** and
relative risk
reduction in stroke in
RCTs of BP lowering



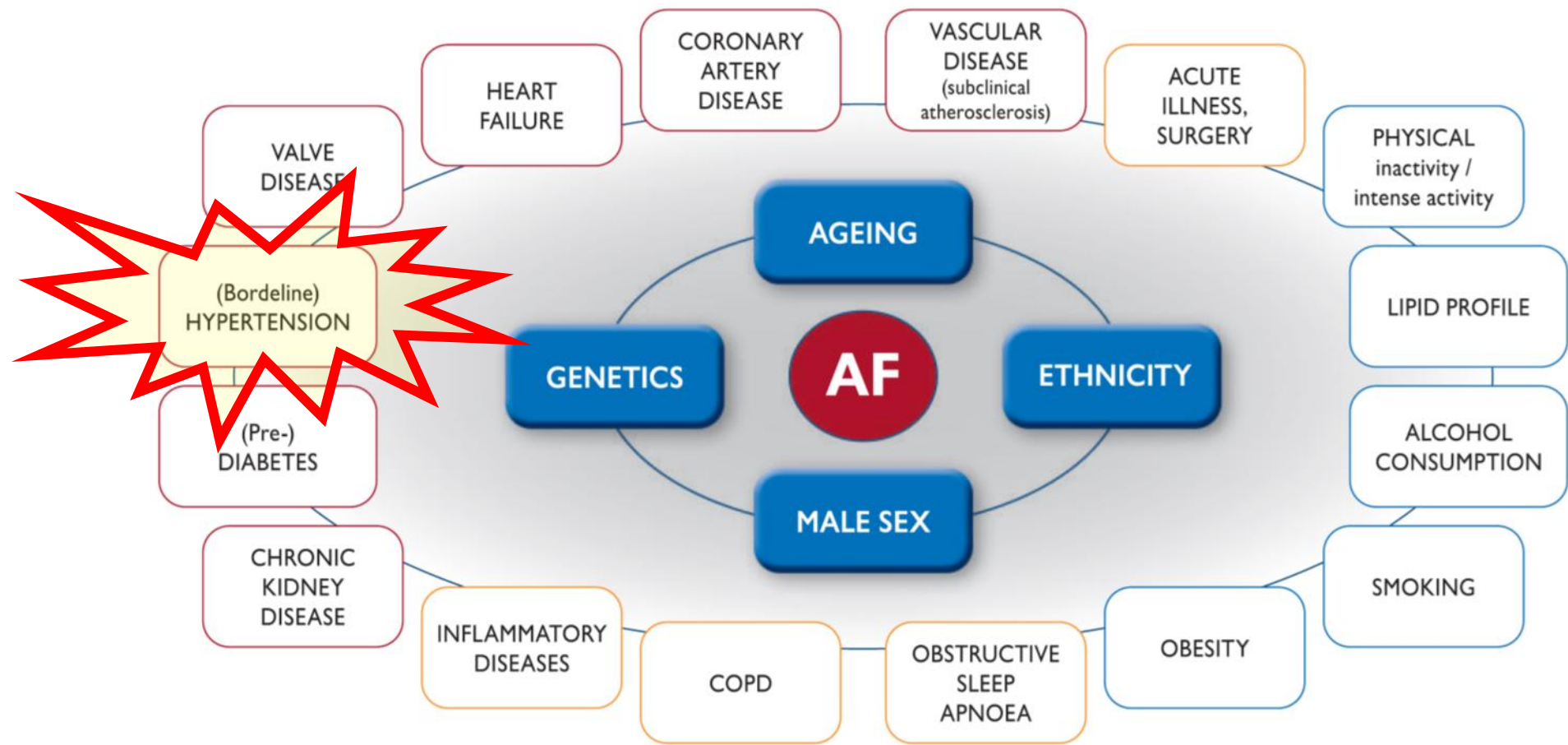
Hypertension

A Harbinger of Stroke and Dementia





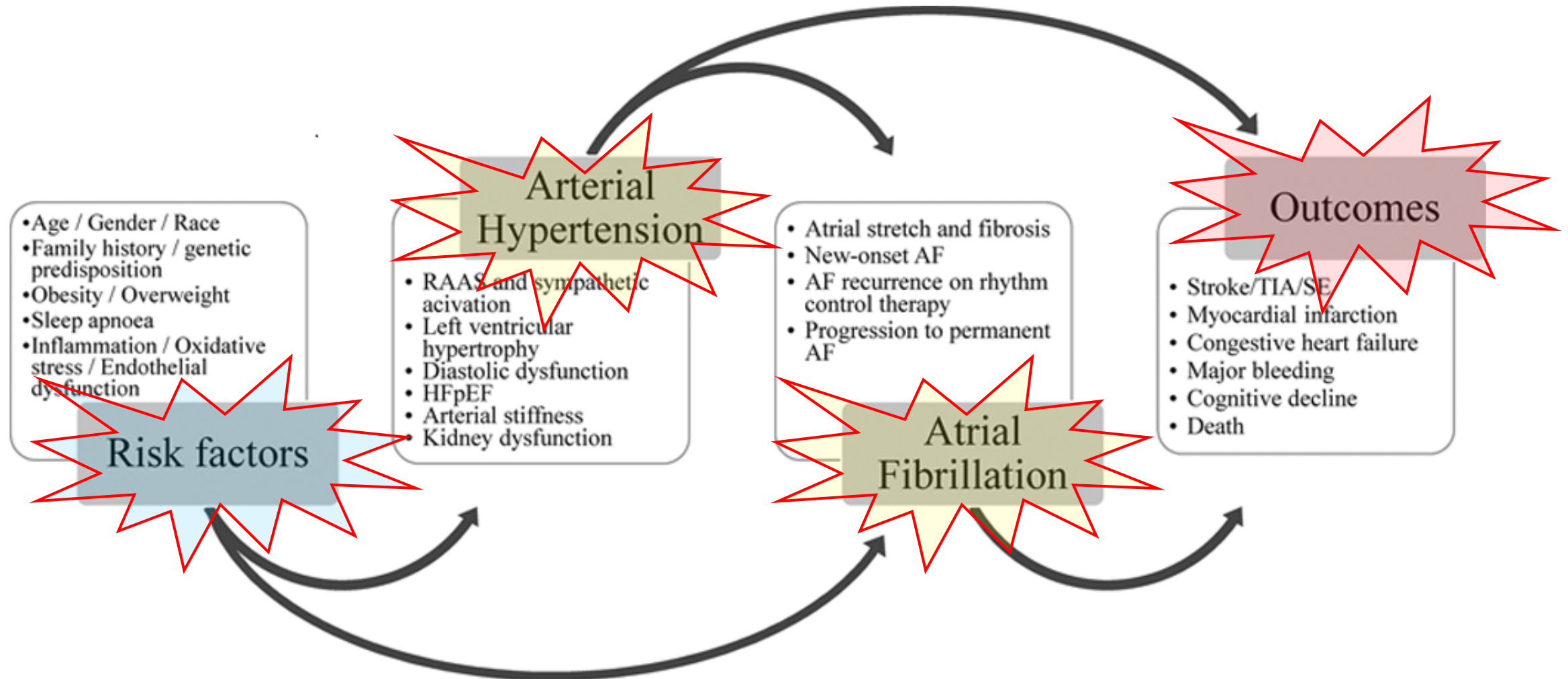
Summary of risk factors for incident AF



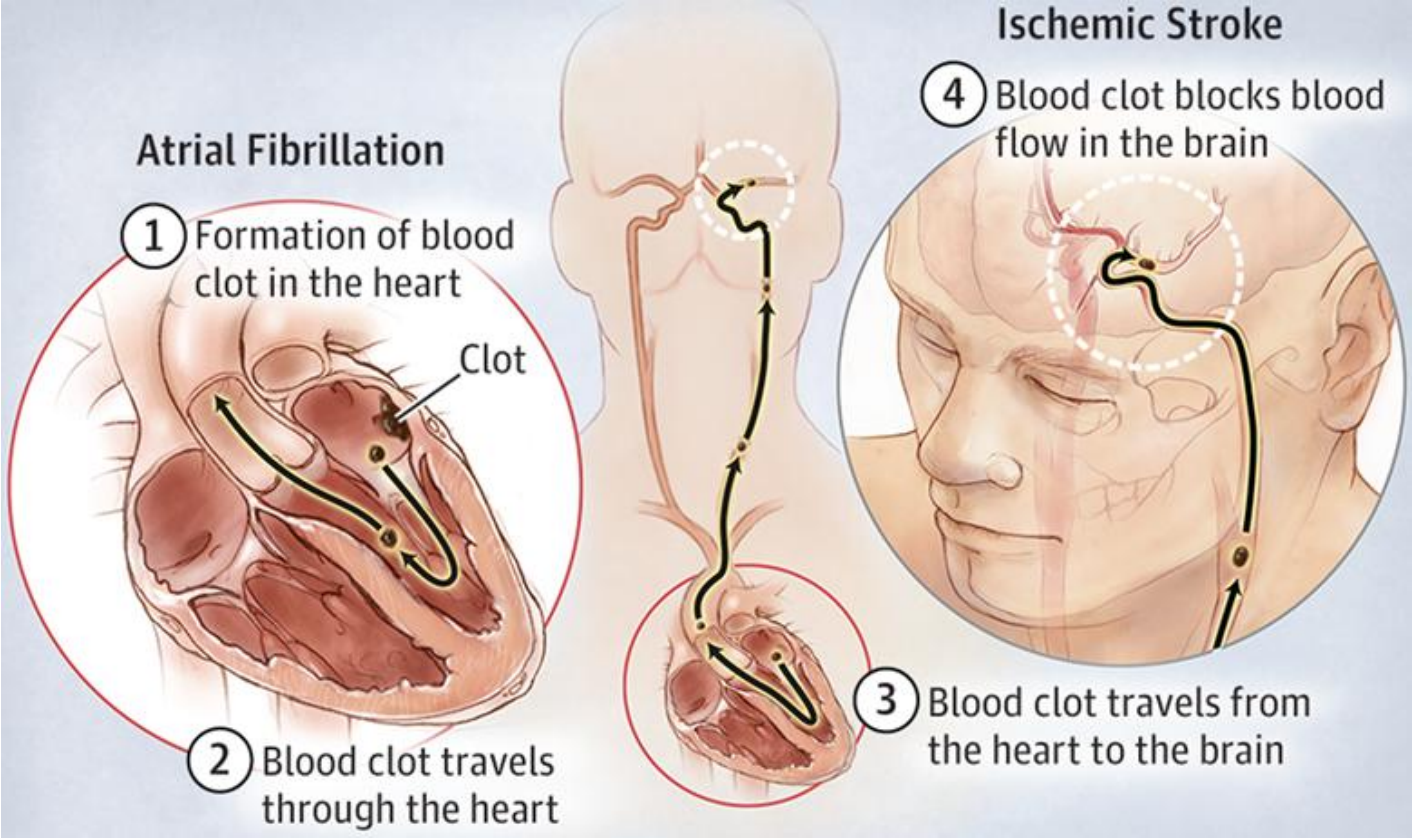
*Hypertension is the most common aetiological factor associated with the development of AF, and patients with hypertension have a **1.7-fold higher risk** of developing AF compared with normotensives*

Atrial Fibrillation and Hypertension

Hypertension and atrial fibrillation axis in the cardiovascular disease continuum

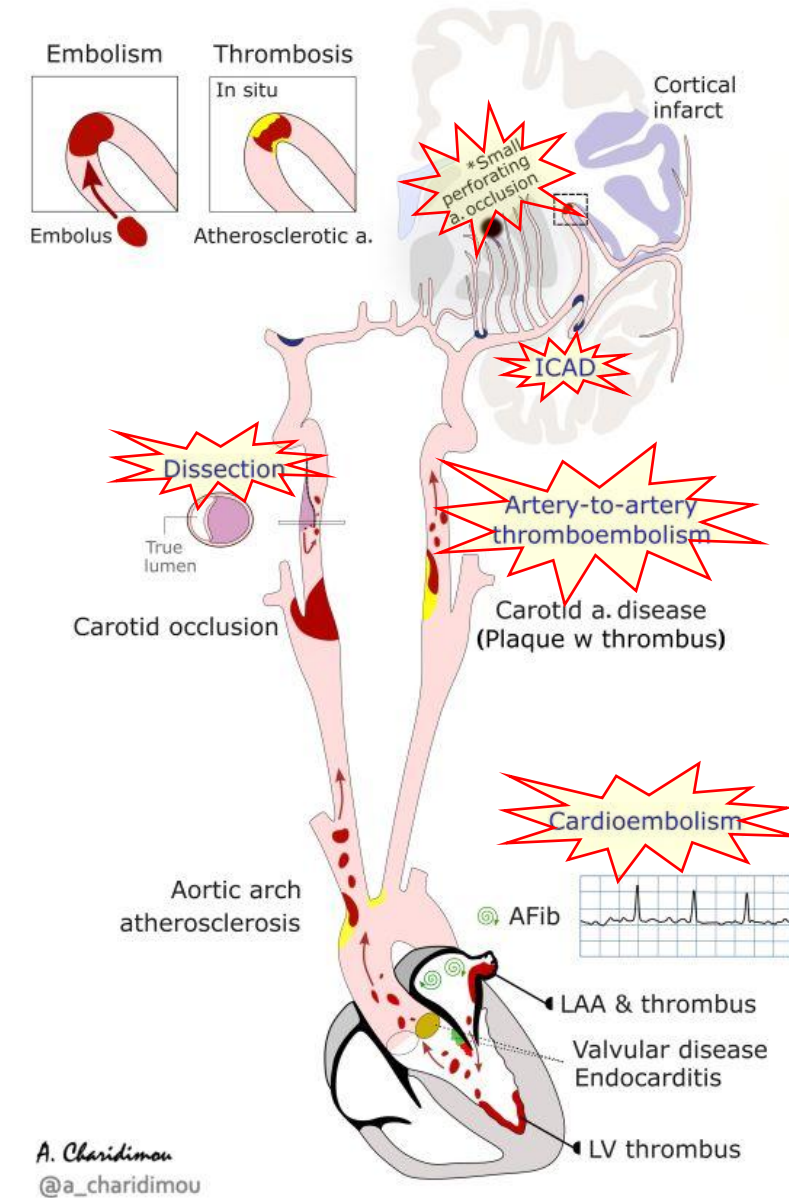
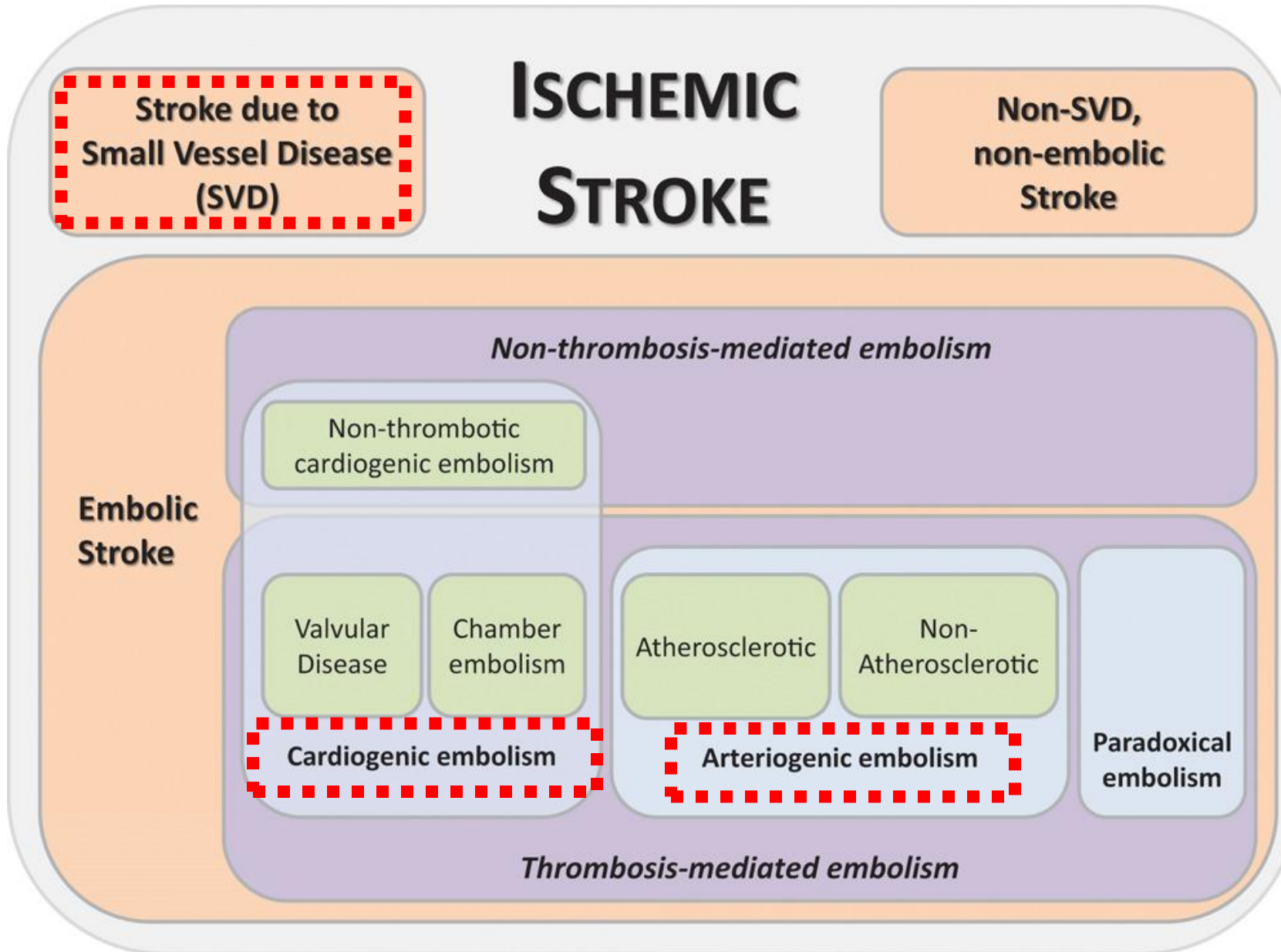


2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)



CHA ₂ DS ₂ -VASc score		Points awarded
Risk factors and definitions		
C	Congestive heart failure Clinical HF, or objective evidence of moderate to severe LV dysfunction, or HCM	1
H	Hypertension or on antihypertensive therapy	1
A	Age 75 years or older	2
D	Diabetes mellitus Treatment with oral hypoglycaemic drugs and/or insulin or fasting blood glucose >125 mg/dL (7 mmol/L)	1
S	Stroke Previous stroke, TIA, or thromboembolism	2
V	Vascular disease Angiographically significant CAD, previous myocardial infarction, PAD, or aortic plaque	1
A	Age 65 – 74 years	1
Sc	Sex category (female)	1
Maximum score		9

Ischemic stroke is an etiologically heterogeneous syndrome



Summary of office blood pressure thresholds for treatment

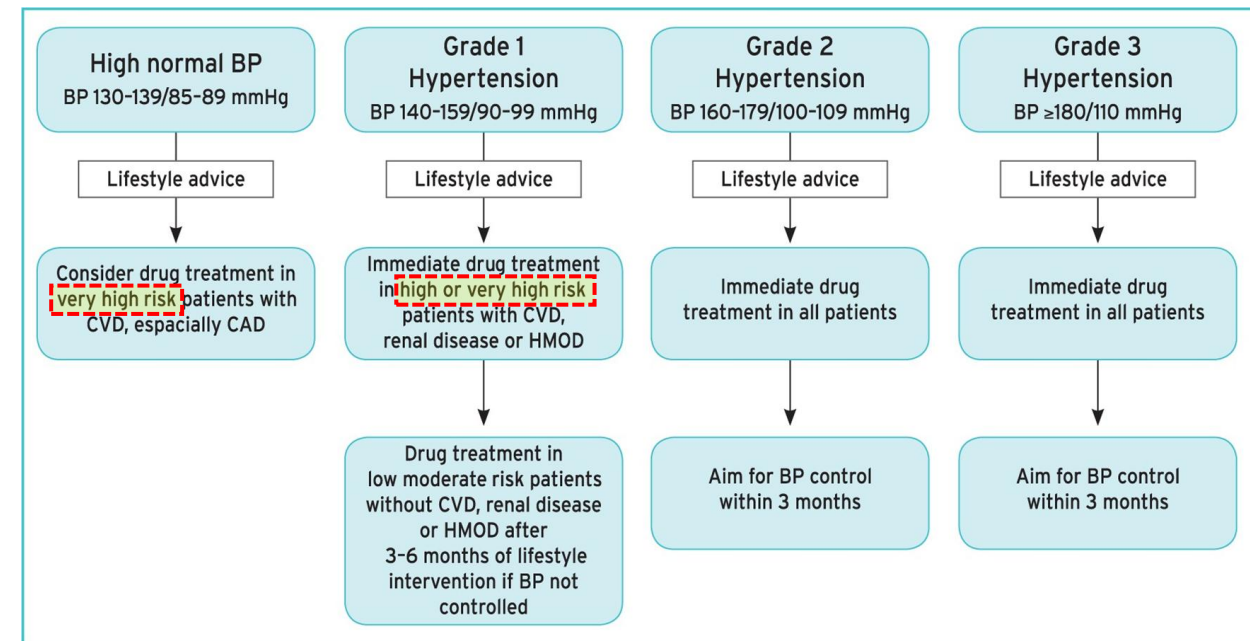
Age group	Office SBP treatment threshold (mmHg)					Office DBP treatment threshold (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke/TIA	
18 - 65 years	≥140	≥140	≥140	≥140 ^a	≥140 ^a	≥90
65 - 79 years	≥140	≥140	≥140	≥140 ^a	≥140 ^a	≥90
≥80 years	≥160	≥160	≥160	≥160	≥160	≥90
Office DBP treatment threshold (mmHg)	≥90	≥90	≥90	≥90	≥90	

BP = blood pressure; CAD = coronary artery disease; CKD = chronic kidney disease; DBP = diastolic blood pressure; SBP = systolic blood pressure; TIA = transient ischaemic attack.

^aTreatment may be considered in these very high-risk patients with high-normal SBP (i.e. SBP 130–140 mmHg).

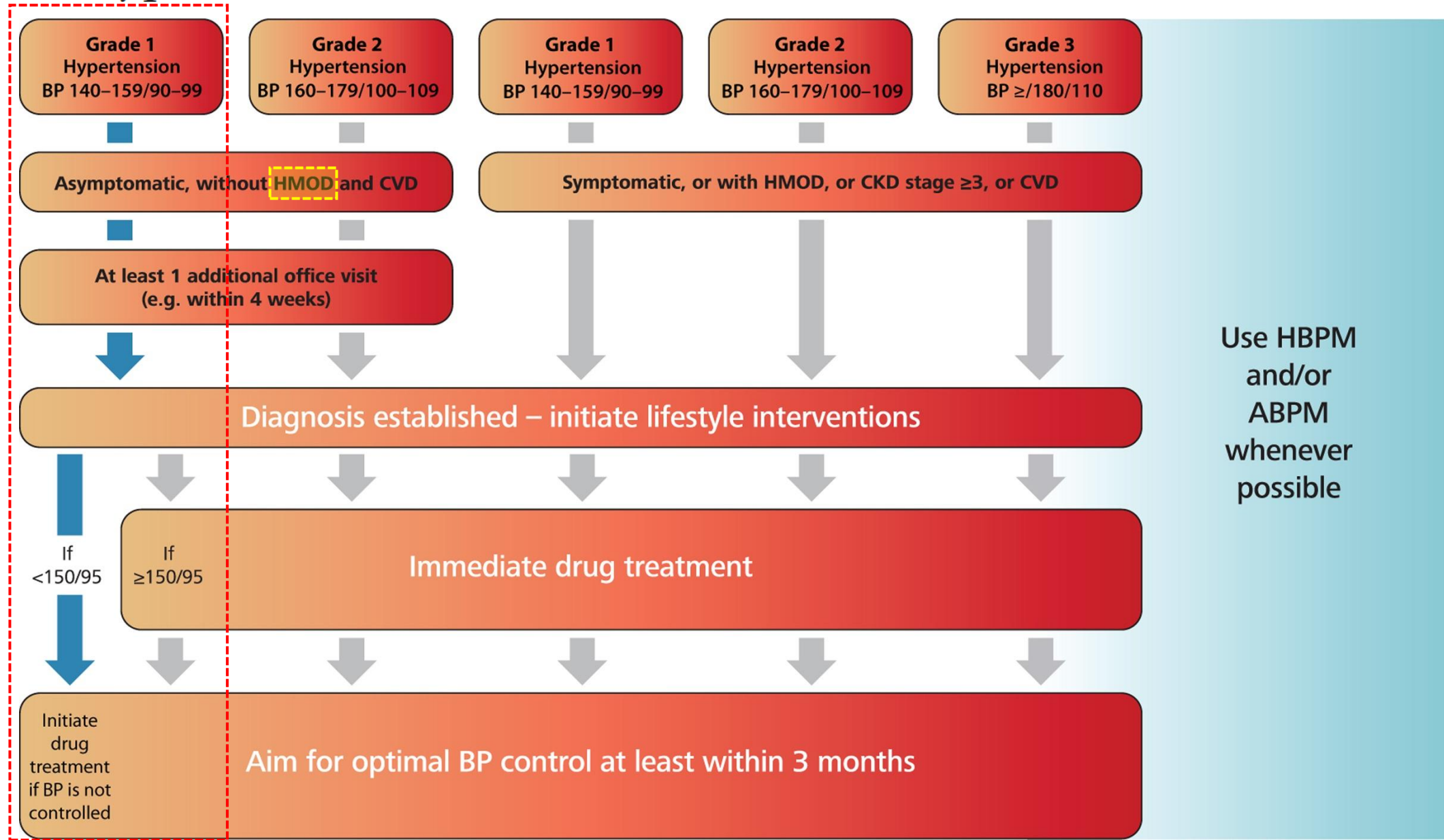
2018 ESC/ESH Guidelines for the management of arterial hypertension

Very high risk	People with any of the following: Documented CVD, either clinical or unequivocal on imaging. ● Clinical CVD includes acute myocardial infarction, acute coronary syndrome, coronary or other arterial revascularization, stroke, TIA, aortic aneurysm, and PAD ● Unequivocal documented CVD on imaging includes significant plaque (i.e. $\geq 50\%$ stenosis) on angiography or ultrasound; it does not include increase in carotid intima-media thickness ● Diabetes mellitus with target organ damage, e.g. proteinuria or a with a major risk factor such as grade 3 hypertension or hypercholesterolaemia ● Severe CKD (eGFR < 30 mL/min/1.73 m²) ● A calculated 10 year SCORE of $\geq 10\%$
High risk	People with any of the following: ● Marked elevation of a single risk factor, particularly cholesterol > 8 mmol/L (> 310 mg/dL), e.g. familial hypercholesterolaemia or grade 3 hypertension (BP $\geq 180/110$ mmHg) ● Most other people with diabetes mellitus (except some young people with type 1 diabetes mellitus and without major risk factors, who may be at moderate-risk) Hypertensive LVH Moderate CKD eGFR 30-59 mL/min/1.73 m²) A calculated 10 year SCORE of 5-10%
Moderate risk	People with: ● A calculated 10 year SCORE of ≥ 1 to $< 5\%$ ● Grade 2 hypertension ● Many middle-aged people belong to this category
Low risk	People with: ● A calculated 10 year SCORE of $< 1\%$



2023 ESH Guidelines for the management of arterial hypertension

Journal of Hypertension 2023, 41:1874–2071



Stroke Risk Factors, Genetics, and Prevention

	Nonmodifiable Risk Factors	Modifiable Risk Factors
Ischemic stroke	Age	Hypertension
	Sex	Current smoking
	Race/ethnicity	Waist-to-hip ratio
		Diet
		Physical inactivity
		Hyperlipidemia
		Diabetes mellitus
		Alcohol consumption
		Cardiac causes
		Apolipoprotein B to A1
	Genetics*	

Diabetes and Cardiovascular Disease

JAMA, May 11, 1979—Vol 241, No. 19

The Framingham Study

Adjusted and unadjusted relative risks of specified events in two years for diabetics vs nondiabetics aged 45 to 74 years at time of examination

Table 3.—Average Annual Age-Adjusted Incidence per 1,000 Specified Cardiovascular Events*

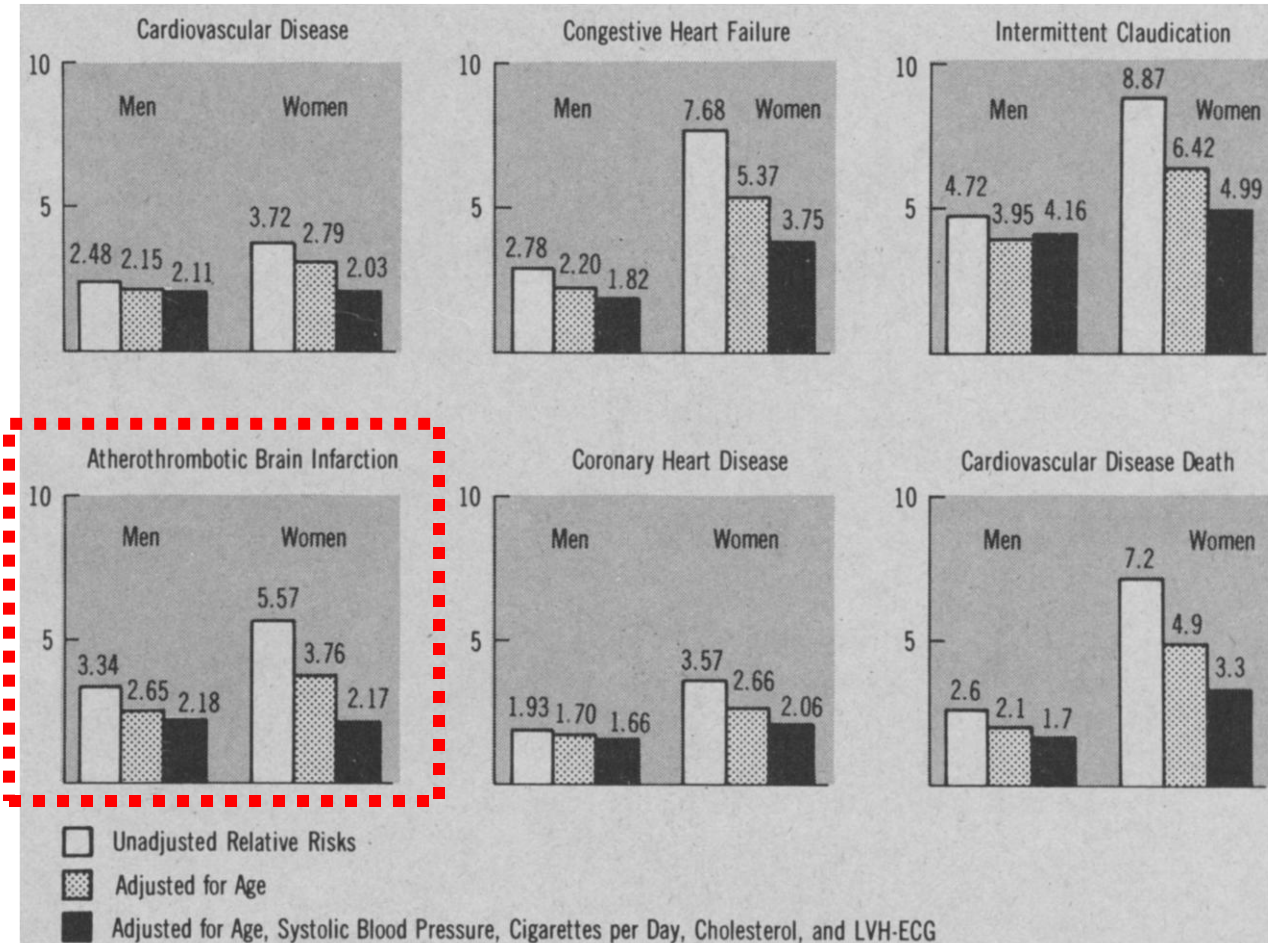
	Men		Women	
	Diabetic	Nondiabetic	Diabetic	Nondiabetic
Cardiovascular disease	39.1	19.1	27.2	10.2
Cardiovascular disease death	17.4	8.5	17.0	3.6
Congestive heart failure	7.6	3.5	11.4	2.2
Intermittent claudication	12.6	3.3	8.4	1.3
Atherothrombotic brain infarction	4.7	1.9	6.2	1.7
Coronary heart disease	24.8	14.9	17.8	6.9

*Framingham cohort including men and women aged 45 to 74 years

Table 2.—Prevalence of Major Risk Attributes*

	Age, yr			
	45-54	55-64	65-74	Total
Men				
No.	7,052	5,024	1,785	13,861
Prevalence of				
Diabetes	2.7	4.8	6.3	3.9
Definite hypertension	16.5	20.6	21.4	18.6
Borderline hypertension	29.8	32.1	37.7	31.7
Left ventricular hypertrophy (LVH)-ECG (definite)	0.9	1.8	2.8	1.5
Cigarette smoking	60.9	50.2	37.6	54.0
Women				
No.	9,081	7,115	2,732	18,928
Prevalence of				
Diabetes	1.8	3.7	5.9	3.1
Definite hypertension	14.2	25.7	33.9	21.4
Borderline hypertension	28.1	35.1	40.6	32.5
LVH-ECG (definite)	0.4	1.4	2.3	1.0
Cigarette smoking	43.9	30.4	19.1	35.2

*The Framingham study 20-year follow-up.



Prospective Associations of Fasting Insulin, Body Fat Distribution, and Diabetes With Risk of Ischemic Stroke

ATHEROSCLEROSIS RISK IN COMMUNITIES (ARIC) STUDY

Table 2—Relative risks of ischemic stroke in relation to diabetes estimated from multivariable proportional hazards models (ARIC)

Model and adjustment variables	Events (n)	Diabetes using fasting glucose			Diabetes using fasting glucose		
			≥140 mg/dl			≥126 mg/dl	
		RR†	95% CI	P value	RR†	95% CI	P value
1. Age, sex, race, ARIC community, smoking, and education	187	3.70	2.7–5.1	<0.0001	3.23	2.4–4.4	<0.0001
2. Model 1 plus systolic blood pressure and antihypertensives	183	2.96	2.1–4.1	<0.0001	2.56	1.8–3.5	<0.0001
3. Model 2 plus HDL and LDL cholesterol	176	2.58	1.8–3.7	<0.0001	2.21	1.6–3.1	<0.0001
4. Model 3 plus von Willebrand factor	175	2.26	1.6–3.2	<0.0001	1.94	1.4–2.8	0.0002
5. Model 4 plus waist-to-hip ratio	175	2.22	1.5–3.2	<0.0001	1.90	1.3–2.7	0.0004

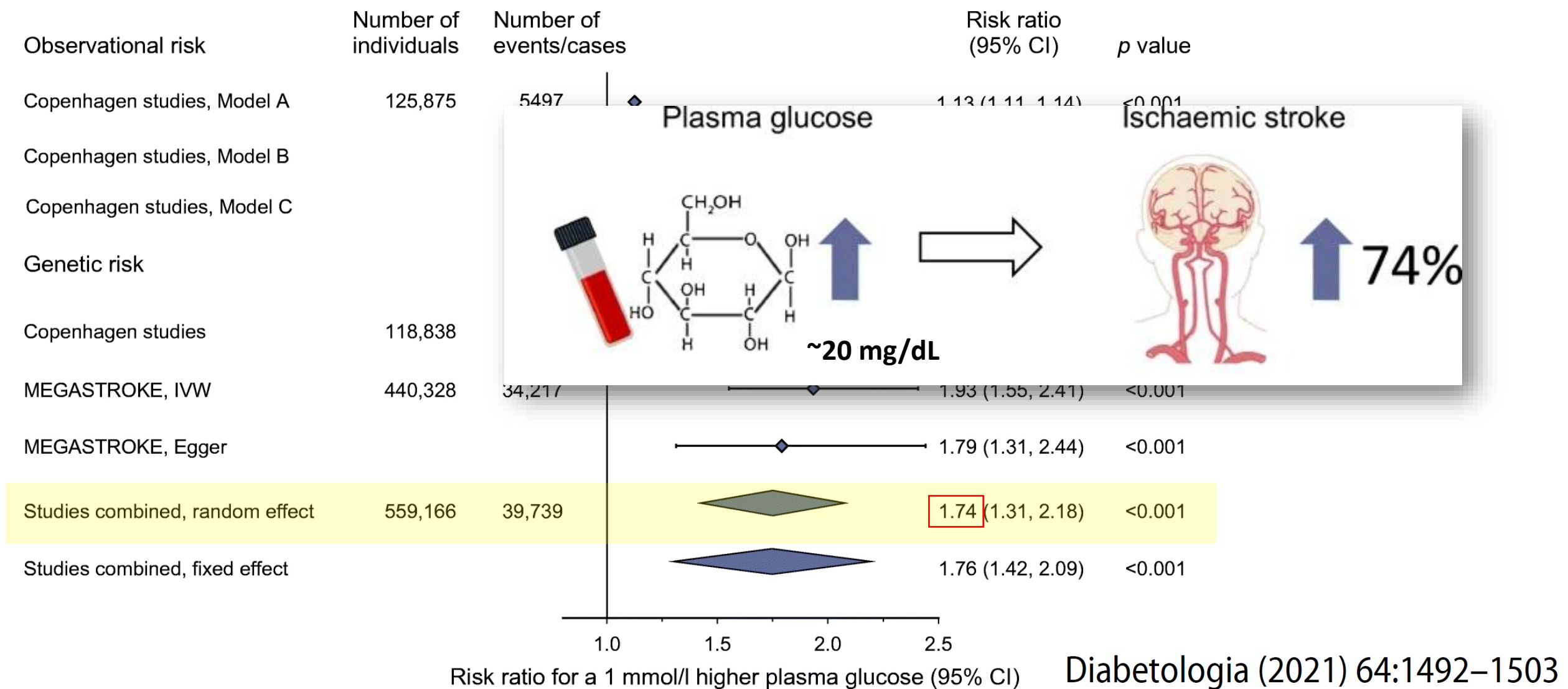
Also included as diabetes: nonfasting glucose ≥200 mg/dl, physician diagnosis of diabetes, or use of hypoglycemic medication. †The reference group is subjects without diabetes. RR, relative risk.

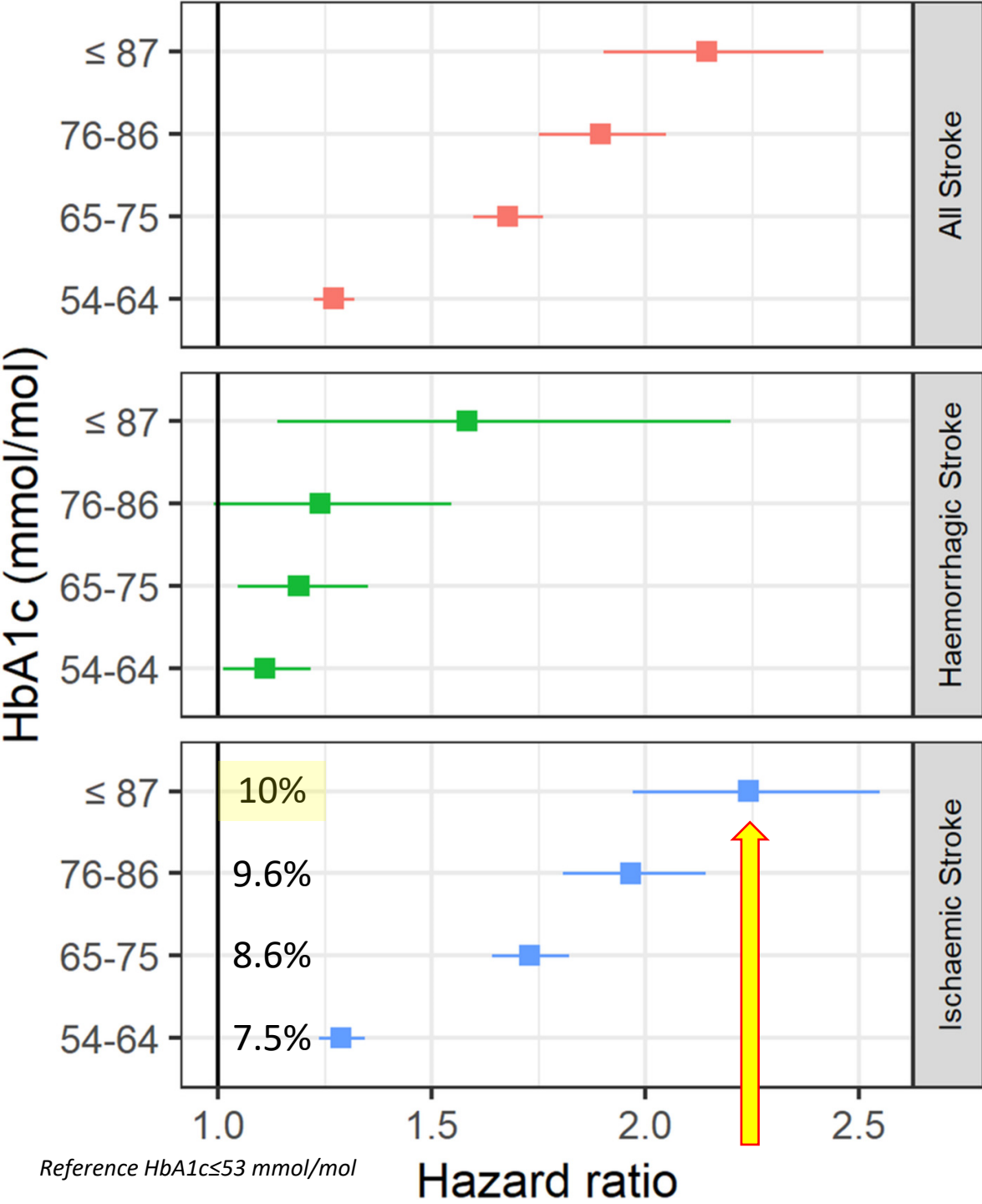
The association of diabetes with ischemic stroke was strong, with relative risks of 2.0–4.0

Diabetes Care 22:1077–1083, 1999

Impact of high glucose levels and glucose lowering on risk of ischaemic stroke: a Mendelian randomisation study and meta-analysis

Risk of ischaemic stroke for a 1 mmol/l higher observationally and causal, genetically determined plasma glucose concentration.





Risk of first stroke in people with type 2 diabetes and its relation to glycaemic control: A nationwide observational study

- All Stroke
- Haemorrhagic Stroke
- Ischaemic Stroke

The risk of a first **stroke** with every 10mmol/mol (1%) increase in **HbA1c** category to a **more-than-double risk** (adjusted HR 2.14, 95% CI 1.90-2.42) in people with the highest HbA1c levels (10%) compared with the reference group (7%)

Outcome of a first stroke divided into ischaemic and haemorrhagic strokes in 406,271 people with type 2 diabetes in Sweden, from 1998-2015, according to glycaemic control

**LONG-TERM COMPLICATIONS OF
DIABETES MELLITUS**

THE NEW ENGLAND JOURNAL OF MEDICINE June 10, 1993

ABC of arterial and venous disease

Vascular complications of diabetes

BMJ VOLUME 320 15 APRIL 2000

Vascular complications of diabetes

Microvascular

Retinopathy

Nephropathy

Neuropathy

Macrovascular

Ischaemic heart disease

Stroke

Peripheral vascular disease

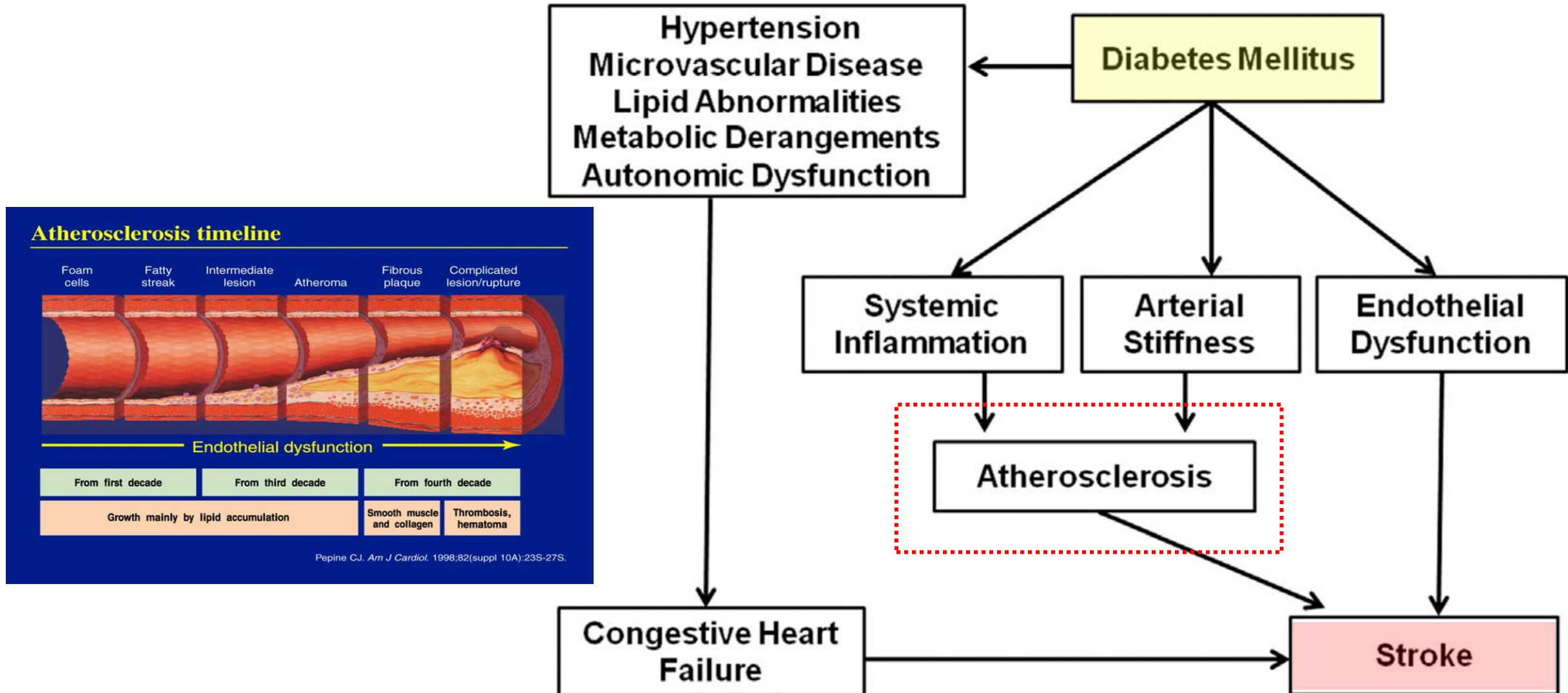
Stroke patterns, etiology, and prognosis in patients with diabetes mellitus

Etiology	Nondiabetic, n = 3,118	Diabetic, n = 572	p	Total, n = 3,690
Large-artery disease, n (%)	966 (31)	240 (42)	<0.0001	1,206 (33)
Small-vessel disease, n (%)	468 (15)	160 (28)		628 (17)
Cardiogenic embolism, n (%)	716 (23)	80 (14)		796 (21)
Other, n (%)	531 (17)	63 (11)		594 (16)
Undetermined, n (%)	437 (14)	29 (5)		466 (13)

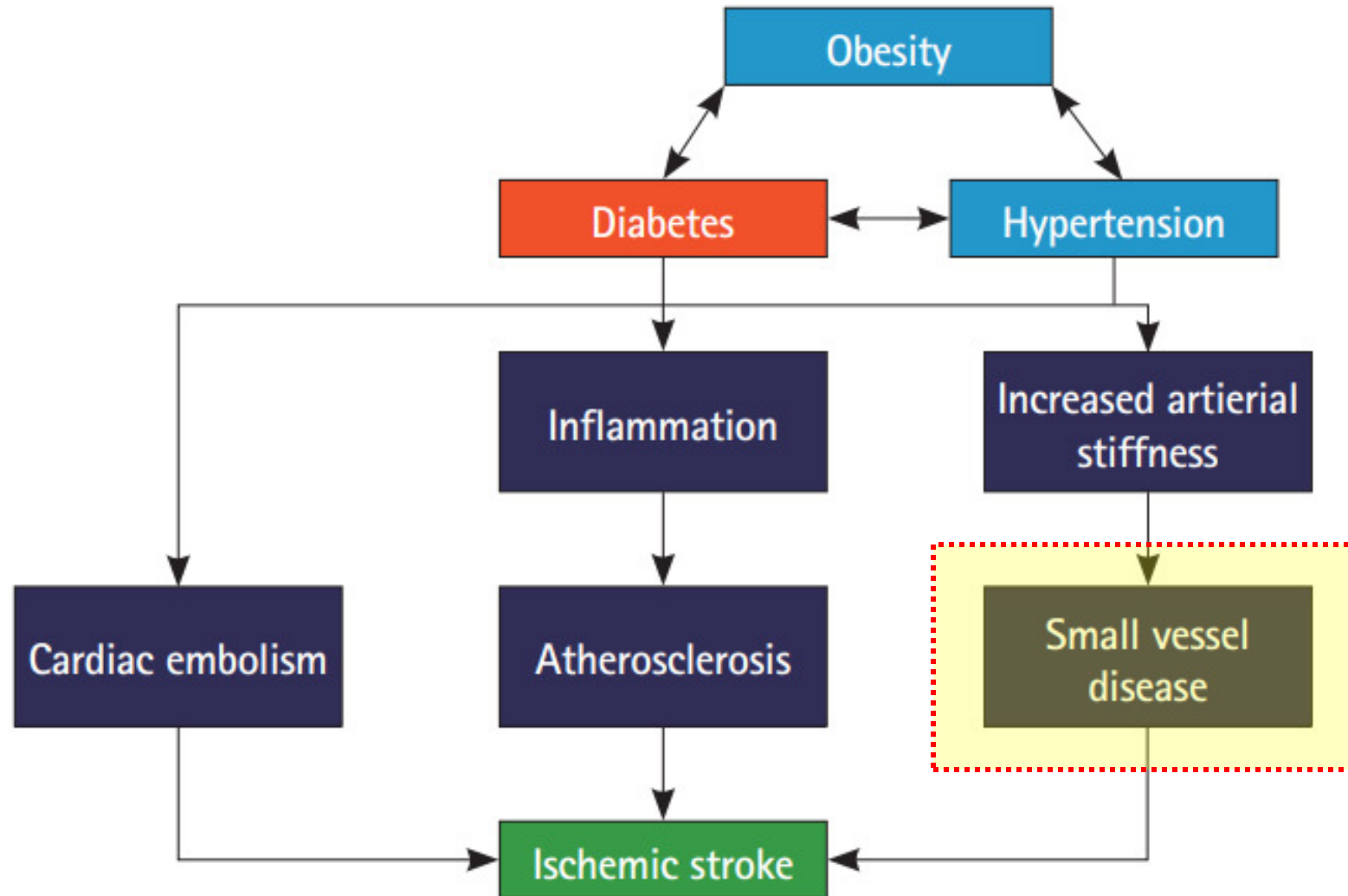
Table 5 Variables associated with small-vessel and large-artery disease and subgroup analysis according to hypertension and age (multiple logistic regression analysis)*

Variable	Small-vessel disease		Large-artery disease	
	OR (95% CI)	p	OR (95% CI)	p
Diabetes	1.78 (1.31–3.82)	0.012	2.02 (1.31–3.02)	0.002
Hypertension	4.12 (3.79–4.62)	0.0001	1.88 (1.29–2.33)	0.0001
Age	1.03 (1.004–1.07)	0.027	1.12 (0.99–1.17)	0.057

Diabetes and Stroke: Epidemiology, Pathophysiology, Pharmaceuticals and Outcomes



Diabetes and Stroke: What Are the Connections?



Risk factors for lacunar infarction syndromes

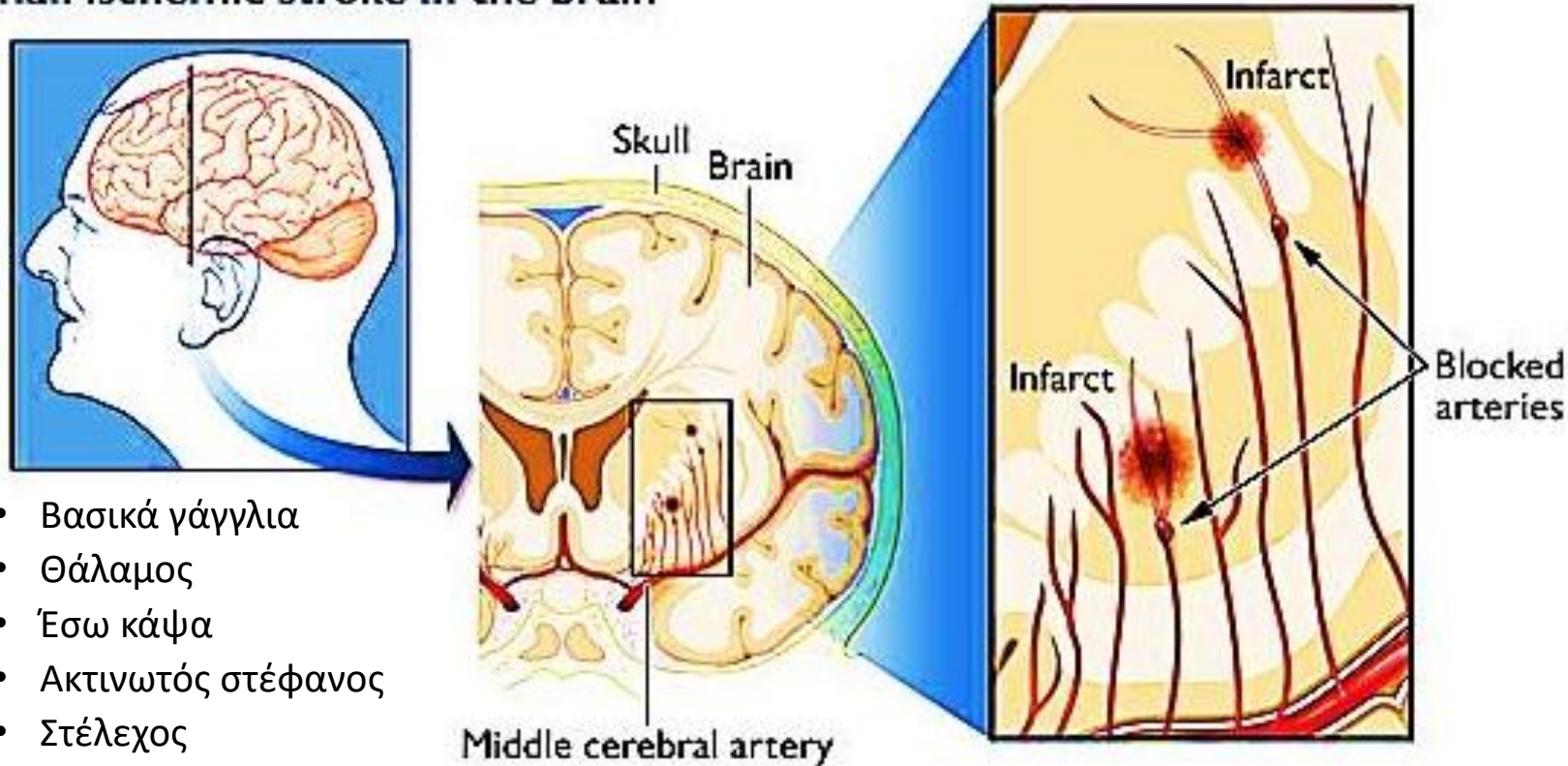
Table 2. Risk of lacunar infarction associated with the examined risk factors estimated by conditional logistic regression

Risk factors	Cases		Controls		Univariate analysis		Multivariate analysis	
	No.	(%)	No.	(%)	OR	(95% CI)	OR	(95% CI)
Hypertension								
No	63	(31)	137	(67)	1.0		1.0	
Yes	140	(69)	66	(33)	8.4	(4.4, 16.2)	8.9	(4.2, 18.8)
High cholesterol								
No	150	(78)	151	(78)	1.0		1.0	
Yes	42	(22)	43	(22)	0.9	(0.5, 1.5)	0.9	(0.5, 1.8)
Heart disease								
No	150	(75)	166	(83)	1.0		1.0	
Yes	51	(25)	34	(17)	1.7	(1.0, 2.8)	1.0	(0.5, 1.9)
Diabetes mellitus								
No	167	(82)	190	(94)	1.0		1.0	
Yes	36	(18)	13	(6)	3.1	(1.6, 6.1)	2.3	(1.0, 5.5)
Alcohol drinking								
Never users	51	(25)	58	(29)	1.0		1.0	
Ever users	152	(75)	145	(71)	1.3	(0.8, 2.2)	1.2	(0.6, 2.6)
Oral contraceptives								
Never users	67	(83)	68	(84)	1.0		1.0	
Ever users	14	(17)	13	(16)	1.1	(0.4, 3.2)	3.4	(0.4, 28.4)
Cigarette smoking								
Never smokers	62	(30)	93	(46)	1.0		1.0	
Ex-smokers	50	(25)	69	(34)	1.1	(0.6, 1.9)	1.5	(0.7, 3.1)
Current smokers	91	(45)	41	(20)	5.4	(2.7, 10.4)	6.6	(2.9, 14.8)
Physical exercise								
Never or rarely	151	(74)	122	(60)	1.0		1.0	
1-2 times per week	28	(14)	27	(13)	0.6	(0.3, 1.2)	1.0	(0.4, 2.3)
≥3 times per week	24	(12)	54	(27)	0.2	(0.1, 0.5)	0.3	(0.1, 0.7)

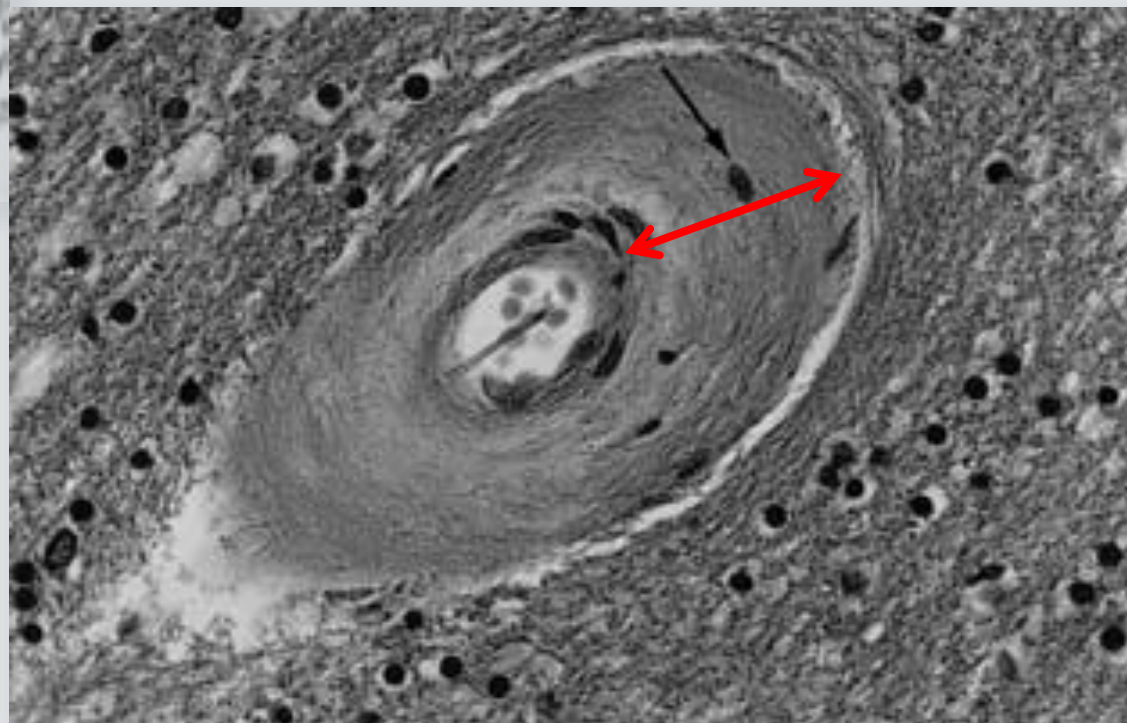
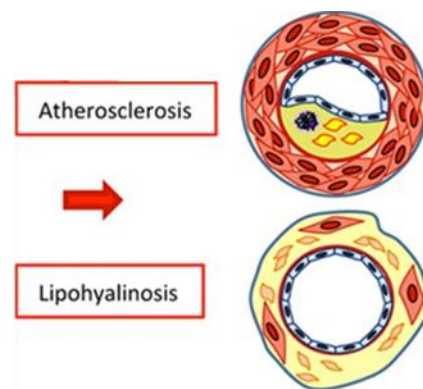
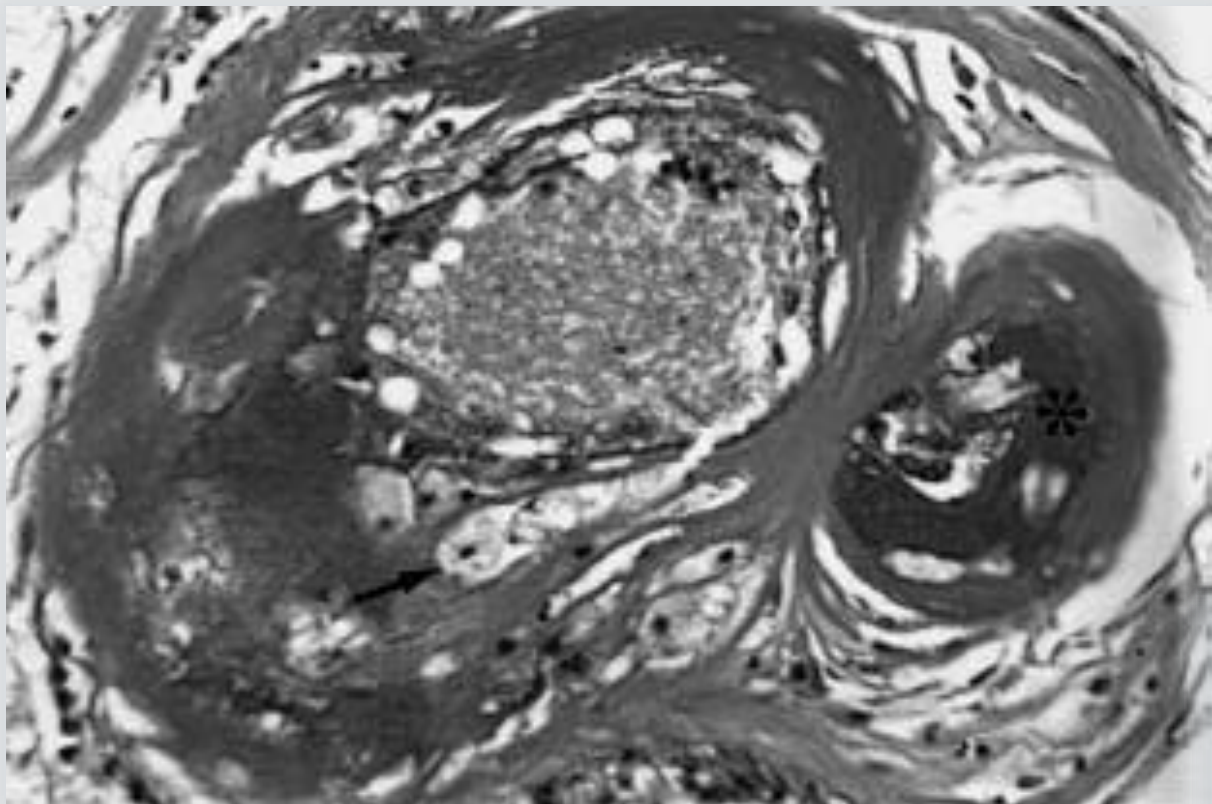
Νόσος Μικρών Αγγείων Κενοχωριώδη → Lacunar

«Μικρά έμφρακτα (<15mm) της υποφλοιώδους περιοχής λόγω απόφραξης μεμονωμένων μικρών διατιτραίνοντων κλάδων»

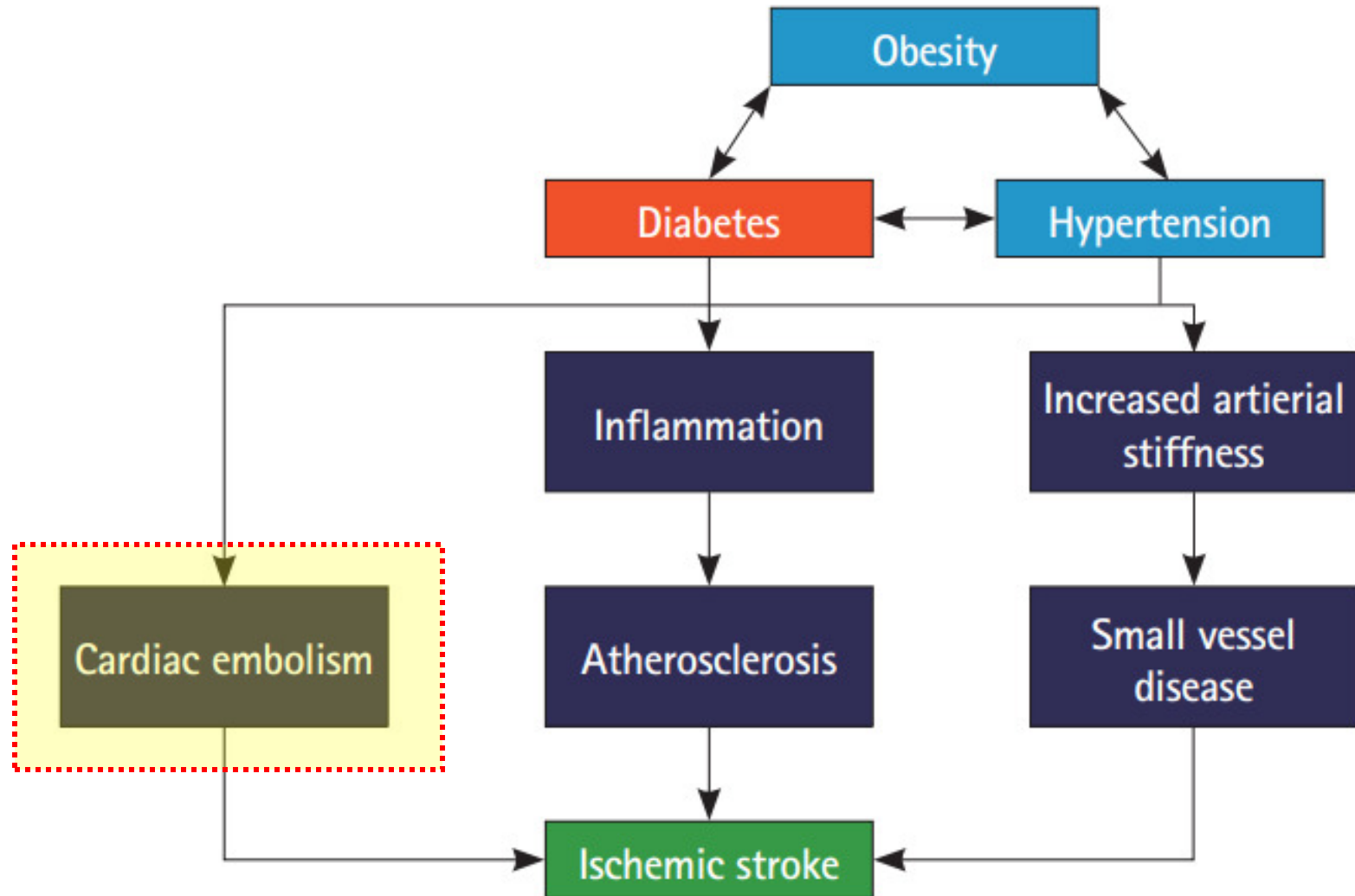
Small ischemic stroke in the brain



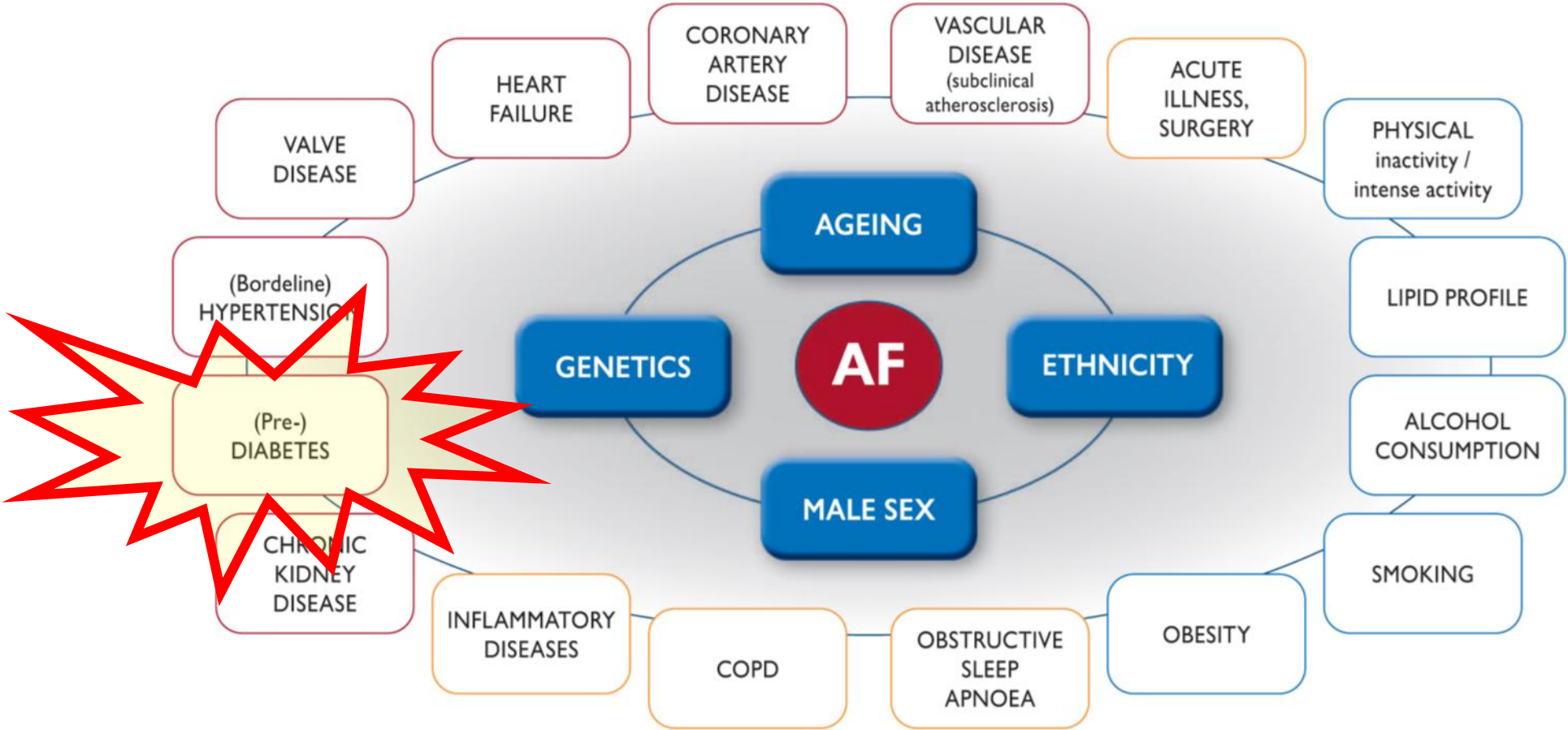
Ann Neurol 2001;50:208–215



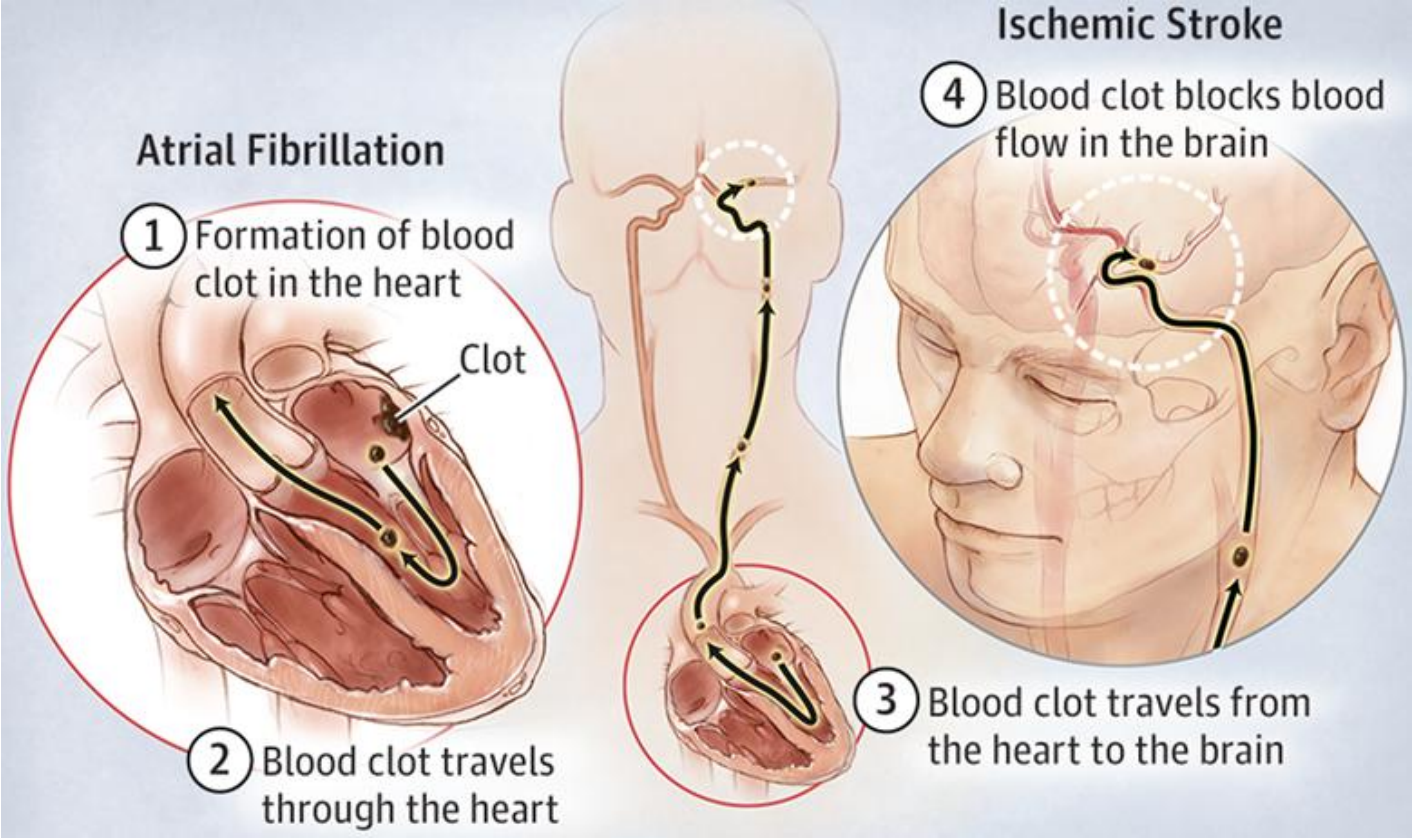
Diabetes and Stroke: What Are the Connections?



Summary of risk factors for incident AF



2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)



CHA ₂ DS ₂ -VASc score		Points awarded
Risk factors and definitions		
C	Congestive heart failure Clinical HF, or objective evidence of moderate to severe LV dysfunction, or HCM	1
H	Hypertension or on antihypertensive therapy	1
A	Age 75 years or older	2
D	Diabetes mellitus Treatment with oral hypoglycaemic drugs and/or insulin or fasting blood glucose >125 mg/dL (7 mmol/L)	1
S	Stroke Previous stroke, TIA, or thromboembolism	2
V	Vascular disease Angiographically significant CAD, previous myocardial infarction, PAD, or aortic plaque	1
A	Age 65 – 74 years	1
Sc	Sex category (female)	1
Maximum score		9

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

Very high CV risk

Patients with T2DM with:

- Clinically established ASCVD or
- Severe TOD or
- 10-year CVD risk $\geq 20\%$ using SCORE2-Diabetes

High CV risk

Patients with T2DM not fulfilling the very high-risk criteria and a:

- 10-year CVD risk 10 to $<20\%$ using SCORE2-Diabetes

Moderate CV risk

Patients with T2DM not fulfilling the very high-risk criteria and a:

- 10-year CVD risk 5 to $<10\%$ using SCORE2-Diabetes

Low CV risk

Patients with T2DM not fulfilling the very high-risk criteria and a:

- 10-year CVD risk $<5\%$ using SCORE2-Diabetes

© ESC 2023

SCORE2-Diabetes risk

Risk predictor	Risk predictor category	Age 40–44	Age 45–49	Age 50–54	Age 55–59	Age 60–64	Age 65–69
Age of diabetes diagnosis (years)	30–34	3	3	3	3	3	3
	35–39	2	2	2	2	2	2
	40–44	1	1	1	1	1	1
	45–49	N/A	0	0	0	0	0
	50–54	N/A	N/A	0	0	0	0
	55–59	N/A	N/A	N/A	–1	–1	–1
	60–64	N/A	N/A	N/A	N/A	–2	–2
	65–69	N/A	N/A	N/A	N/A	N/A	–3
Smoking status	Non-smoker	–9	–5	0	4	9	13
	Current smoker	–2	2	6	9	13	17
Systolic blood pressure (mmHg)	100–119	–1	–1	–1	–1	–1	0
	120–139	1	1	1	1	1	0
	140–159	3	3	3	2	2	1
	≥ 160	6	5	4	4	3	2
Total cholesterol (mmol/L)	3.0–3.9	–4	–4	–3	–3	–3	–2
	4.0–4.9	–3	–2	–2	–2	–2	–1
	5.0–5.9	–1	–1	–1	–1	–1	0
	6.0–6.9	1	1	1	1	1	0
	≥ 7.0	3	3	2	2	2	1
HDL cholesterol (mmol/L)	0.5–0.9	2	1	1	1	1	1
	1.0–1.4	0	0	0	0	0	0
	≥ 1.5	–1	–1	–1	–1	–1	–1
HbA1c (mmol/mol)	30–39	1	1	0	0	0	0
	40–49	2	2	2	2	1	1
	50–59	4	3	3	3	2	2
	60–69	5	5	4	4	3	3
	≥ 70	7	6	5	5	4	4
eGFR (mL/min/1.73 m ²)	30–44	8	7	6	6	5	4
	45–59	4	4	3	3	3	2
	60–89	1	1	1	1	1	1
	≥ 90	–1	–1	–1	0	0	0

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; SCORE2-Diabetes, type 2 diabetes-specific 10-year CVD risk score; T2DM, type 2 diabetes mellitus; TOD, target-organ damage; UACR, urinary albumin-to-creatinine ratio.

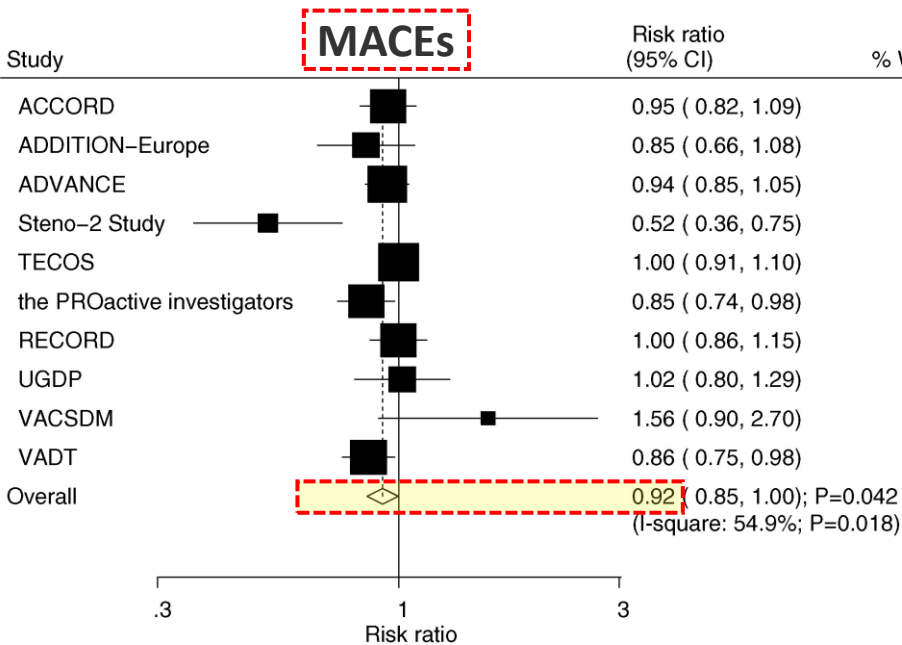
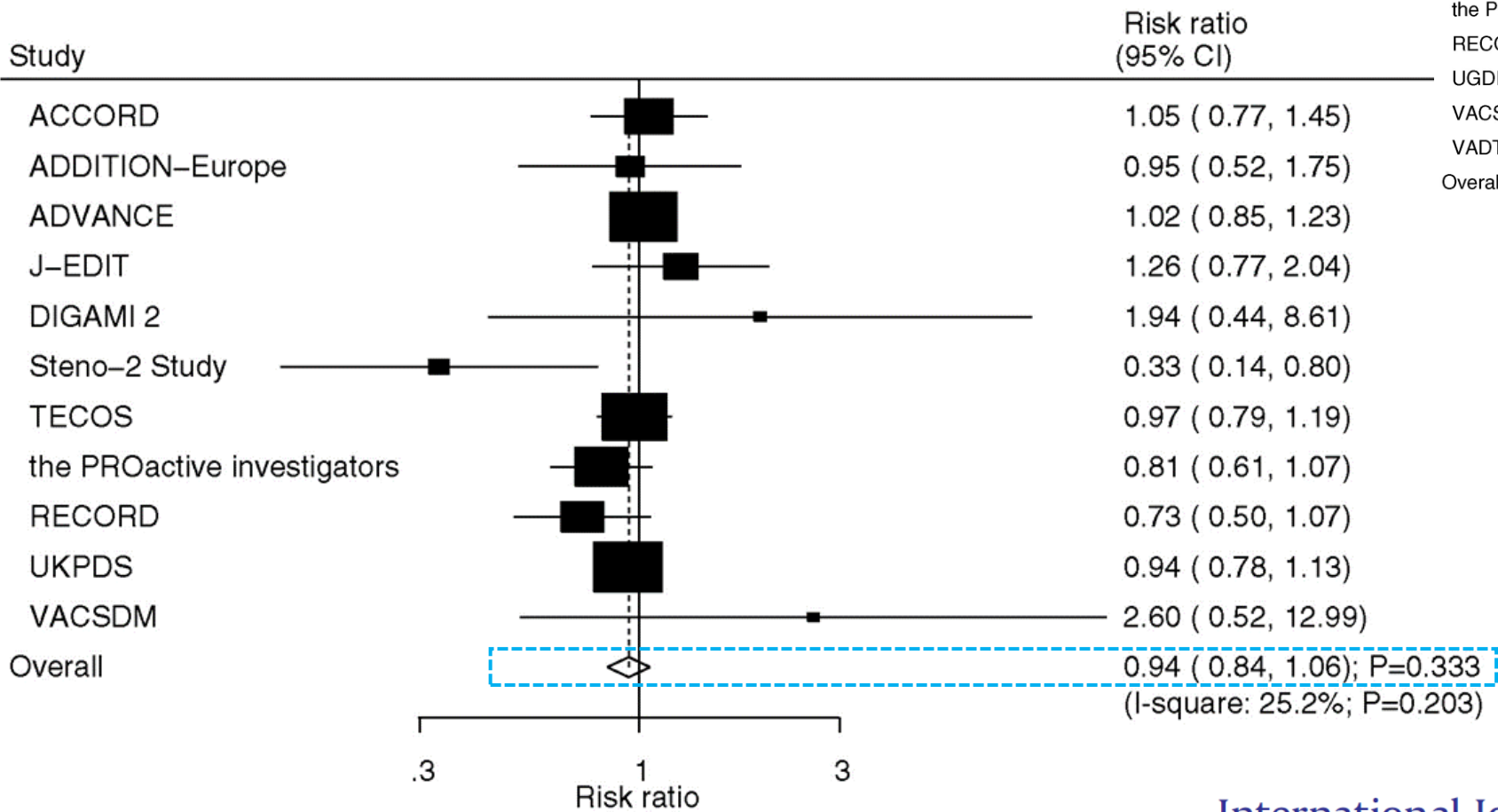
Severe TOD defined as eGFR <45 mL/min/1.73 m² irrespective of albuminuria; or eGFR 45–59 mL/min/1.73 m² and microalbuminuria (UACR 30–300 mg/g; stage A2); or proteinuria (UACR >300 mg/g; stage A3); or presence of microvascular disease in at least three different sites [e.g. microalbuminuria (stage A2) plus retinopathy plus neuropathy].^{43–45}

2019 ESC Guidelines on **diabetes**, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

Recommendations	Class ^a	Level ^b
It is recommended to apply tight glucose control, targeting a near-normal HbA1c (<7.0% or <53 mmol/mol), to decrease microvascular complications in individuals with DM. ^{145–149}	I	A
It is recommended that HbA1c targets are individualized according to the duration of DM, comorbidities, and age. ^{122,150}	I	C
Avoidance of hypoglycaemia is recommended. ^{136,139,140,151}	I	C
The use of structured self-monitoring of blood glucose and/or continuous glucose monitoring should be considered to facilitate optimal glycaemic control. ^{141–144}	IIa	A
An HbA1c target of <7.0% (or <53 mmol/mol) should be considered for the prevention of macrovascular complications in individuals with DM.	IIa	C

Effects of intensive glucose lowering in treatment of type 2 diabetes mellitus on cardiovascular outcomes: A meta-analysis of data from 58,160 patients in 13 randomized controlled trials

B. stroke



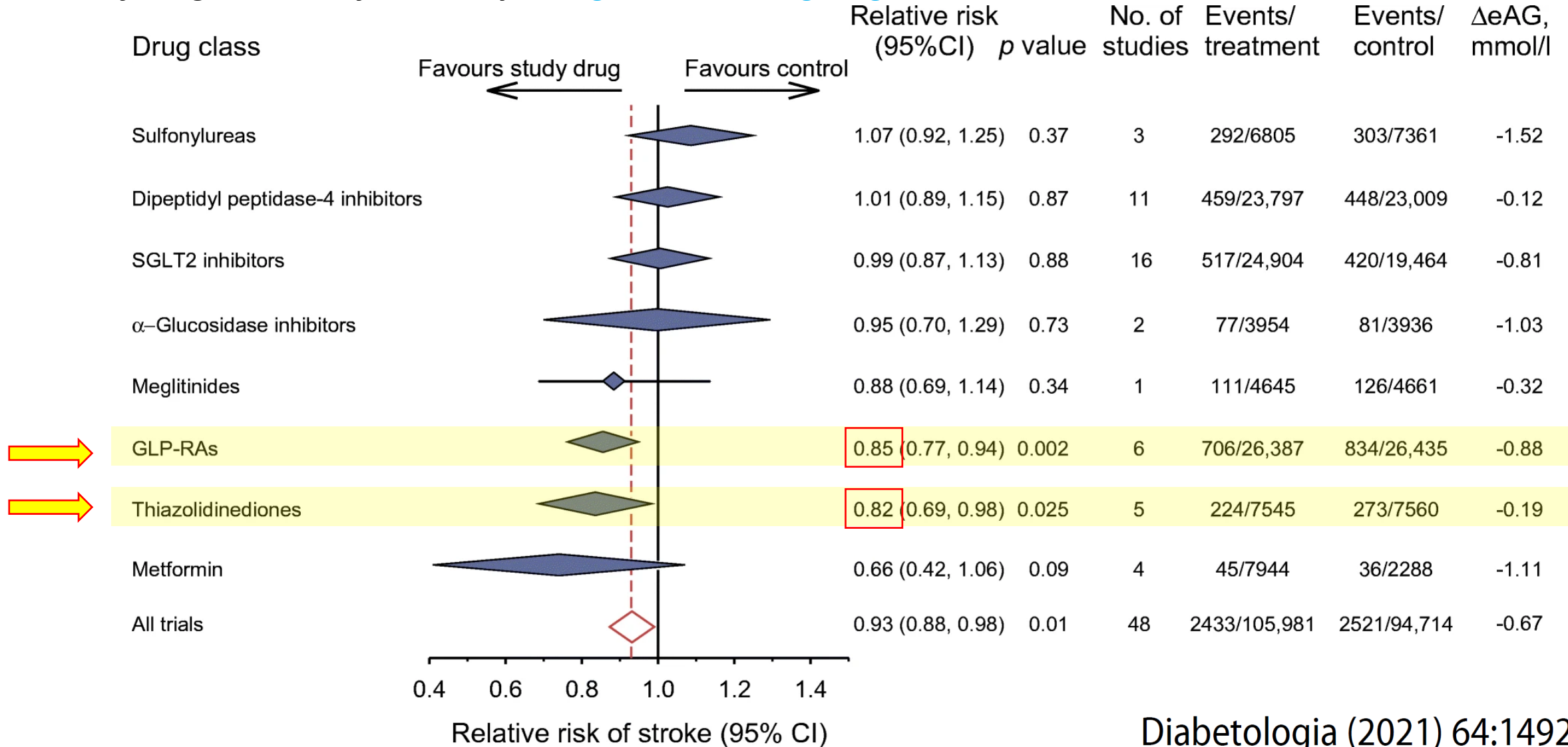
Conclusion

T2DM patients who received intensive glucose lowering therapy are associated with a reduced risk of MACEs and MI, whereas it has **no significant effect** on the risk of total mortality, cardiac death, **stroke**, and congestive heart failure.

These effects might differ when stratified by baseline characteristics in T2DM patients.

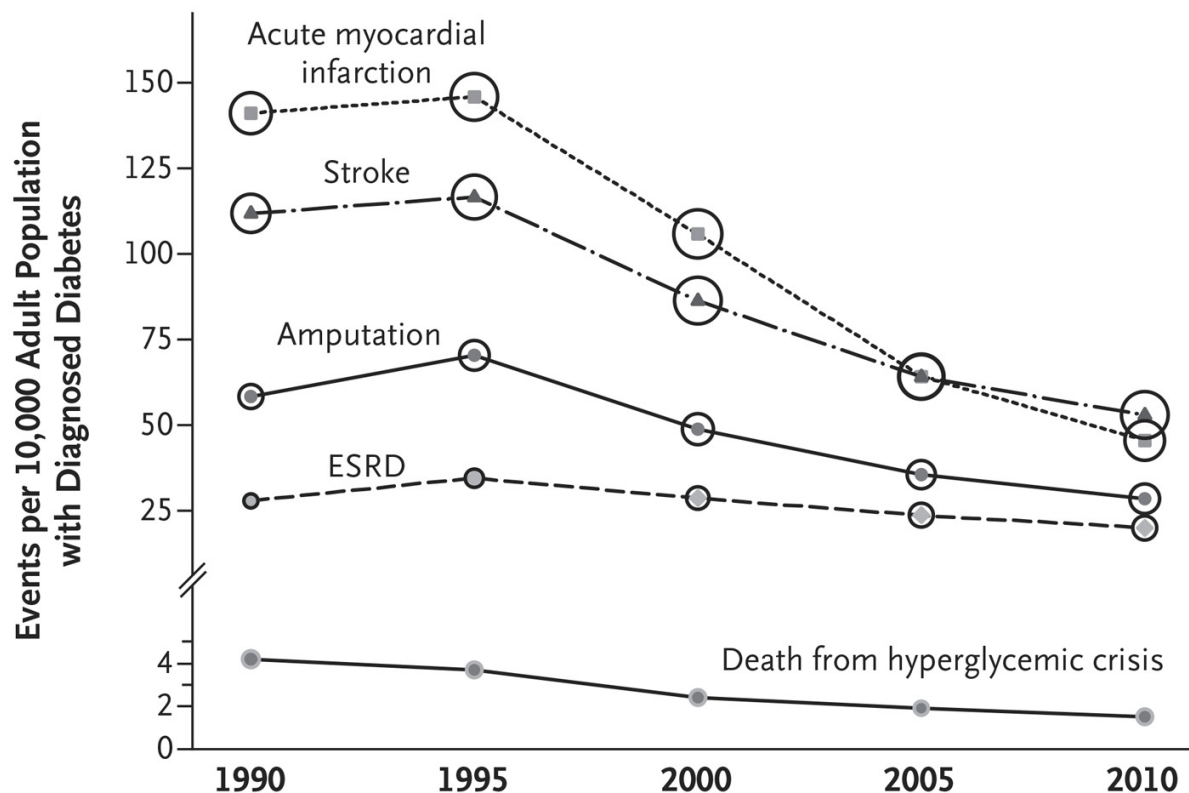
Impact of high glucose levels and glucose lowering on risk of ischaemic stroke: a Mendelian randomisation study and meta-analysis

Meta-analyses of **risk of stroke** (fatal and non-fatal) for randomised clinical intervention trials of more than 12 months' duration for eight classes of commonly used **glucose-lowering drugs**

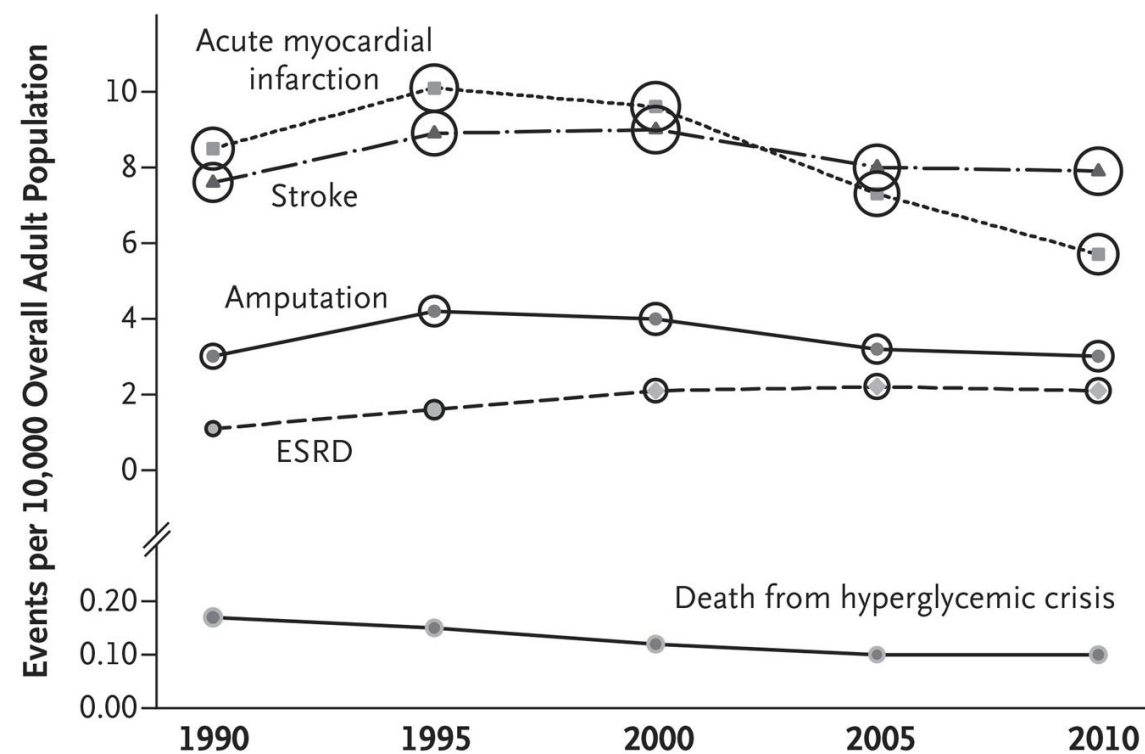


Changes in Diabetes-Related Complications in the United States, 1990–2010

A Population with Diabetes



B Population with or without Diabetes

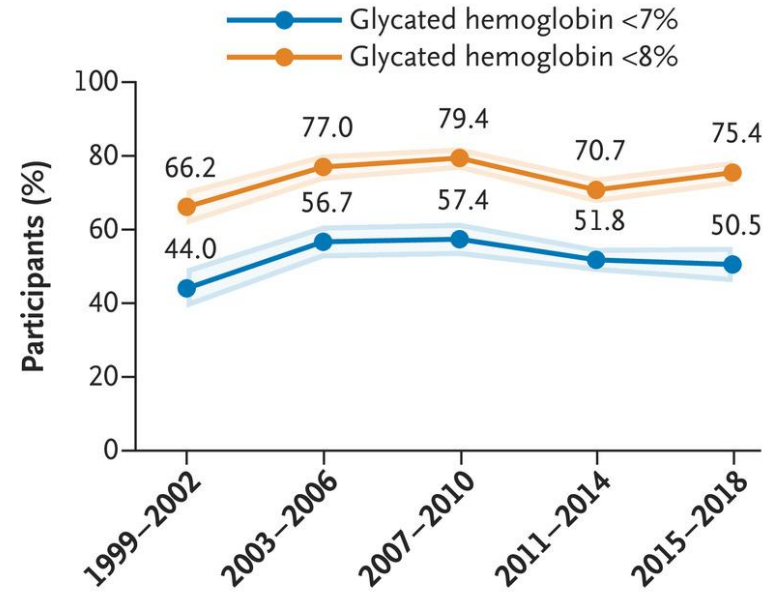


Rates of diabetes-related complications have declined substantially in the past two decades, but a large burden of disease persists because of the continued increase in the prevalence of diabetes

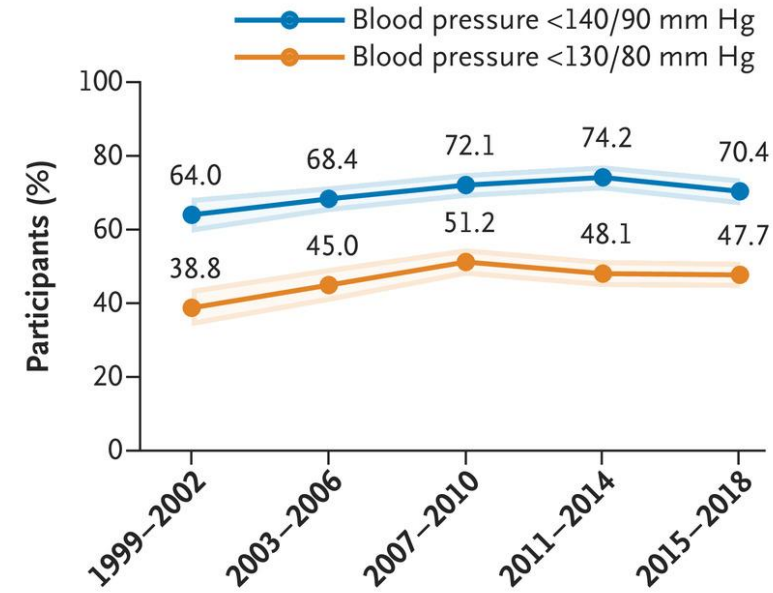
Trends in Diabetes Treatment and Control in U.S. Adults, 1999–2018

N Engl J Med 2021;384:2219-28

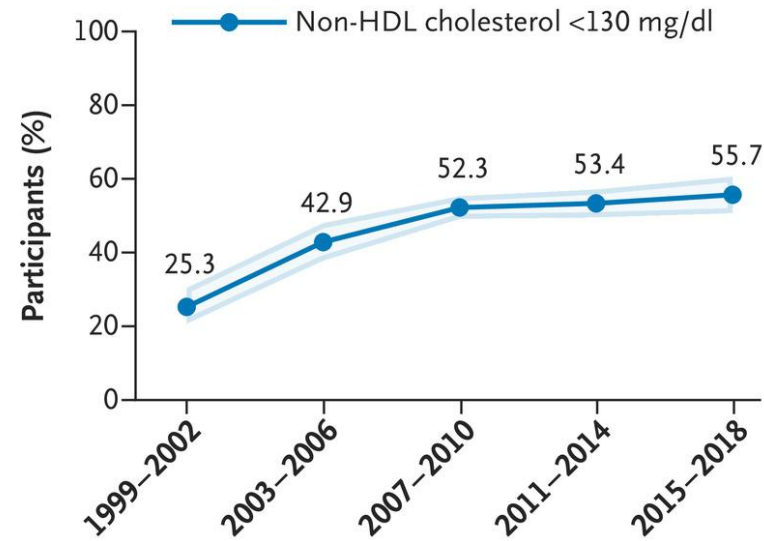
A Glycemic Control



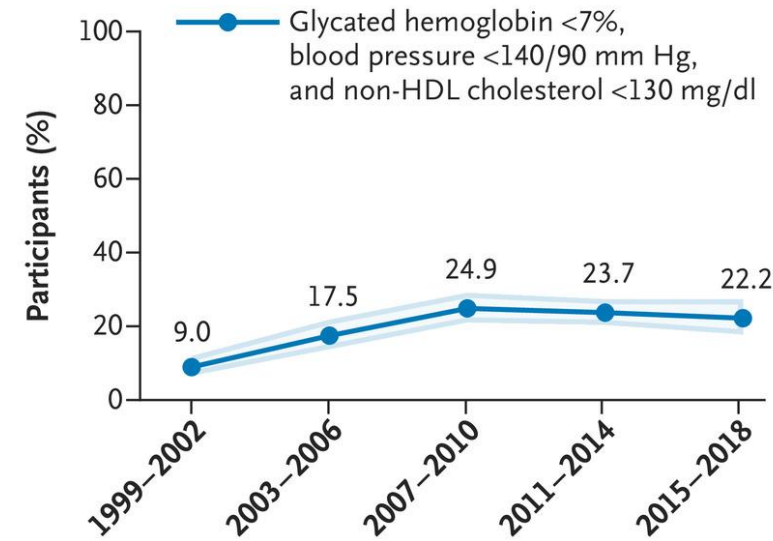
B Blood-Pressure Control



C Lipid Control

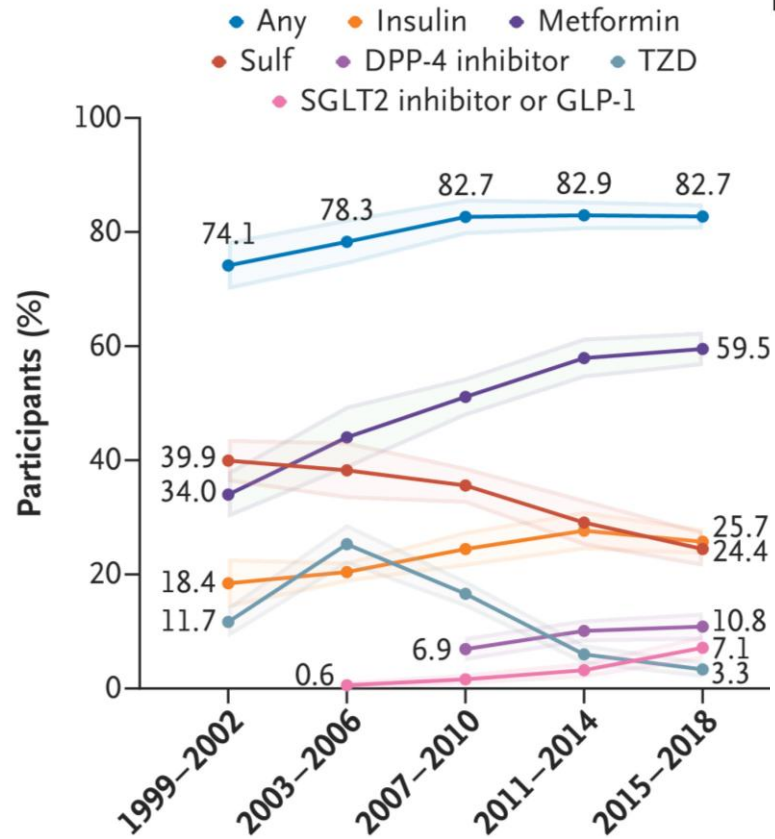


D All Risk Factors Controlled

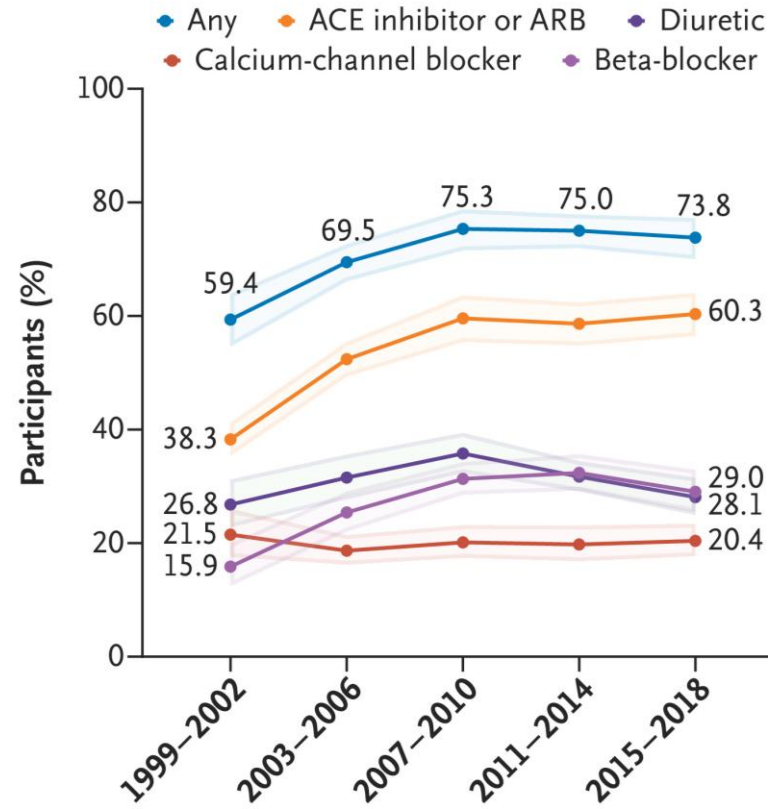


Trends in Diabetes Treatment and Control in U.S. Adults, 1999–2018

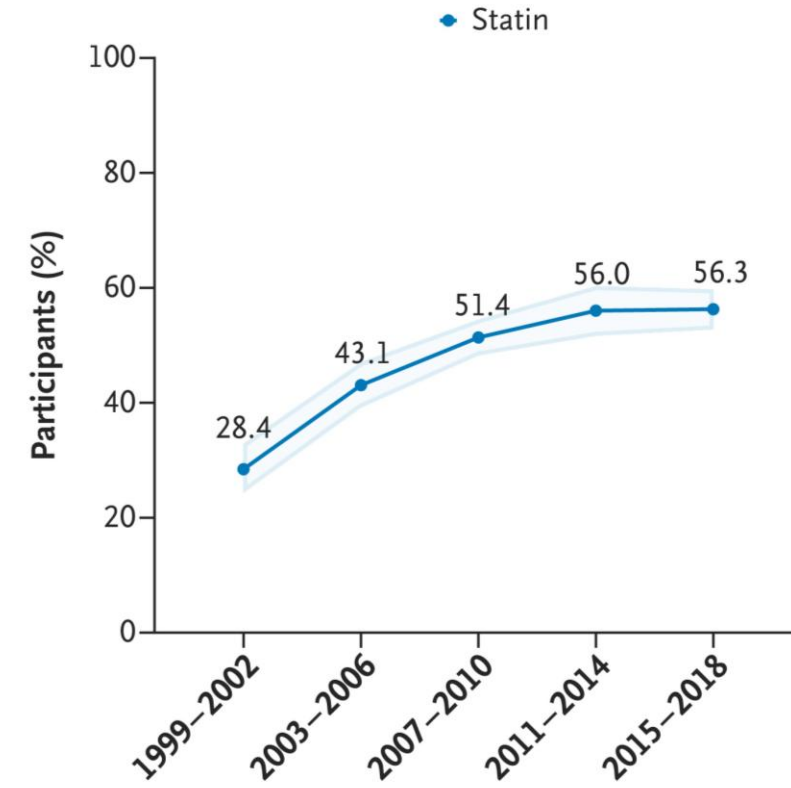
A Use of Glucose-Lowering Medication



B Use of Blood-Pressure-Lowering Medication



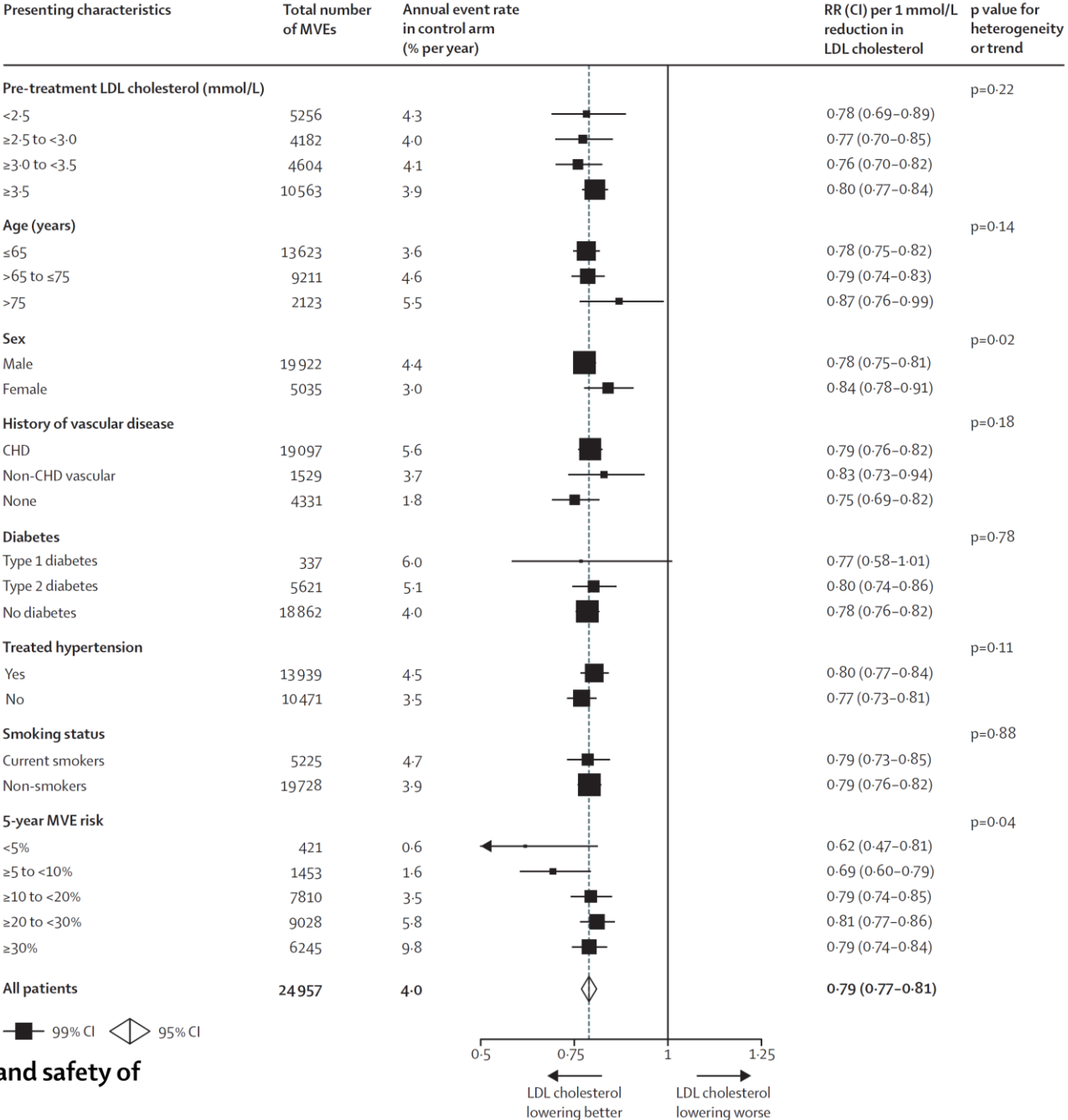
C Use of Lipid-Lowering Medication



Stroke Risk Factors, Genetics, and Prevention

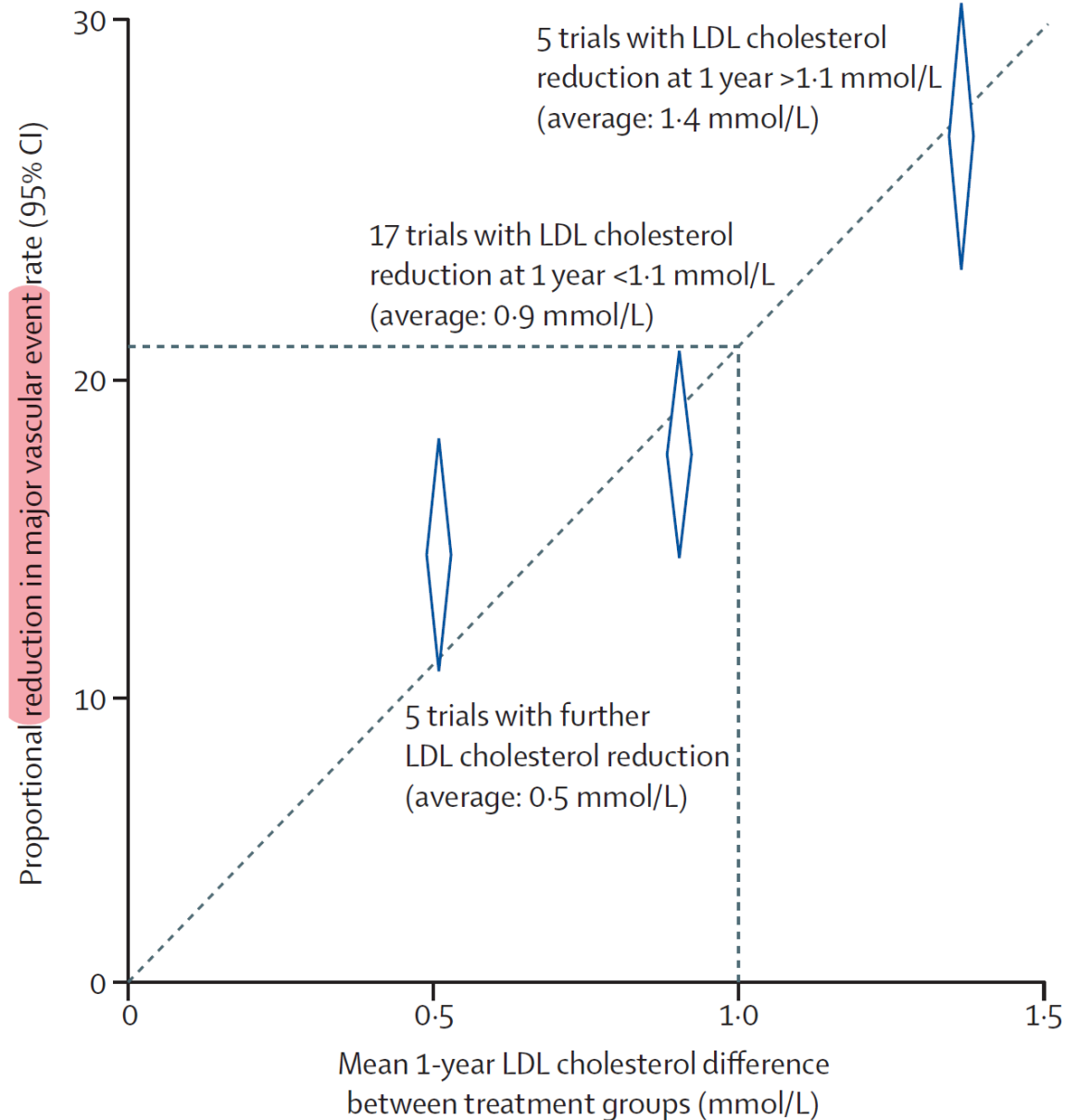
	Nonmodifiable Risk Factors	Modifiable Risk Factors
Ischemic stroke	Age	Hypertension
	Sex	Current smoking
	Race/ethnicity	Waist-to-hip ratio
		Diet
		Physical inactivity
		Hyperlipidemia
		Diabetes mellitus
		Alcohol consumption
		Cardiac causes
		Apolipoprotein B to A1
	Genetics*	

Figure 1: Similar proportional reductions in risks of major vascular events per mmol/L LDL cholesterol reduction in randomised trials of statin therapy among people with different presenting characteristics

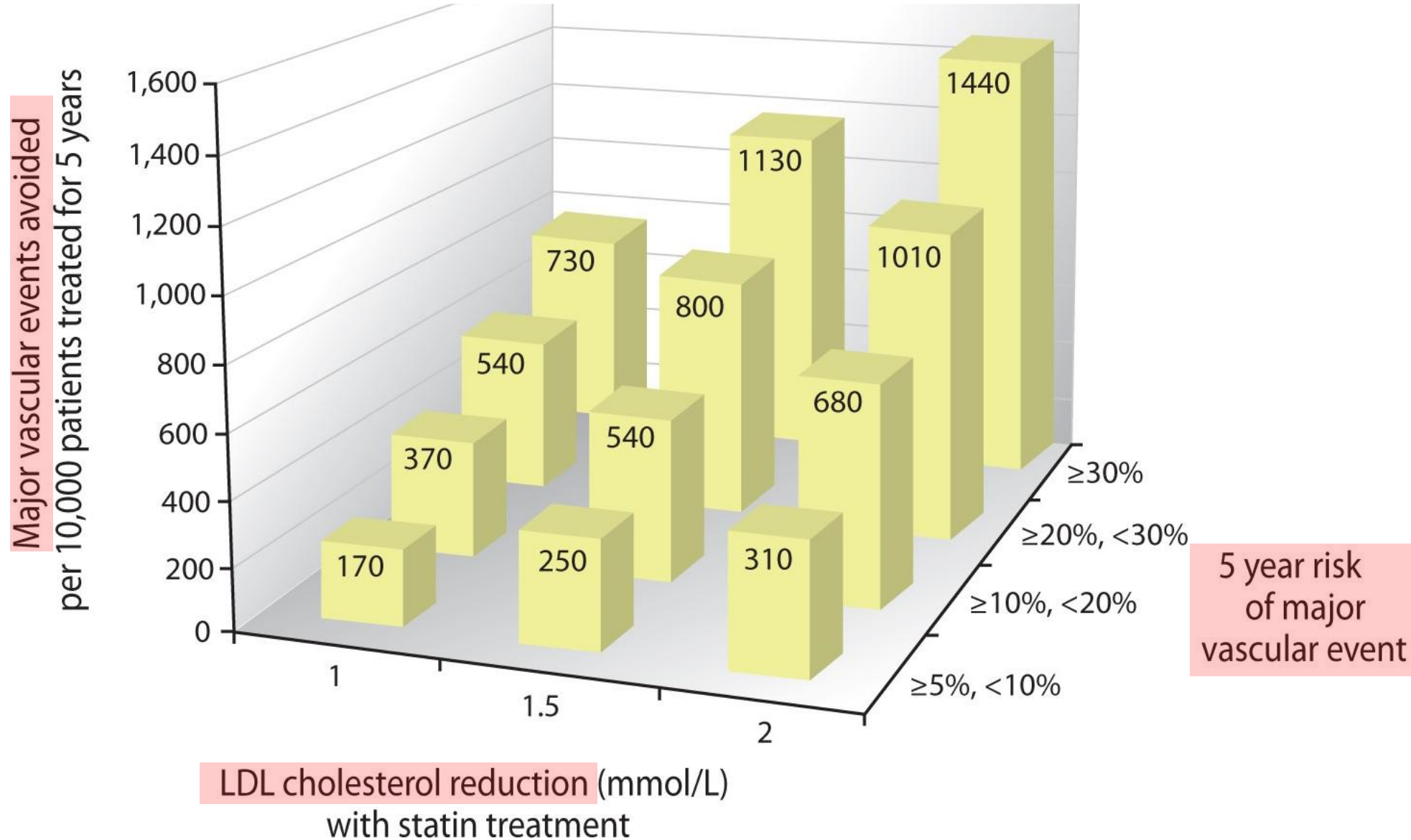


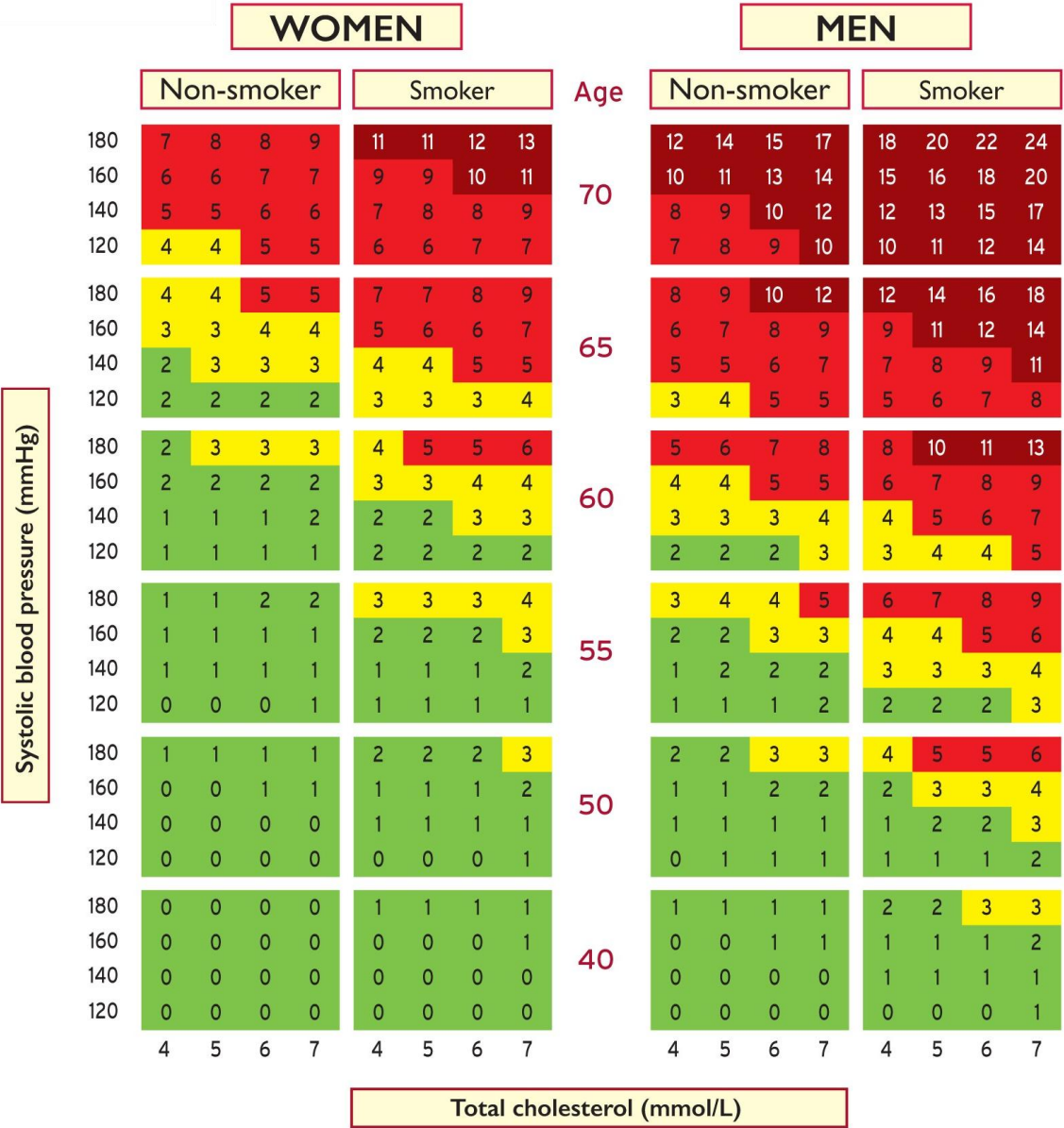
Interpretation of the evidence for the efficacy and safety of statin therapy

Interpretation of the evidence for the efficacy and safety of statin therapy



Interpretation of the evidence for the efficacy and safety of statin therapy





<3% 3-4% 5-9% ≥10%

2019 ESC/EAS Guidelines for the management of **dyslipidaemias**: lipid modification to reduce cardiovascular risk

^a Target organ damage is defined as microalbuminuria, retinopathy, or neuropathy.

Very-high-risk

People with any of the following:
Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound.

DM with target organ damage,^a or at least three major risk factors, or early onset of T1DM of long duration (>20 years).

Severe CKD (eGFR <30 mL/min/1.73 m²).

A calculated SCORE ≥10% for 10-year risk of fatal CVD.

FH with ASCVD or with another major risk factor.

High-risk

People with:

Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg.

Patients with FH without other major risk factors.

Patients with DM without target organ damage,^a with DM duration ≥10 years or another additional risk factor.

Moderate CKD (eGFR 30–59 mL/min/1.73 m²).

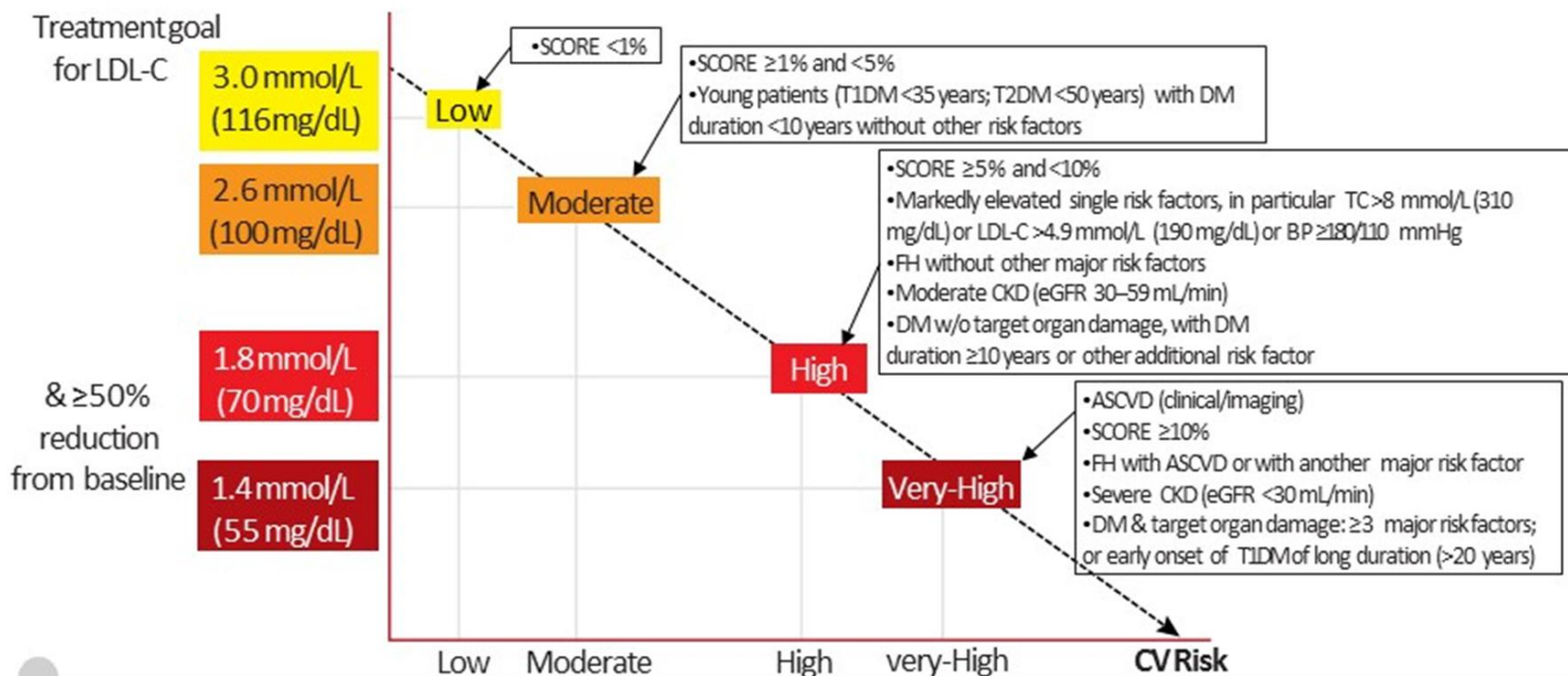
A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.

Moderate-risk

Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1% and <5% for 10-year risk of fatal CVD.

Low-risk

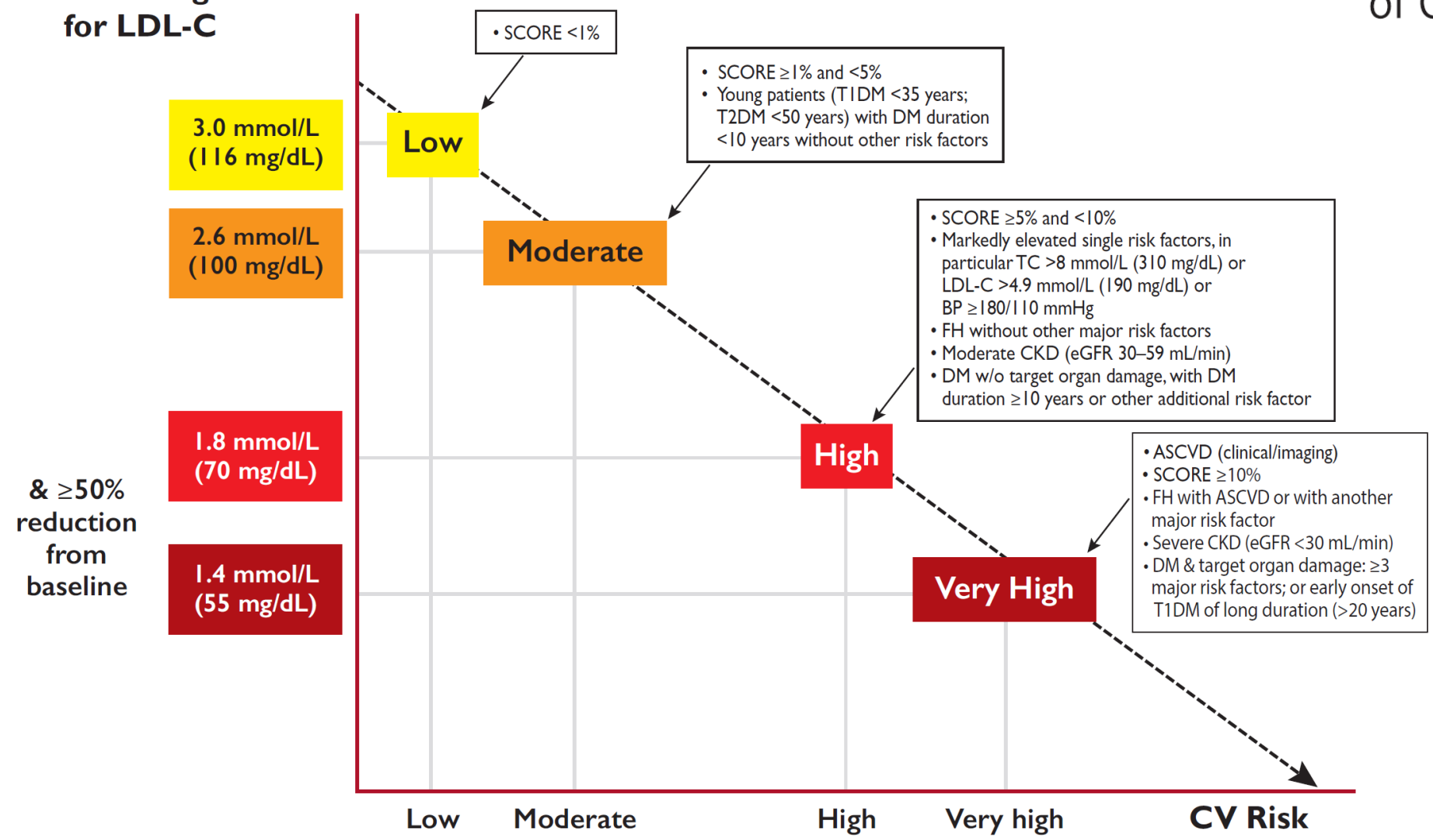
Calculated SCORE <1% for 10-year risk of fatal CVD.



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2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

Treatment goal for LDL-C



& ≥50% reduction from baseline

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

LDL-C	Very-high risk in primary or secondary prevention: A therapeutic regimen that achieves $\geq 50\%$ LDL-C reduction from baseline^b and an LDL-C goal of <1.4 mmol/L (<55 mg/dL). No current statin use: this is likely to require high-intensity LDL-lowering therapy. Current LDL-lowering treatment: an increased treatment intensity is required. High risk: A therapeutic regimen that achieves $\geq 50\%$ LDL-C reduction from baseline^b and an LDL-C goal of <1.8 mmol/L (<70 mg/dL). Moderate risk: A goal of <2.6 mmol/L (<100 mg/dL). Low risk: A goal of <3.0 mmol/L (<116 mg/dL).
Non-HDL-C	Non-HDL-C secondary goals are <2.2 , 2.6 , and 3.4 mmol/L (<85 , 100 , and 130 mg/dL) for very-high-, high-, and moderate-risk people, respectively.
ApoB	ApoB secondary goals are <65 , 80 , and 100 mg/dL for very-high-, high-, and moderate-risk people, respectively.
Triglycerides	No goal, but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk

Total CV risk (SCORE) %		Untreated LDL-C levels					
		<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥190 mg/dL)
Primary prevention	<1, low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class ^a /Level ^b	I/C	I/C	I/C	I/C	Ila/A	Ila/A
	≥1 to <5, or moderate risk (see Table 4)	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class ^a /Level ^b	I/C	I/C	Ila/A	Ila/A	Ila/A	Ila/A
	≥5 to <10, or high-risk (see Table 4)	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class ^a /Level ^b	Ila/A	Ila/A	Ila/A	I/A	I/A	I/A
	≥10, or at very-high risk due to a risk condition (see Table 4)	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class ^a /Level ^b	Ila/B	Ila/A	I/A	I/A	I/A	I/A

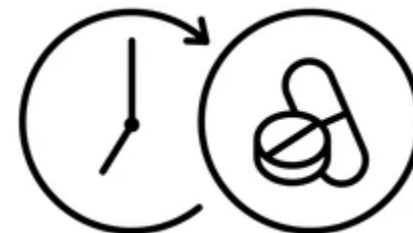
Table 8 Impact of specific lifestyle changes on lipid levels

	Magnitude of the effect	Level
Lifestyle interventions to reduce TC and LDL-C levels		
Avoid dietary trans fats	++	A
Reduce dietary saturated fats	++	A
Increase dietary fibre	++	A
Use functional foods enriched with phytosterols	++	A
Use red yeast rice nutraceuticals	++	A
Reduce excessive body weight	++	A
Reduce dietary cholesterol	+	B
Increase habitual physical activity	+	B
Lifestyle interventions to reduce TG-rich lipoprotein levels		
Reduce excessive body weight	+	A
Reduce alcohol intake	+++	A
Increase habitual physical activity	++	A
Reduce total amount of dietary carbohydrates	++	A
Use supplements of n-3 polyunsaturated fats	++	A
Reduce intake of mono- and disaccharides	++	B
Replace saturated fats with mono- or polyunsaturated fats	+	B
Lifestyle interventions to increase HDL-C levels		
Avoid dietary trans fats	++	A
Increase habitual physical activity	+++	A
Reduce excessive body weight	++	A
Reduce dietary carbohydrates and replace them with unsaturated fats	++	A
Modest consumption in those who take alcohol may be continued	++	B
Quit smoking	+	B

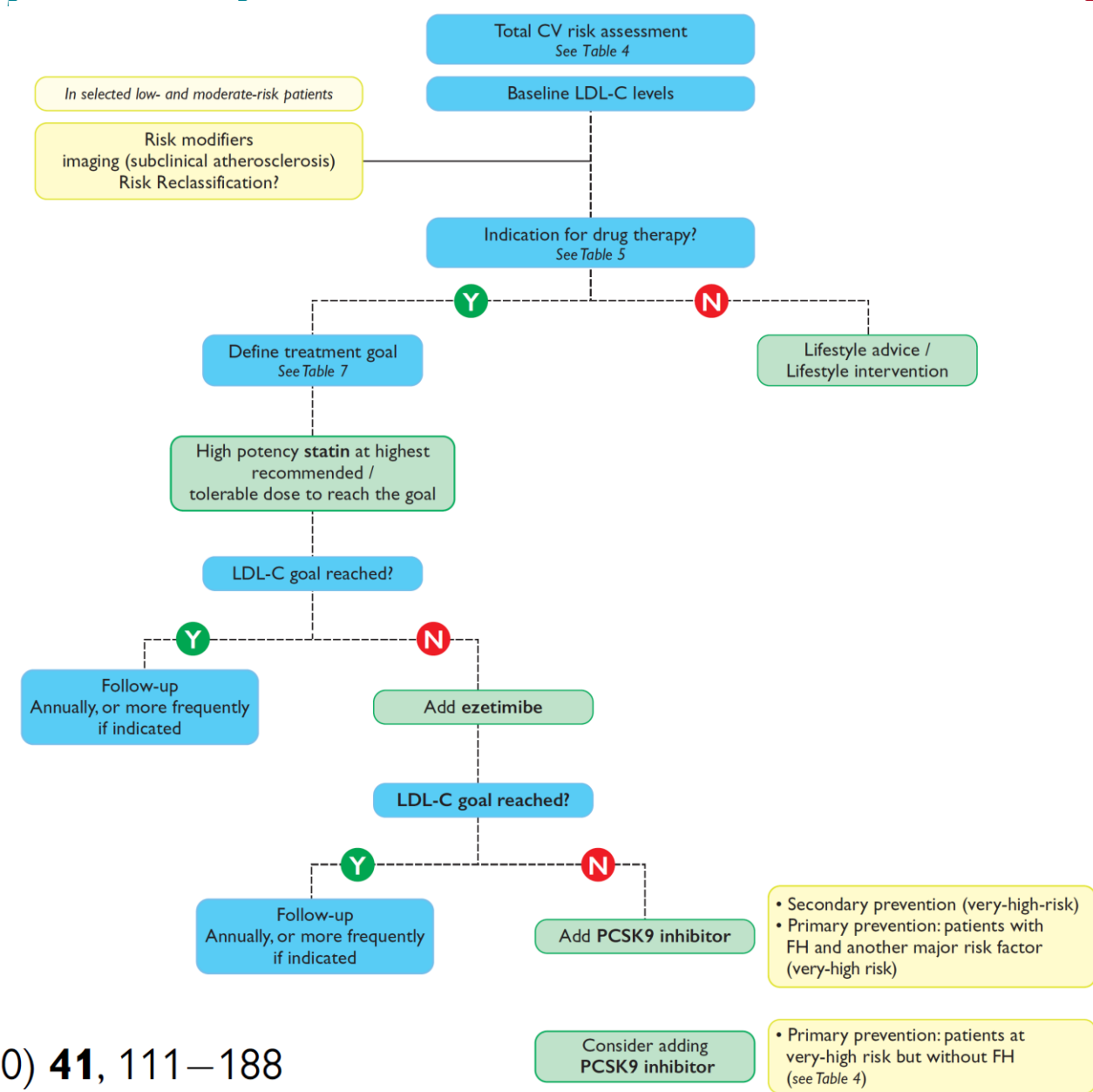


The initial non-pharmacological approach is very important in patients at very high risk of future CV events, such as stroke or TIA patients:

- *increasing the potential of a better physician-to-patient interaction,*
- &
- *adherence to treatment.*



2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*



Interpretation of the evidence for the efficacy and safety of statin therapy

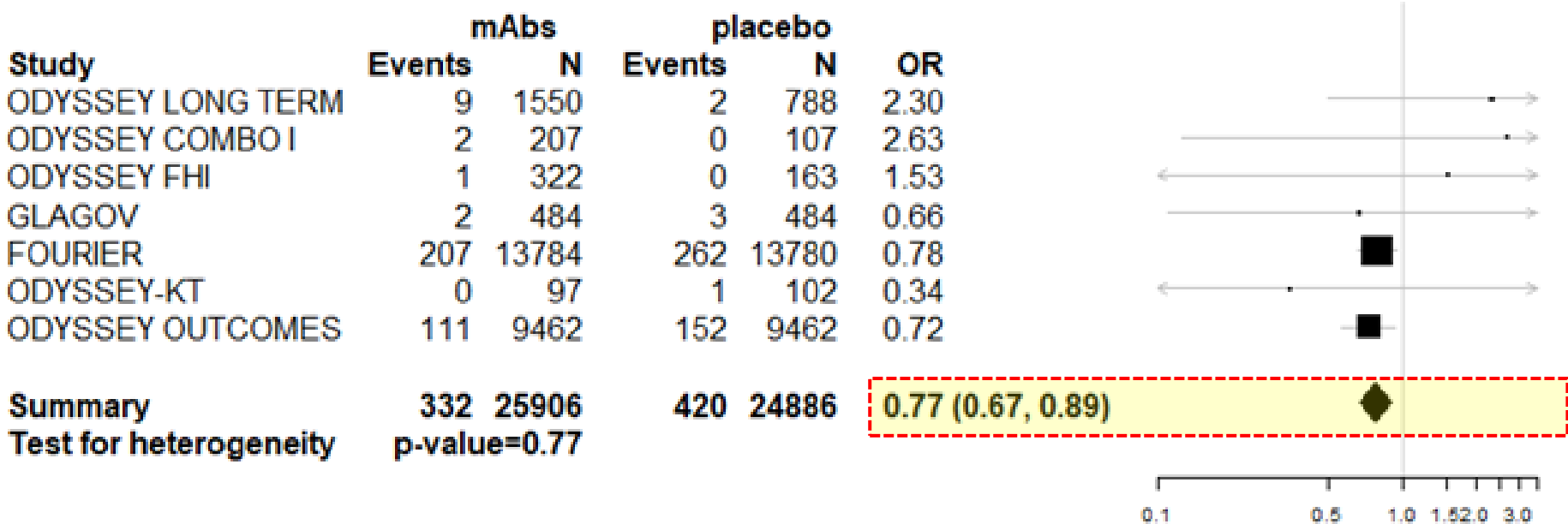
	Daily dose of different statins				
	5 mg	10 mg	20 mg	40 mg	80 mg
Pravastatin	15%	20%	24%	29%	33%
Simvastatin	23%	27%	32%	37%	42%
Atorvastatin	31%	37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	58%

Shaded boxes indicate regimens that can produce about a halving or more in LDL cholesterol concentrations (largely irrespective of patient characteristics, including presenting concentrations of cholesterol). The 2016 cost for generic atorvastatin 40 mg daily in the UK is about £2 per 28 days of treatment,¹⁸⁴ rosuvastatin 20 mg daily currently costs about £25 per month,¹⁸⁵ but it became available as a generic in the USA during 2016.

Table 3: Average relative reductions in LDL cholesterol concentrations with different doses of commonly used statins^{160,163}

Cardiovascular events with PCSK9 inhibitors: an updated meta-analysis of randomised controlled trials

Effect of monoclonal antibody therapy on **stroke**



2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

Intensity of lipid lowering treatment

Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%

Monitor for statin-related
adverse effects



2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

Table 10 Drugs potentially interacting with statins metabolized by cytochrome P450 3A4 leading to increased risk of myopathy and rhabdomyolysis

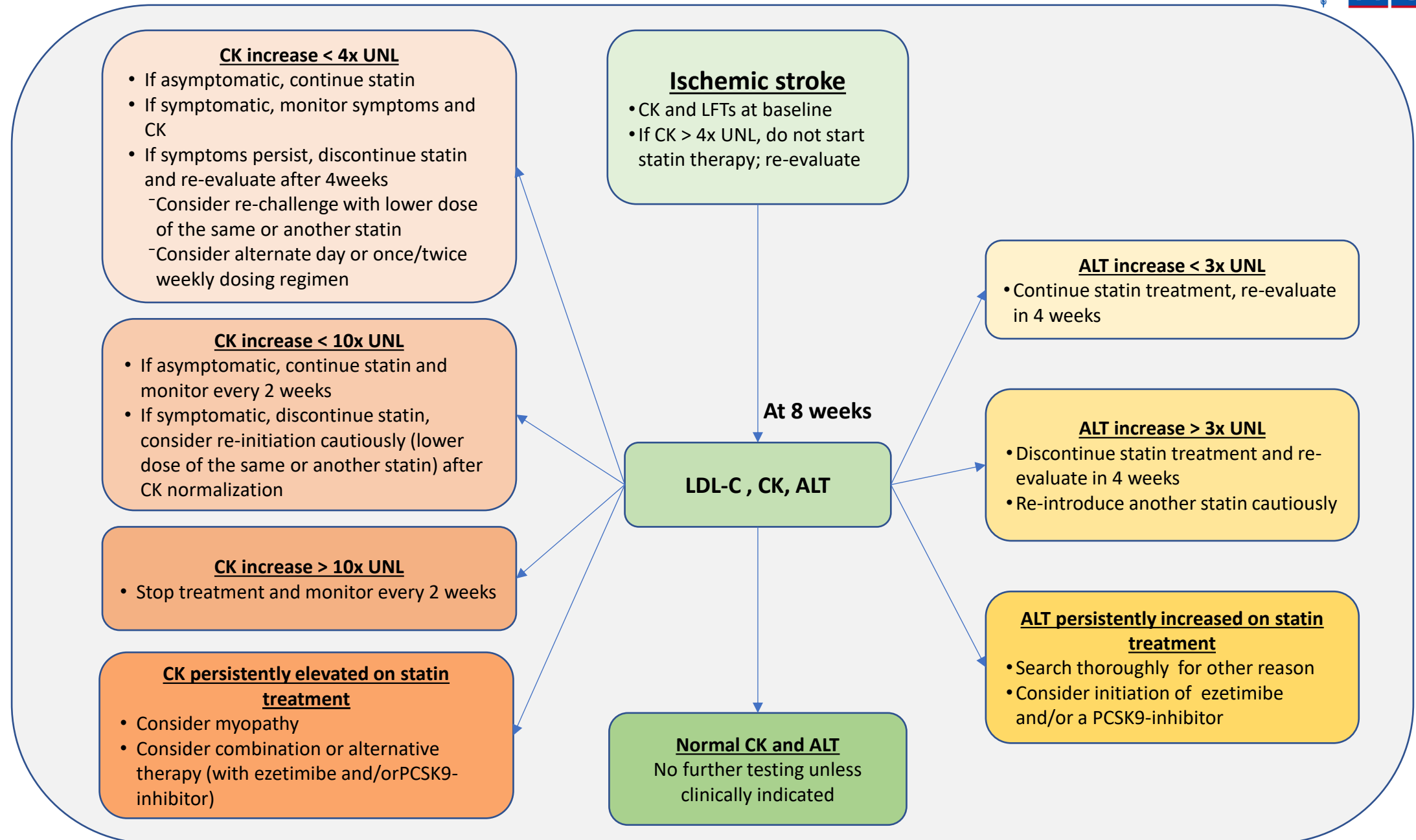
Anti-infective agents	Calcium antagonists	Other
Itraconazole	Verapamil	Ciclosporin
Ketoconazole	Diltiazem	Danazol
Posaconazole	Amlodipine	Amiodarone
Erythromycin		Ranolazine
Clarithromycin		Grapefruit juice
Telithromycin		Nefazodone
HIV protease inhibitors		Gemfibrozil



Patients with ischemic stroke or TIA should be monitored for statin-related adverse effects.

If a patient develops statin-related adverse effects, **another statin regimen** (lower dose of the same statin or another statin or alternate statin administration) should be used.

If the adverse effects recur following change of statin regimen, statin therapy should be permanently discontinued and **ezetimibe and/or a PCSK9 inhibitor** should be prescribed (2C).



2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*



Recommendations for the treatment of dyslipidaemias in older people (aged >65 years)

Recommendations	Class ^a	Level ^b
Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients. ²¹⁷	I	A
Treatment with statins is recommended for primary prevention, according to the level of risk, in older people aged ≤75 years. ²¹⁷	I	A
Initiation of statin treatment for primary prevention in older people aged >75 years may be considered, if at high-risk or above. ²¹⁷	IIb	B
It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals.	I	C

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*



Testing lipids

How often should lipids be tested?

- Before starting lipid-lowering drug treatment, at least two measurements should be made, with an interval of 1–12 weeks, with the exception of conditions where prompt drug treatment is suggested, such as ACS and very high-risk patients.

How often should a patient's lipids be tested after starting lipid-lowering treatment?

- After starting treatment: 8 (± 4) weeks.
- After adjustment of treatment: 8 (± 4) weeks until the goal is achieved.

How often should lipids be tested once a patient has achieved the target or optimal lipid level?

- Annually (unless there are adherence problems or other specific reasons for more frequent reviews).

Primary and Secondary Prevention of Ischemic Stroke and Cerebral Hemorrhage

JACC Focus Seminar

ANTITHROMBOTIC THERAPY

Aspirin:
4,000 years and still learning

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the salicylates*

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HEROIN HYDROCHL
The sedative for coughs

GUARCOL CURE
The anesthetic

HEROIN
*The sedative for
coughs*

LYCETOL
The uric acid solvent

SALOPHEN
*The antirheumatic and
antineuralgic*

FERRO-SOMATOSE
The iron preparation

HEMICRANIN
The anesthetic

SULFONAL
The antirheumatic

IODOTHYRINE
The iodine preparation

SOMATOSE
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SYCOSE
The anesthetic

PHENACETIN
The anesthetic

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The anesthetic

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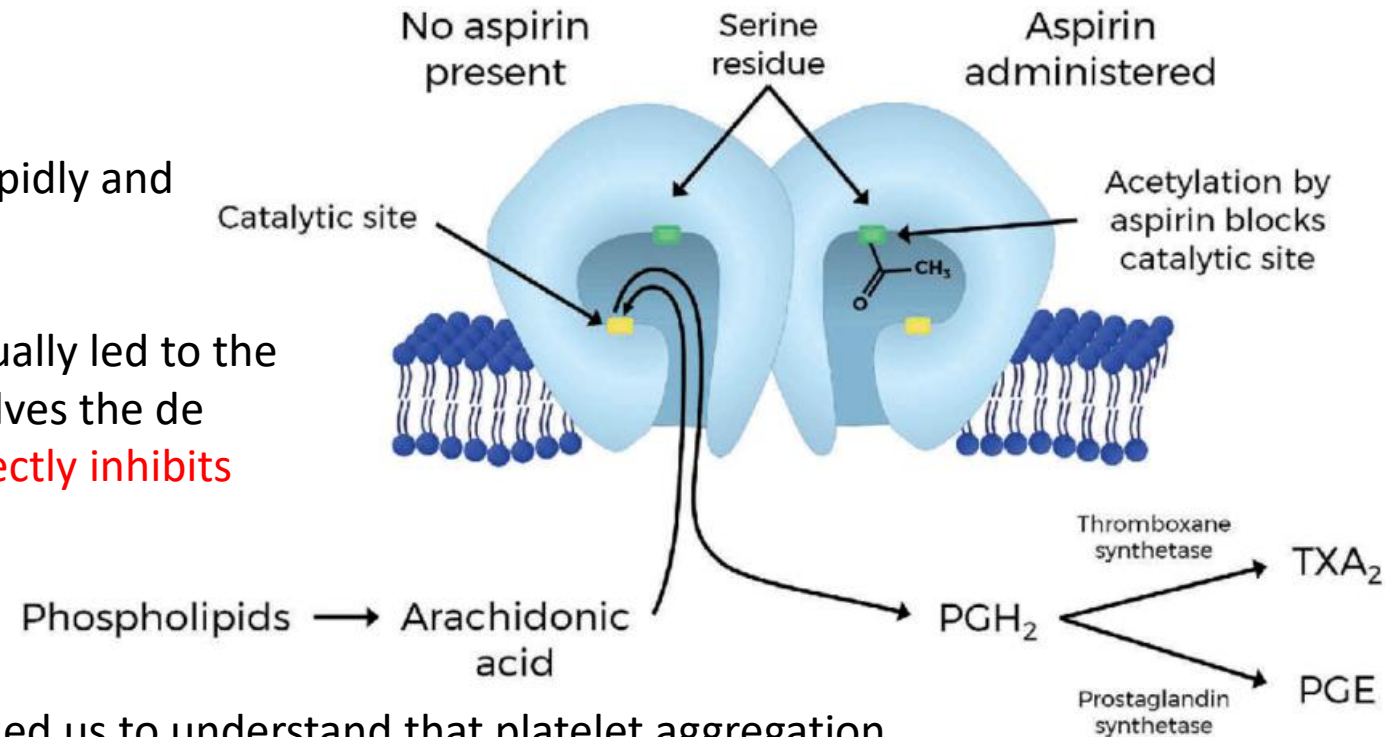
Aspirin: 4,000 years and still learning

Aspirin: The Story of a Wonder Drug

BMJ VOLUME 329 11 DECEMBER 2004

■ LEARNING HOW ASPIRIN WORKS (AND A FEW OTHER THINGS)

- In the late 1960s, **Weiss** et al reported that aspirin rapidly and irreversibly **inhibits platelet aggregation**.
- In parallel, using biological assays in work that eventually led to the Nobel Prize, **Vane** discovered that **inflammation** involves the de novo synthesis of **prostaglandins** and that **aspirin directly inhibits this synthesis**.
- Further work connecting these lines of investigation led us to understand that platelet aggregation is enhanced by the prostaglandin derivative **thromboxane A₂**, produced by **cy-clooxygenase-1**, and that **aspirin irreversibly inhibits this enzyme by acetylation**.



An aspirin a day? Clinical utility of aspirin therapy for the primary prevention of cardiovascular disease

LEARNING WHEN TO USE ASPIRIN

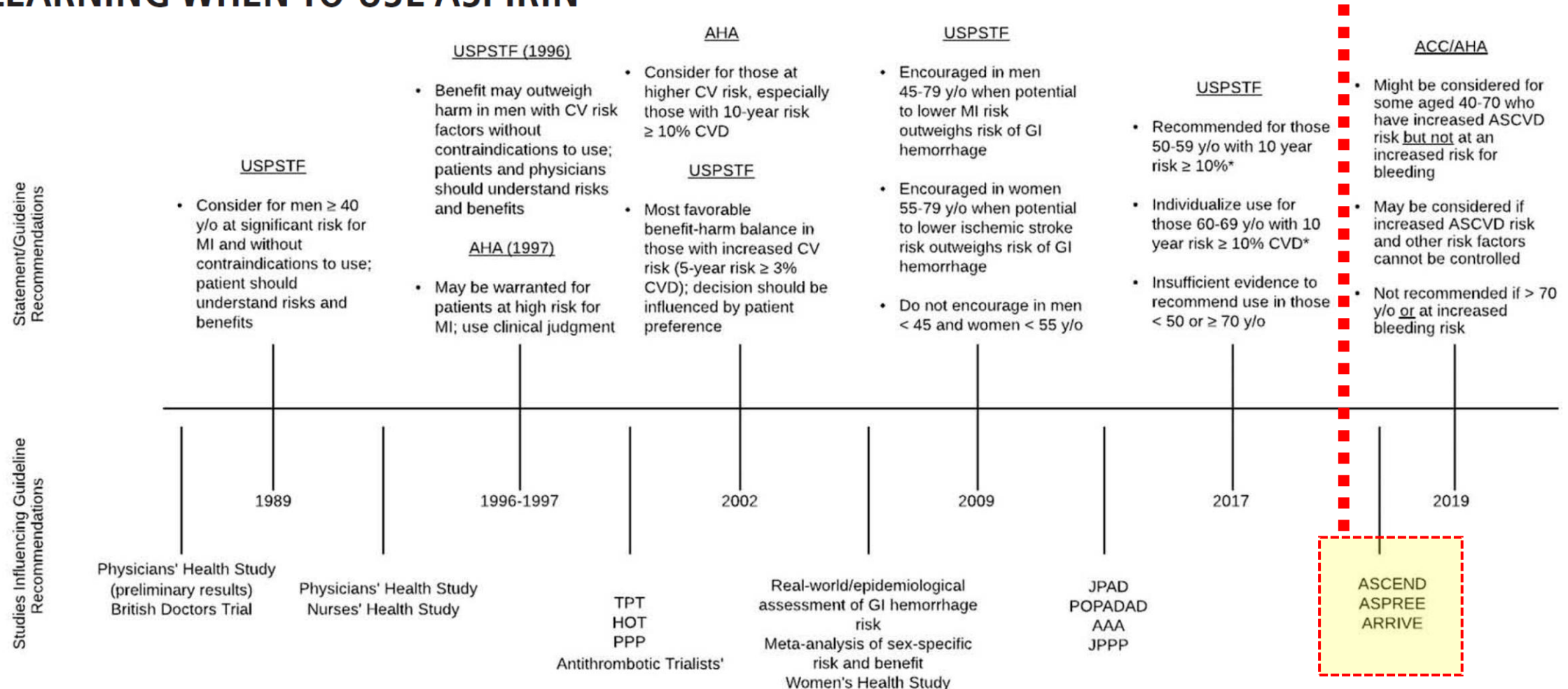


Table 1. Trials of Aspirin for Primary Cardiovascular Prevention

Study	Year	Patients	Aspirin Dose	DM*	Mean or Median Follow-Up	Study Population	Primary Outcome Measure	Significant Efficacy
BDT ³⁰	1988	5139	300–500 mg/d	2%	5.6 y	Healthy men	CV death	No
PHS ³¹	1989	22 071	325 mg every other day	4%	5 y	Healthy men	CV death	No
ETDRS ³²	1992	3711	650 mg/d	100%	5 y	DM†	All-cause mortality	No
ACBS ³³	1995	372	325 mg/d	19%	2.4 y	Carotid stenosis	Death, MI, stroke, TIA, stroke, MI, UA	No
HOT ³⁴	1998	18 790	75 mg/d	8%	3.8 y	<u>Hypertension</u>	CV death, MI, stroke	Yes
TPT ³⁵	1998	5085	75 mg/d	NR	6.7 y	<u>CV risk factors</u>	Coronary death and MI	Yes
PPP ³⁶	2001	4495	100 mg/d	17%	3.7 y	CV risk factors	CV death, nonfatal MI, stroke	No
ECLAP ³⁷	2004	518	100 mg/d	5%	3 y	<u>Polycythemia vera</u>	CV death, nonfatal MI, stroke, PE, VT	Yes
WHS ³⁸	2005	39 876	100 mg every other day	3%	10.1 y	Healthy women	CV death, nonfatal MI, stroke	No
CLIPS ³⁹	2007	366	100 mg/d	78%	2 y	<u>PAD</u>	CV death, MI, stroke	Yes
APLASA ⁴⁰	2007	98	81 mg/d	8%	2.3 y	AA syndrome	Acute thrombosis	No
POPADAD ⁴¹	2008	1276	100 mg/d	100%	6.7 y	Diabetes, PAD	CV death, nonfatal MI, stroke, CLI	No
JPAD ⁴²	2008	2539	81–100 mg/d	100%	4.4 y	DM	Ischemic heart disease, stroke, PAD	No
AAA ⁴³	2010	3350	100 mg/d	3%	8.2 yr	PAD	CV death, MI, stroke, revascularization	No
JPPP ⁴⁴	2014	14 464	100 mg/d	34%	5.0 yr	CV risk factors	CV death, nonfatal MI, stroke	No

Aspirin for Primary Prevention of Atherosclerotic Cardiovascular Disease

Advances in Diagnosis and Treatment

Table 1. Summary of the Major Aspirin Primary Prevention Trials

Trial (Acronym)	Aspirin Dose (Daily, Unless Noted)	Control Group	No. of Subjects (Aspirin/Control), Sex, Mean Age, y	Relative Risk (95% CI), Aspirin/Control Number of Events			
				Nonfatal MI	Nonfatal Stroke	Cardiovascular Mortality	All-Cause Mortality
British Doctors' Study (BDS) ²⁶	300-500 mg	No aspirin	3429/1710, M, 61	0.97 (0.67-1.41), 80/41	1.13 (0.72-1.77), 61/27	1.01 (0.74-1.37), 119/59	0.89 (0.74-1.08), 270/151
Physicians' Health Study (PHS) ²⁷	325 mg every other day	Placebo	11 037/11 034, M, 53	0.59 (0.47-0.74), 129/213	1.20 (0.91-1.59), 110/92	0.92 (0.66-1.28), 66/72	0.96 (0.80-1.14), 217/227
Early Treatment Diabetic Retinopathy Study (ETDRS) ²⁸	650 mg	Placebo	1856/1855, M/F, ~50	0.83 (P ≤ .05), 524 (combined)	1.26 (0.89-1.80), 67/53	0.89 (0.76-1.04), 244/275	0.93 (0.79-1.09), 284/305
Thrombosis Prevention Trial (TPT) ²⁹	75 mg	Placebo	1268/1272, M, 57	0.65 (0.45-0.92), 47/73	0.64 (0.34-1.20), 16/25	1.05 (0.69-1.61), 42/40	1.03 (0.80-1.32), 113/110
Hypertension Optimal Treatment (HOT) ³⁰	75 mg	Placebo	9399/9391, M/F, 61	0.60 (0.45-0.81), 68/113	0.99 (0.78-1.24), ^a 146/148	0.95 (0.75-1.20), 133/140	0.93 (0.79-1.09), 284/305
Primary Prevention Project (PPP) ³¹	100 mg	No aspirin	2226/2269, M/F, 64	0.69 (0.36-1.33), 15/22	0.84 (0.42-1.67), 15/18	0.56 (0.31-1.01), 17/31	0.81 (0.58-1.13), 62/78
Women's Health Study (WHS) ³²	100 mg every other day	Placebo	19 934/19 942, F, 54	1.01 (0.83-1.24), 184/181	0.81 (0.67-0.97), 198/244	0.95 (0.74-1.22), 120/126	0.95 (0.85-1.06), 609/642
Prevention of Progression of Arterial Disease and Diabetes (POPADAD) ³³	100 mg	Placebo	638/638, M/F, 60	0.98 (0.69-1.40), 55/56	0.71 (0.45-1.12), 29/41	1.23 (0.80-1.89), 43/35	0.93 (0.72-1.21), 94/101
Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) ³⁴	81-100 mg	No aspirin	1262/1277, M/F, 65	1.35 (0.57-3.19), 12/9	1.01 (0.60-1.72), 27/27	0.10 (0.01-0.79), 1/10	0.91 (0.57-1.43), 33/38
Aspirin for Asymptomatic Atherosclerosis (AAA) ³⁵	100 mg	Placebo	1675/1675, M/F, 62	0.91 (0.65-1.28), 62/68	0.97 (0.62-1.52), 37/38	1.17 (0.72-1.89), 43/35	0.95 (0.85-1.06), 609/642
Japanese Primary Prevention Project (JPPP) ³⁶	100 mg	No aspirin	7220/7244, M/F, 70	0.53 (0.31-0.91), 20/38	1.00 (0.77-1.31), 109/109	1.02 (0.71-1.47), 58/57	0.98 (0.84-1.15), 297/303
Total ^b	All doses		118 445	0.78 (0.71-0.87)	0.95 (0.85-1.06)	0.94 (0.86-1.03)	0.94 (0.89-0.99)
Low-dose aspirin trials ^b	≤100 mg		87 524	0.83 (0.74-0.94)	0.86 (0.76-0.98)	0.97 (0.85-1.10)	0.95 (0.89-1.01)

Table 2. Summary of Recent Meta-Analyses of Aspirin for Primary Cardiovascular Prevention

Study Characteristic	ATT ⁴⁵	Bartolucci ⁴⁶	Raju ⁴⁷	Berger ⁴⁸	Seshasai ⁴⁹	Xie ⁵⁰	Raju ⁵¹	Guirguis-Blake ^{52,53}
Publication date	2009	2011	2011	2011	2012	2014	2015	2016
Type	Patient level	Study level	Study level	Study level	Study level	Study level	Study level	Study level
Pooled patients	95 000	100 038	100 076	102 621	102 621	107 686	114 734	118 445
Summary measure	RaR (95% CI)	OR (95% CI)	RR (95% CI)	RR (95% CI)	OR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Studies included	6	9	9	9	9	14	10	11
Follow-up	330,000 PY	NR	3.8–10.1 yr	710,053 PY	≈700,000 PY	734,170 PY	NR	3.6–10.1 y
Serious vascular events	0.88 (0.82–0.94)*	0.87 (0.80–0.93)*	0.88 (0.83–0.94)*	0.90 (0.85–0.96)*	0.90 (0.85–0.96)*	0.90 (0.85–0.95)*	0.89 (0.82–0.97)*	NR
Any MI	NR	NR	0.83 (0.69–1.00)*	0.86 (0.74–1.00)*	NR	0.86 (0.75–0.98)*	0.78 (0.65–0.94)*	NR
Fatal MI	NR	NR	NR	NR	1.06 (0.83–1.37)	NR	NR	NR
Nonfatal MI	0.77 (0.69–0.86)*	0.81 (0.67–0.99)*	NR	NR	0.80 (0.67–0.96)*	NR	0.80 (0.64–0.99)*	0.78 (0.71–0.87)*
All-cause death	NR	0.95 (0.88–1.01)	0.94 (0.88–1.00)*	0.94 (0.89–1.00)	0.94 (0.88–1.00)	0.94 (0.89–0.99)*	0.94 (0.89–1.00)	0.94 (0.89–0.99)*
Cardiovascular	0.97 (0.87–1.09)	0.96 (0.80–1.14)	0.96 (0.84–1.09)	0.99 (0.85–1.14)	0.99 (0.85–1.15)	1.04 (0.86–1.25)	0.95 (0.84–1.07)	0.94 (0.86–1.03)
Any stroke	0.95 (0.85–1.06)	0.92 (0.83–1.02)	NR	0.94 (0.84–1.06)	0.94 (0.84–1.06)	0.95 (0.87–1.05)	0.94 (0.84–1.06)	0.95 (0.85–1.06)
Hemorrhagic	1.32 (1.00–1.75)*	NR	1.36 (1.01–1.82)*	1.35 (1.01–1.81)*	NR	1.34 (1.01–1.79)*	1.43 (1.10–1.86)*	1.33 (1.03–1.71)*
Ischemic	0.86 (0.74–1.00)*	NR	0.86 (0.75–0.98)*	0.87 (0.73–1.02)	NR	0.86 (0.75–0.98)*	NR	NR
Major bleeding	1.54 (1.30–1.82)*	NR	1.66 (1.41–1.95)*	1.62 (1.31–2.00)*	NR	1.55 (1.35–1.78)*	1.69 (1.43–1.98)*	NR
Gastrointestinal	NR	NR	1.37 (1.15–1.62)*	1.29 (1.24–1.47)*	NR	NR	1.64 (1.30–2.07)*	1.59 (1.32–1.91)*

*Statistically significant.

Guidelines for the Primary Prevention of Stroke

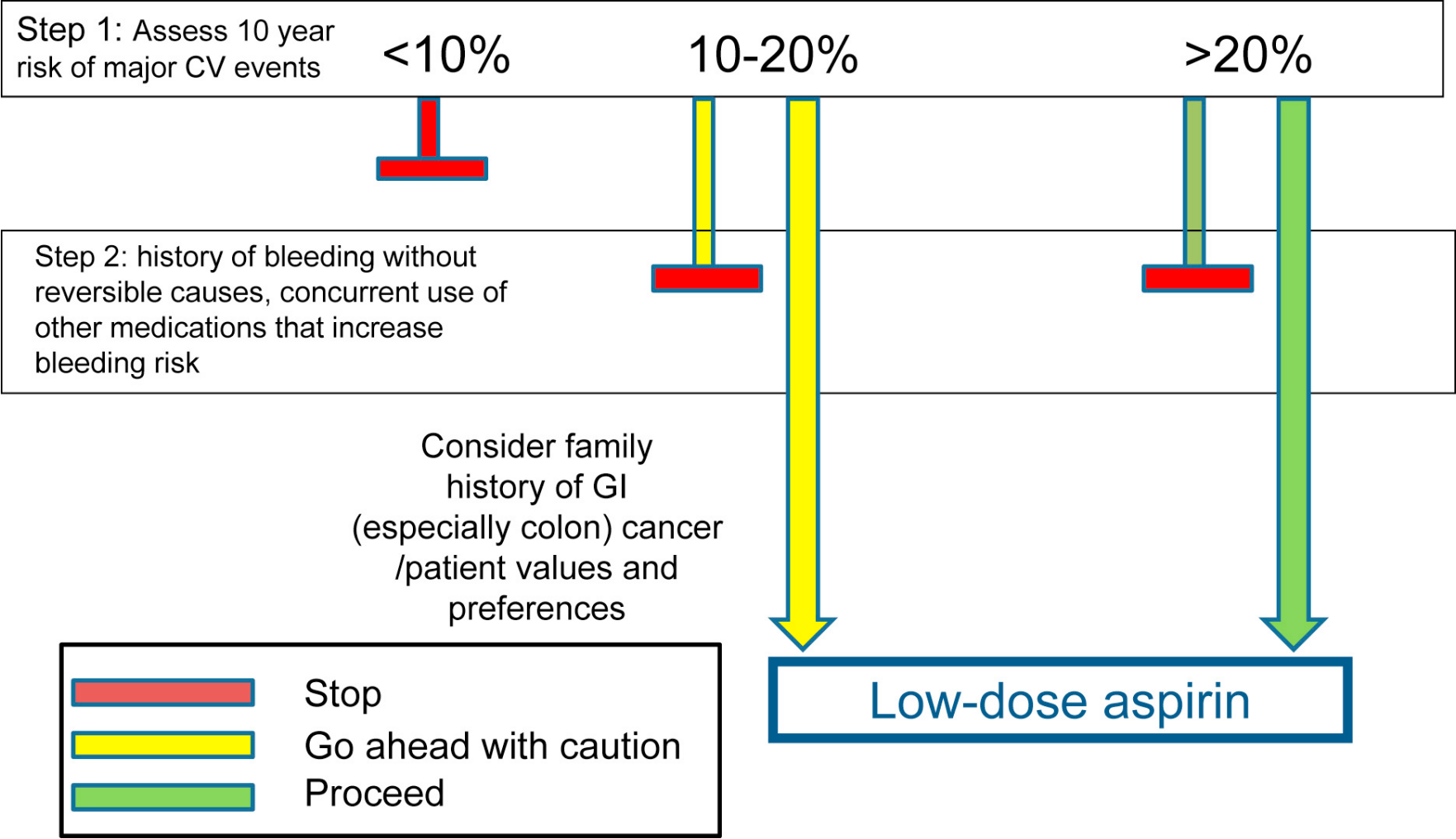
A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

Section	2014 Recommendation	Description of Change from 2011
Diabetes mellitus	Control of blood pressure in accordance with an AHA/ACC/CDC advisory to a target of <140/90 mm Hg is recommended in patients with type 1 or type 2 diabetes mellitus (<i>Class I; Level of Evidence A</i>).	Reworded to reference AHA/ACC/CDC advisory
	The usefulness of aspirin for primary stroke prevention for patients with diabetes mellitus but low 10-y risk of cardiovascular disease is unclear (<i>Class IIb; Level of Evidence B</i>).	Deleted the phrase “however, administering aspirin may be reasonable”
Antiplatelet agents and aspirin	The use of aspirin for cardiovascular (including but not specific to stroke) prophylaxis is reasonable for people whose risk is sufficiently high (10-y risk >10%) for the benefits to outweigh the risks associated with treatment. A cardiovascular risk calculator to assist in estimating 10-y risk can be found online at http://my.americanheart.org/cvriskcalculator (<i>Class IIa; Level of Evidence A</i>).	Reworded to include cardiovascular risk calculator and link; changed from Class I to IIa
	Aspirin might be considered for the prevention of a first stroke in people with chronic kidney disease (ie, estimated glomerular filtration rate <45 mL·min ⁻¹ ·1.73 m ⁻²) (<i>Class IIb; Level of Evidence C</i>). This recommendation <u>does not apply to severe</u> kidney disease (stage 4 or 5; estimated glomerular filtration rate <30 mL·min ⁻¹ ·1.73 m ⁻²).	New recommendation
	Cilostazol may be reasonable for the prevention of a first stroke in people with peripheral arterial disease (<i>Class IIb; Level of Evidence B</i>).	New recommendation
	As a result of a lack of relevant clinical trials, antiplatelet regimens other than aspirin and cilostazol are not recommended for the prevention of a first stroke (<i>Class III; Level of Evidence C</i>).	New recommendation

Aspirin Therapy in Primary Cardiovascular Disease Prevention

J Am Coll Cardiol 2014;64:319-27

A Position Paper of the European Society of Cardiology Working Group on Thrombosis



Aspirin for Primary Cardiovascular Risk Prevention and Beyond in Diabetes Mellitus

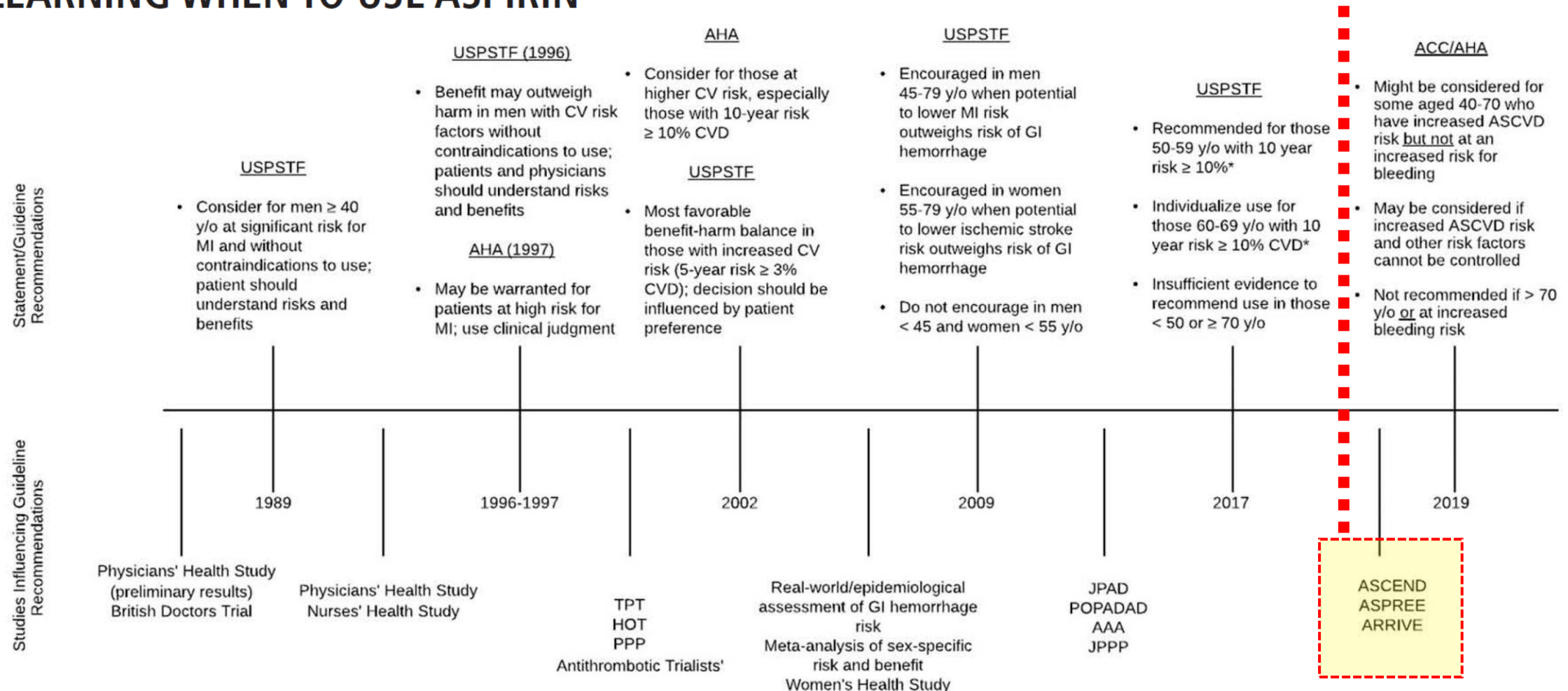
Figure 3. Risk stratification approach for aspirin use in primary prevention of cardiovascular disease for a patient with diabetes mellitus, on the background assumption of optimal management of other cardiovascular disease risk factors.

		Family history of CRC		No family history of CRC	
Age (years)	10-year CVD risk	HBR	no HBR	HBR	no HBR
<50	<5%	No ASA	No ASA	No ASA	No ASA
<50	5–10%	No ASA	Initiate ASA	No ASA	Clinical judgment
50–59	5–10%	No ASA	Initiate ASA	No ASA	Clinical judgment
50–59	10–20%	Clinical judgment	Initiate ASA	No ASA	Initiate ASA
60–69	10–20%	Clinical judgment	Initiate ASA	No ASA	Clinical judgment
≥70	≥20%	No ASA	Clinical judgment	No ASA	Clinical judgment

High bleeding risk (HBR) is defined as a **history of bleeding without reversible causes** and concurrent use of other **medications that increase bleeding risk**. **Clinical judgment** includes a balanced assessment of **risk and benefits** of aspirin therapy and factors patients' **preference and willingness** to comply with aspirin for the subsequent 10 years. **CRC** indicates **colorectal cancer**; and CVD, cardiovascular disease

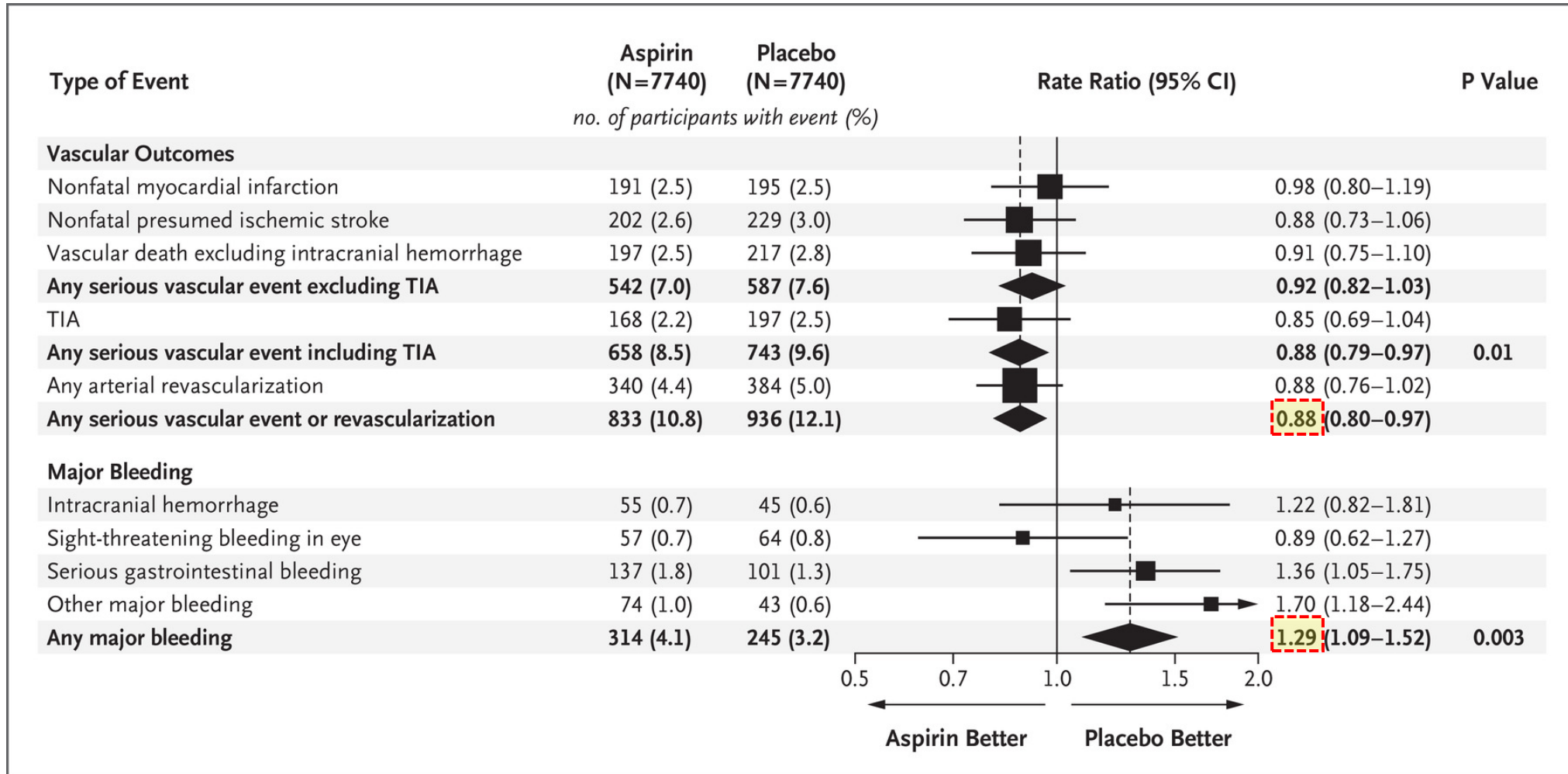
An aspirin a day? Clinical utility of aspirin therapy for the primary prevention of cardiovascular disease

LEARNING WHEN TO USE ASPIRIN



Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

ASCEND

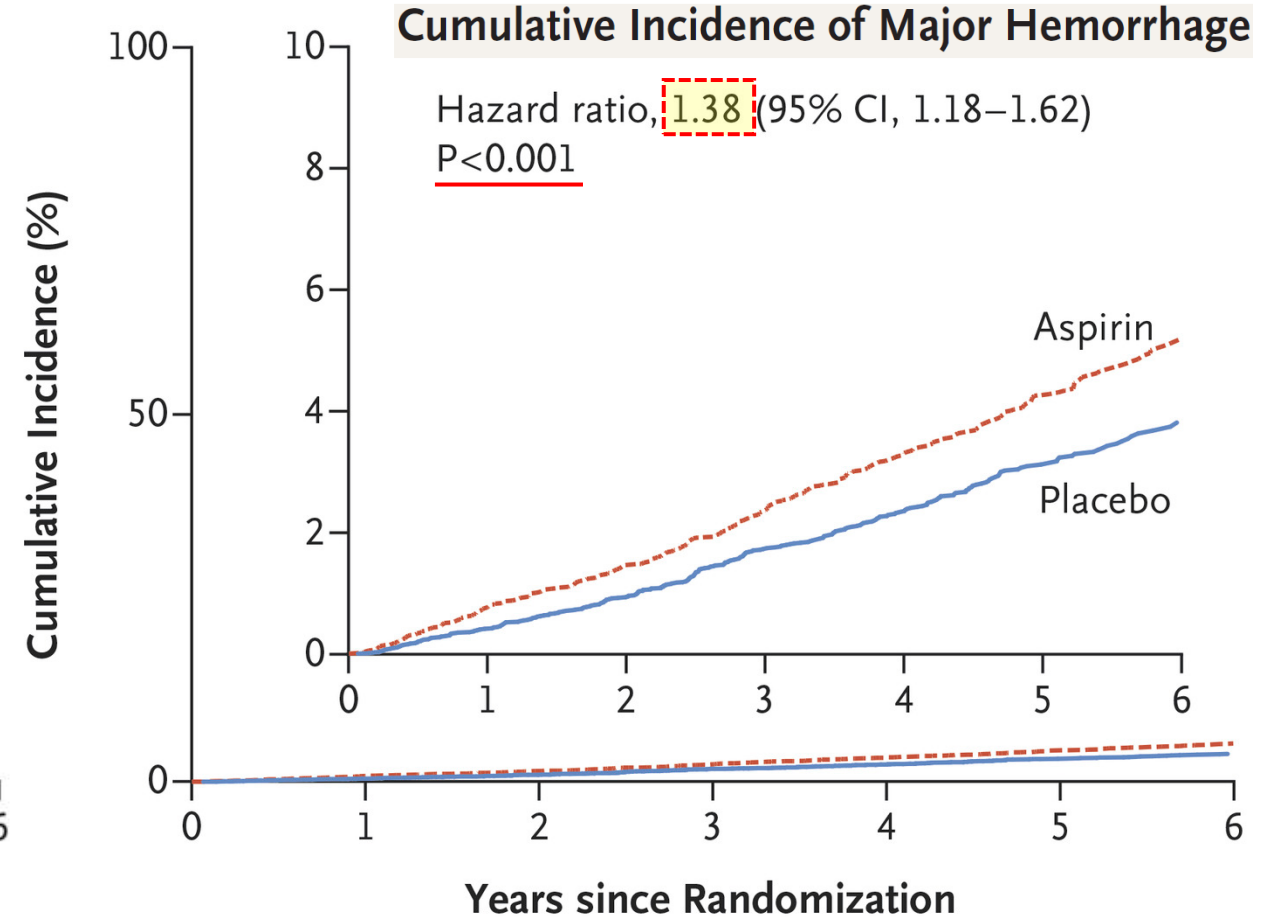
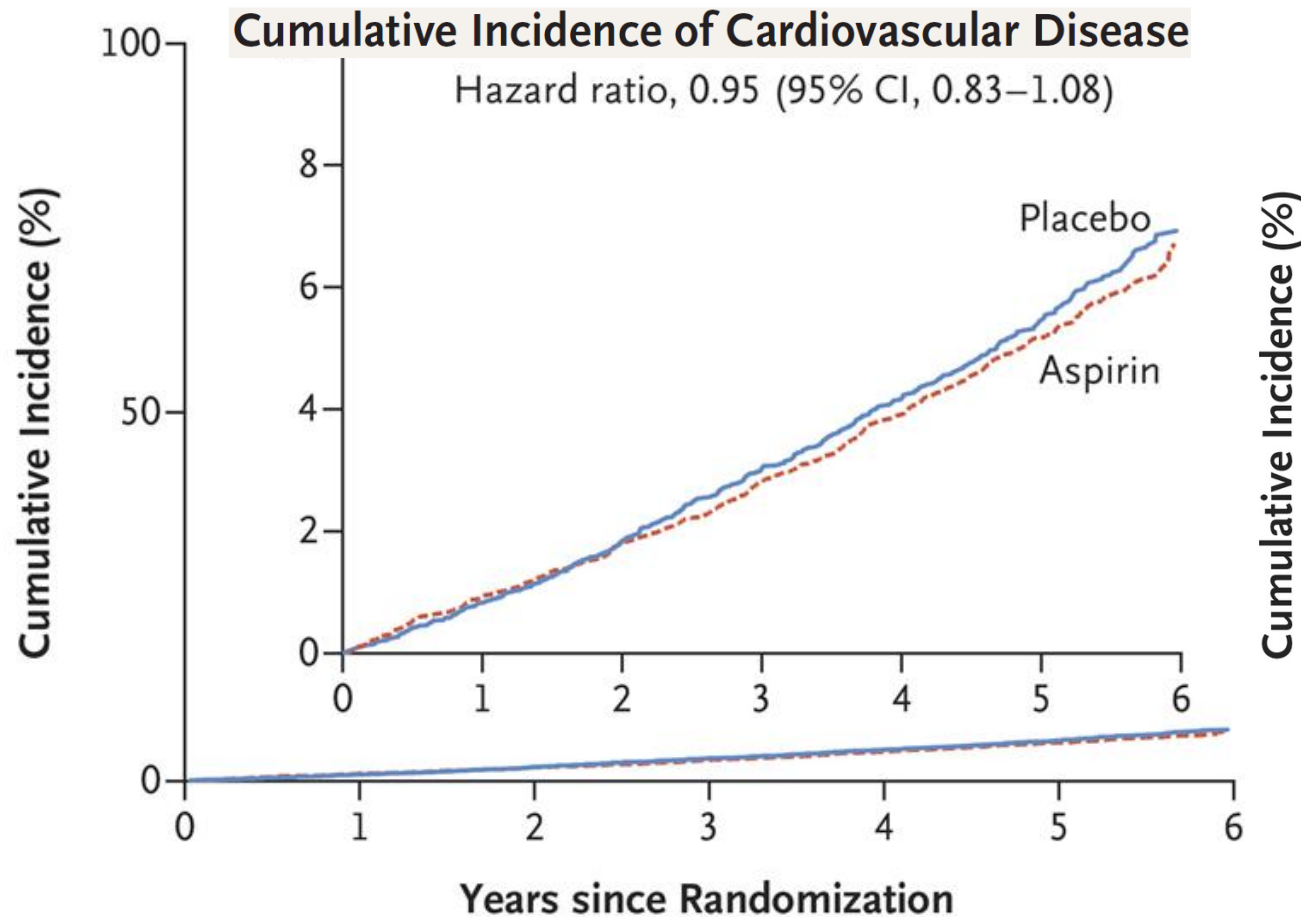


Effect of Aspirin on Cardiovascular Events and Bleeding in the **Healthy Elderly**

ASPREE

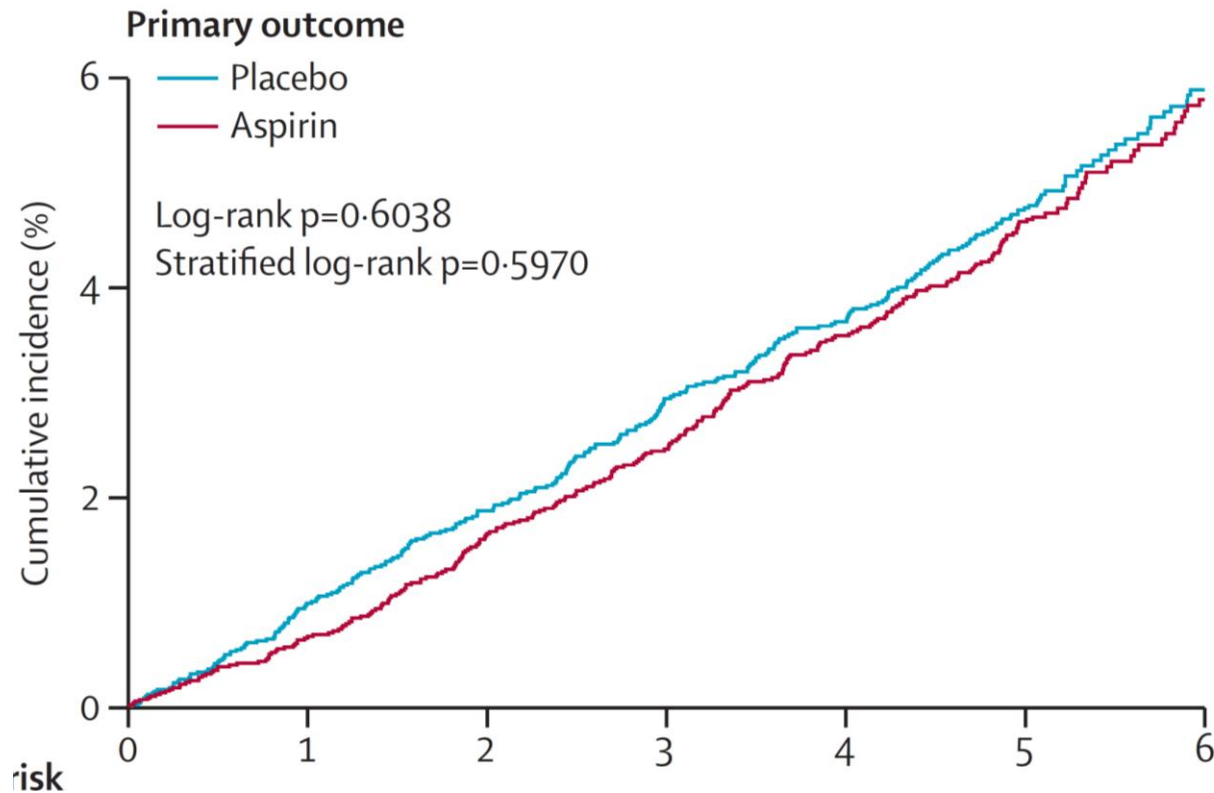
Conclusions

The use of low-dose aspirin as a primary prevention strategy in older adults resulted in a **significantly higher risk of major hemorrhage** and *did not result in a significantly lower risk of cardiovascular disease* than placebo.

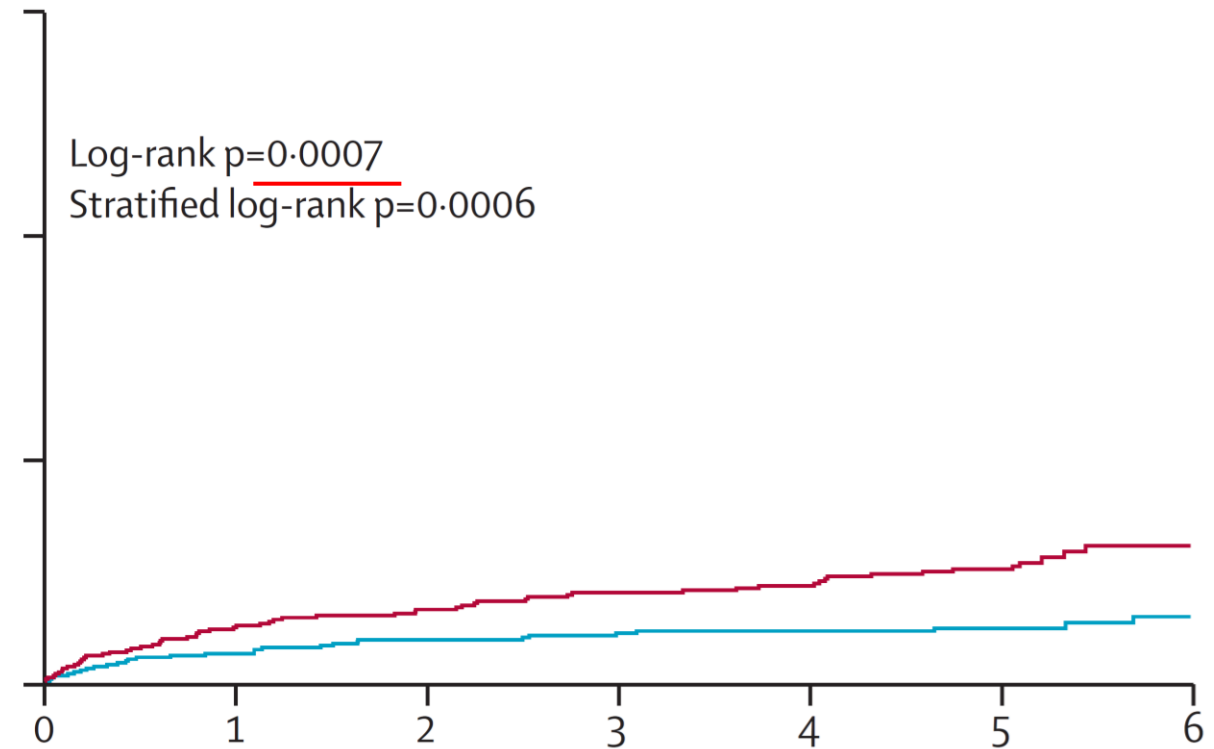


Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial

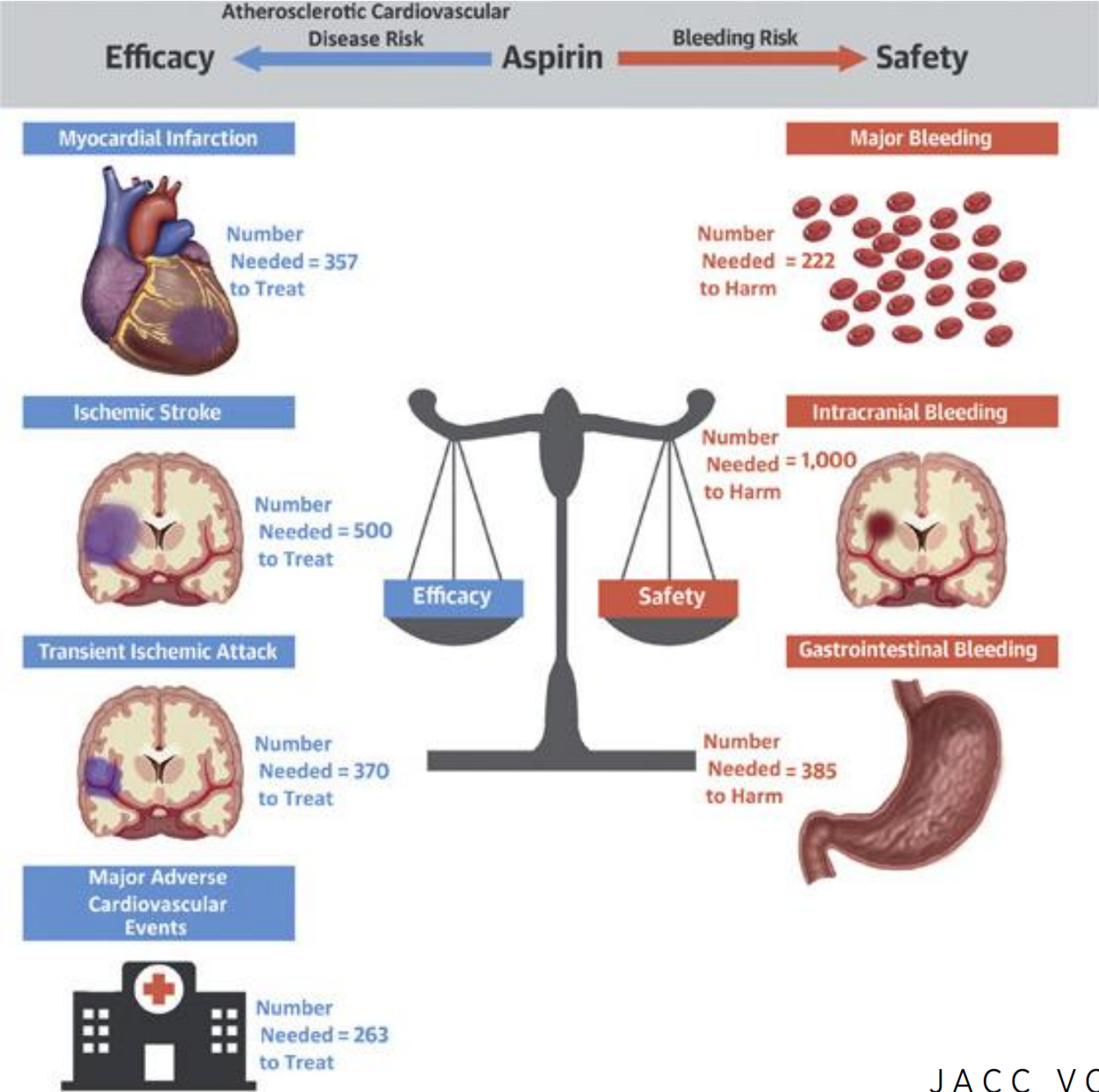
ARRIVE



Gastrointestinal bleeding



Aspirin for Primary Prevention of Cardiovascular Events



2021 ESC Guidelines on cardiovascular disease prevention in clinical practice

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

Recommendations for Aspirin Use Referenced studies that support recommendations are summarized in Online Data Supplements 17 and 18.		
COR	LOE	Recommendations
IIb	A	1. Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk. ^{54,6-1-54,6-8}
III: Harm	B-R	2. Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age. ^{54,6-9}
III: Harm	C-LD	3. Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding. ^{54,6-10}

Circulation. 2019;140:e596–e646

Recommendations	Class ^a	Level ^b
In patients with DM at high or very high CVD risk, low-dose aspirin may be considered for primary prevention in the absence of clear contraindications. ^{5,624,625}	IIb	A
Antiplatelet therapy is not recommended in individuals with low/moderate CV risk due to the increased risk of major bleeding. ^{624,626–630}	III	A

© ESC 2021

European Heart Journal (2021) **42**, 3227–3337

ANTIPLATELET AGENTS

10. Cardiovascular Disease and Risk Management: *Standards of Care in Diabetes—2023*

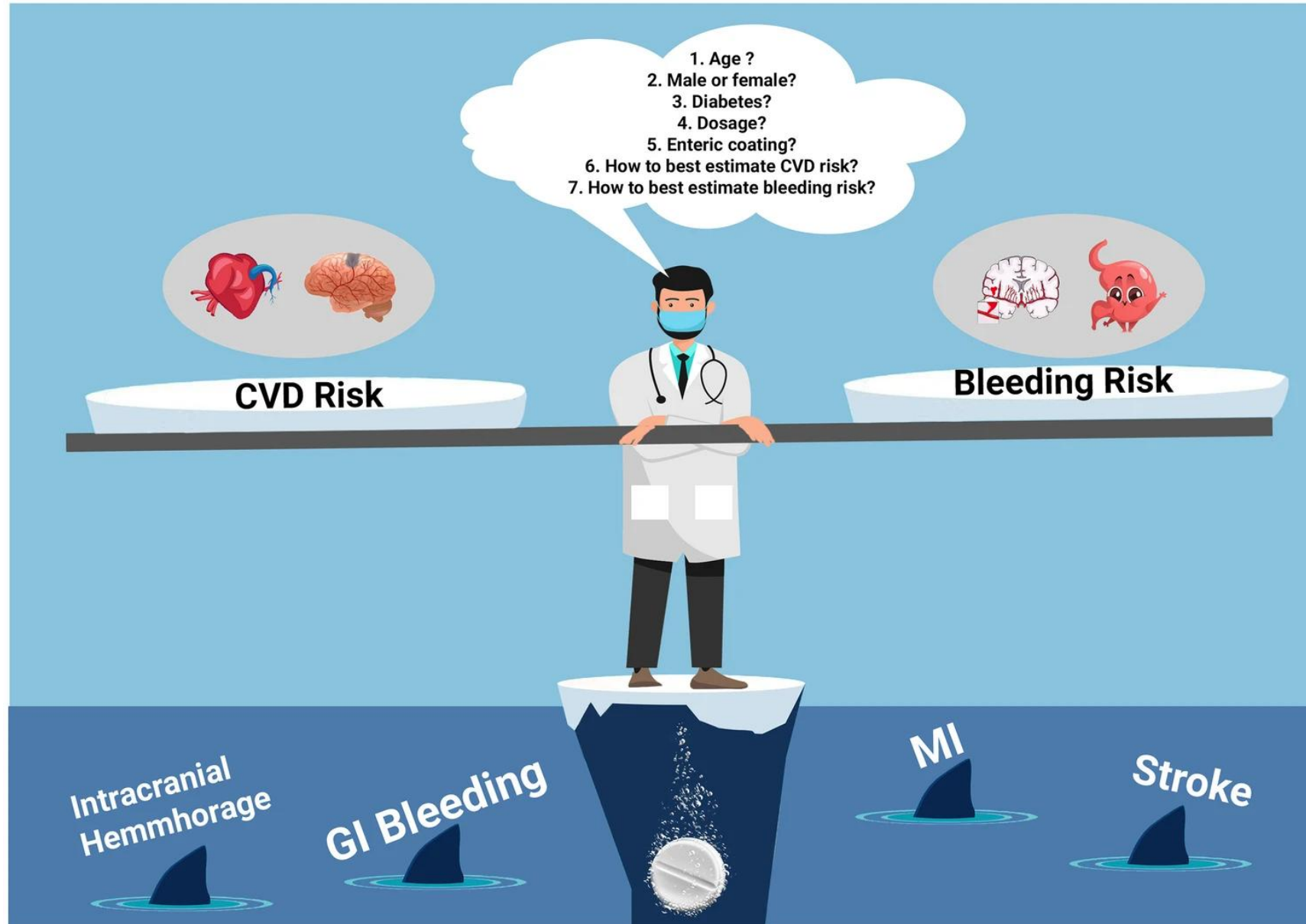
Recommendations

10.38 Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a comprehensive discussion with the patient on the benefits versus the comparable increased risk of bleeding. **A**

Diabetes Care 2023;46(Suppl. 1):S158–S190

Aspirin for Primary Prevention of Cardiovascular Diseases: “WALTZ” with the Evidence

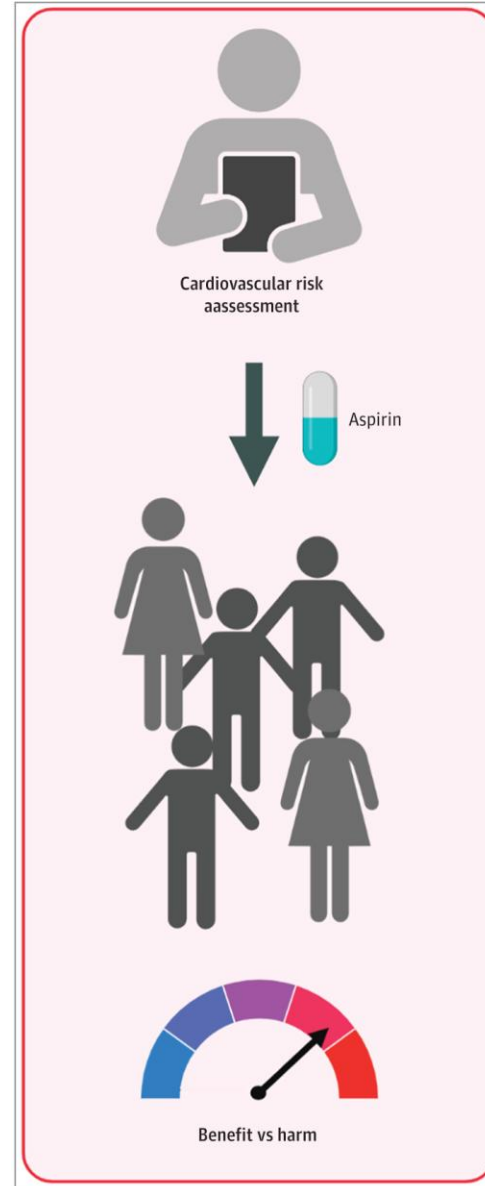
Kyriakos Dimitriadis¹ · Emilia Lazarou¹ · Panagiotis Tsioufis¹ · Stergios Soulaïdopoulos¹ · Konstantinos Tsioufis¹



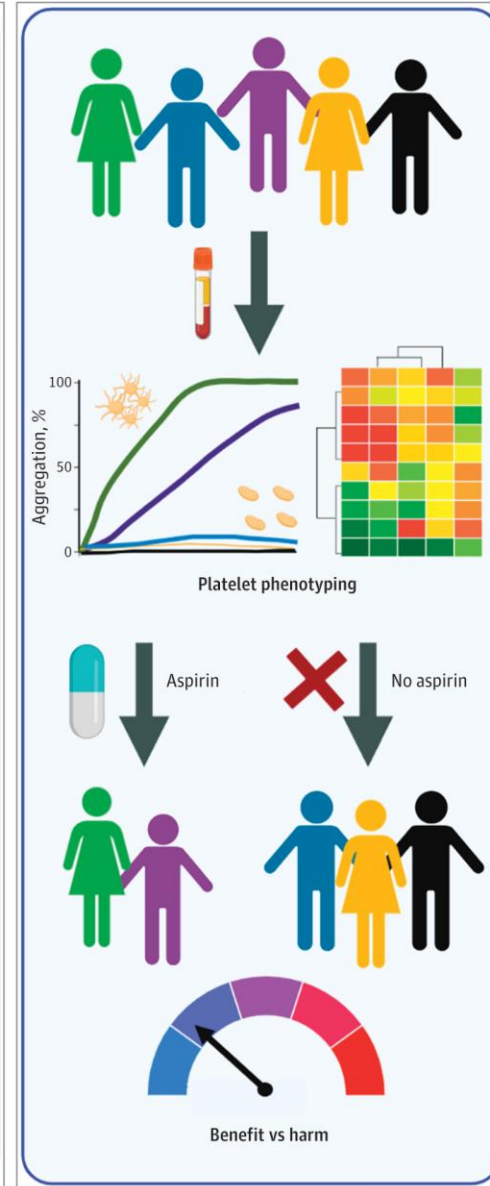
Aspirin for Primary Prevention—Time to Rethink Our Approach

Jeffrey S. Berger, MD, MS

A Traditional approach



B Personalized approach



Heart Disease and Stroke Statistics—2023 Update: A Report From the American Heart Association



Primary and Secondary Prevention of Ischemic Stroke and Cerebral Hemorrhage

JACC VOL. 75, NO. 15, 2020

APRIL 21, 2020:1804-18

JACC Focus Seminar

TABLE 2 Summary of the Effectiveness of Intervention for the Primary Prevention of First-Ever Stroke

Intervention	Risk Ratio	Stroke Risk per Year (%)		Relative Risk Reduction (95% CI) (%)	Absolute Risk Reduction (%)
		Control	Intervention		
Nil		0.14			
Blood pressure-lowering (by 10-mm Hg systolic)	1.54	0.22	0.13	41 (33-48)	0.09
LDL cholesterol-lowering (by 1.0 mmol/l)	1.27	0.18	0.14	21 (6-33)	0.04
Anticoagulation (for atrial fibrillation)	5.00	0.70	0.25	64 (49-74)	0.45
Cigarette smoking-cessation	1.45	0.20	0.14	31 (25-36)	0.06

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ «ΚΑΡΔΙΟΜΕΤΑΒΟΛΙΚΗ ΙΑΤΡΙΚΗ»

Πρωτογενής Πρόληψη ΑΕΕ
Δευτερογενής πρόληψη (αντιθρομβωτική αγωγή)

Κακαλέτσης Νικόλαος

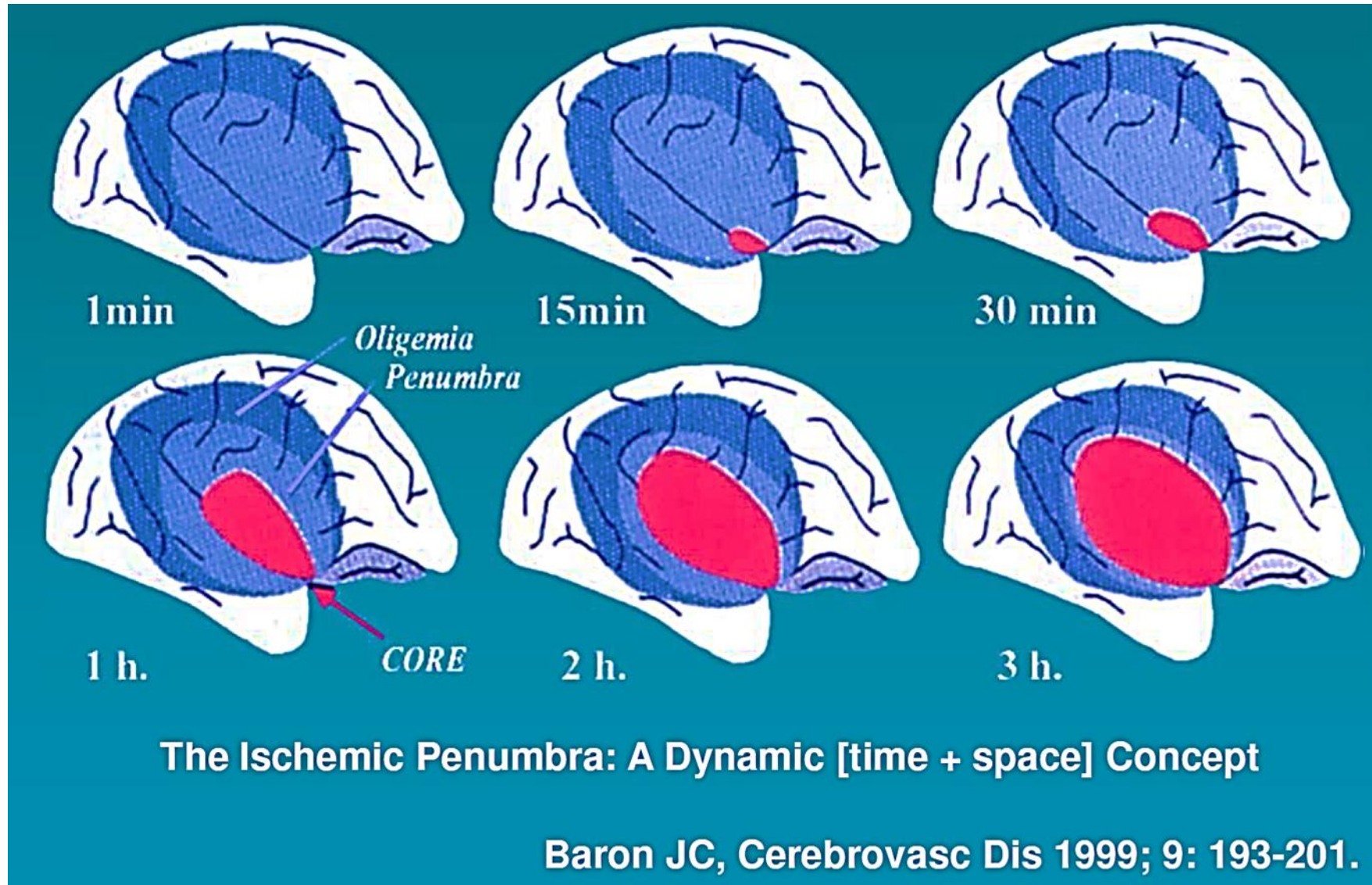
Παθολόγος

Επιμελητής Β', Β' Παθολογική Κλινική, Γ.Ν.Θ. Ιπποκράτειο

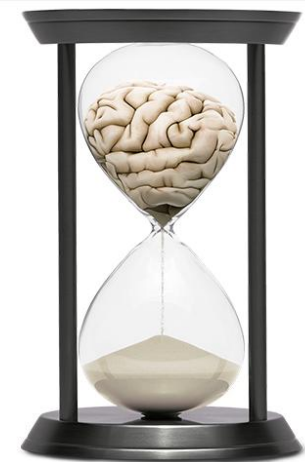
Μεταδιδακτορικός Ερευνητής Ιατρικής Σχολής Α.Π.Θ.

Stroke Research Fellow, HUS Helsinki University Hospital and University of Helsinki, Finland

Growth of Infarction



Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials



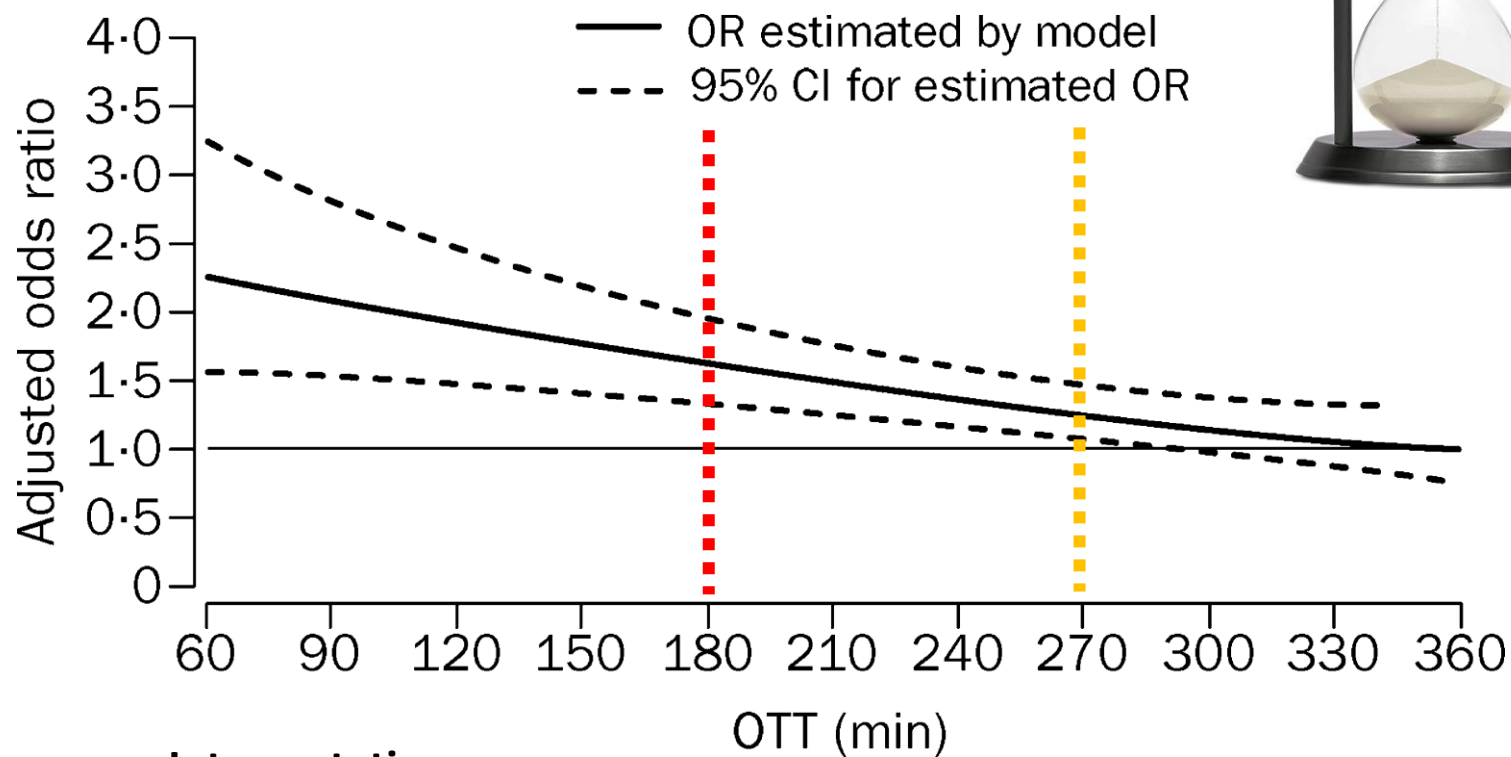
**ΣΥΣΤΑΣΕΙΣ ΓΙΑ ΤΗΝ ΕΝΔΟΦΛΕΒΙΑ
ΘΡΟΜΒΟΛΥΣΗ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΟΞΕΥ
ΙΣΧΑΙΜΙΚΟ ΑΓΓΕΙΑΚΟ ΕΓΚΕΦΑΛΙΚΟ
ΕΠΕΙΣΟΔΙΟ.**



Ένας κλινικός οδηγός από τον Ελληνικό Οργανισμό
Εγκεφαλικών

1. Κάθε ασθενής με συμπτώματα οξέος ΑΕΕ θα πρέπει να αντιμετωπίζεται ως πιθανός υποψήφιος για θεραπεία με ενδοφλέβια θρομβόλυση εφόσον βρίσκεται εντός 4,5 ωρών από την έναρξη των συμπτωμάτων (Σύσταση 1Α). Στο πλαίσιο αυτό, θα πρέπει να του παραχωρείται άμεση πρόσβαση στον αξονικό ή μαγνητικό τομογράφο, ώστε να υποβληθεί σε επείγουσα απεικόνιση του εγκεφάλου όσο το δυνατόν ταχύτερα για να αποκλειστεί το ενδεχόμενο ενδοκράνιας αιμορραγίας (Σύσταση 1Γ).

HEART VESSELS & BRAIN | ΙΟΥΛΙΟΣ - ΣΕΠΤΕΜΒΡΙΟΣ 2017



Interpretation

The sooner that rt-PA is given to stroke patients, the greater the benefit, especially if started within 90 min. Our results suggest a potential benefit beyond 3 h, but this potential might come with some risks.

Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials

ΣΥΣΤΑΣΕΙΣ ΓΙΑ ΤΗΝ ΜΗΧΑΝΙΚΗ ΘΡΟΜΒΕΚΤΟΜΗ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΟΞΥ ΙΣΧΑΙΜΙΚΟ ΑΓΓΕΙΑΚΟ ΕΓΚΕΦΑΛΙΚΟ ΕΠΕΙΣΟΔΙΟ.

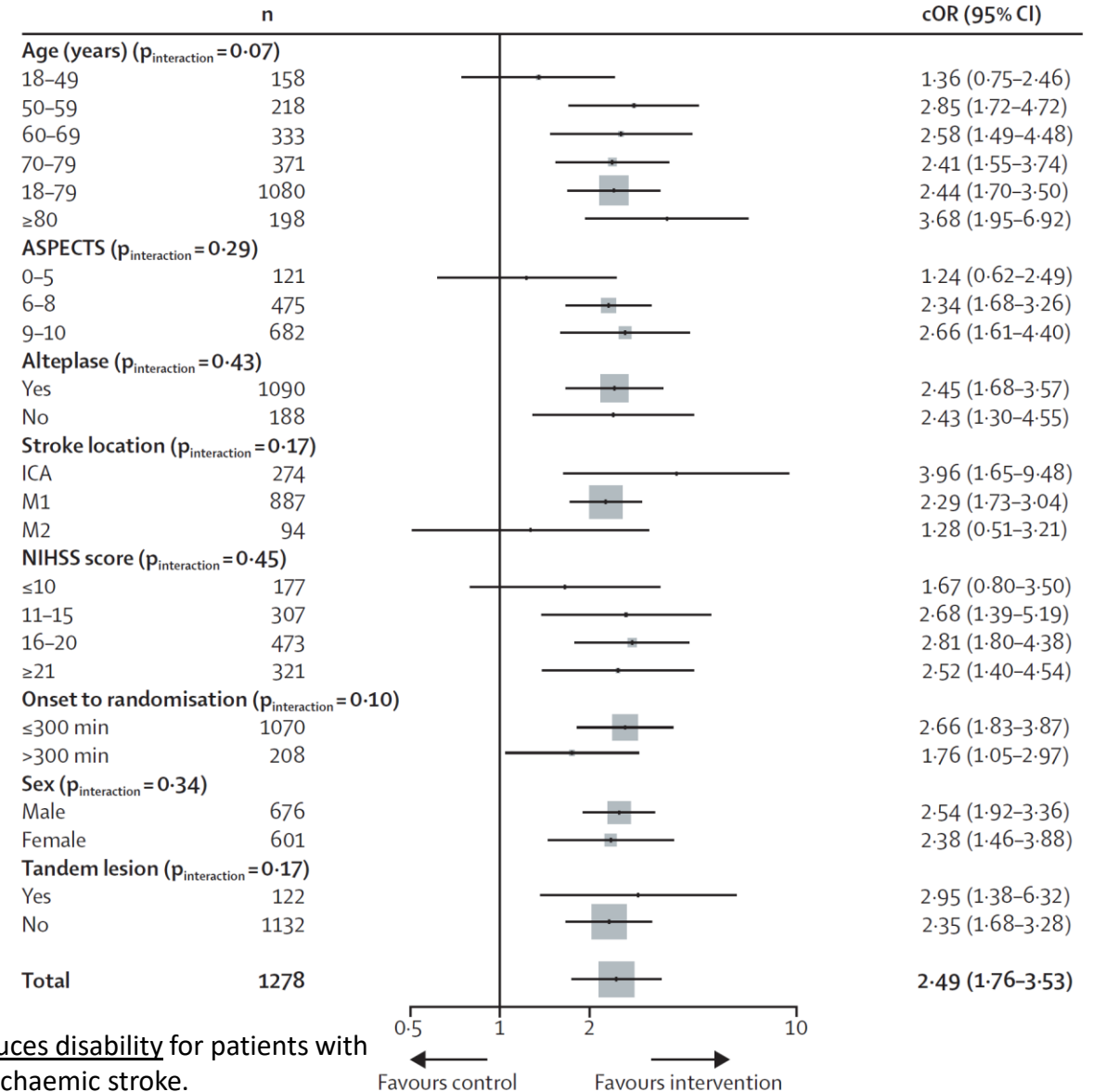
Ένας κλινικός οδηγός από τον Ελληνικό Οργανισμό Εγκεφαλικών.



1. Σε ασθενείς με σημαντικά νευρολογικά συμπτώματα λόγω ισχαιμικού αγγειακού εγκεφαλικού επεισοδίου (ΑΕΕ) με απόφραξη μεγάλου κλάδου της πρόσθιας ενδοκράνιας κυκλοφορίας, συνιστάται ενδαγγειακή θεραπεία με μηχανική θρομβεκτομή έως 6 ώρες μετά την έναρξη των συμπτωμάτων (1Α). Η παρουσία συνυπάρχουσας σύστοιχης εξωκράνιας καρωτιδικής νόσου δεν αποτελεί αντένδειξη (2Β). Μετά την πάροδο των 6 ωρών συνιστάται θρομβεκτομή σε επιλεγμένους ασθενείς (1Α). Επί απουσίας αντενδείξεων, οι ασθενείς θα πρέπει να λαμβάνουν προηγούμενως ενδοφλέβια θρομβόλυση με αλτεπλάση εφόσον αυτή δύναται να χορηγηθεί εντός 4.5 ωρών από την έναρξη της συμπτωματολογίας (1Α).

HEART VESSELS & BRAIN | ΑΠΡΙΛΙΟΣ - ΙΟΥΝΙΟΣ 2017

- MR CLEAN
- ESCAPE
- REVASCAT
- SWIFT PRIME
- EXTEND IA



In conclusion, **endovascular thrombectomy reduces disability** for patients with large vessel anterior circulation ischaemic stroke.

Benefits are seen across a wide range of age and initial stroke severity and apply to patients **irrespective** of eligibility for **intravenous alteplase**.

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ «ΚΑΡΔΙΟΜΕΤΑΒΟΛΙΚΗ ΙΑΤΡΙΚΗ»

Πρωτογενής Πρόληψη ΑΕΕ
Δευτερογενής πρόληψη (αντιθρομβωτική αγωγή)

Κακαλέτσης Νικόλαος

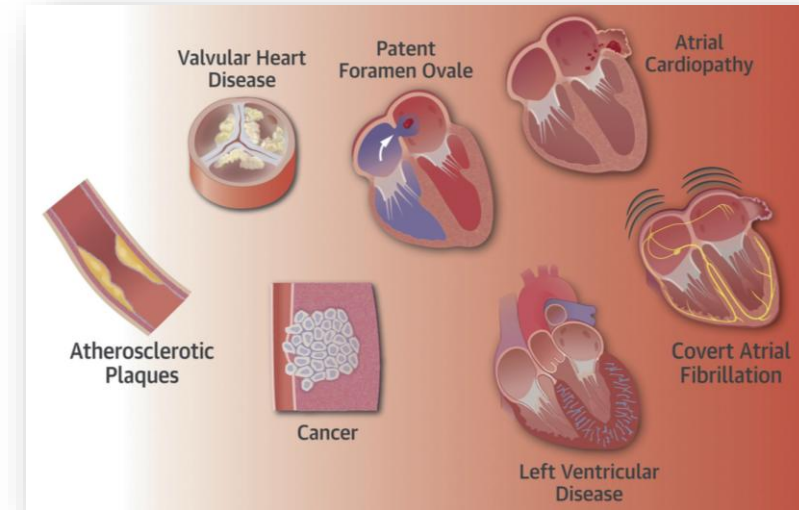
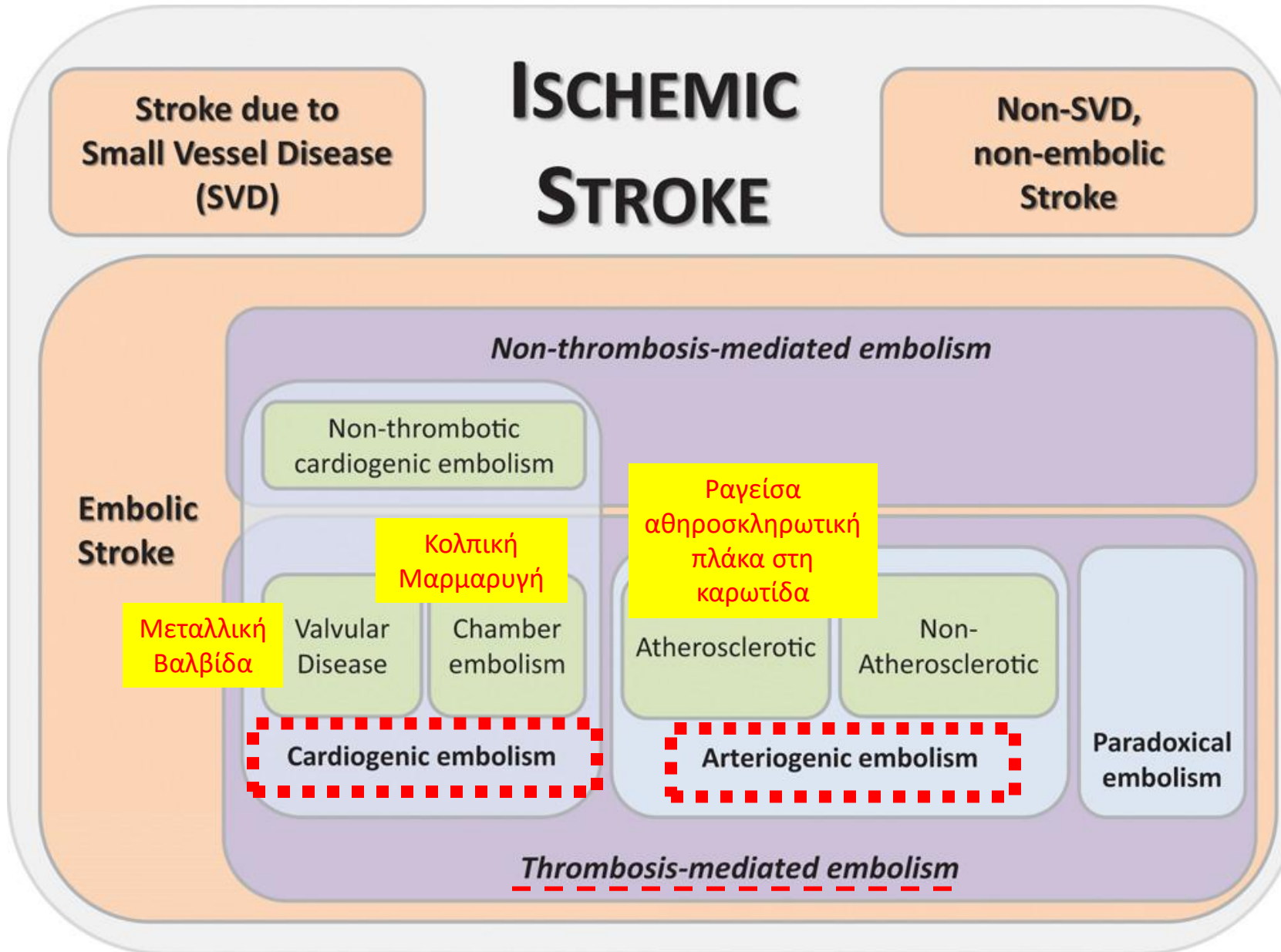
Παθολόγος

Επιμελητής Β', Β' Παθολογική Κλινική, Γ.Ν.Θ. Ιπποκράτειο

Μεταδιδακτορικός Ερευνητής Ιατρικής Σχολής Α.Π.Θ.

Stroke Research Fellow, HUS Helsinki University Hospital and University of Helsinki, Finland

Ischemic stroke is an etiologically heterogeneous syndrome



Ntaios G. Embolic Stroke of Undetermined Source: JACC Review Topic of the Week. J Am Coll Cardiol. 2020 Jan 28;75(3):333-340.

In order to optimize the **secondary prevention strategy** in a patient with ischemic stroke, it is rational to identify the underlying etiologic pathology.

Hellenic Journal of Atherosclerosis

ΚΛΙΝΙΚΟΣ ΟΔΗΓΟΣ

Συστάσεις για την αντιθρομβωτική αγωγή
σε ασθενείς με ισχαιμικό εγκεφαλικό επεισόδιο

Γ. Ντάιος, Γ. Ανδρικόπουλος, Ε. Αρναούτογλου, Ε. Βαβουρανάκης,
Γ. Γεροτζιάφας, Ε. Κορομπόκη, Μ. Ματσάγκας, Χ. Μηλιώνης,
Β. Παπαβασιλείου, Α. Πλωμαρίτογλου, Δ. Ρίχτερ, Σ. Σουρμελής, Κ. Σπέγγος,
Κ. Τάκης, Κ. Τζιόμαλος, Α. Τσελέπη, Α. Ι. Χατζητόλιος, Κ. Βέμμος

*Ένας κλινικός οδηγός από τον Ελληνικό Οργανισμό Εγκεφαλικών
και το Ινστιτούτο Μελέτης και Εκπαίδευσης στη Θρόμβωση
και την Αντιθρομβωτική Αγωγή*



ΑΘΗΝΑ, 2017



OFFICIAL THREE-MONTHLY JOURNAL
OF THE HELLENIC ATHEROSCLEROSIS SOCIETY

www.hjatherosclerosis.com

Ισχαιμικό ΑΕΕ / Παροδικό ΑΕΕ

Μη καρδιοεμβολικό

Καρδιοεμβολικό

TIA

ABCD²<4

ABCD²≥4

NIHSS<4

NIHSS≥4

Ασπιρίνη 100mgx1 &
Κλοπιδογρέλη 75mgx1

21 ημέρες

10 ημέρες ή
εξιτήριο

- Ασπιρίνη (50-325mg x1)
- Κλοπιδογρέλη (75mg x1)
- Τριφλουζάλη (600mg x1)
- Ασπιρίνη/διπυριδαμόλη (25mg/200mg x2)

TIA

NIHSS<8

NIHSS 8-16

NIHSS>16

Ασπιρίνη 160-300mg x1

1^η

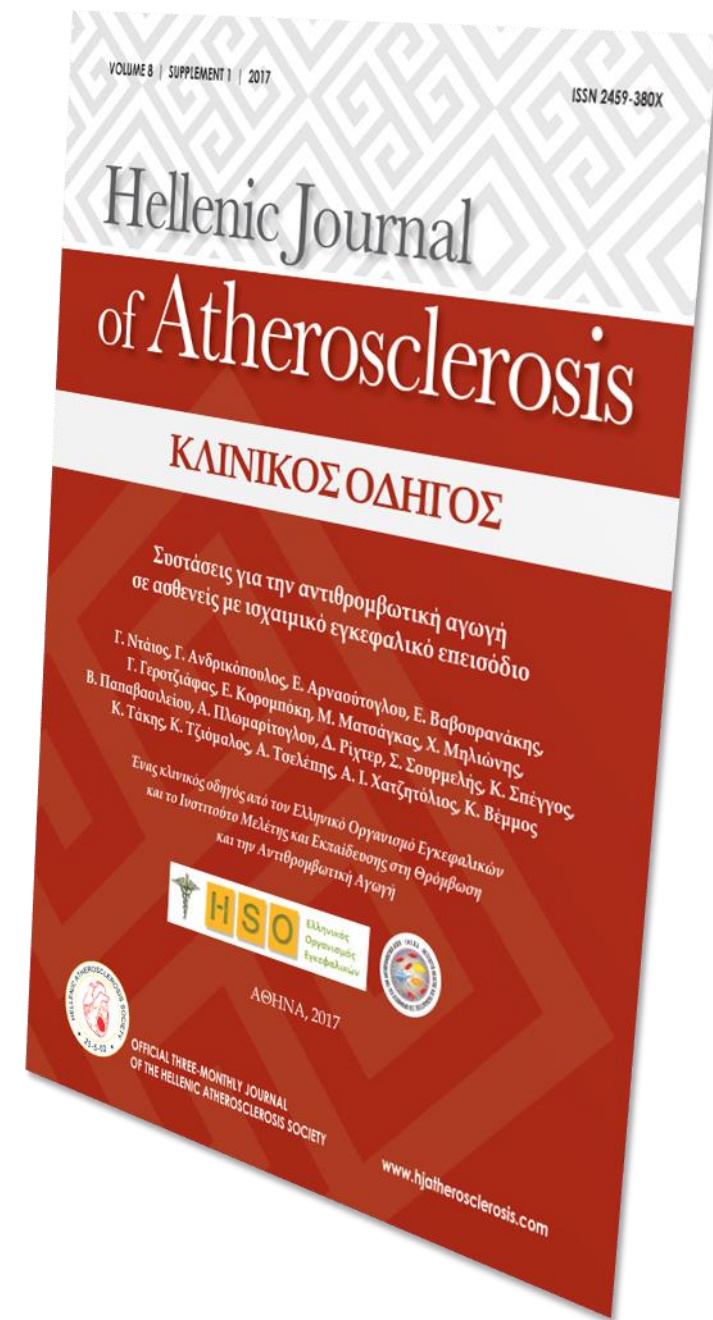
3^η

7^η

14^η

NOAC ή Sintrom

1. Ασθενείς με **ισχαιμικό** (εγκατεστημένο ή παροδικό) εγκεφαλικό επεισόδιο χωρίς κολπική μαρμαρυγή ή μεταλλική βαλβίδα ή άλλη ένδειξη για αντιπηκτική αγωγή πρέπει να λαμβάνουν **αντιαιμοπεταλιακή αγωγή** (1A).

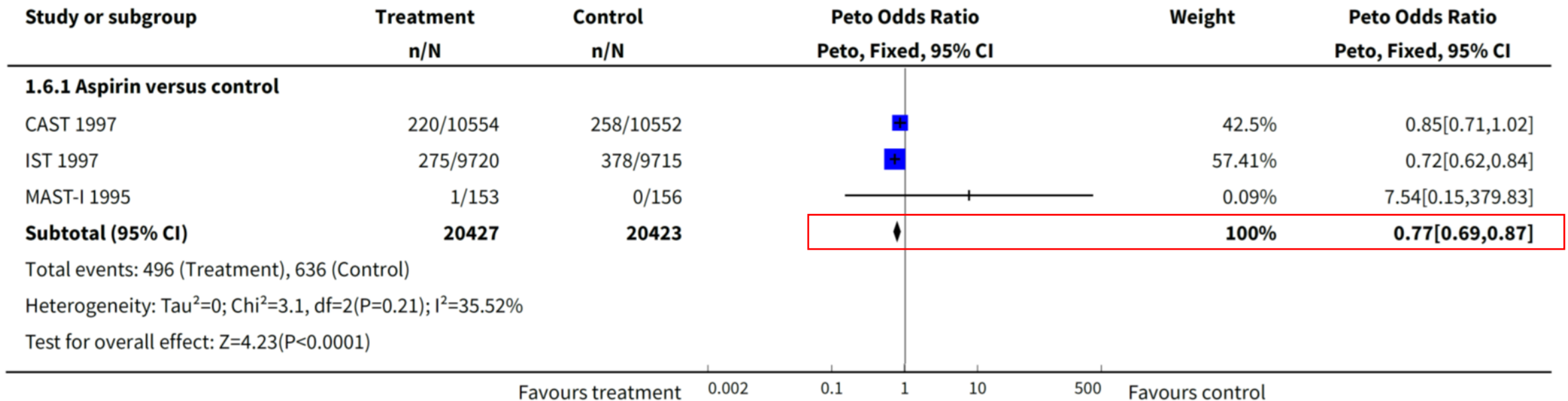


Oral antiplatelet therapy for acute ischaemic stroke (Review)

Sandercock PAG, Counsell C, Tseng MC, Cecconi E

Study	Participants	Stroke	Intervention	Age	FU
CAST Chinese Acute Stroke Trial	21,106	<48h	aspirin 160mg vs placebo	28% >70 years	4 weeks or discharge
IST International Stroke Trial	19,435	<48h	sc heparin (5000 IU or 12 500 IU 12 hourly), aspirin 300 mg, both, or neither	61% >70 years	14 days or discharge
MAST-I Multicentre Acute Stroke Trial-Italy	309	<6h	aspirin 300 mg oral (or iv/rectal) 24 hourly vs no treatment	46% 61-75 years	10 days

Analysis 1.6. Comparison 1 Antiplatelet drug versus control in acute presumed ischaemic stroke, Outcome 6 Recurrent ischaemic/unknown stroke during treatment period.



Antiplatelet therapy with **aspirin 160 mg to 300 mg** daily, given orally (or by nasogastric tube or per rectum in people who cannot swallow) and started **within 48 hours** of onset of presumed ischaemic stroke, reduced the risk of early recurrent ischaemic stroke without a major risk of early haemorrhagic complications; long-term outcomes were improved.

Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

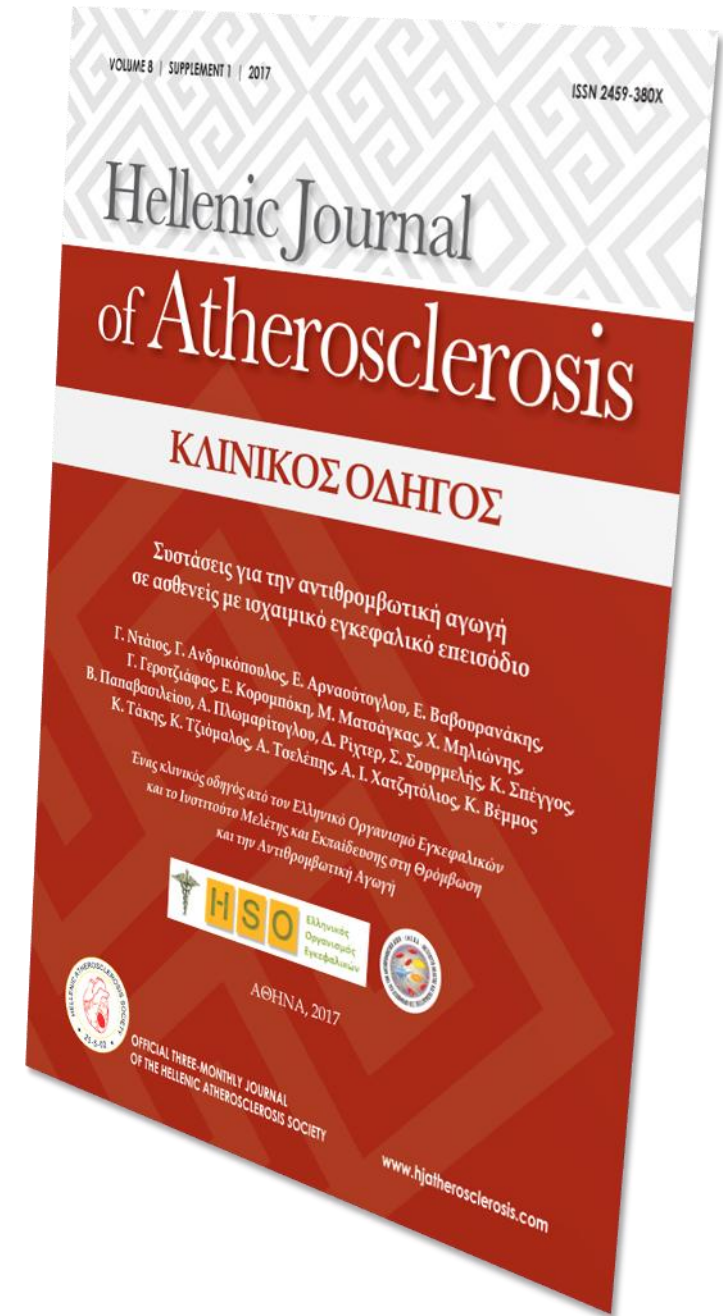
Endorsed by the Society for Academic Emergency Medicine and The Neurocritical Care Society

3.9. Antiplatelet Treatment	COR	LOE	New, Revised, or Unchanged
1. Administration of aspirin is recommended in patients with AIS within 24 to 48 hours after onset. For those treated with IV alteplase, aspirin administration is generally delayed until 24 hours later but might be considered in the presence of concomitant conditions for which such treatment given in the absence of IV alteplase is known to provide substantial benefit or withholding such treatment is known to cause substantial risk.	I	A	Recommendation revised from 2013 AIS Guidelines.

4. Ασθενείς με οξύ ισχαιμικό εγκεφαλικό επεισόδιο πρέπει να λαμβάνουν **ασπιρίνη** (325 mg) αμέσως μόλις αποκλειστεί η αιμορραγία εγκεφάλου (1Α). Σε ασθενείς που έχουν υποβληθεί σε **ενδοφλέβια θρομβόλυση**, η αντιαιμοπεταλιακή αγωγή πρέπει να καθυστερεί 24 ώρες και να ξεκινά αφού αποκλειστεί η αιμορραγία εγκεφάλου (1Γ).

9. Σε ασθενείς με οξύ **ισχαιμικό** εγκεφαλικό επεισόδιο και ένδειξη αντιπηκτικής αγωγής, η έναρξη της αντιπηκτικής αγωγής πρέπει να καθυστερεί για κάποιο χρονικό διάστημα ώστε να μειωθεί ο κίνδυνος αιμορραγικής μετατροπής του εγκεφαλικού εμφράκτου ...

Στο μεσοδιάστημα ο ασθενής θα πρέπει να λαμβάνει **ασπιρίνη**.



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NOAC ή Sintrom

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1^η

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14^η

NOAC ή Sintrom

	ΒΑΘΜΟΙ
1. Επίπεδο συνείδησης	
1Α) Γενικό επίπεδο συνείδησης	
• Εγρήγορση με έντονες ανταποκρίσεις.	0
• Απουσία εγρήγορσης – απαιτούνται μικρά ερεθίσματα για να επιτευχθεί ανταπόκριση, να δοθούν απαντήσεις ή να εκτελεσθούν εντολές.	1
• Βυθιότητα – Απαιτούνται επανειλημμένα ερεθίσματα για να μπορέσει ο ασθενής να παρακολουθήσει τον εξεταστή ή πολύ έντονα ακόμη και επώδυνα ερεθίσματα για να προκληθεί κινητική αντίδραση	2
• Κώμα – Μόνο αντανακλαστικές αντιδράσεις (κινητικές ή του αυτόνομου νευρικού) ή πλήρης απουσία οποιασδήποτε αντίδρασης	3
1Β) Ερώτηση ηλικίας και τρέχοντος μήνα	
• Σωστές απαντήσεις και στις δύο ερωτήσεις	0
• Μια μόνο σωστή απάντηση	1
• Καμία σωστή απάντηση	2
1Γ) Άνοιγμα και κλείσιμο βλεφάρων και σχηματισμός γροθιάς με το μη παρετικό άκρο	
• Σωστή εκτέλεση και των δύο δοκιμασιών	0
• Σωστή εκτέλεση μιας μόνο δοκιμασίας	1
• Καμία δοκιμασία δεν εκτελείται σωστά	2
2. Κινήσεις οφθαλμών (οριζόντιο επίπεδο)	
• Φυσιολογικές	0
• Μερική πάρεση – ανώμαλη κίνηση οφθαλμού τουλάχιστον σε έναν οφθαλμό	1
• Συζυγής απόκλιση οφθαλμών ή παράλυση που δεν διορθώνονται κατά την προσπάθεια ελέγχου του οφθαλμοκινητικού αντανακλαστικού (oculocephalic maneuver)	2
3. Οπτικά πεδία	
• Καμία απώλεια όρασης	0
• Μερική ημιανοψία	1
• Πλήρης ημιανοψία	2
• Αμφοτερόπλευρη ημιανοψία (τύφλωση που συμπεριλαμβάνει την φλοιϊκή αιτιολογία τύφλωση)	3
4. Πάρεση μυών προσώπου	
• Φυσιολογικές συμμετρικές κινήσεις προσώπου	0
• Ήπια έκπτωση μυϊκής ισχύος (αποπλάτυνση της ρινοχειλικής αύλακας, ασυμμετρία στο χαμόγελο)	1

• Μερική πάρεση (πλήρης ή σχεδόν πλήρης παράλυση μόνο στο κατώτερο τμήμα του προσώπου)		2
• Πλήρης έτερο- ή αμφοτερό-πλευρη πάρεση (ανώτερο και κατώτερο τμήμα του προσώπου)		3
5. Μυϊκή ισχύς άνω άκρων (κάθε άνω άκρο εξετάζεται για 10 δευτερόλεπτα και βαθμολογείται χωριστά)	Δ	A
• Το άκρο διατηρείται στην αρχική θέση εξέτασης	0	0
• Προοδευτική πτώση άνω άκρου, χωρίς να ακουμπήσει στο σώμα ή το κρεβάτι εντός των 10 δευτερολέπτων	1	1
• Προοδευτική πτώση άνω άκρου, που ακουμπά στο σώμα ή το κρεβάτι πριν την παρέλευση των 10 δευτερολέπτων	2	2
• Καμία ένδειξη προσπάθειας διατήρησης στη θέση εξέτασης (καμία προσπάθεια αντιβαρικής κίνησης)	3	3
• Δεν παρατηρείται καμία ένδειξη μυϊκής ισχύος στο άκρο (π.χ. κίνηση δακτύλων)	4	4
6. Μυϊκή ισχύς κάτω άκρων (κάθε κάτω άκρο εξετάζεται για 5 δευτερόλεπτα και βαθμολογείται χωριστά)	Δ	A
• Το άκρο διατηρείται στην αρχική θέση εξέτασης	0	0
• Προοδευτική πτώση κάτω άκρου, χωρίς να ακουμπήσει στο σώμα ή το κρεβάτι εντός των 5 δευτερολέπτων	1	1
• Προοδευτική πτώση κάτω άκρου, που ακουμπά στο σώμα ή το κρεβάτι πριν την παρέλευση των 5 δευτερολέπτων	2	2
• Καμία ένδειξη προσπάθειας διατήρησης στη θέση εξέτασης (καμία προσπάθεια αντιβαρικής κίνησης)	3	3
• Δεν παρατηρείται καμία ένδειξη μυϊκής ισχύος στο άκρο (π.χ. κίνηση δακτύλων)	4	4
7. Αταξία άκρου/ων (δοκιμασίες δείκτη-ρινός) και πτέρνας-κνήμης)		
• Απουσία αταξίας		0
• Αταξία σε ένα μόνο άκρο		1
• Αταξία σε δύο άκρα		2
8. Αισθητικότητα		
• Φυσιολογική		0
• Ήπια ή ενδιάμεσης βαρύτητας απώλεια αισθητικότητας (ο ασθενής όμως μπορεί ακόμη να αισθανθεί ότι τον αγγίζουμε στη διάρκεια της δοκιμασίας)		1
• Σοβαρή ή πλήρης απώλεια της αισθητικότητας (ο ασθενής δεν έχει την αίσθηση του αγγίγματος, του νυγμού ή του επώδυνου ερεθίσματος που προκαλεί ο εξεταστής)		2
9. Λόγος/Αφασία (εκτίμηση με τη χρήση των εικόνων της αυθεντικής κλίμακας)		
• Φυσιολογικός λόγος, καμία ένδειξη αφασίας		0

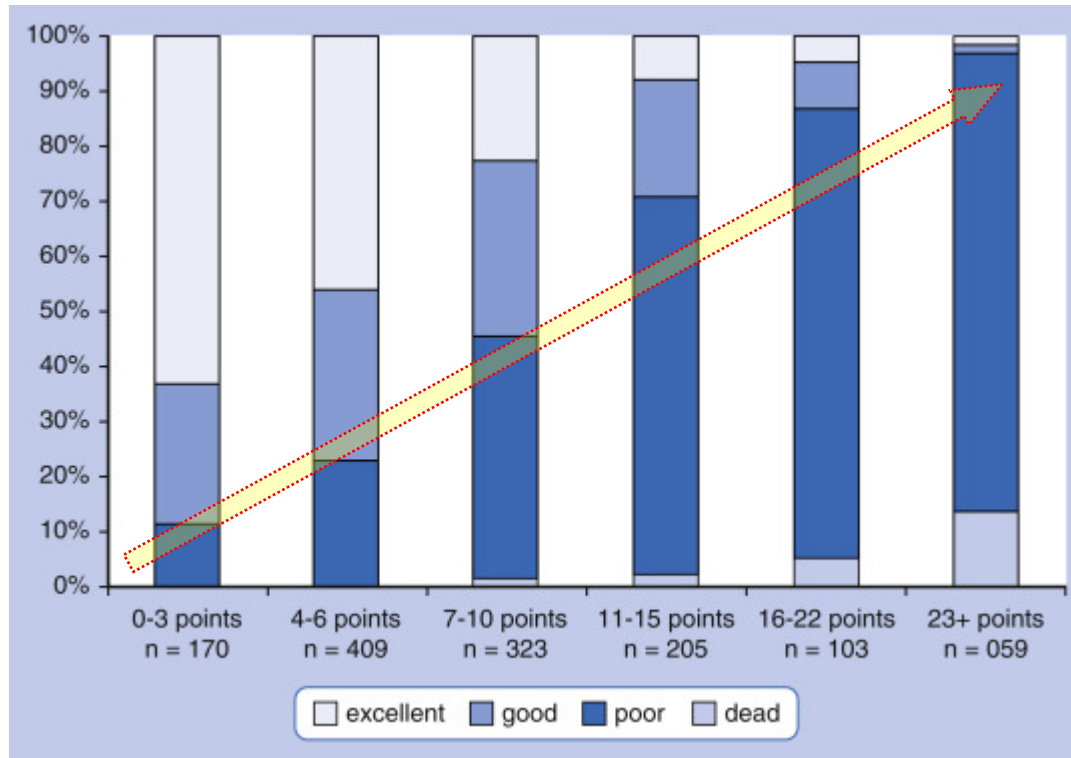
ΣΥΣΤΑΣΕΙΣ ΓΙΑ ΤΗΝ ΕΝΔΟΦΛΕΒΙΑ ΘΡΟΜΒΟΛΥΣΗ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΟΞΥ ΙΣΧΑΙΜΙΚΟ ΑΓΓΕΙΑΚΟ ΕΓΚΕΦΑΛΙΚΟ ΕΠΕΙΣΟΔΙΟ.

Ένας κλινικός οδηγός από τον Ελληνικό Οργανισμό Εγκεφαλικών

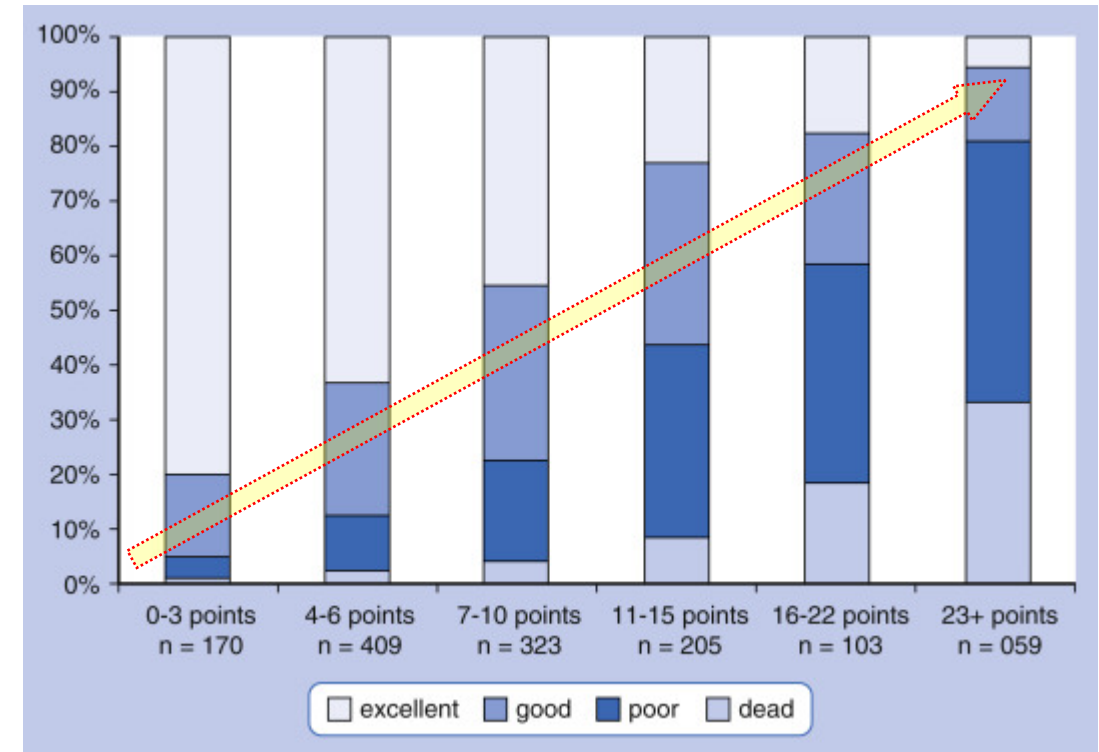
• Ήπια ή ενδιάμεσης βαρύτητας αφασία	1
• Σοβαρή αφασία	2
• Πλήρης απουσία λόγου, σφαιρική αφασία	3
10. Δυσαρθρία	
• Απουσία δυσαρθρίας	0
• Ήπια ή ενδιάμεσης βαρύτητας δυσαρθρία	1
• Σοβαρή δυσαρθρία (ακατάληπτος λόγος που δεν μπορεί να αποδοθεί σε αφασία) ή αναρθρία	2
11. Αναγνώριση ταυτόχρονων αμφοτερόπλευρων ερεθισμάτων	
• Καμία διαταραχή	0
• Αδυναμία αναγνώρισης ενός εκ των οπτικών, απτικών και οπτικοχωρικών ακουστικών ερεθισμάτων	1
• Αδυναμία αναγνώρισης τουλάχιστον δύο διαφορετικών τύπων ερεθισμάτων. Ο ασθενής μπορεί να μην αναγνωρίζει κάποιο από τα άκρα του ή να προσανατολίζεται μόνο προς μια μεριά του χώρου.	2

Συνιστάται η **εξάσκηση** αλλά και **διαδικτυακή εκπαίδευση** των επαγγελματιών υγείας που εμπλέκονται στην αντιμετώπιση ασθενών με αγγειακά εγκεφαλικά επεισόδια στην κλίμακα NIHSS πριν από τη χρήση του παραπάνω πίνακα.

National Institutes of Health Stroke Scale



Effect of baseline National Institutes of Health Stroke Scale score on outcome at **7 days**.



Effect of baseline National Institutes of Health Stroke Scale score on outcome at **3 months**.

NIH Stroke Scale/Score (NIHSS)★

Calculates the NIH Stroke Scale for quantifying stroke severity.

INSTRUCTIONS

The NIH Stroke Scale has many caveats buried within it. If your patient has prior known neurologic deficits e.g. prior weakness, hemi- or quadriplegia, blindness, etc. or is intubated, has a language barrier, etc., it becomes especially complicated. In those cases, consult the [NIH Stroke Scale website](#). MDCalc's version is an attempt to clarify many of these confusing caveats, but cannot and should not be substituted for the official protocol.

Rules:

- Score what you see, not what you think.
- Score the first response, not the best response (except Item 9 - Best Language).
- Don't coach.

When to Use ▾

Pearls/Pitfalls ▾

Why Use ▾

1A: Level of consciousness
May be assessed casually while taking history

Alert; keenly responsive	0
Arouses to minor stimulation	+1
Requires repeated stimulation to arouse	+2
Movements to pain	+2
Postures or unresponsive	+3

8 points

NIH Stroke Scale

Copy Results 📄

Next Steps >>>

About the Creator



Dr. Patrick D. Lyden

[Are you Dr. Patrick D. Lyden?](#)

Also from MDCalc...

Related Calcs

- [tPA Contraindications](#)
- [Modified NIH Stroke Scale](#)
- [THRIVE Score](#)

You might be interested in...

Partner Content



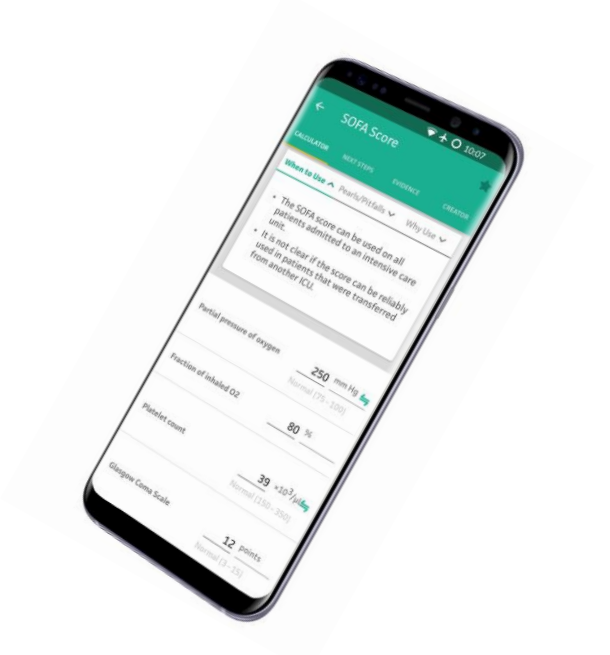
[MDCalc Stroke CME](#)
Get up to 10 hours of stroke CME



[Calculated Decisions: NIHSS](#)
Emergency Medicine Practice

Content Contributors

- [Daniel Runde, MD](#)



ABCD²

Score for TIA

	ABCD2 items (score: 0–7)	Points
A	Age: ≥ 60 years	1
B	Blood pressure: $\geq 140/90$ mm Hg	1
C	Clinical features:	
	-unilateral weakness or -speech impairment without weakness	2 1
D	Duration of symptoms:	
	≥ 60 minutes or 10–59 minutes	2 1
D	Diabetes: (on medication/insulin)	1

Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack

S Claiborne Johnston, Peter M Rothwell, Mai N Nguyen-Huynh, Matthew F Giles, Jacob S Elkins, Allan L Bernstein, Stephen Sidney

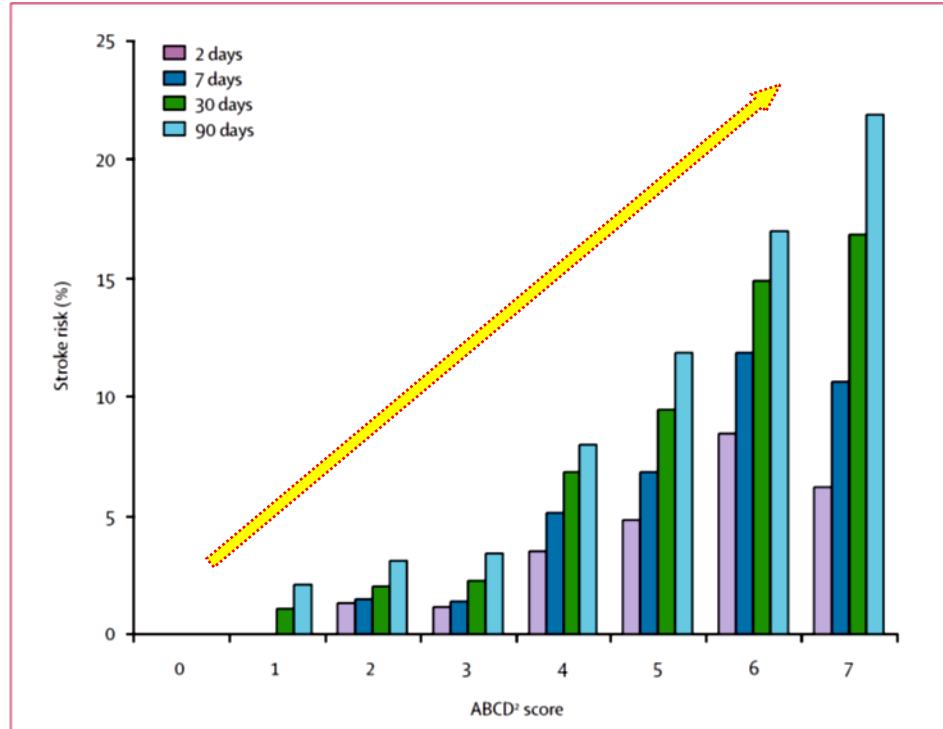


Figure: Short-term risk of stroke by ABCD² score in six groups combined (n=4799)

Lancet 2007; 369: 283–92

Higher ABCD² Score Predicts Patients Most Likely to Have True Transient Ischemic Attack

S. Andrew Josephson, MD; Stephen Sidney, MD, MPH; Trinh N. Pham, MA;
Allan L. Bernstein, MD; S. Claiborne Johnston, MD, PhD

Conclusions

Among patients diagnosed by emergency department physicians with TIA, higher ABCD² score was associated with a greater likelihood that the diagnosis was confirmed on expert review. The predictive power of the ABCD² model is therefore partially explained by identification of those patients likely to have experienced a true TIA, an important aspect of the score when used **by non-neurologists**. However, higher ABCD² scores still remained predictive of 90-day stroke rate in the group of patients judged to have a true TIA by an expert neurologist.

Stroke 2008;49:3096-3098

ABCD² Score for TIA ★

Estimates the risk of stroke after a suspected transient ischemic attack (TIA).

When to Use ▾	Pearls/Pitfalls ▾	Why Use ▾
Age ≥ 60 years	No 0	Yes +1
BP ≥ 140/90 mmHg Initial BP. Either SBP ≥ 140 or DBP ≥ 90.	No 0	Yes +1
Clinical features of the TIA		
	Unilateral weakness	+2
	Speech disturbance without weakness	+1
	Other symptoms	0
Duration of symptoms		
	<10 minutes	0
	10-59 minutes	+1
	≥ 60 minutes	+2
History of diabetes	No 0	Yes +1

6 points

Per the validation study, 6-7 points: High Risk

2-Day Stroke Risk: 8.1%

7-Day Stroke Risk: 11.7%

90-Day Stroke Risk: 17.8%

Copy Results 📄

Next Steps >>>

About the Creator



Dr. S. Claiborne Johnston

[Are you Dr. S. Claiborne Johnston?](#)

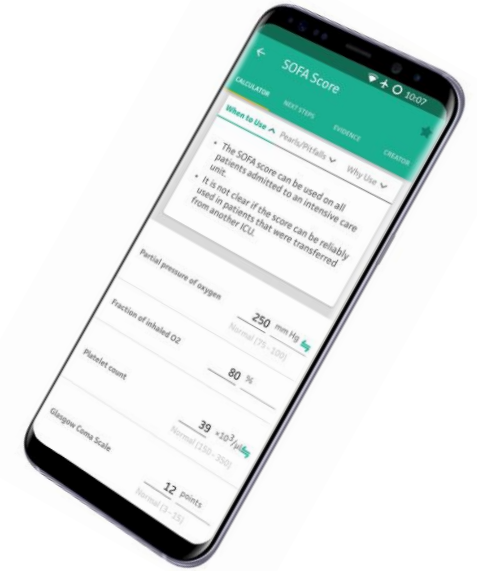
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Related Calcs

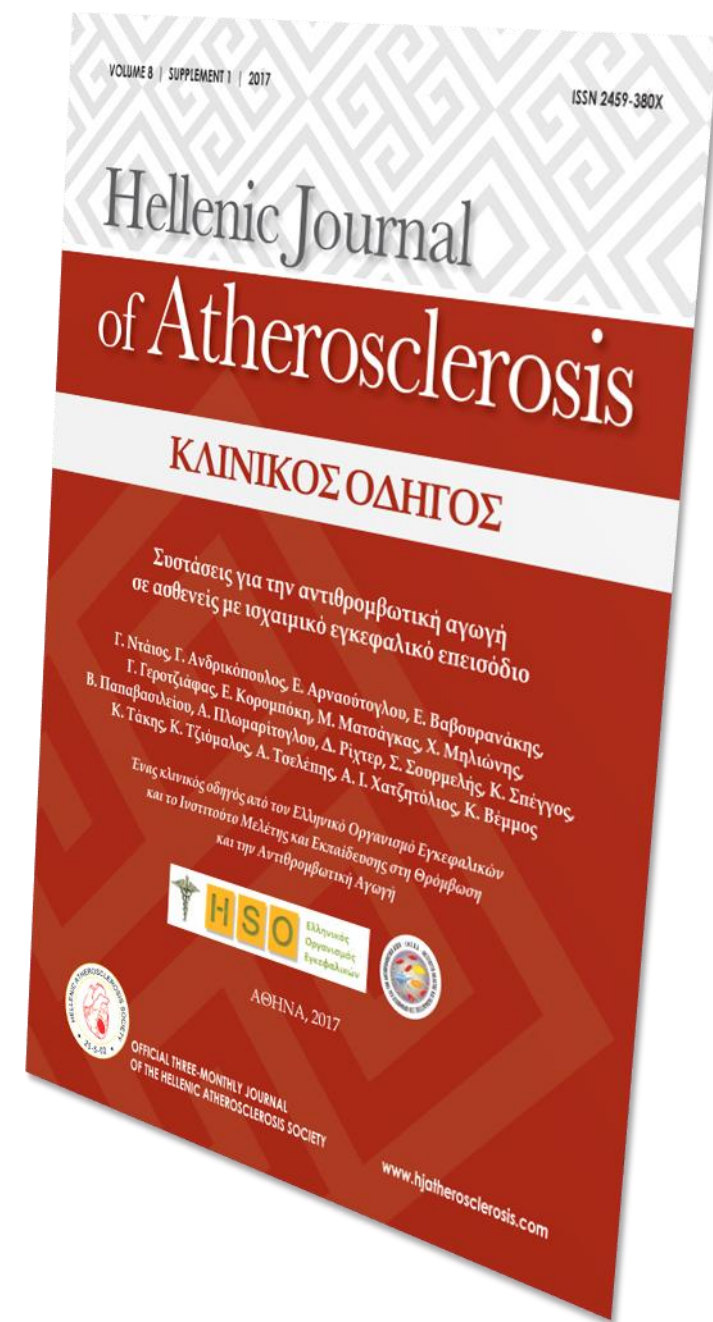
- [CHADS₂ Score](#)
- [THRIVE Score](#)
- [Modified Rankin Score](#)

Content Contributors

- [Daniel Runde, MD](#)



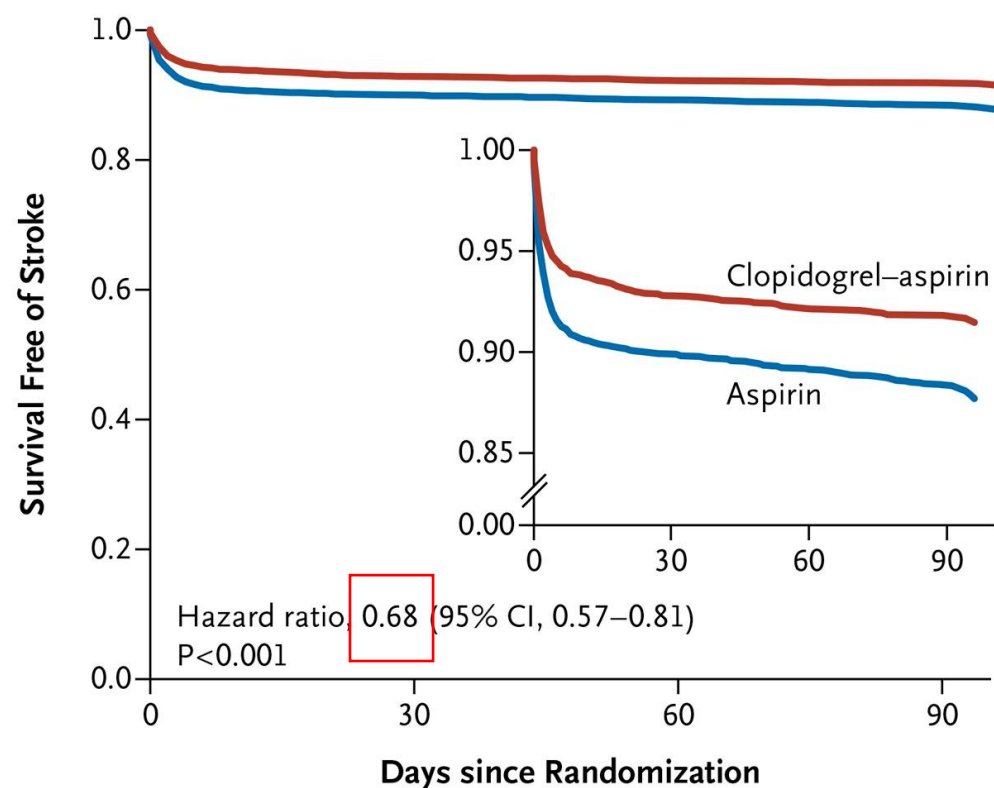
5. Ασθενείς με παροδικό εγκεφαλικό επεισόδιο υψηλού κινδύνου ($ABCD2 \geq 4$) ή μικρής βαρύτητας εγκατεστημένο ισχαιμικό εγκεφαλικό επεισόδιο ($NIHSS$ score κατά την εισαγωγή <4) χωρίς κολπική μαρμαρυγή ή μεταλλική βαλβίδα ή άλλη ένδειξη για αντιπηκτική αγωγή θα μπορούσαν να λάβουν διπλή αντιαιμοπεταλιακή αγωγή με ασπιρίνη και κλοπιδογρέλη για 21 ημέρες μετά το επεισόδιο (2B). Στη συνέχεια πρέπει να συνεχίσουν να λαμβάνουν αντιαιμοπεταλιακή αγωγή όπως αυτή περιγράφεται στο εδάφιο 2.



ORIGINAL ARTICLE

Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack

- Randomized, double-blind, placebo-controlled trial conducted at 114 centers in China,
- **5,170** patients within 24 hours after the onset of minor ischemic stroke or high-risk TIA
- combination therapy with **clopidogrel and aspirin** (clopidogrel at an initial dose of 300 mg, followed by 75 mg per day for 90 days, plus aspirin at a dose of 75 mg per day for the first 21 days) or to **placebo plus aspirin** (75 mg per day for 90 days). All participants received open-label aspirin at a clinician-determined dose of 75 to 300 mg on day 1.
- The primary outcome was **stroke (ischemic or hemorrhagic)** during 90 days of follow-up in an intention-to-treat analysis.



No. at Risk				
Aspirin	2586	2307	2287	1906
Clopidogrel-aspirin	2584	2376	2361	1989

CHANCE

Table 2. Efficacy and Safety Outcomes.

Outcome	Aspirin (N = 2586)		Clopidogrel and Aspirin (N = 2584)		Hazard Ratio (95% CI)	P Value
	Patients with Event no.	Event Rate %	Patients with Event no.	Event Rate %		
Primary outcome						
Stroke	303	11.7	212	8.2	0.68 (0.57–0.81)	<0.001
Secondary outcomes						
Stroke, myocardial infarction, or death from cardiovascular causes	307	11.9	216	8.4	0.69 (0.58–0.82)	<0.001
Ischemic stroke	295	11.4	204	7.9	0.67 (0.56–0.81)	<0.001
Hemorrhagic stroke	8	0.3	8	0.3	1.01 (0.38–2.70)	0.98
Myocardial infarction	2	0.1	3	0.1	1.44 (0.24–8.63)	0.69
Death from cardiovascular causes	5	0.2	6	0.2	1.16 (0.35–3.79)	0.81
Death from any cause	10	0.4	10	0.4	0.97 (0.40–2.33)	0.94
Transient ischemic attack	47	1.8	39	1.5	0.82 (0.53–1.26)	0.36
Safety outcomes						
Bleeding*						
Severe	4	0.2	4	0.2	0.94 (0.24–3.79)	0.94
Moderate	4	0.2	3	0.1	0.73 (0.16–3.26)	0.68
Mild	19	0.7	30	1.2	1.57 (0.88–2.79)	0.12
Any bleeding	41	1.6	60	2.3	1.41 (0.95–2.10)	0.09

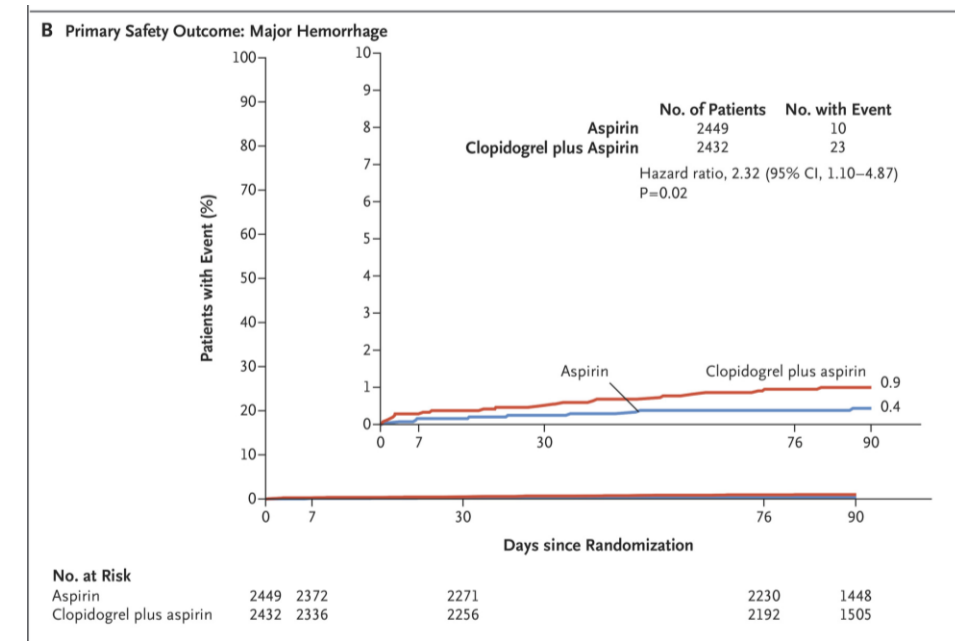
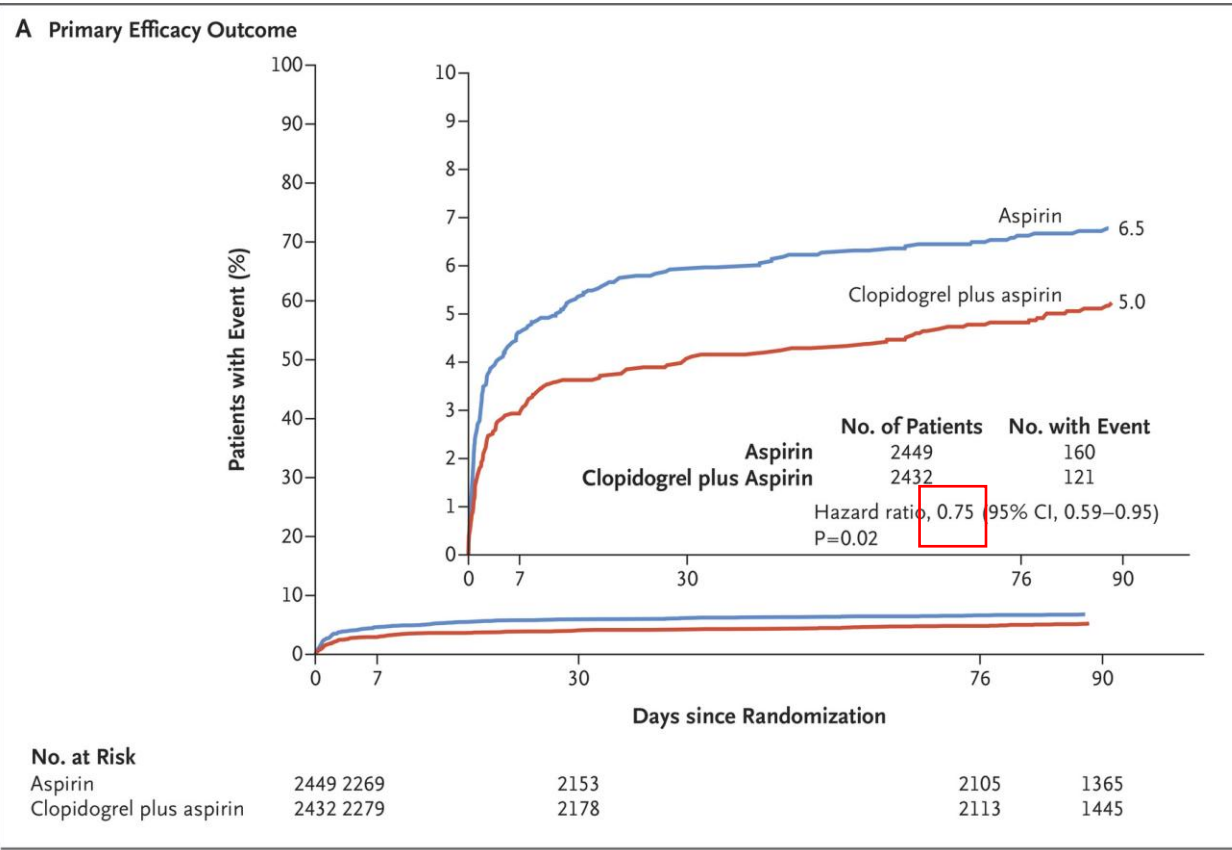
Conclusions

Among patients with TIA or minor stroke who can be treated within 24 hours after the onset of symptoms, the **combination of clopidogrel and aspirin is superior** to aspirin alone for reducing the risk of stroke in the first 90 days and **does not increase the risk of hemorrhage**.

Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA

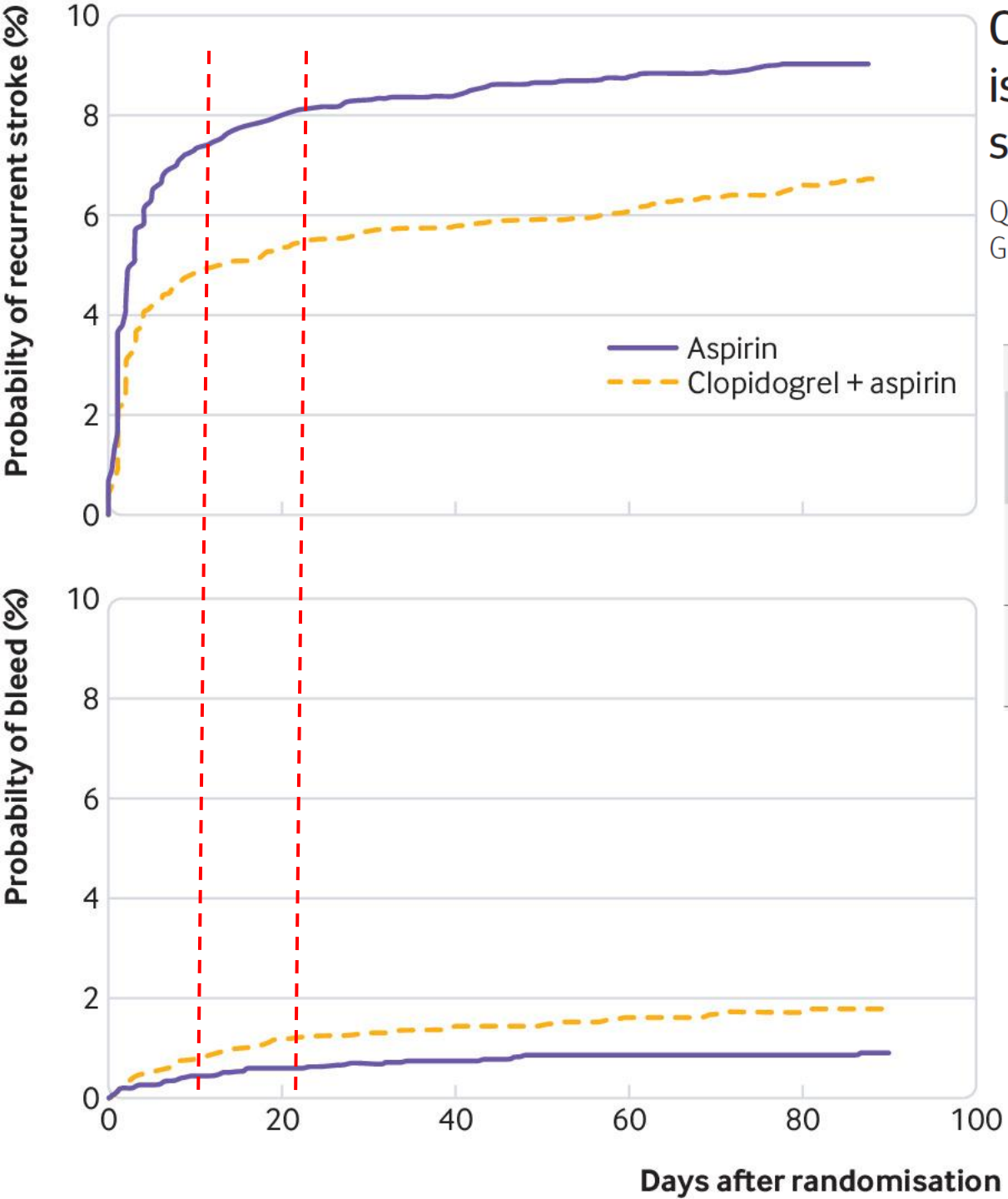
POINT

- Randomized, double-blind, placebo-controlled trial
- **4,881** patients (269 international sites) with minor ischemic stroke or high-risk TIA
- Clopidogrel at a loading dose of 600 mg on day 1, followed by **75 mg per day, plus aspirin** (at a dose of 50 to 325 mg per day) or the same range of doses of **aspirin alone**.
- Primary efficacy outcome in a time-to-event analysis was the risk of a composite of **major ischemic events**, which was defined as ischemic stroke, myocardial infarction, or death from an ischemic vascular event, at 90 days.



Conclusions

In patients with minor ischemic stroke or high-risk TIA, those who received a combination of clopidogrel and aspirin had a **lower risk of major ischemic events** but a **higher risk of major hemorrhage** at 90 days than those who received aspirin alone.



Clopidogrel plus aspirin versus aspirin alone for acute minor ischaemic stroke or high risk transient ischaemic attack: systematic review and meta-analysis

Qiukui Hao,^{1,2} Malavika Tampi,³ Martin O'Donnell,⁴ Farid Foroutan,² Reed AC Siemieniuk,² Gordon Guyatt²

10,447 participants

BMJ 2018;364:k5108

Table 3 | GRADE evidence profile: Dual antiplatelet with clopidogrel and aspirin for 10-21 days versus 22-90 days after transient ischaemic attack (TIA) or minor stroke

Outcome; timeframe	Study results and measurements	Absolute effect estimates	
		Stop clopidogrel, continue aspirin	Continue clopidogrel and aspirin
Ischaemic stroke; 90 days	Odds ratio 1.47 (95% CI 0.84 to 2.56) Based on data from 4406 patients in one study. Follow-up 90 days	10/1000 Difference: 4 more per 1000 (95% CI 2 fewer to 11 more)	14/1000
Moderate or severe bleeding; 90 days	Odds ratio 2.20 (95% CI 0.83 to 5.78) Based on data from 4599 patients in one study. Follow-up 90 days	3/1000 Difference: 3 more per 1000 (95% CI 1 fewer to 7 more)	6/1000

Conclusion

Dual antiplatelet therapy with clopidogrel and aspirin given within 24 hours after high-risk TIA or minor ischaemic stroke reduces the risk of subsequent stroke by about 2%, with few serious adverse consequences. Discontinuation of dual antiplatelet therapy as early as 10 days, and no later than 21 days, after initiation is likely to maximise its net benefit.

Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Endorsed by the Society for Academic Emergency Medicine and The Neurocritical Care Society

3.9. Antiplatelet Treatment	COR	LOE	New, Revised, or Unchanged
2. In patients presenting with minor noncardioembolic ischemic stroke (NIHSS score ≤ 3) who did not receive IV alteplase, treatment with dual antiplatelet therapy (aspirin and clopidogrel) started within 24 hours after symptom onset and continued for 21 days is effective in reducing recurrent ischemic stroke for a period of up to 90 days from symptom onset.	I	A	New recommendation.

European Stroke Organisation expedited recommendation for the use of short-term dual antiplatelet therapy early after minor stroke and high-risk TIA

European Stroke Journal

0(0) 1–5

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Recommendation 1

In people with a non-cardioembolic minor ischaemic stroke (NIHSS score of 3 or less) or high-risk TIA (ABCD2 score of 4 or more) in the past 24 hours, we recommend 21-days of dual antiplatelet therapy with aspirin and clopidogrel, followed by antiplatelet monotherapy thereafter.

Quality of evidence: High ⊕⊕⊕⊕

Strength of recommendation: Strong for intervention ↑↑

Expert consensus statement

In people with acute non-cardioembolic low risk TIA or in whom the diagnosis is uncertain, 11/11 experts voted against use of dual antiplatelet therapy over monotherapy

Ισχαιμικό ΑΕΕ / Παροδικό ΑΕΕ

Μη καρδιοεμβολικό

Καρδιοεμβολικό

TIA

ABCD²<4

ABCD²≥4

NIHSS<4

NIHSS≥4

TIA

NIHSS<8

NIHSS 8-16

NIHSS>16

Ασπιρίνη 100mgx1 &
Κλοπιδογρέλη 75mgx1

21 ημέρες

10 ημέρες ή
εξιτήριο

Ασπιρίνη 160-300mg x1

1^η

3^η

7^η

14^η

- Ασπιρίνη (50-325mg x1)
- Κλοπιδογρέλη (75mg x1)
- Τριφλουζάλη (600mg x1)
- Ασπιρίνη/διπυριδαμόλη (25mg/200mg x2)

NOAC ή Sintrom

Ισχαιμικό ΑΕΕ / Παροδικό ΑΕΕ

Μη καρδιοεμβολικό

Καρδιοεμβολικό

TIA

ABCD²<4

ABCD²≥4

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1^η

3^η

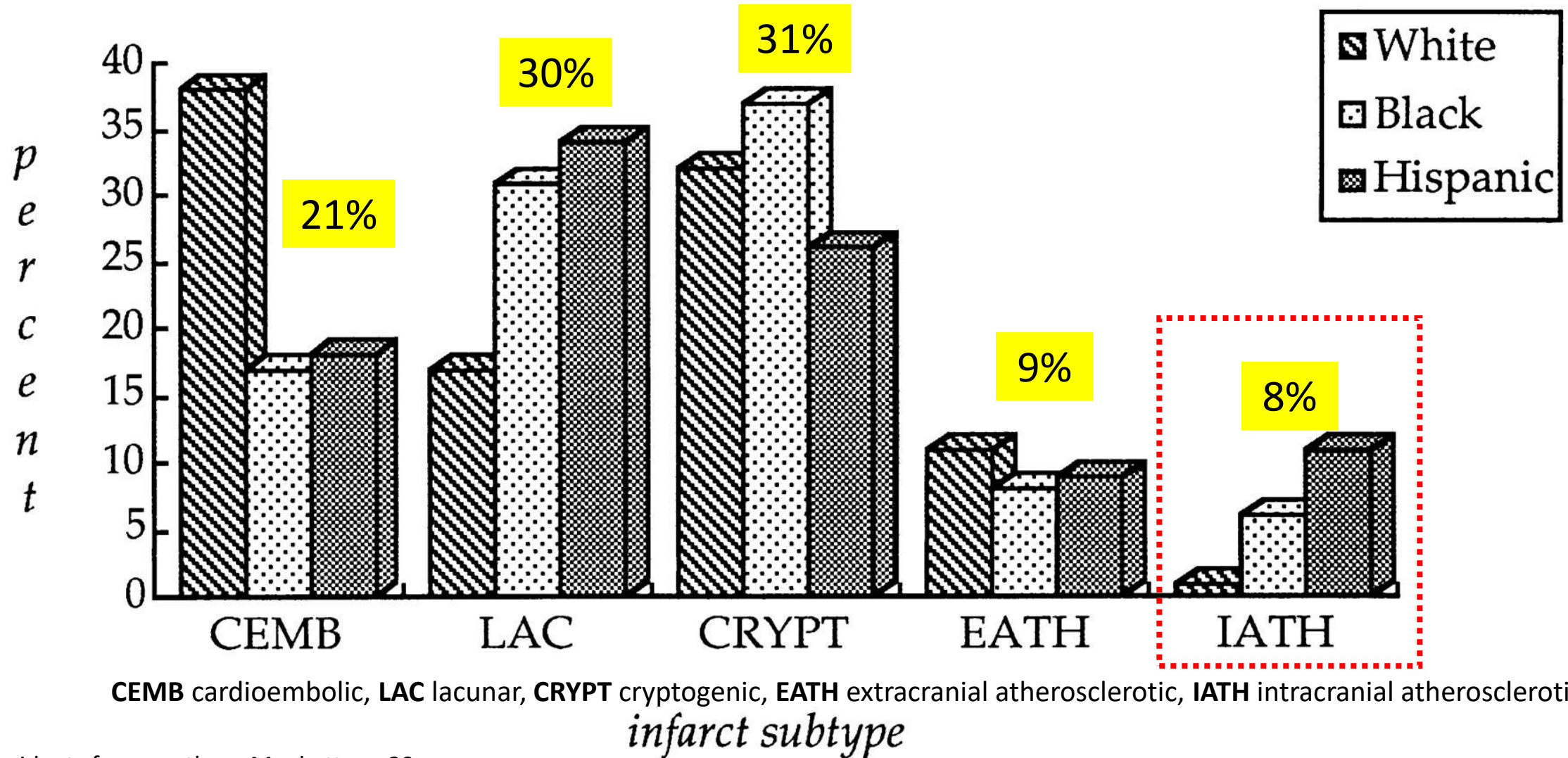
7^η

14^η

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NOAC ή Sintrom

Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The Northern Manhattan Stroke Study



438 Residents from northern Manhattan >39 years hospitalized for acute ischemic stroke (black 35%, Hispanic 46%, white 19%)

Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA

THALES

NIHSS ≤ 5 or
TIA +ABCD² ≥ 6 or
Intra-/ extracranial stenosis $>50\%$

Table 2. Efficacy and Safety Outcomes.*

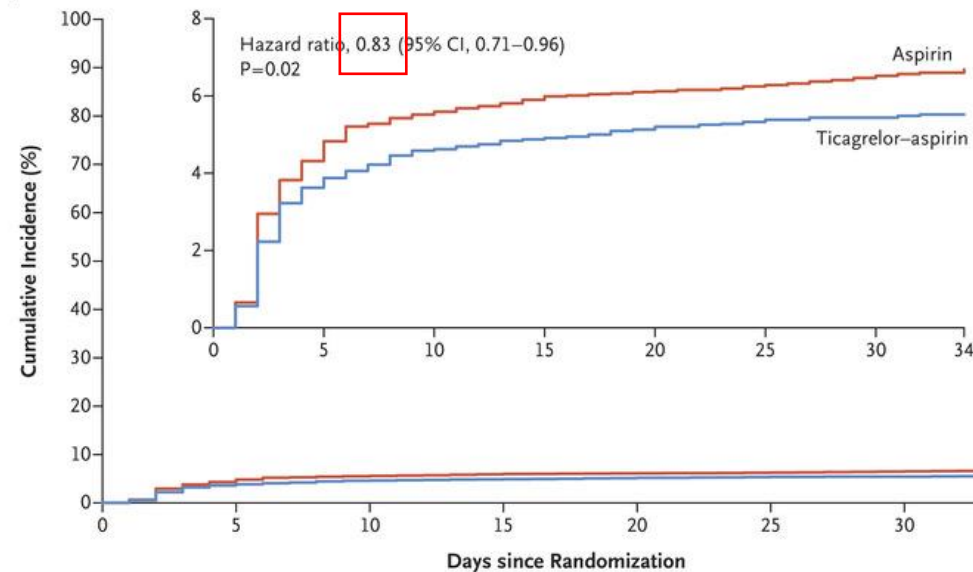
Outcome	Ticagrelor–Aspirin Group (N = 5523)		Aspirin Group (N = 5493)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate†	Patients with Event	Event Rate‡		
	no. (%)	%	no. (%)	%		
Primary outcome						
Stroke or death	303 (5.5)	5.4	362 (6.6)	6.5	0.83 (0.71–0.96)	0.02
Stroke	284 (5.1)	5.1	347 (6.3)	6.3	0.81 (0.69–0.95)	
Death	36 (0.7)	0.6	27 (0.5)	0.5	1.33 (0.81–2.19)	
Secondary outcomes						
Ischemic stroke	276 (5.0)	5.0	345 (6.3)	6.2	0.79 (0.68–0.93)	0.004
Overall disability‡	1282 (23.8)	NA	1284 (24.1)	NA	0.98 (0.89–1.07)	0.61
Safety outcomes						
Severe bleeding	28 (0.5)	0.5	7 (0.1)	0.1	3.99 (1.74–9.14)	0.001
Intracranial hemorrhage or fatal bleeding	22 (0.4)	0.4	6 (0.1)	0.1	3.66 (1.48–9.02)	0.005
Fatal bleeding	11 (0.2)		2 (<0.1)			
Intracranial hemorrhage	20 (0.4)	0.4	6 (0.1)	0.1	3.33 (1.34–8.28)	0.01
Hemorrhagic stroke	10 (0.2)		2 (<0.1)			
Moderate or severe bleeding	36 (0.7)	0.6	11 (0.2)	0.2	3.27 (1.67–6.43)	<0.001
Premature permanent discontinuation of trial treatment owing to bleeding	152 (2.8)	2.9	32 (0.6)	0.6	4.80 (3.28–7.02)	<0.001

* NA denotes not applicable.

† Event rates are Kaplan–Meier estimates of the percentage of patients with events.

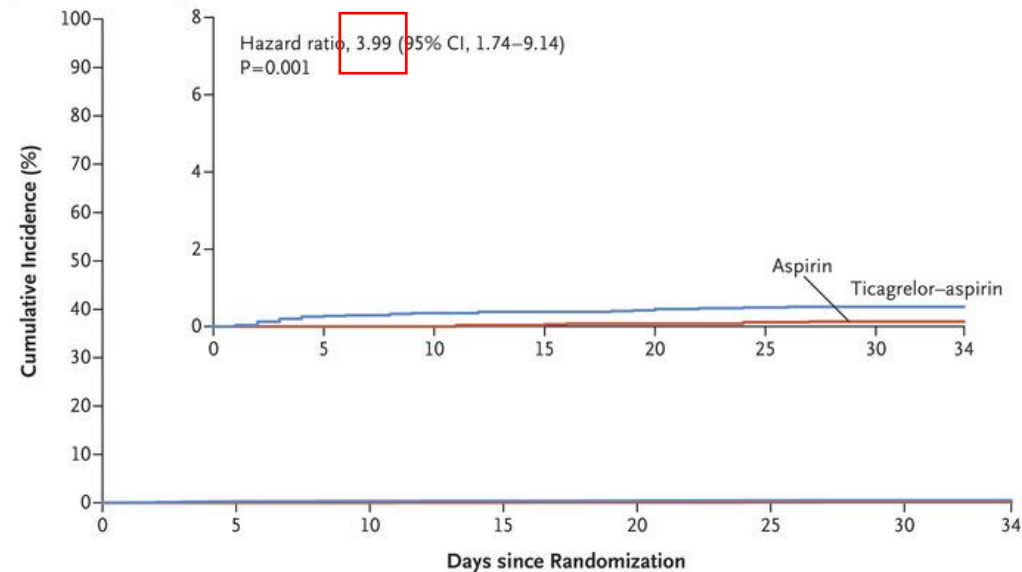
‡ Overall disability was determined by a score greater than 1 on the modified Rankin scale. The odds ratio is shown rather than the hazard ratio (5386 patients in the ticagrelor–aspirin group and 5333 patients in the aspirin group).

A Probability of Stroke or Death



No. at Risk								
Ticagrelor–aspirin	5523	5314	5257	5241	5227	5215	5209	1091
Aspirin	5493	5253	5181	5159	5146	5138	5126	1135

B Probability of Severe Bleeding



No. at Risk								
Ticagrelor–aspirin	5523	5495	5471	5467	5463	5457	5456	1146
Aspirin	5493	5486	5464	5459	5454	5451	5450	1216

European Stroke Organisation expedited recommendation for the use of short-term dual antiplatelet therapy early after minor stroke and high-risk TIA

European Stroke Journal
0(0) 1–5
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Recommendation 2

In people with non-cardioembolic mild to moderate ischaemic stroke (NIHSS of 5 or less) or high-risk TIA (ABCD2 score of 6 or more or other high-risk features*) in the past 24 hours, we suggest 30-days of dual antiplatelet therapy with aspirin and ticagrelor followed by antiplatelet monotherapy thereafter.

*defined as either intracranial atherosclerotic disease or at least 50% stenosis in an internal carotid artery that could account for the presentation.

Quality of evidence: Moderate ⊕⊕⊕

Strength of recommendation: Weak for intervention ↑?

2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack

A Guideline From the American Heart Association/American Stroke Association

Recommendations for Intracranial Large Artery Atherosclerosis			COR	LOE	Recommendations	2b	THALES B-NR	3. In patients with recent (within 24 hours) minor stroke or high-risk TIA and concomitant ipsilateral >30% stenosis of a major intracranial artery, the addition of ticagrelor 90 mg twice a day to aspirin for up to 30 days might be considered to further reduce recurrent stroke risk. ³⁴⁰
Referenced studies that support recommendations are summarized in online Data Supplements 20–27.								
			Antithrombotic Therapy					
1	WASID B-R SAMMPRIS	1. In patients with a stroke or TIA caused by 50% to 99% stenosis of a major intracranial artery, aspirin 325 mg/d is recommended in preference to warfarin to reduce the risk of recurrent ischemic stroke and vascular death. ^{335,336}	2b	TOSS-I C-LD TOSS-II	4. In patients with stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, the addition of cilostazol 200 mg/day to aspirin or clopidogrel might be considered to reduce recurrent stroke risk. ^{341–344}			
2a	SAMMPRIS WASID B-NR CHANCE CLAIR	2. In patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70%–99%) of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for up to 90 days is reasonable to further reduce recurrent stroke risk. ^{336–339}	2b	C-EO	5. In patients with stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, the usefulness of clopidogrel alone, the combination of aspirin and dipyridamole, ticagrelor alone, or cilostazol alone for secondary stroke prevention is not well established.			

Ισχαιμικό ΑΕΕ / Παροδικό ΑΕΕ

Μη καρδιοεμβολικό

Καρδιοεμβολικό

TIA

ABCD²<4

ABCD²≥4

NIHSS<4

NIHSS≥4

TIA

NIHSS<8

NIHSS 8-16

NIHSS>16

Ασπιρίνη 100mgx1 &
Κλοπιδογρέλη 75mgx1

Ασπιρίνη 160-300mg x1

21 ημέρες

10 ημέρες ή
εξιτήριο

1^η

3^η

7^η

14^η

- Ασπιρίνη (50-325mg x1)
- Κλοπιδογρέλη (75mg x1)
- Τριφλουζάλη (600mg x1)
- Ασπιρίνη/διπυριδαμόλη (25mg/200mg x2)

NOAC ή Sintrom

Ισχαιμικό ΑΕΕ / Παροδικό ΑΕΕ

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TIA

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*21 ημέρες

10 ημέρες ή
εξιτήριο

1^η

3^η

7^η

14^η

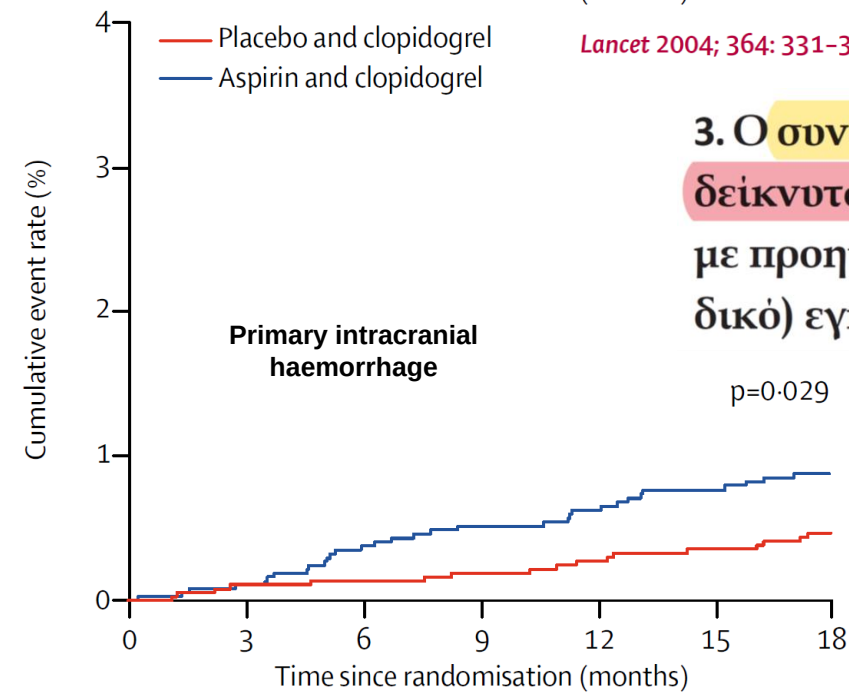
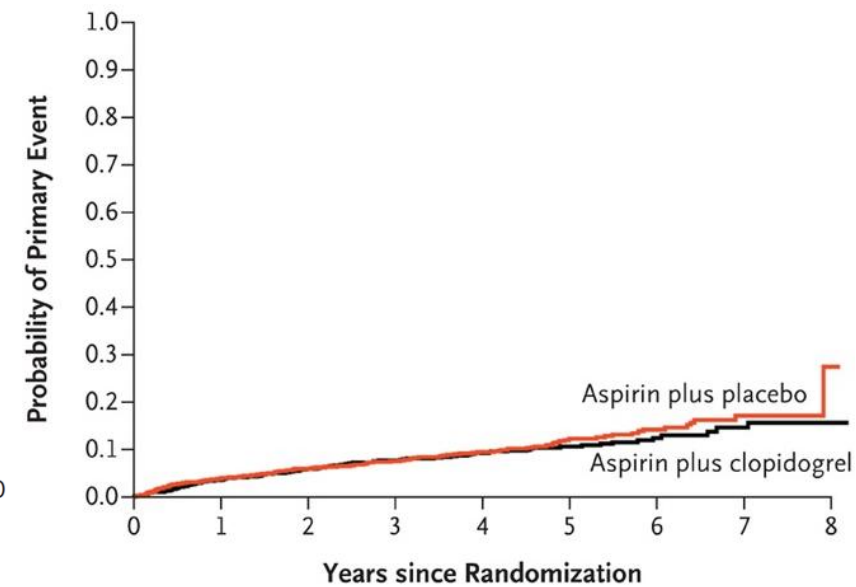
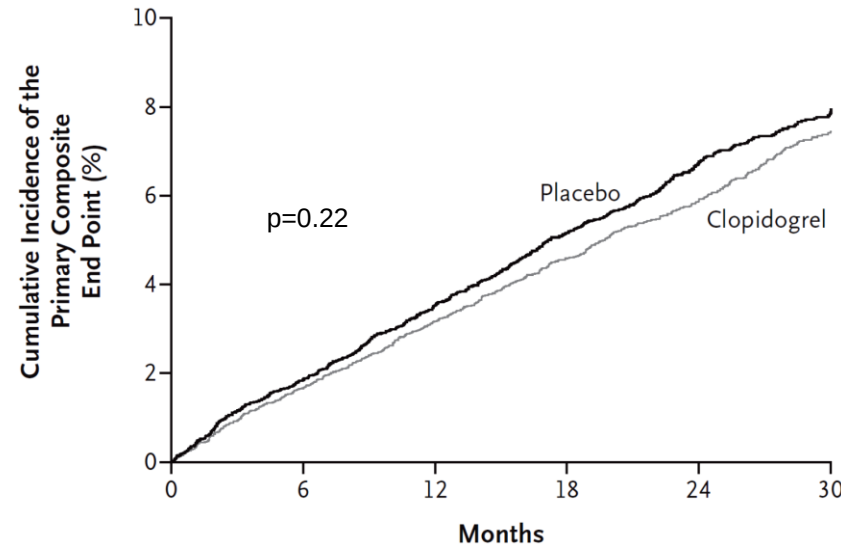
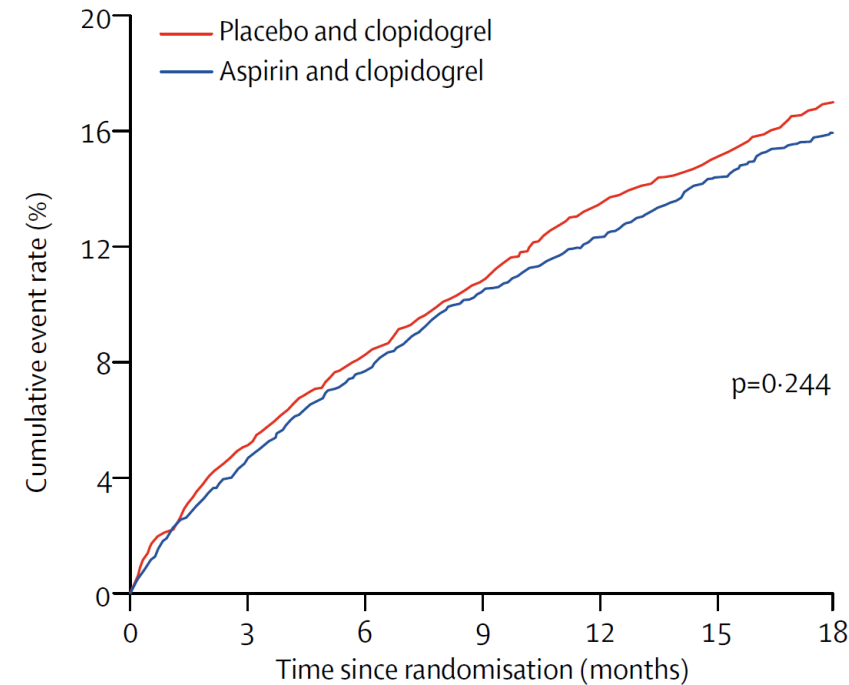
- Ασπιρίνη (50-325mg x1)
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- Τριφλουζάλη (600mg x1)
- Ασπιρίνη/διυριδαμόλη (25mg/200mg x2)

NOAC ή Sintrom

MATCH: Clopidogrel/aspirin vs clopidogrel / Major vascular event

CHARISMA: Clopidogrel/aspirin vs aspirin / Major vascular event

SPS3: Aspirin/clopidogrel vs aspirin / Stroke recurrence



Lancet 2004; 364: 331-37

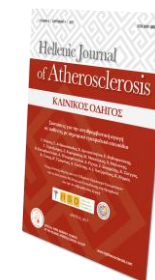
N Engl J Med 2006;354:1706-17

N Engl J Med 2012;367:817-25

**3. Ο συνδυασμός ασπιρίνης με κλοπιδογρέλη αντεν-
δείκνυται για μακροχρόνια χορήγηση σε ασθενείς
με προηγούμενο ισχαιμικό (εγκατεστημένο ή παρο-
δικό) εγκεφαλικό επεισόδιο (1Α).**

Table 2. Primary Efficacy Outcomes.*

Outcome	Aspirin plus Placebo (N=1503)		Aspirin plus Clopidogrel (N=1517)		Hazard Ratio (95% CI)	P Value
	no.	rate (%/yr)	no.	rate (%/yr)		
All strokes (ischemic and hemorrhagic)	138	2.7	125	2.5	0.92 (0.72–1.16)	0.48
Ischemic stroke	124	2.4	100	2.0	0.82 (0.63–1.09)	0.13
Intracranial hemorrhage	13	0.25	21	0.42	1.65 (0.83–3.31)	0.15
Unknown†	1	0.02	4	0.08	3.97 (0.44–35.47)	0.22
Disabling or fatal stroke‡	40	0.78	42	0.84	1.06 (0.69–1.64)	0.79
Transient ischemic attack without stroke	39	0.78	28	0.57	0.73 (0.45–1.18)	0.19
Myocardial infarction	38	0.71	31	0.59	0.84 (0.52–1.35)	0.47
Other thromboembolic events§	12	0.22	21	0.40	1.81 (0.89–3.68)	0.10
Major vascular event¶	174	3.4	153	3.1	0.89 (0.72–1.11)	0.29
All deaths	77	1.4	113	2.1	1.52 (1.14–2.04)	0.004
Vascular causes	19	0.35	27	0.51	1.46 (0.81–2.64)	0.20
Cerebral	9	0.17	10	0.19	1.13 (0.46–2.78)	0.79
Noncerebral	10	0.18	17	0.32	1.77 (0.81–3.87)	0.15
Probable vascular causes	6	0.11	18	0.34	3.09 (1.23–7.80)	0.02
Nonvascular causes	31	0.57	39	0.73	1.31 (0.82–2.10)	0.26
Uncertain	21	0.39	29	0.55	1.41 (0.82–2.52)	0.21



Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke
 A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

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6.6.1. Noncardioembolic Stroke	COR	LOE	New, Revised, or Unchanged
1. For patients with noncardioembolic AIS, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events.	I	A	Recommendation reworded for clarity from 2014 Secondary Prevention. COR and LOE unchanged. See Table XCV in online Data Supplement 1 for original wording.
2. For early secondary prevention in patients with noncardioembolic AIS, the selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance, relative known efficacy of the agents, and other clinical characteristics.	I	C-EO	Recommendation reworded for clarity from 2014 Secondary Prevention. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording.

Ισχαιμικό ΑΕΕ / Παροδικό ΑΕΕ

Μη καρδιοεμβολικό

Καρδιοεμβολικό

TIA

$ABCD^2 < 4$

$ABCD^2 \geq 4$

$NIHSS < 4$

$NIHSS \geq 4$

TIA

$NIHSS < 8$

$NIHSS 8-16$

$NIHSS > 16$

* Ασπιρίνη 100mgx1 &
Κλοπιδογρέλη 75mgx1

Ασπιρίνη 160-300mg x1

*21 ημέρες

10 ημέρες ή
εξιτήριο

1^η

3^η

7^η

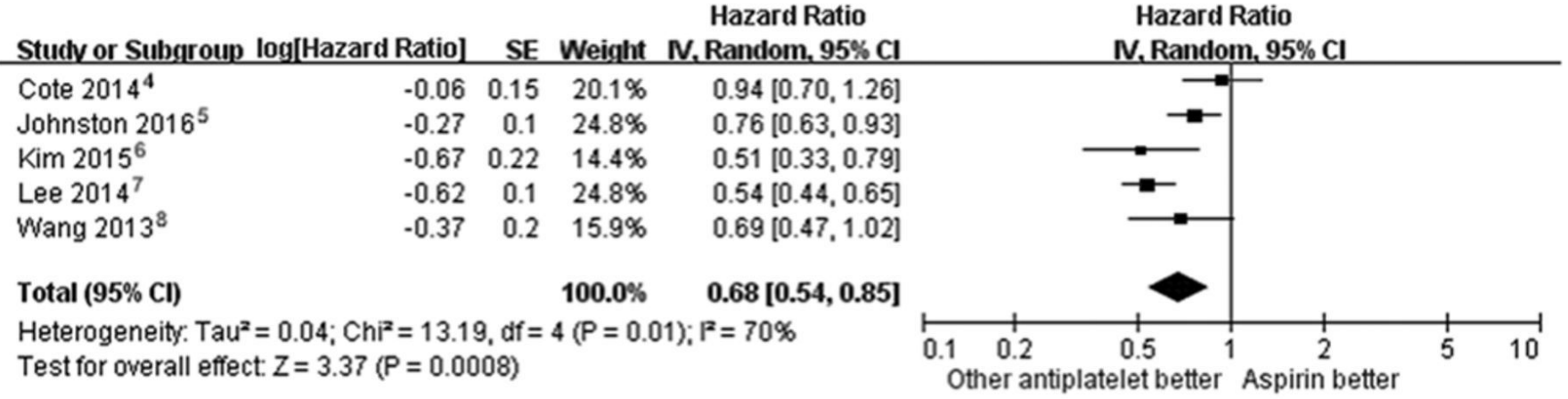
14^η

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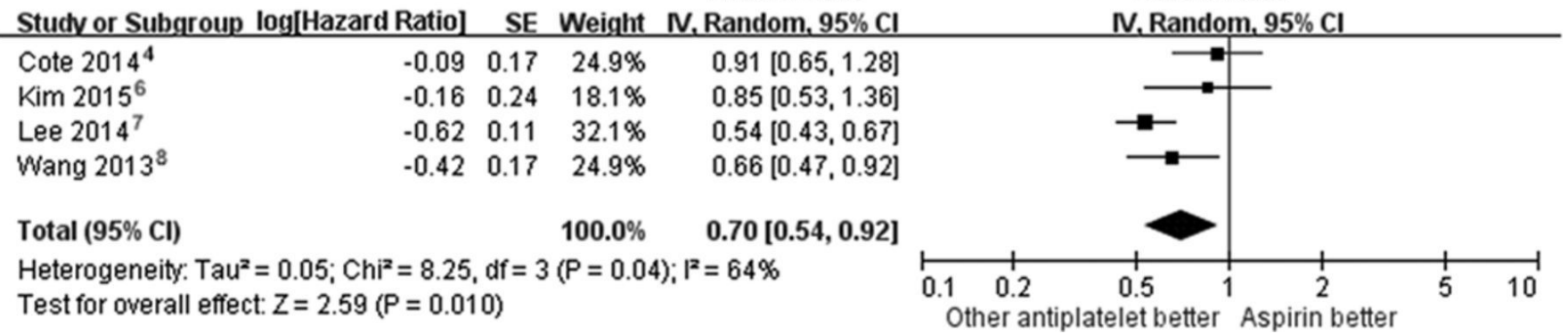
NOAC ή Sintrom

Lee M, Saver JL, Hong KS, Rao NM, Wu YL, Ovbiagele B.
 Antiplatelet Regimen for Patients With Breakthrough Strokes While on Aspirin:
 A Systematic Review and Meta-Analysis.
 Stroke. 2017 Sep;48(9):2610-2613

A



B



Hazard ratio with 95% confidence interval (CI) estimates for (A) major adverse cardiovascular events and (B) recurrent stroke (active treatment vs control) by individual study and pooled

Conclusions

Among patients who experience an ischemic stroke or transient ischemic attack while on aspirin monotherapy, the addition of or a switch to another antiplatelet agent, especially in the first days after index event, is associated with fewer future vascular events, including stroke.

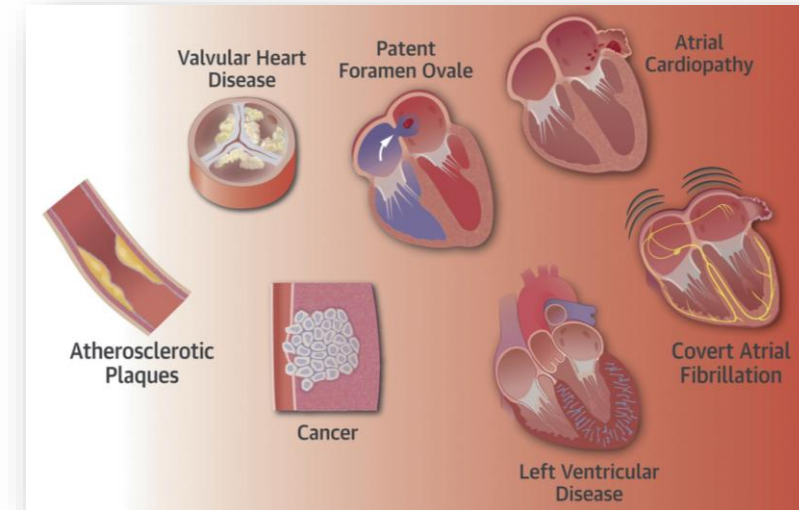
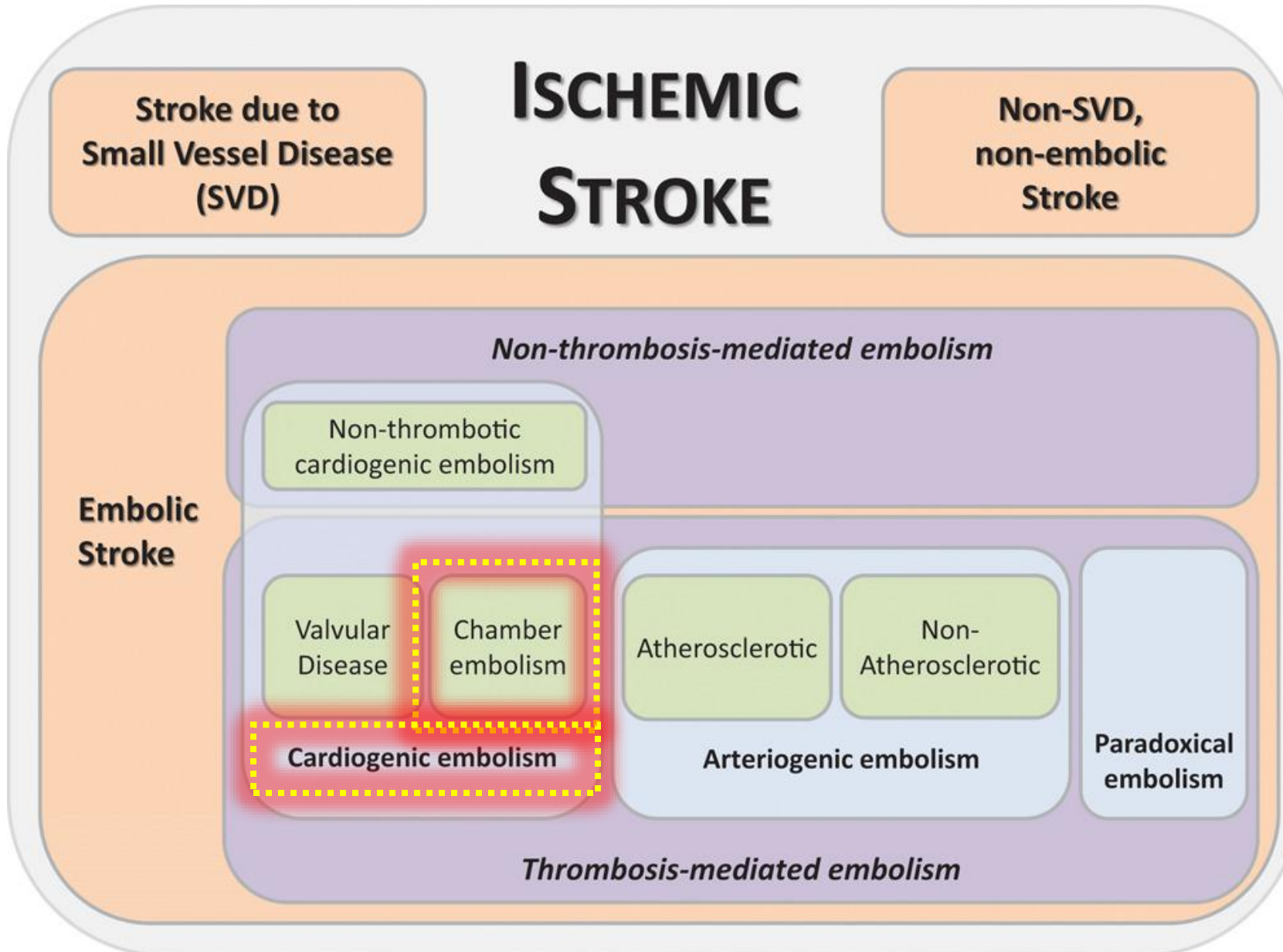
*The studies analyzed included **large registries** in addition to **randomized trials**.
 It was possible that the pooled results were biased because of confounding by indication.
 Therefore, these observational data can only be seen **as suggestive** rather than evidence-based guide for clinical practice.*

Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke
A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

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6.6.1. Noncardioembolic Stroke	COR	LOE	New, Revised, or Unchanged
3. For patients who have a noncardioembolic AIS while taking aspirin, increasing the dose of aspirin or switching to an alternative antiplatelet agent for additional benefit in secondary stroke prevention is not well established.	IIb	B-R	Recommendation revised from 2014 Secondary Prevention.

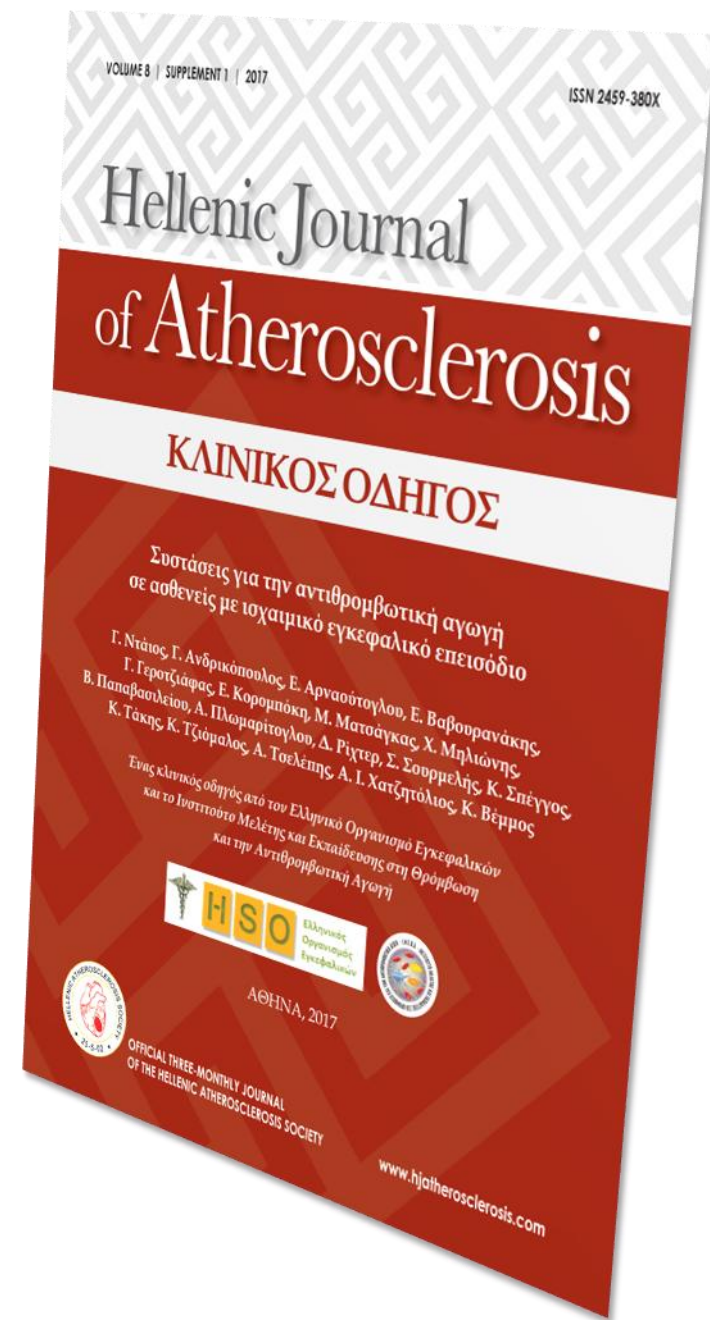
Ischemic stroke is an etiologically heterogeneous syndrome

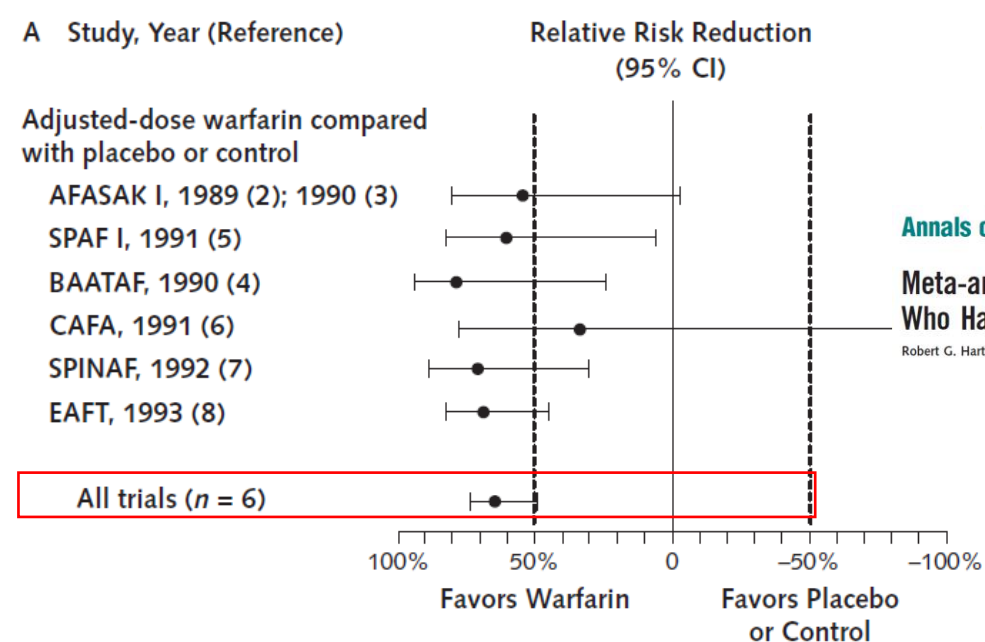


Ntaios G. Embolic Stroke of Undetermined Source: JACC Review Topic of the Week. J Am Coll Cardiol. 2020 Jan 28;75(3):333-340.

In order to optimize the secondary prevention strategy in a patient with ischemic stroke, it is rational to identify the underlying etiologic pathology.

6. Ασθενείς με **ισχαιμικό** (εγκατεστημένο ή παροδικό) εγκεφαλικό επεισόδιο και παροξυσμική, εμμένουσα ή χρόνια κολπική μαρμαρυγή πρέπει να λαμβάνουν **αντιπηκτική αγωγή** (1A). Η αντιαιμοπεταλιακή αγωγή σε ασθενείς με ισχαιμικό (εγκατεστημένο ή παροδικό) εγκεφαλικό επεισόδιο και παροξυσμική, εμμένουσα ή χρόνια κολπική μαρμαρυγή είναι σαφώς υποδεέστερη της αντιπηκτικής αγωγής και πρέπει να μην προτιμάται έναντι της αντιπηκτικής (1A). Σε ασθενείς στους οποίους δεν δύναται να χορηγηθεί αντιπηκτική αγωγή, μπορεί να χορηγηθεί ασπιρίνη (1A).



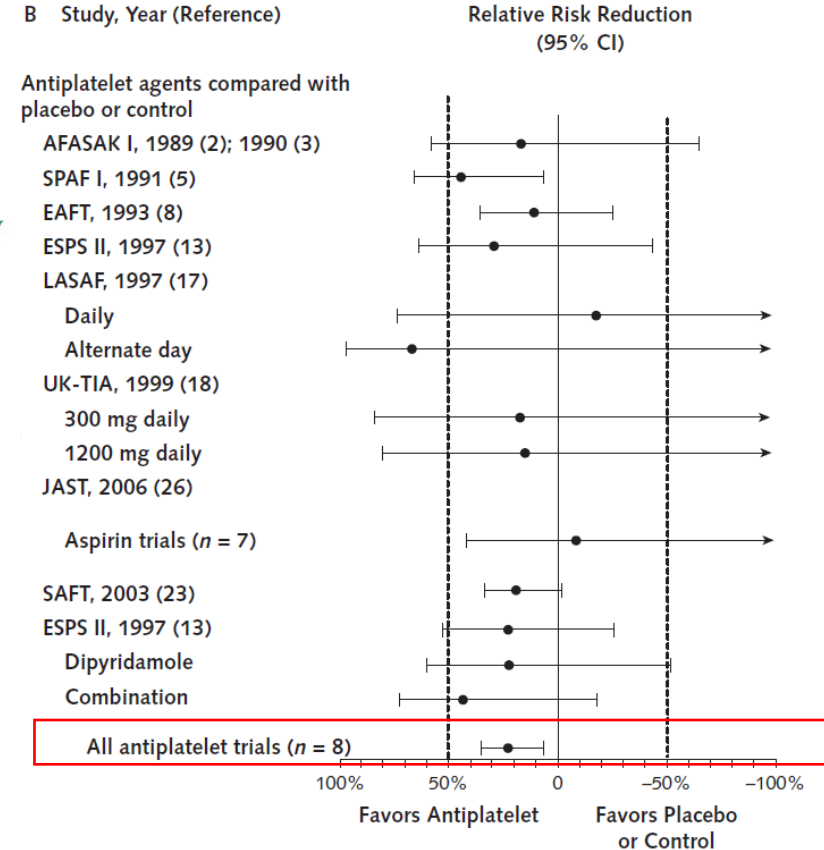


Annals of Internal Medicine

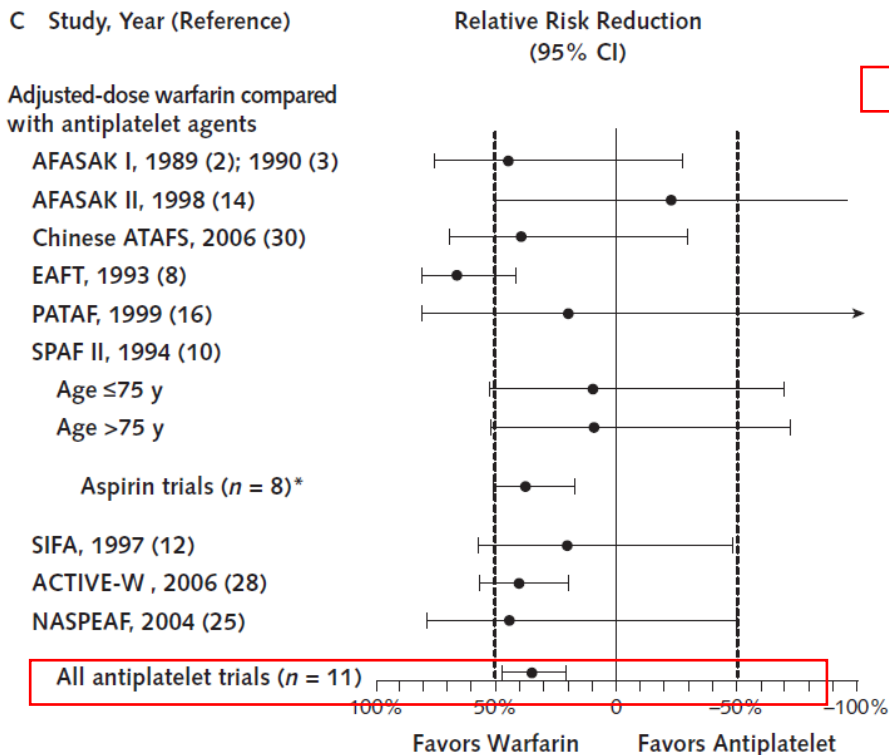
Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation

Robert G. Hart, MD; Lesly A. Pearce, MS; and Maria I. Aguilar, MD

REVIEW

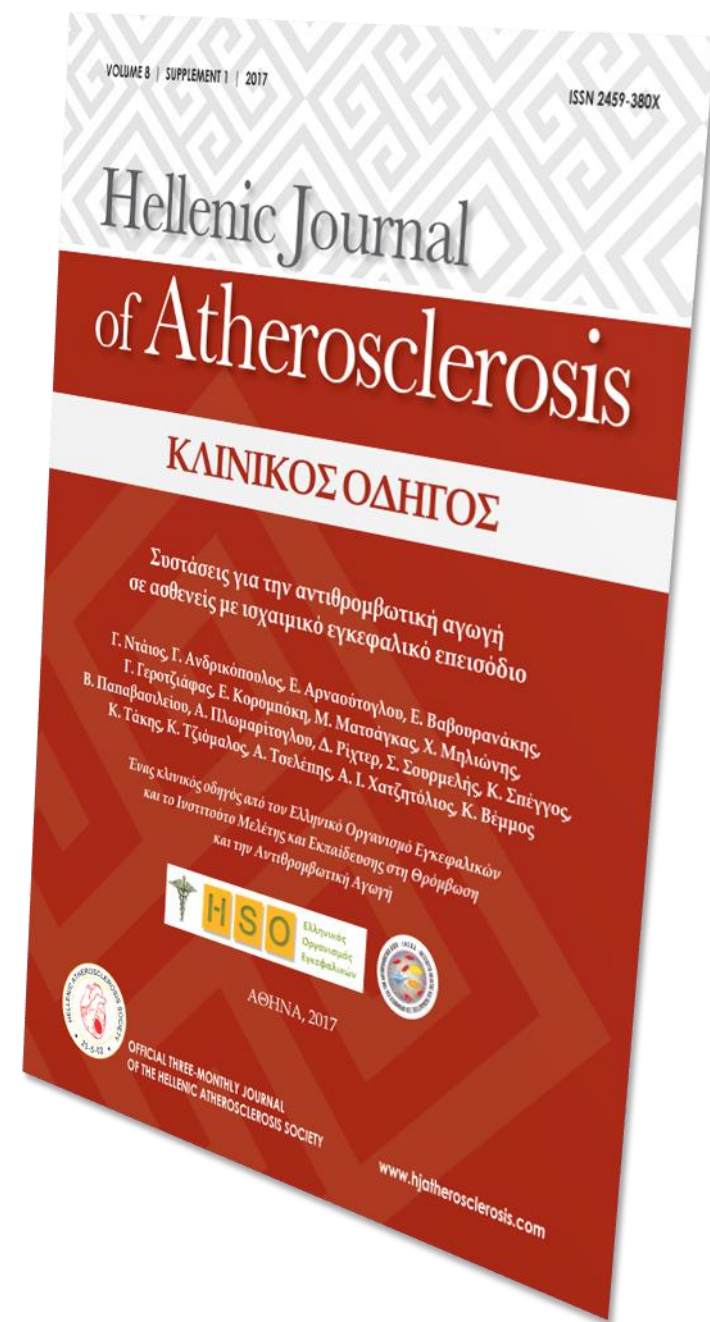


Η αντιαιμοπεταλιακή αγωγή σε ασθενείς με ισχαιμικό (εγκεφαλοεπιδόδιο ή παροδικό) εγκεφαλικό επεισόδιο και παροξυσμική, εμμένουσα ή χρόνια κοιλιακή μαρμαρυγή είναι σαφώς υποδεέστερη της αντιπηκτικής αγωγής και πρέπει να **μην προτιμάται** έναντι της αντιπηκτικής



Ασθενείς με ισχαιμικό (εγκεφαλοεπιδόδιο ή παροδικό) εγκεφαλικό επεισόδιο και παροξυσμική, εμμένουσα ή χρόνια κοιλιακή μαρμαρυγή πρέπει να λαμβάνουν **αντιπηκτική αγωγή**

7. Οι επιλογές **αντιπηκτικής αγωγής** σε ασθενείς με ισχαιμικό (εγκατεστημένο ή παροδικό) εγκεφαλικό επεισόδιο και παροξυσμική, εμμένουσα ή χρόνια κολπική μαρμαρυγή μη βαλβιδικής αιτιολογίας είναι οι **ανταγωνιστές της βιταμίνης Κ** (ασενοκουμαρόλη ή βαρφαρίνη) (1Α), οι άμεσοι ανταγωνιστές της θρομβίνης (**νταμπιγκαντράνη**) (1Α) και οι αναστολείς του παράγοντα Χα (**ριβαροξαμπάνη, απιξαμπάνη ή εντοξαμπάνη ή**) (1Α).



ROCKET AF

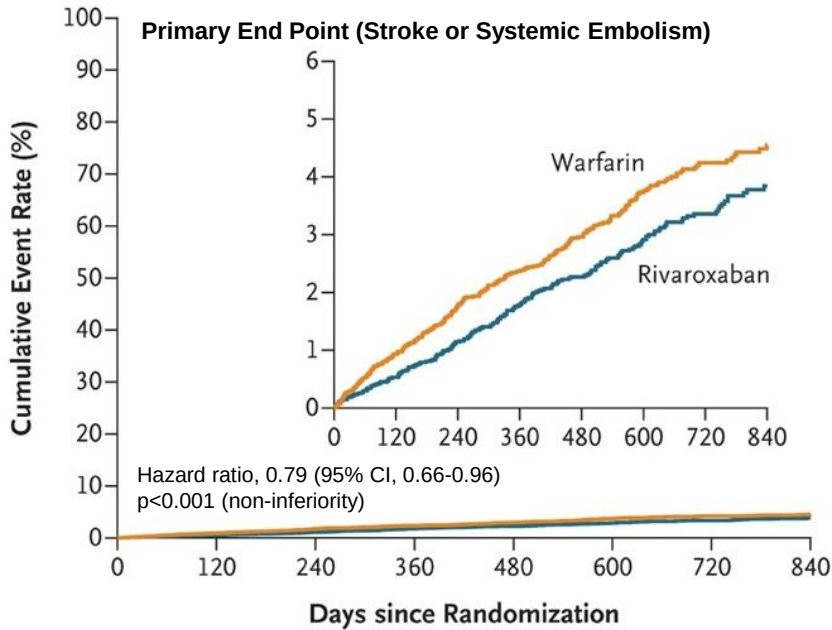
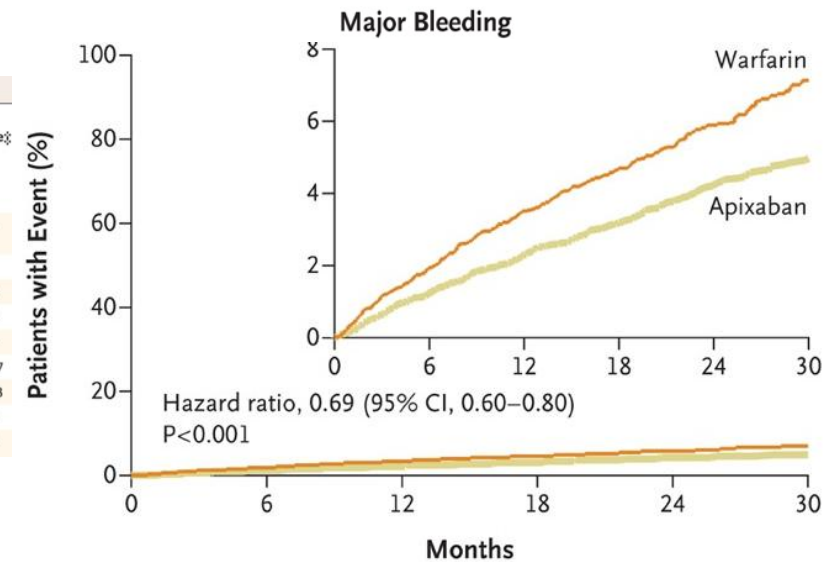
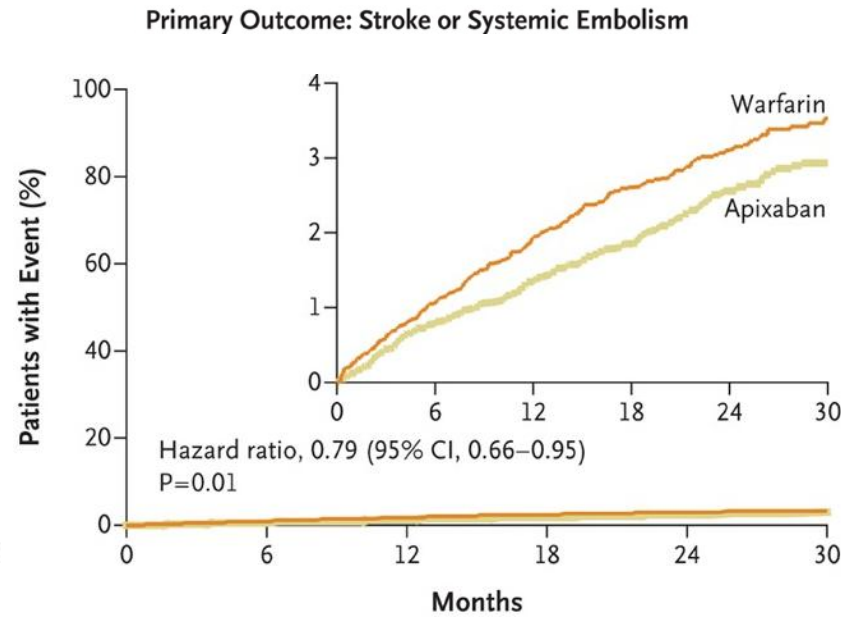


Table 3. Rates of Bleeding Events.^a

Variable	Rivaroxaban (N=7111)		Warfarin (N=7125)		Hazard Ratio (95% CI) [†]	P Value [‡]
	Events no. (%)	Event Rate no./100 patient-yr	Events no. (%)	Event Rate no./100 patient-yr		
Principal safety end point: major and nonmajor clinically relevant bleeding [§]	1475 (20.7)	14.9	1449 (20.3)	14.5	1.03 (0.96–1.11)	0.44
Major bleeding						
Any	395 (5.6)	3.6	386 (5.4)	3.4	1.04 (0.90–1.20)	0.58
Decrease in hemoglobin ≥ 2 g/dl	305 (4.3)	2.8	254 (3.6)	2.3	1.22 (1.03–1.44)	0.02
Transfusion	183 (2.6)	1.6	149 (2.1)	1.3	1.25 (1.01–1.55)	0.04
Critical bleeding [¶]	91 (1.3)	0.8	133 (1.9)	1.2	0.69 (0.53–0.91)	0.007
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5	0.50 (0.31–0.79)	0.003
Intracranial hemorrhage	55 (0.8)	0.5	84 (1.2)	0.7	0.67 (0.47–0.93)	0.02
Nonmajor clinically relevant bleeding	1185 (16.7)	11.8	1151 (16.2)	11.4	1.04 (0.96–1.13)	0.35

ARISTOTLE



N Engl J Med 2011;365:981-92

RE-LY

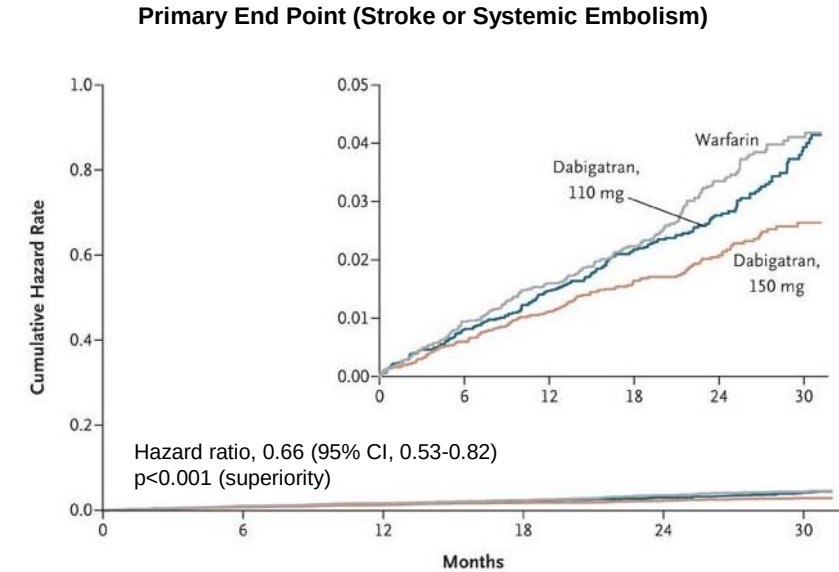


Table 3. Safety Outcomes, According to Treatment Group.^a

Event	Dabigatran, 110 mg		Dabigatran, 150 mg		Warfarin		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin	
	no. of patients	%/yr	no. of patients	%/yr	no. of patients	%/yr	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Major bleeding	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003	0.93 (0.81–1.07)	0.31
Life-threatening	145	1.22	175	1.45	212	1.80	0.68 (0.55–0.83)	<0.001	0.81 (0.66–0.99)	0.04
Non-life threatening	198	1.66	226	1.88	208	1.76	0.94 (0.78–1.15)	0.56	1.07 (0.89–1.29)	0.47
Gastrointestinal [†]	133	1.12	182	1.51	120	1.02	1.10 (0.86–1.41)	0.43	1.50 (1.19–1.89)	<0.001
Minor bleeding	1566	13.16	1787	14.84	1931	16.37	0.79 (0.74–0.84)	<0.001	0.91 (0.85–0.97)	0.005
Major or minor bleeding	1740	14.62	1977	16.42	2142	18.15	0.78 (0.74–0.83)	<0.001	0.91 (0.86–0.97)	0.002
Intracranial bleeding	27	0.23	36	0.30	87	0.74	0.31 (0.20–0.47)	<0.001	0.40 (0.27–0.60)	<0.001
Extracranial bleeding	299	2.51	342	2.84	315	2.67	0.94 (0.80–1.10)	0.45	1.07 (0.92–1.25)	0.38
Net clinical benefit outcome [‡]	844	7.09	832	6.91	901	7.64	0.92 (0.84–1.02)	0.10	0.91 (0.82–1.00)	0.04

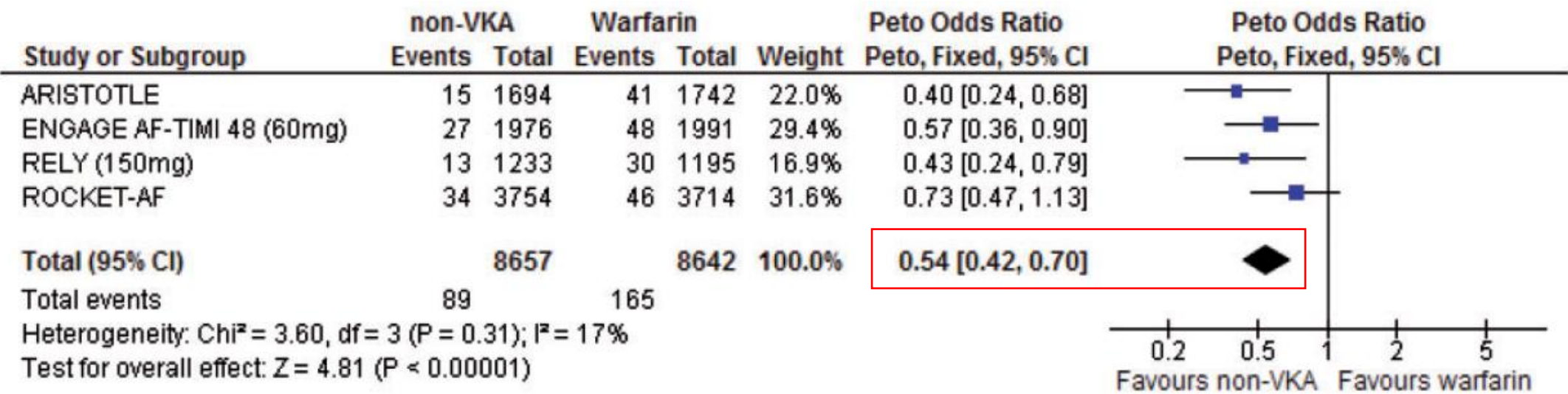
N Engl J Med 2009;361:1139-51

N Engl J Med 2011;365:883-91

Nonvitamin-K-antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and previous stroke or transient ischemic attack: An updated systematic review and meta-analysis of randomized controlled trials

George Ntaios¹, Vasileios Papavasileiou², Hans-Chris Diener³, Konstantinos Makaritsis¹ and Patrik Michel⁴

Forest plot of the effects of non-VKAs versus warfarin on safety outcomes: **intracranial bleeding**



2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)

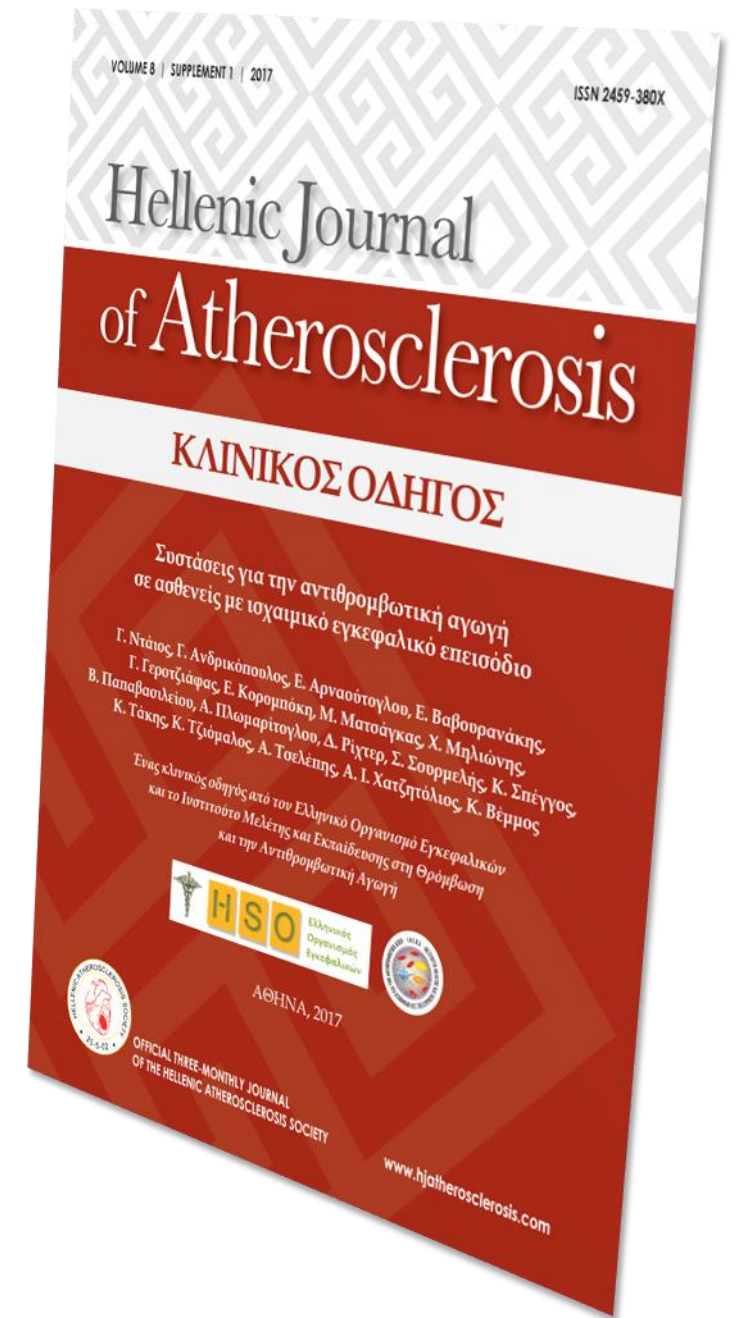
Recommendations for secondary stroke prevention in AF patients after acute ischaemic stroke	Class ^a	Level ^b
In AF patients with an ischaemic stroke or TIA, long-term secondary prevention of stroke using OAC is recommended if there is no strict contraindication to OAC use, with a preference for NOACs over VKAs in NOAC-eligible patients. ^{1125–1130}	I	A
In AF patients presenting with acute ischaemic stroke, very early anticoagulation (<48 h) using UFH, LMWH, or VKAs is not recommended. ¹⁰⁹⁵	III	B

10. Οι αλληλεπιδράσεις της νταμπιγκαντράνης, ριβαροξαμπάνης, απιξαμπάνης ή εντοξαμπάνης και με φάρμακα και τροφές είναι πολύ λιγότερες σε σχέση με τους ανταγωνιστές της βιταμίνης K (1Γ).

11. Σε ασθενείς υπό νταμπιγκαντράνη, ριβαροξαμπάνη, απιξαμπάνη ή εντοξαμπάνη, δεν υπάρχει λόγος ελέγχου του INR και πρέπει να αποφεύγεται (1Γ).

13. Η αντιθρομβωτική αγωγή σε ασθενείς με κολπικό πτερυγισμό πρέπει να ακολουθεί τις ίδιες αρχές με την κολπική μαρμαρυγή (1Γ).

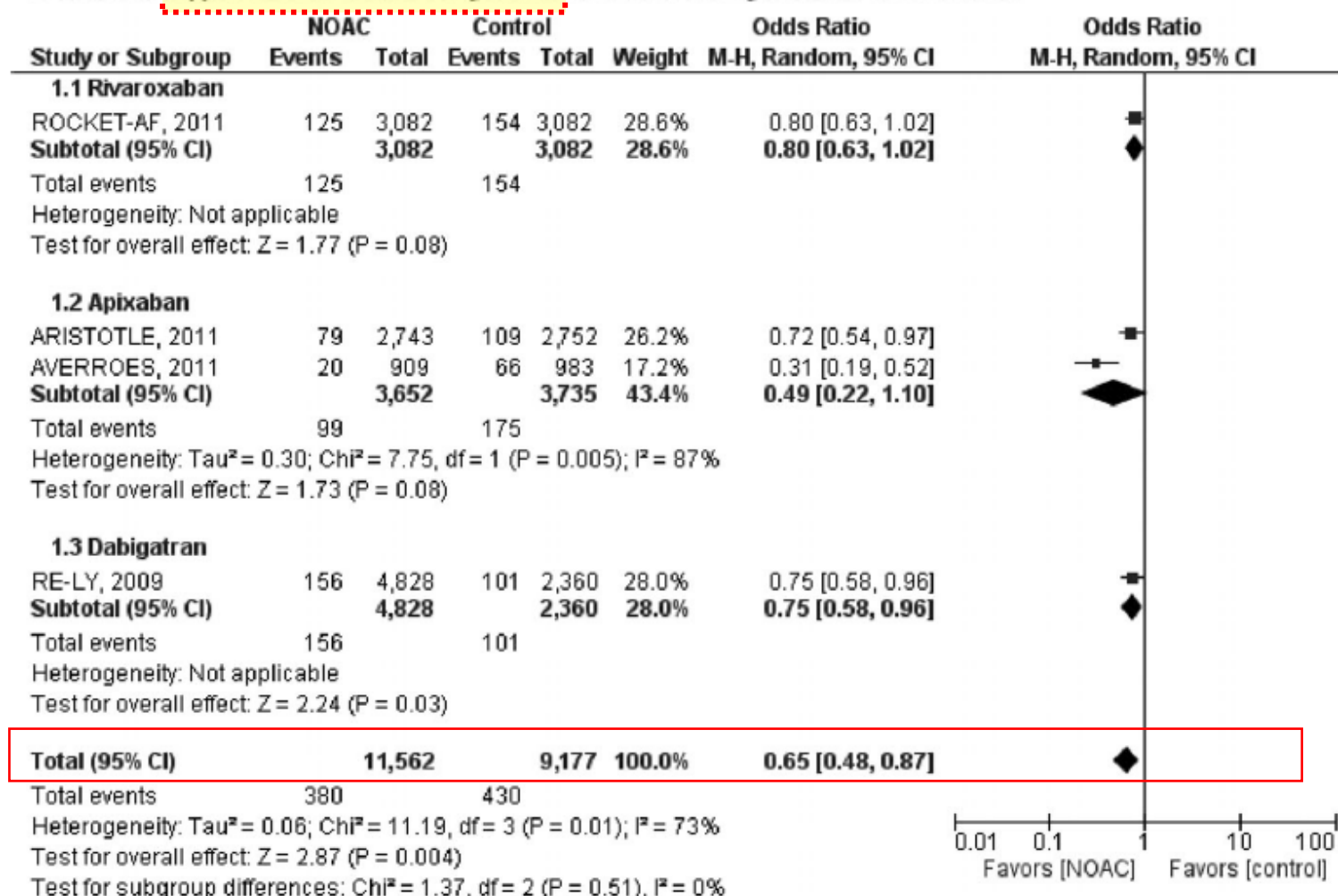
14. Η ηλικία του ασθενούς δεν αποτελεί αντένδειξη για την χορήγηση αντιπηκτικής αγωγής. Και οι ηλικιωμένοι ασθενείς με κολπική μαρμαρυγή πρέπει να λαμβάνουν αντιπηκτική αγωγή εάν δεν υπάρχει αντένδειξη (1Α).



New Oral Anticoagulants in Elderly Adults: Evidence from a Meta-Analysis of Randomized Trials

Partha Sardar, MD,* Saurav Chatterjee, MD,[†] Shobhana Chaudhari, MD,*
and Gregory Y. H. Lip, MD[‡]

Patients aged more than 75 years: Stroke or systemic embolism

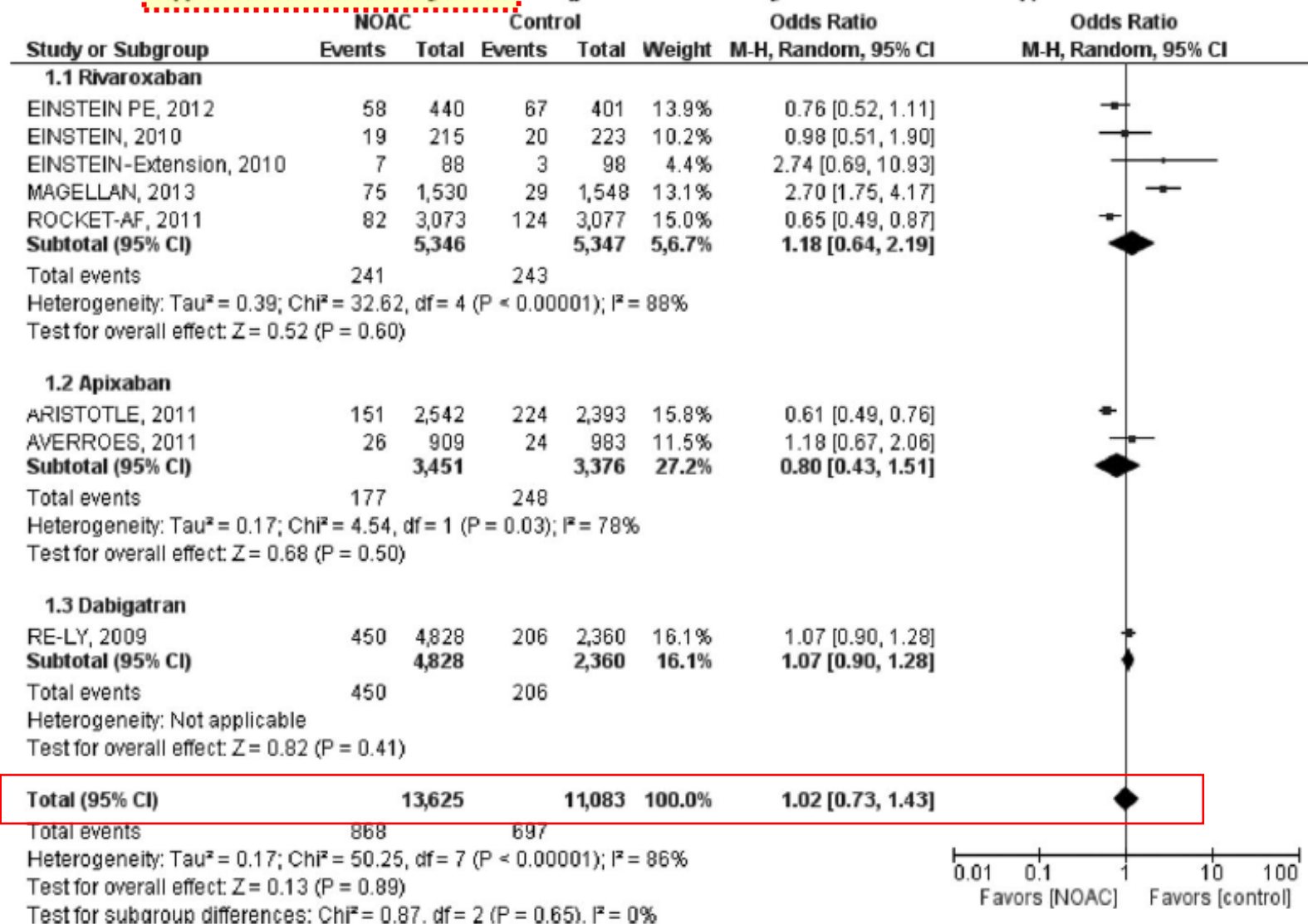


New Oral Anticoagulants in Elderly Adults: Evidence from a Meta-Analysis of Randomized Trials

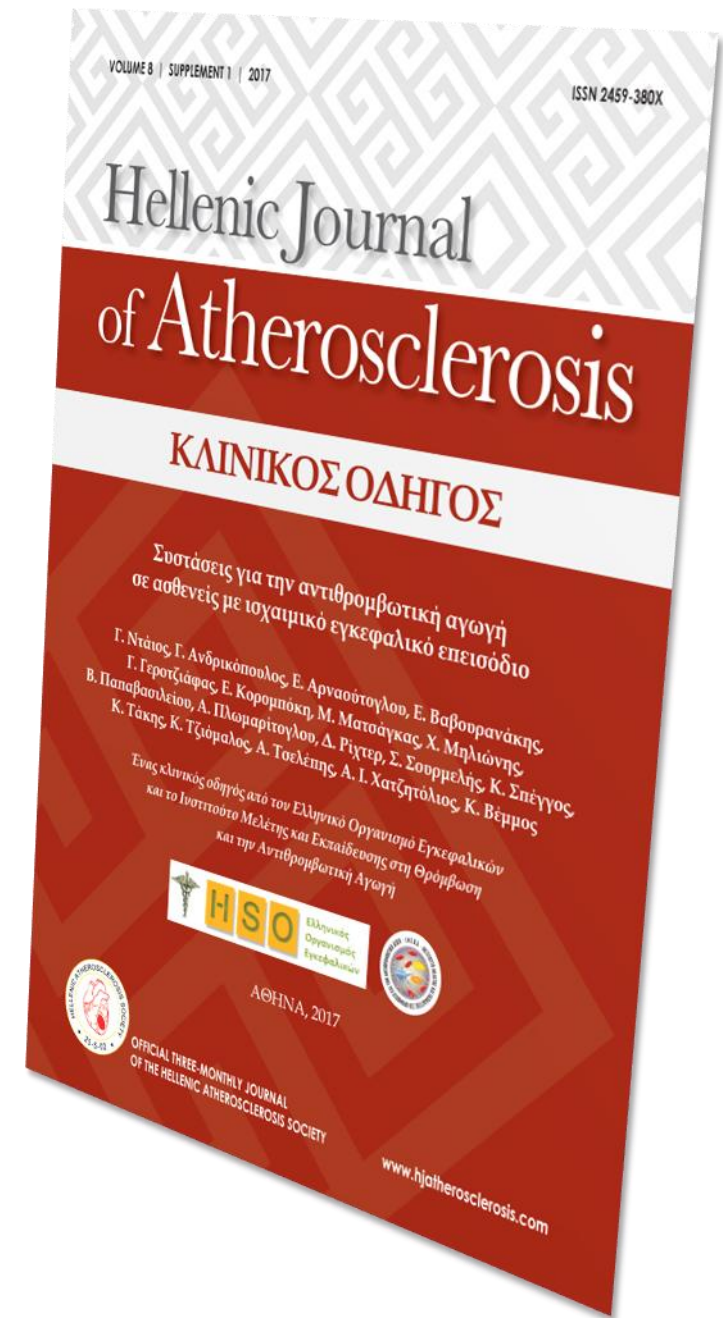
Partha Sardar, MD,* Saurav Chatterjee, MD,[†] Shobhana Chaudhari, MD,*

and Gregory Y. H. Lip,

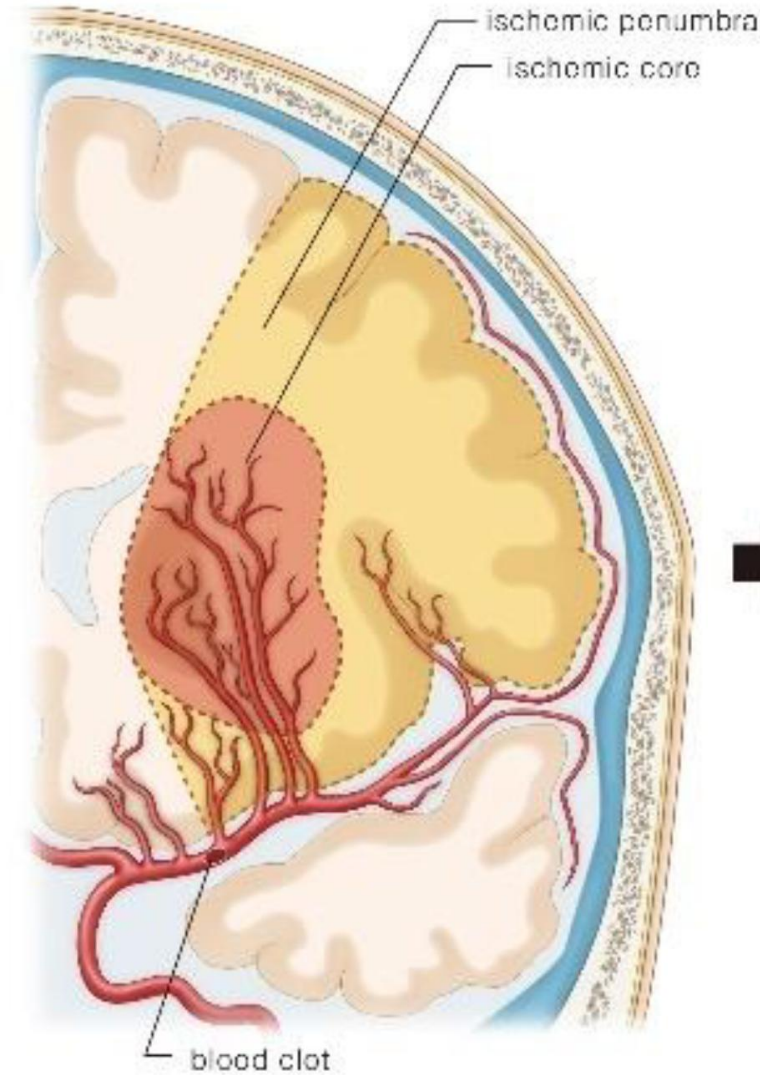
Patients aged more than 75 years: Major or clinically relevant bleeding



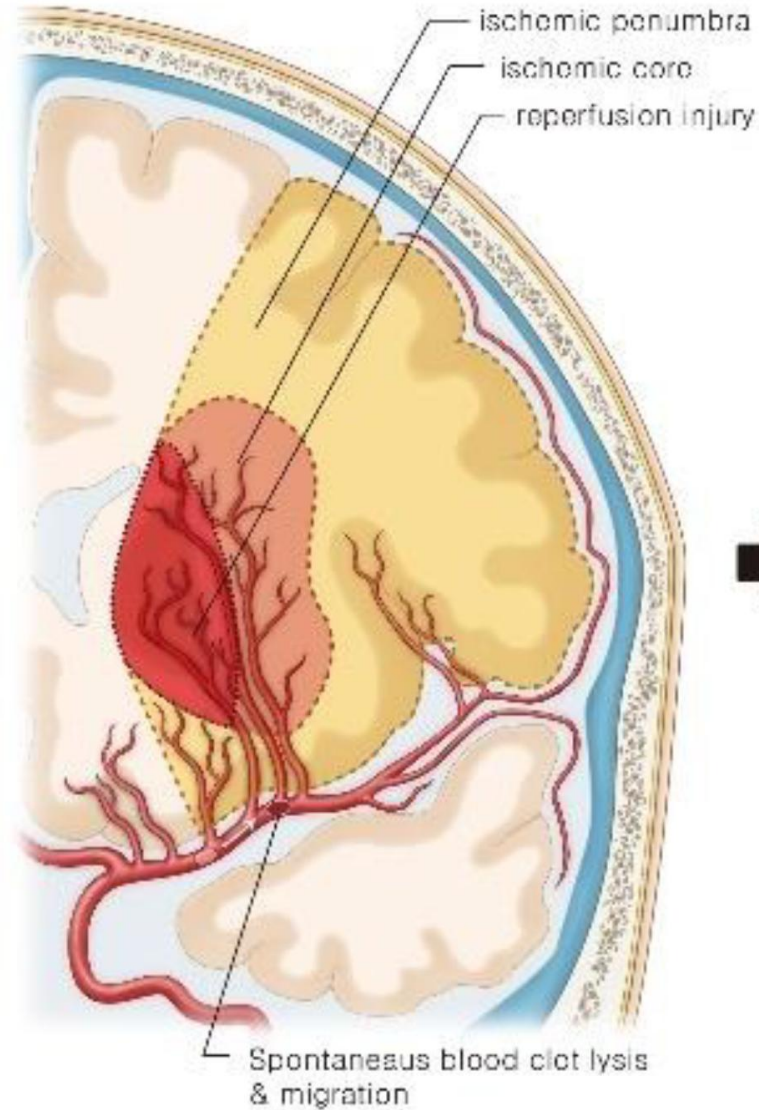
9. Σε ασθενείς με οξύ ισχαιμικό εγκεφαλικό επεισόδιο και ένδειξη αντιπηκτικής αγωγής, η έναρξη της αντιπηκτικής αγωγής πρέπει να καθυστερεί για κάποιο χρονικό διάστημα ώστε να μειωθεί ο κίνδυνος αιμορραγικής μετατροπής του εγκεφαλικού εμφράκτου. Ο προτεινόμενος χρόνος έναρξης της αντιπηκτικής αγωγής είναι την 1η ημέρα σε ασθενείς με παροδικό ισχαιμικό εγκεφαλικό επεισόδιο, την 3η ημέρα σε ασθενείς με μικρής βαρύτητας ισχαιμικό εγκεφαλικό (NIHSS score κατά την εισαγωγή ≤ 8), την 6η ημέρα σε ασθενείς με μέτριας βαρύτητας ισχαιμικό εγκεφαλικό (NIHSS score κατά την εισαγωγή 8-16) και την 12η ημέρα σε ασθενείς με υψηλής βαρύτητας ισχαιμικό εγκεφαλικό (NIHSS score κατά την εισαγωγή ≥ 16) (2Γ). Στο μεσοδιάστημα ο ασθενής θα πρέπει να λαμβάνει ασπιρίνη.



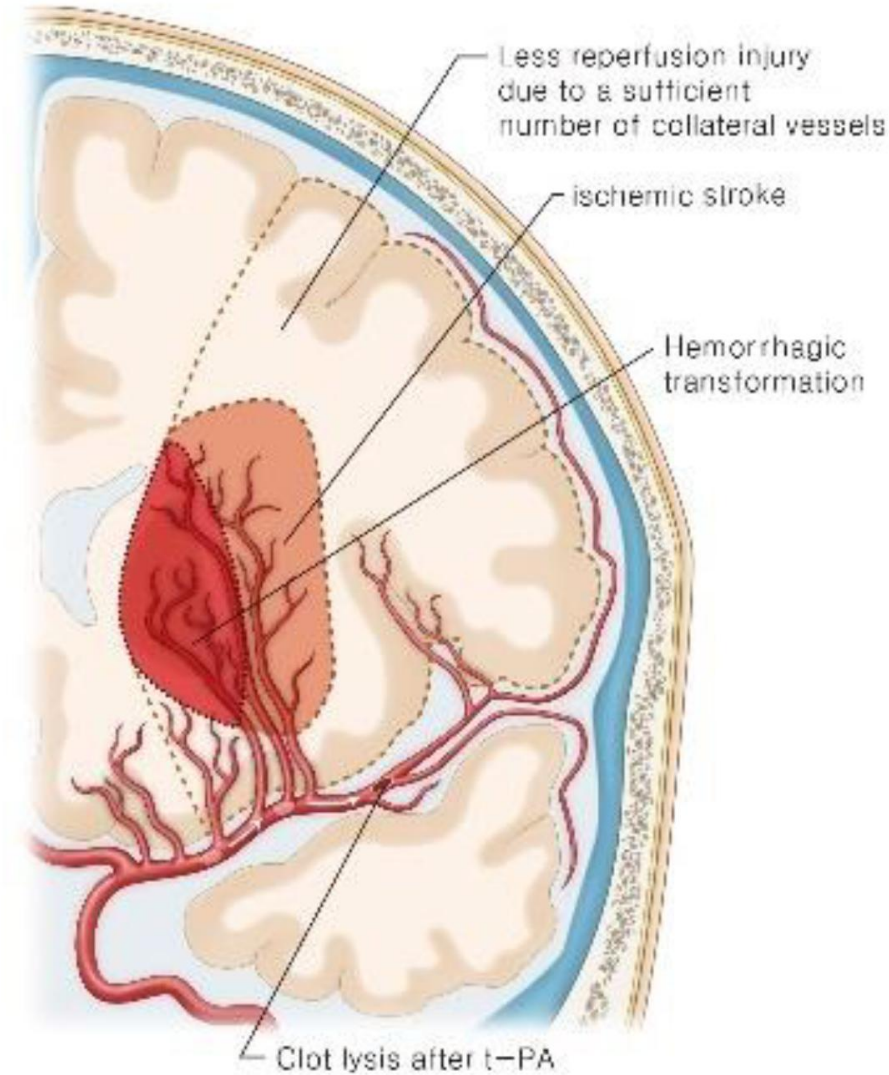
Hemorrhagic Transformation of Infarction



<Before visiting the hospital>



<At the time of hospital visit>



<After using thrombolytic agent>

Timing of anticoagulation after recent ischaemic stroke in patients with atrial fibrillation

It is suspected (though not supported by evidence) that early initiation of anticoagulation might exacerbate or cause parenchymal haemorrhage, with potentially serious clinical consequences.¹⁸ This concern has led clinicians to delay anticoagulation, although the independent contribution of haemorrhagic transformation of the infarct to clinical worsening remains uncertain¹⁹ and evidence from randomised controlled trials is not available.

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

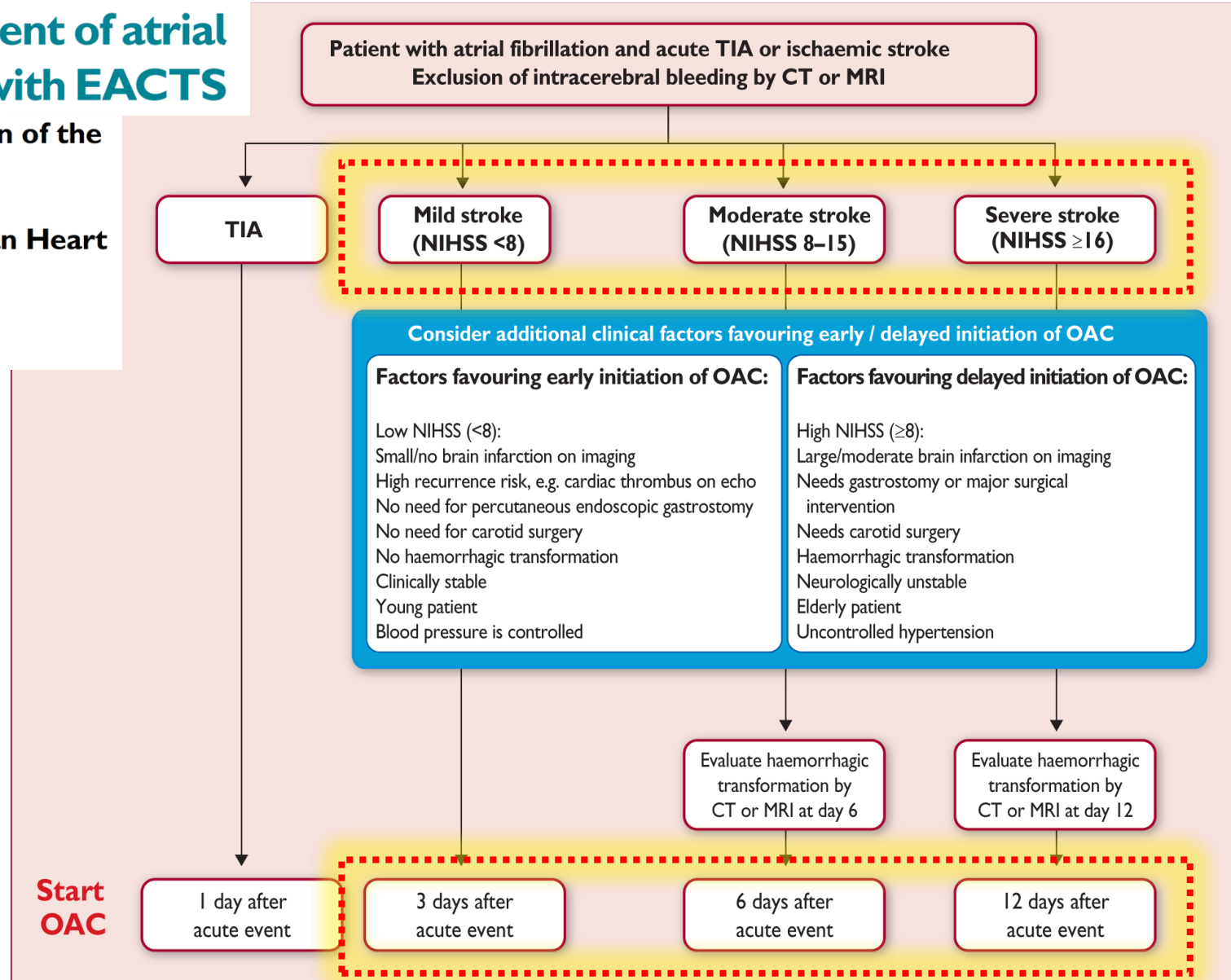
The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC

Endorsed by the European Stroke Organisation (ESO)

European Heart Journal (2016) 37, 2893–2962

“1-3-6-12-day rule”

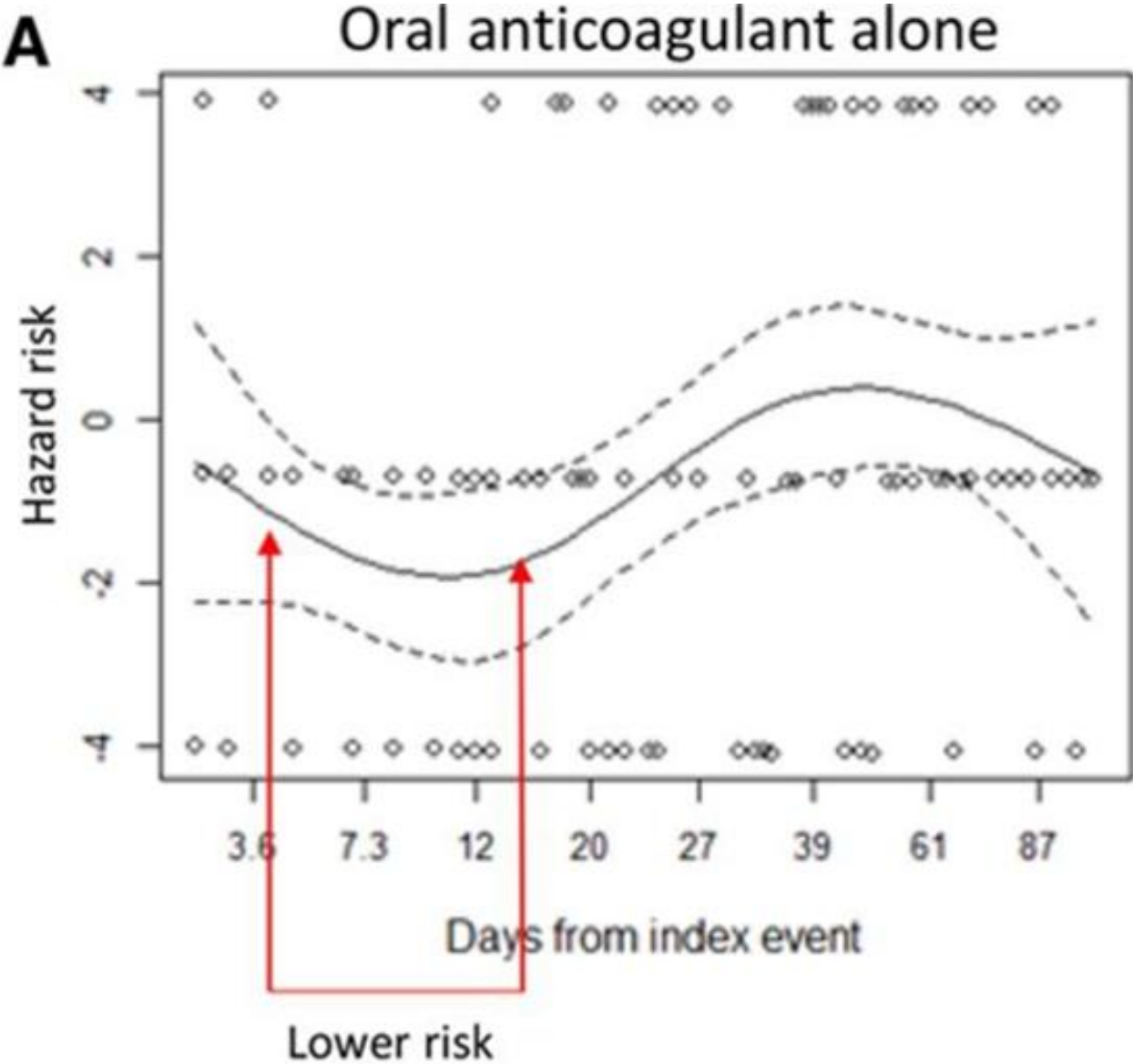


AF = atrial fibrillation; CT = computed tomography; NIHSS = National Institutes of Health stroke severity scale (available at http://www.strokecenter.org/wp-content/uploads/2011/08/NIH_Stroke_Scale.pdf); OAC = oral anticoagulation; TIA = transient ischaemic attack

*Initiation or continuation of anticoagulation in atrial fibrillation patients after a stroke or transient ischaemic attack. This approach is based on **consensus** rather than prospective data.*

Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation
Effect of Anticoagulation and Its Timing: The RAF Study

Prospective *Observational* Study
1.029 patients



Time of Initiating Anticoagulant Treatment	All Outcome Events, HR (95% CI)	Ischemic Outcome Events, HR (95% CI)	Hemorrhagic Outcome Events, HR (95% CI)
Within 7 days	1.35 (0.82–2.22)	1.19 (0.76–1.81)	1.72 (0.75–4.00)
Within 14 days	0.71 (0.47–2.50)	0.61 (0.35–1.06)	1.81 (0.75–4.00)
Between 2 and 14 days	0.67 (0.39–1.14)	0.59 (0.27–1.29)	0.72 (0.29–1.78)
Between 3 and 14 days	0.58 (0.33–1.03)	0.50 (0.23–1.12)	0.51 (0.18–1.47)
Between 4 and 14 days	0.53 (0.30–0.93)	0.43 (0.19–0.97)	0.39 (0.12–1.19)
Between 5 and 14 days	0.47 (0.25–0.87)	0.40 (0.17–0.86)	0.33 (0.10–1.15)
Between 6 and 14 days	0.42 (0.22–0.81)	0.30 (0.11–0.80)	0.37 (0.10–1.37)
Between 7 and 14 days	0.43 (0.23–0.83)	0.25 (0.10–0.65)	0.42 (0.11–1.51)
Between 8 and 14 days	0.42 (0.21–0.87)	0.24 (0.08–0.69)	0.56 (0.15–2.12)
Between 9 and 14 days	0.43 (0.21–0.86)	0.22 (0.07–0.62)	0.48 (0.13–1.78)
Between 10 and 14 days	0.30 (0.13–0.71)	0.18 (0.05–0.63)	0.20 (0.02–1.75)
Between 11 and 14 days	0.29 (0.12–0.71)	0.16 (0.05–0.56)	0.24 (0.03–1.77)
Between 12 and 14 days	0.21 (0.08–0.57)	0.12 (0.03–0.45)	0.27 (0.03–2.17)
Between 13 and 14 days	0.38 (0.13–1.08)	0.21 (0.05–0.85)	0.36 (0.04–3.22)
Day 14	0.38 (0.13–1.11)	0.20 (0.05–0.85)	0.36 (0.04–3.22)

AHA/ASA Guideline



Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Endorsed by the Society for Academic Emergency Medicine and The Neurocritical Care Society

6.6.2. Atrial Fibrillation	COR	LOE	New, Revised, or Unchanged
1. For most patients with an AIS in the setting of atrial fibrillation, it is reasonable to initiate oral anticoagulation between 4 and 14 days after the onset of neurological symptoms.	Ia	B-NR	Recommendation revised from 2014 Secondary Prevention.

Recommendations. We cannot make recommendations about the **optimal time** for initiating **anticoagulation** treatment in patients with acute ischemic stroke based on randomised trials. We encourage inclusion of patients in ongoing randomised controlled trials testing the efficacy and safety of early anticoagulation to answer this question.

Quality of evidence: Low

Strength of recommendation: Weak

Antithrombotic treatment for secondary prevention of stroke and other thromboembolic events in patients with stroke or transient ischemic attack and non-valvular atrial fibrillation:

A European Stroke Organisation guideline

Expert opinion (Delphi vote: 6/7 agree, 1/7 disagree).
We suggest **antiplatelet** therapy **in the first 48 h** after ischemic stroke associated with AF.

We consider it reasonable to start **anticoagulant** therapy at **day 3 or 4** from the index stroke in patients with mild stroke and small infarcts (<1.5 cm) and **at day 7** for moderate infarcts.

For large infarcts, **anticoagulation** treatment might be best delayed for **14 days** after the index stroke.

Ισχαιμικό ΑΕΕ / Παροδικό ΑΕΕ

Μη καρδιοεμβολικό

Καρδιοεμβολικό

TIA

$ABCD^2 < 4$

$ABCD^2 \geq 4$

$NIHSS < 4$

$NIHSS \geq 4$

TIA

$NIHSS < 8$

$NIHSS 8-16$

$NIHSS > 16$

* Ασπιρίνη 100mgx1 &
Κλοπιδογρέλη 75mgx1

Ασπιρίνη 160-300mg x1

*21 ημέρες

10 ημέρες ή
εξιτήριο

1^η

3^η

CT

7^η

CT

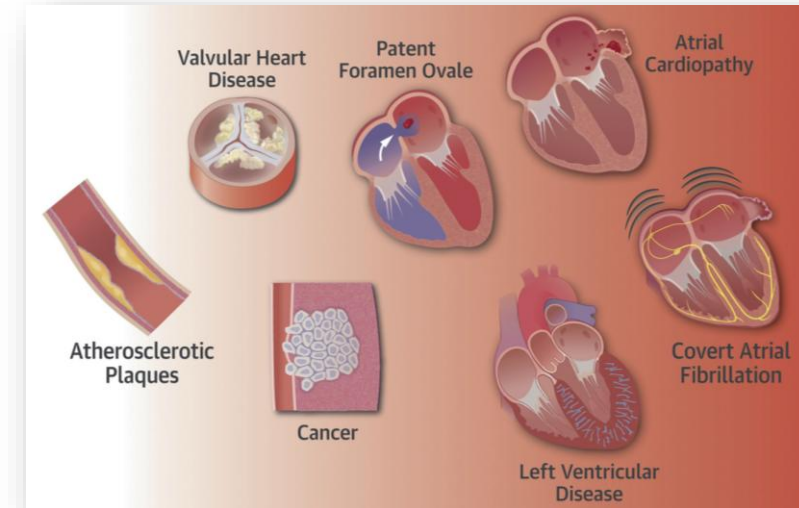
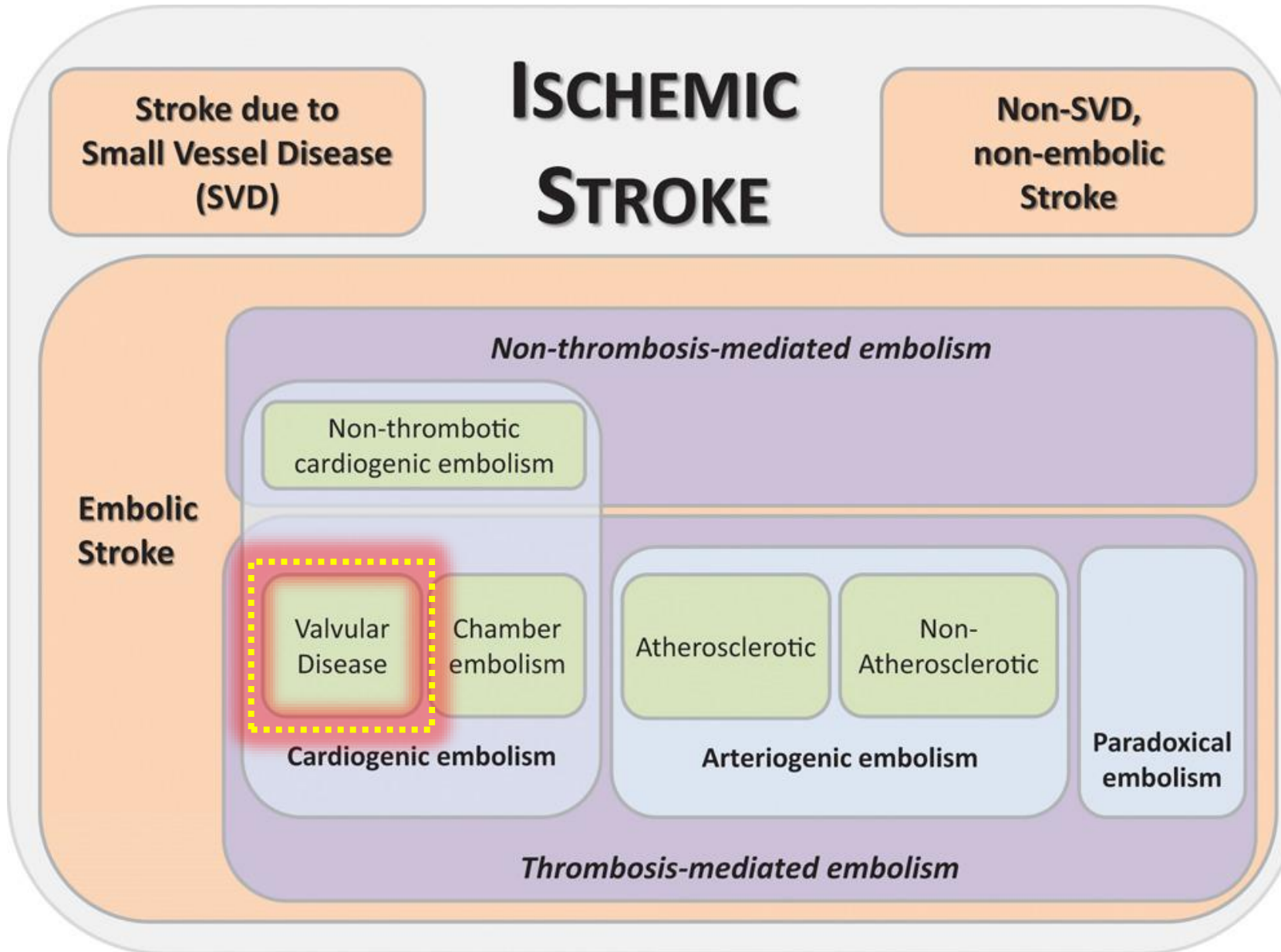
14^η

CT

- Ασπιρίνη (50-325mg x1)
- Κλοπιδογρέλη (75mg x1)
- Τριφλουζάλη (600mg x1)
- Ασπιρίνη/διπυριδαμόλη (25mg/200mg x2)

NOAC ή Sintrom

Ischemic stroke is an etiologically heterogeneous syndrome

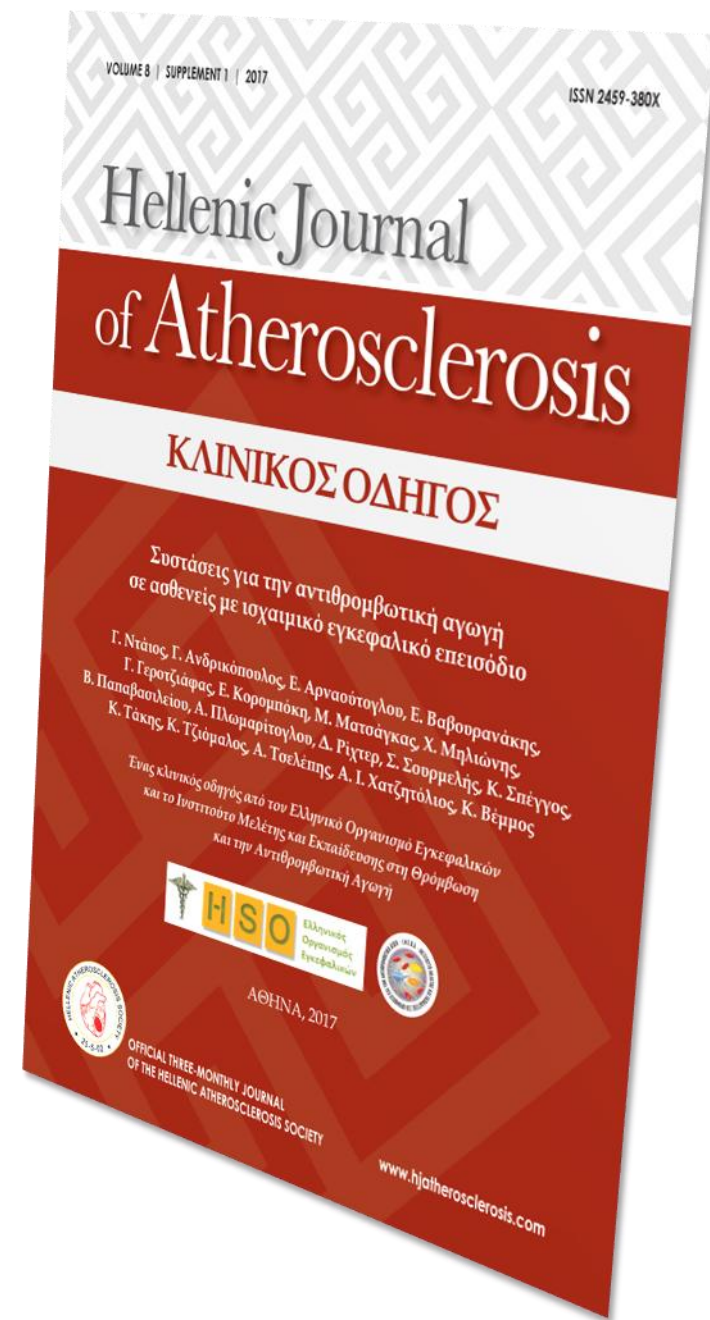


Ntaios G. Embolic Stroke of Undetermined Source: JACC Review Topic of the Week. J Am Coll Cardiol. 2020 Jan 28;75(3):333-340.

In order to optimize the **secondary prevention strategy** in a patient with ischemic stroke, it is rational to identify the underlying etiologic pathology.

12. Ασθενείς με **ισχαιμικό** (εγκεφατεστημένο ή παροδικό) εγκεφαλικό επεισόδιο και παροξυσμική, εμμένουσα ή χρόνια κολπική μαρμαρυγή σε έδαφος βαλβιδοπάθειας της μιτροειδούς ρευματικής αιτιολογίας πρέπει να λαμβάνουν **ανταγωνιστές της βιταμίνης K** (ασενοκουμαρόλη ή βαρφαρίνη) με στόχο εύρος INR 2,0-3,0 (1Γ).

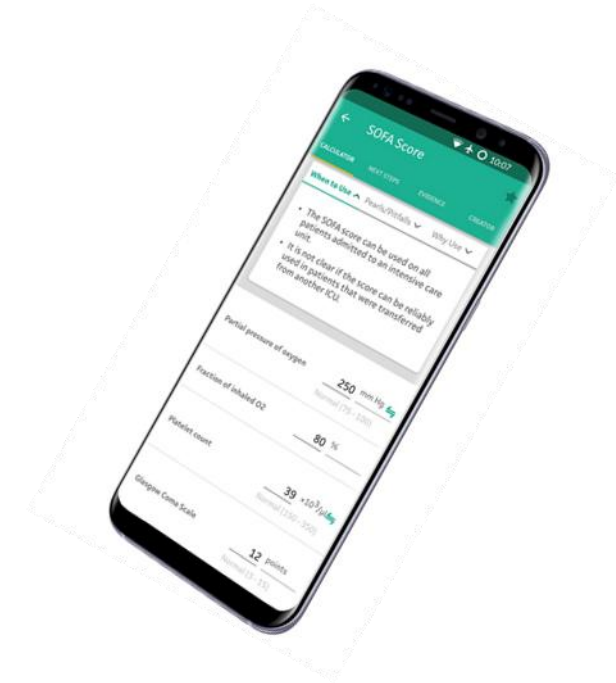
15. Σε ασθενείς με **ισχαιμικό** (εγκεφατεστημένο ή παροδικό) εγκεφαλικό επεισόδιο και μεταλλική καρδιακή βαλβίδα πρέπει να χορηγείται **ανταγωνιστής της βιταμίνης K** (ασενοκουμαρόλη ή βαρφαρίνη). Οι ασθενείς πρέπει να προβαίνουν σε τακτικό έλεγχο του INR (τουλάχιστον άπαξ μηνιαίως) και τιτλοποίηση της δόσης με στόχο εύρος INR 2,5-3,5 ανάλογα με τον τύπο και τη θέση της βαλβίδας καθώς και την παρουσία προηγούμενου θρομβοεμβολικού επεισοδίου (1Α).



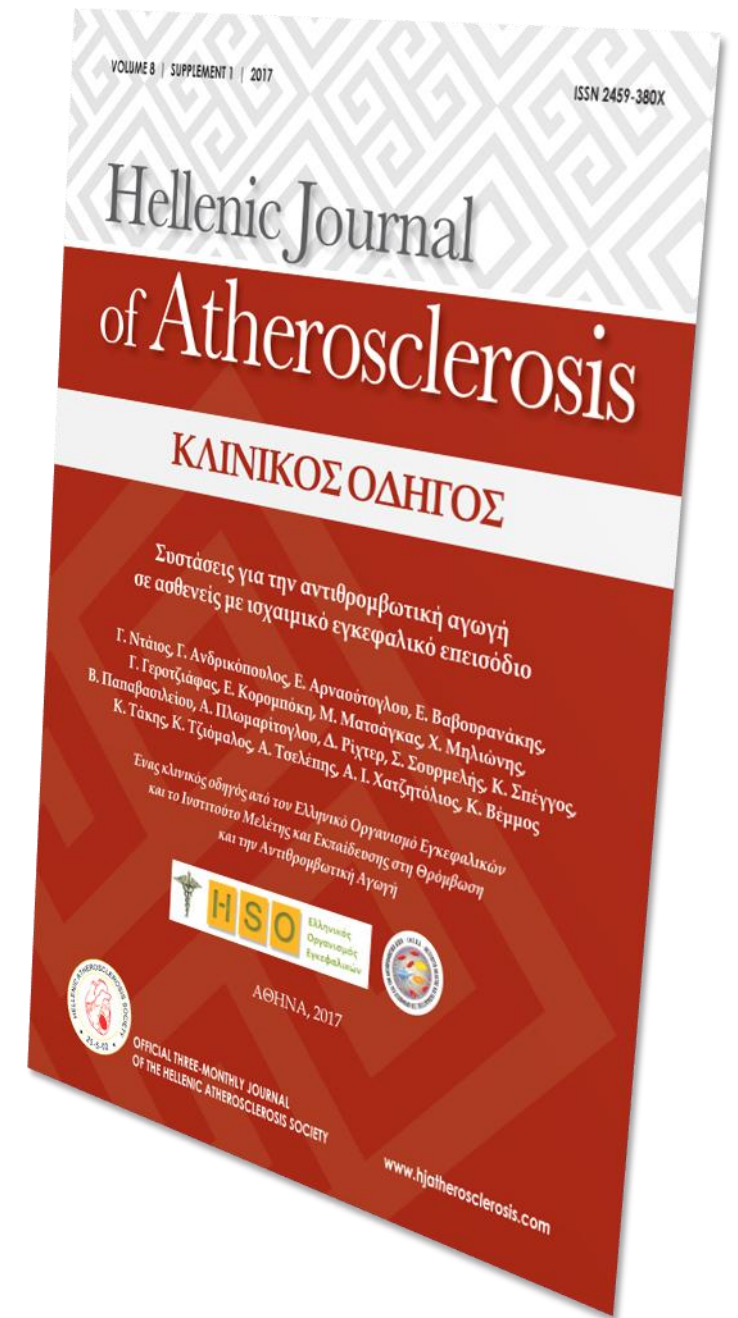
2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)

HAS-BLED score

Risk factors and definitions		Points awarded
H	Uncontrolled hypertension SBP >160 mmHg	1
A	Abnormal renal and/or hepatic function Dialysis, transplant, serum creatinine >200 µmol/L, cirrhosis, bilirubin > × 2 upper limit of normal, AST/ALT/ALP >3 × upper limit of normal	1 point for each
S	Stroke Previous ischaemic or haemorrhagic ^a stroke	1
B	Bleeding history or predisposition Previous major haemorrhage or anaemia or severe thrombocytopenia	1
L	Labile INR^b TTR <60% in patient receiving VKA	1
E	Elderly Aged >65 years or extreme frailty	1
D	Drugs or excessive alcohol drinking Concomitant use of antiplatelet or NSAID; and/or excessive ^c alcohol per week	1 point for each
Maximum score		9



20. Συστήνεται η χορήγηση **ηπαρίνης χαμηλού μοριακού βάρους** σε προφυλακτική δόση σε ασθενείς με οξύ ισχαιμικό εγκεφαλικό επεισόδιο οι οποίοι δεν είναι περιπατητικοί και στους οποίους το όφελος της μείωσης του κινδύνου φλεβικής θρομβοεμβολής ξεπερνά την αύξηση του κινδύνου αιμορραγίας (1A).



European Stroke Organisation (ESO) guidelines for prophylaxis for venous thromboembolism in immobile patients with acute ischaemic stroke

Figure 3.4 The effect on prophylactic anticoagulants on PE during treatment

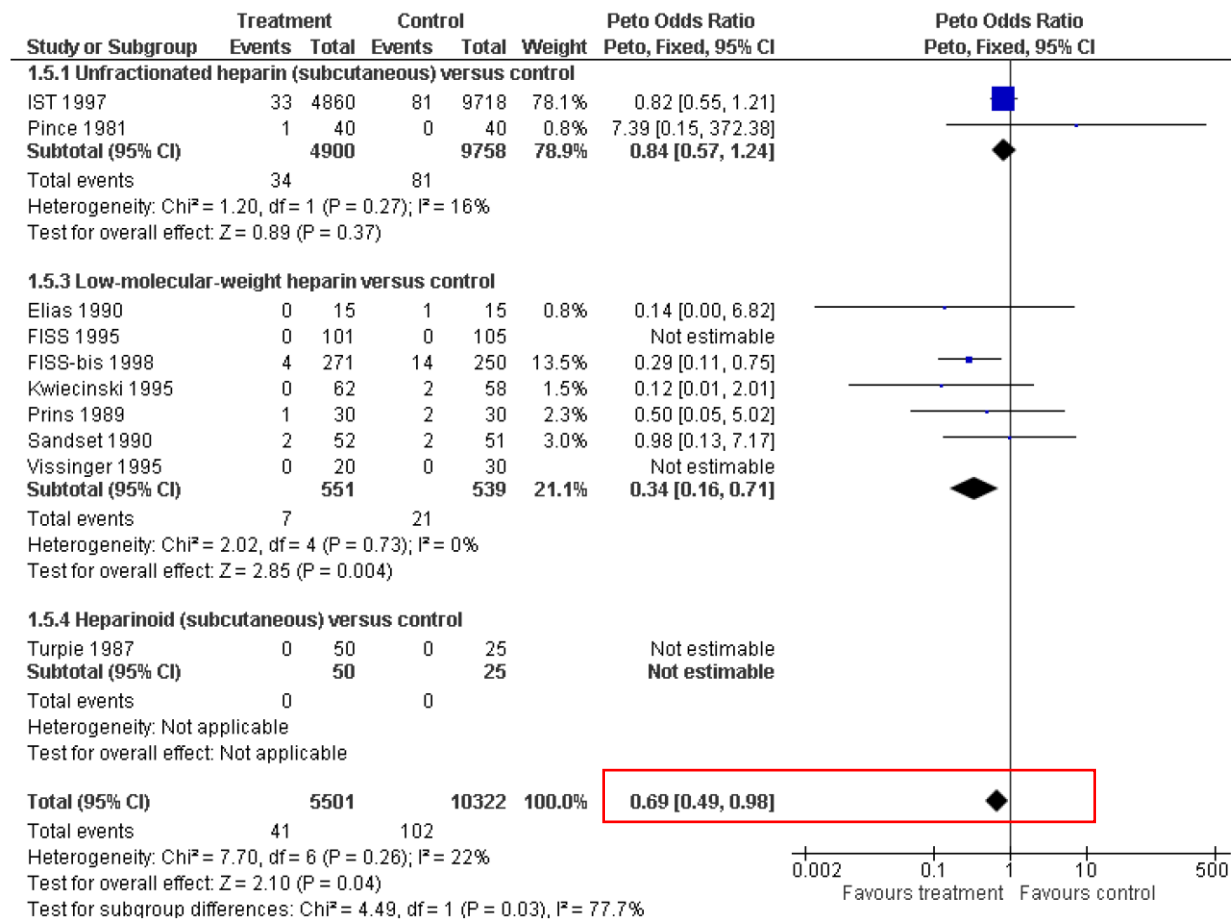


Figure 3.6 The effect on prophylactic anticoagulants on any DVT (including Isotope scanning) only during treatment

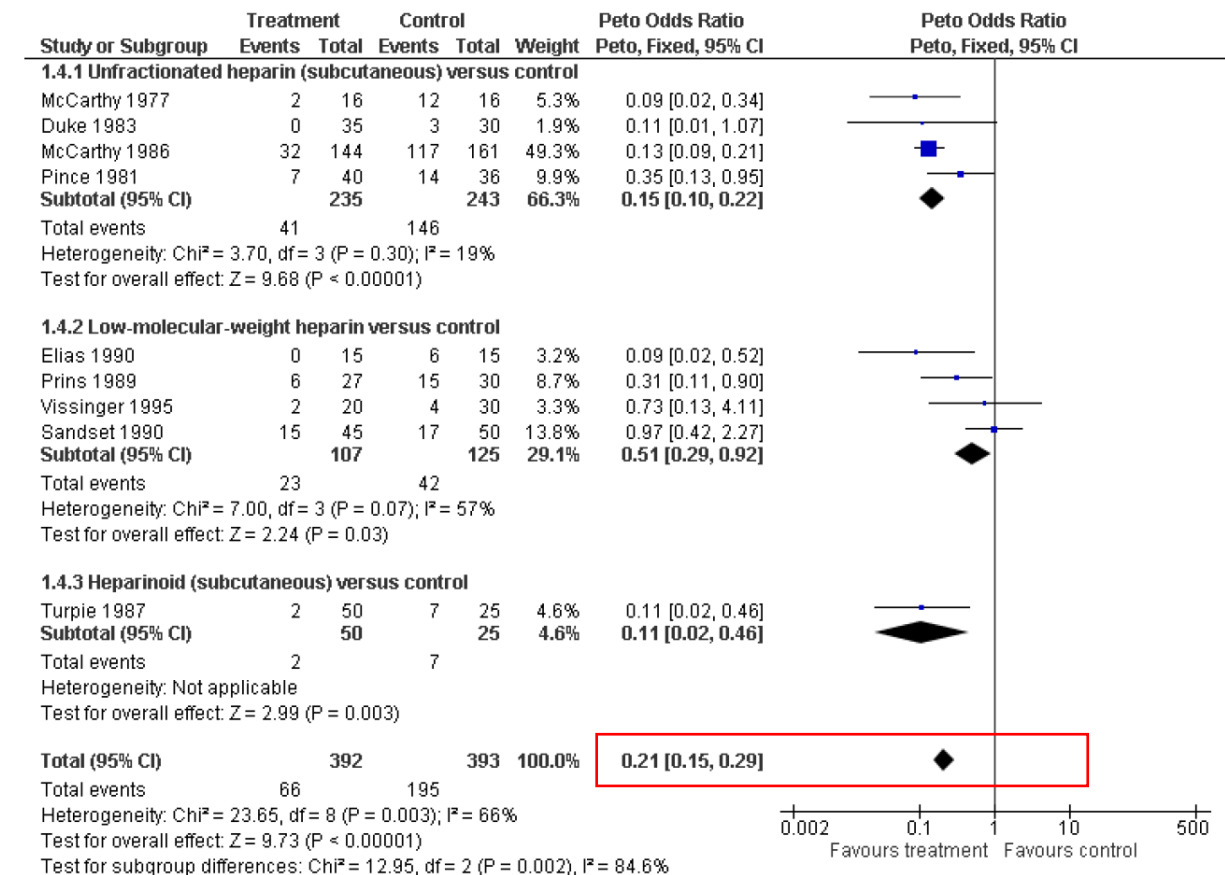


Figure 3.3 The effect of prophylactic anticoagulation on symptomatic intracranial bleeding during treatment period

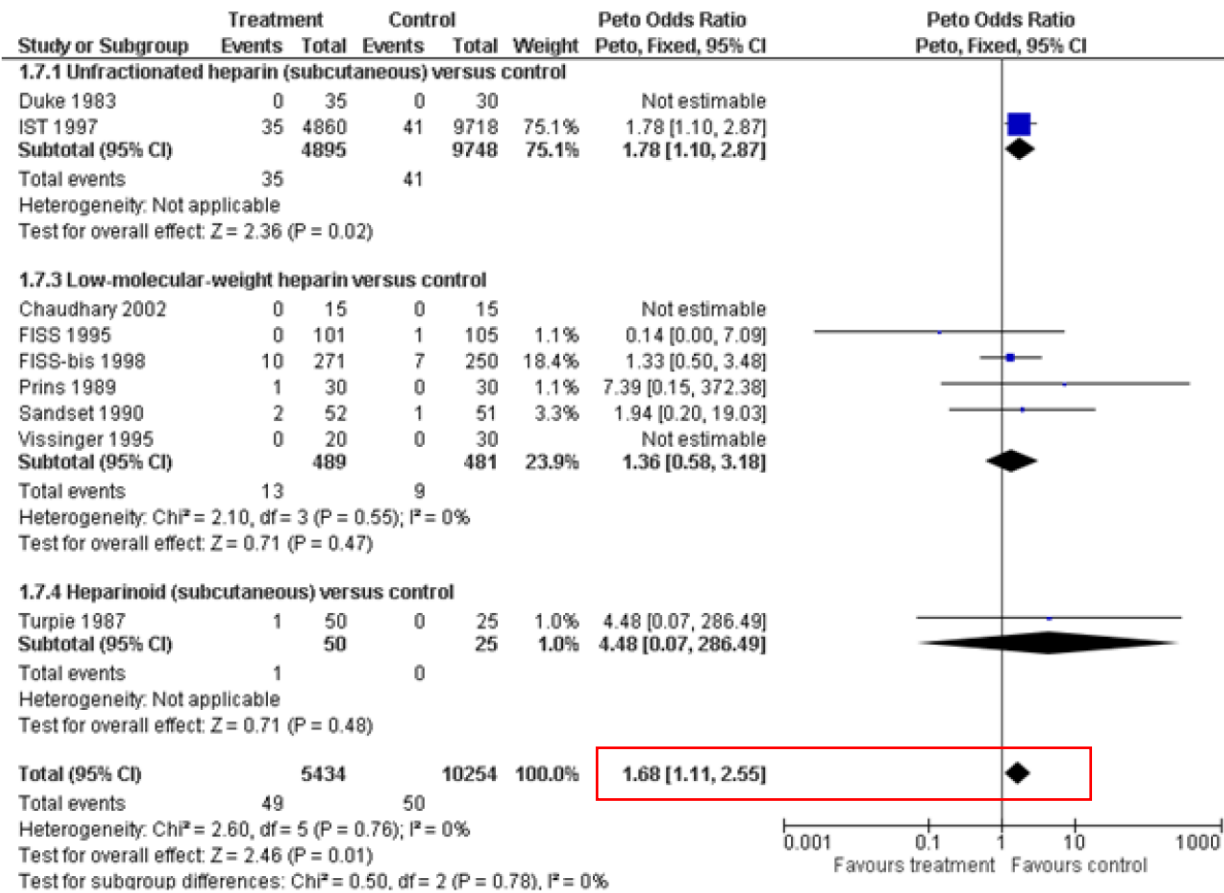
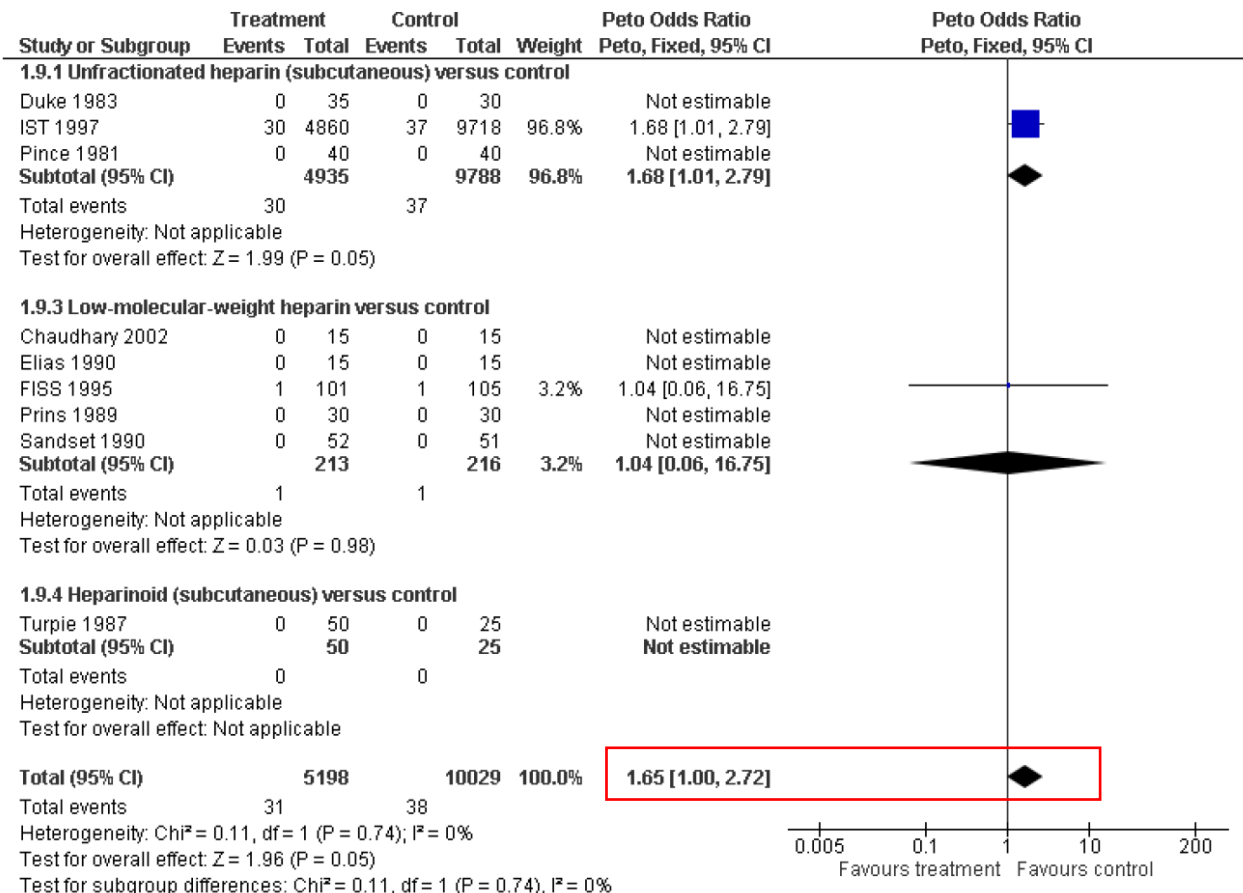


Figure 3.5 The effect of prophylactic anticoagulation on symptomatic extracranial bleeding during treatment period



European Stroke Organisation (ESO) guidelines for prophylaxis for venous thromboembolism in immobile patients with acute ischaemic stroke

Figure 3.2 The effect of prophylactic anticoagulants on death during treatment

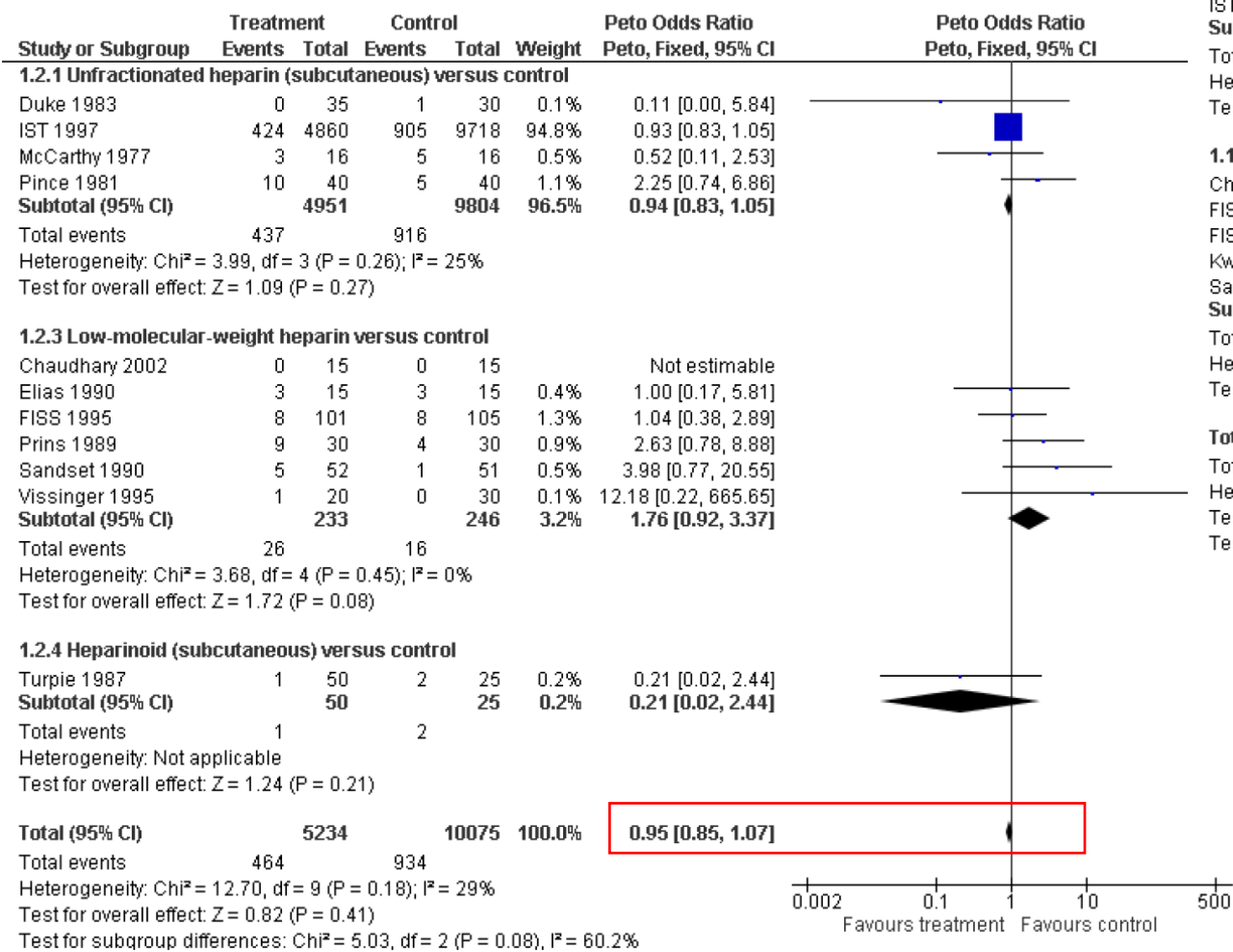
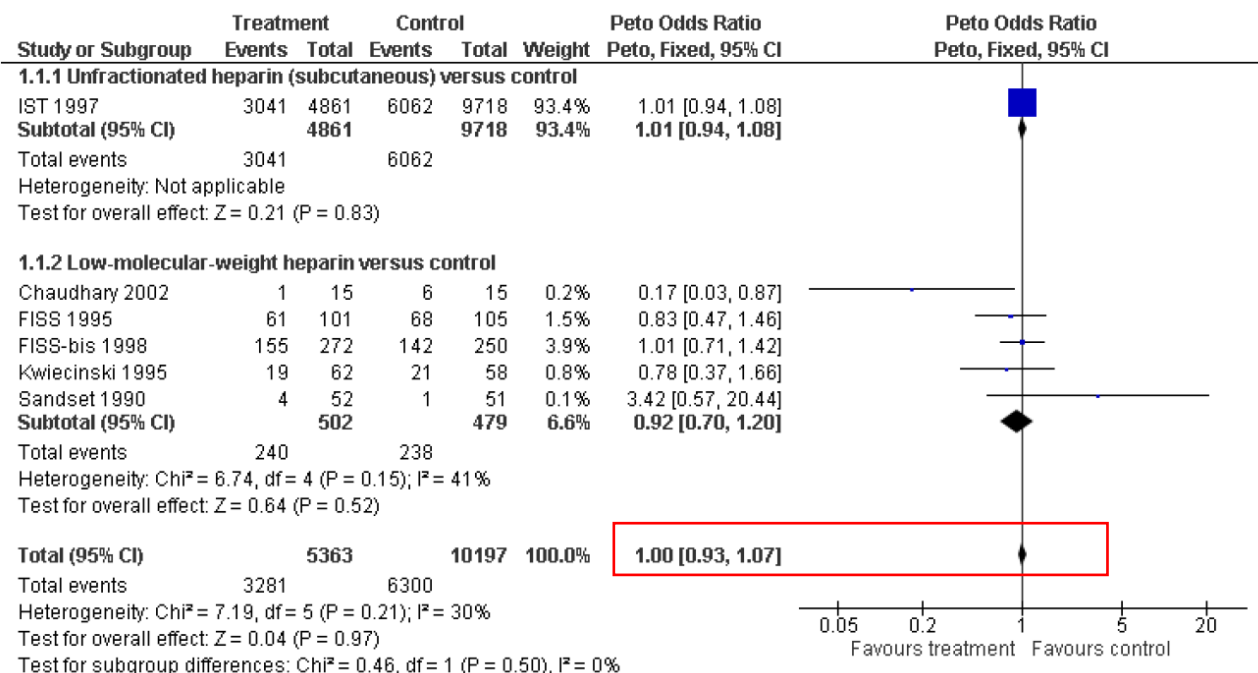


Figure 3.1 The effect on prophylactic anticoagulants of death or dependency at final follow up



European Stroke Organisation (ESO) guidelines for prophylaxis for venous thromboembolism in immobile patients with acute ischaemic stroke

Recommendation

Prophylactic anticoagulation with unfractionated heparin (UFH) (5000U $\times$ 2, or $\times$ 3 daily) or low molecular weight heparin (LMWH) or heparinoid should be considered in immobile patients with ischaemic stroke in whom the benefits of reducing the risk of venous thromboembolism is high enough to offset the increased risks of intracranial and extracranial bleeding associated with their use.

Quality of evidence: Moderate $\oplus\oplus\oplus$

Strength of recommendation: Weak for $\uparrow$?

Recommendation

Where a judgement has been made that prophylactic anticoagulation is indicated LMWH or heparinoid should be considered instead of UFH because of its greater reduction in risk of DVT, the greater convenience, reduced staff costs and patient comfort associated single daily dose vs. multiple daily injections but these advantages should be weighed against the higher risk of extracranial bleeding, higher drug costs and risks in elderly patients with poor renal function

Quality of evidence: Moderate $\oplus\oplus\oplus$

Strength of recommendation: Weak $\uparrow$?

Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Endorsed by the Society for Academic Emergency Medicine and The Neurocritical Care Society

4.9. Deep Vein Thrombosis Prophylaxis	COR	LOE	New, Revised, or Unchanged
2. The benefit of prophylactic-dose subcutaneous heparin (unfractionated heparin [UFH] or LMWH) in patients with AIS is not well established.	IIb	A	New recommendation.
3. When prophylactic anticoagulation is used, the benefit of prophylactic-dose LMWH over prophylactic-dose UFH is uncertain.	IIb	B-R	New recommendation.

Ισχαιμικό ΑΕΕ / Παροδικό ΑΕΕ

Μη καρδιοεμβολικό

Καρδιοεμβολικό

TIA

ABCD²<4

ABCD²≥4

NIHSS<4

NIHSS≥4

TIA

NIHSS<8

NIHSS 8-16

NIHSS>16

* Ασπιρίνη 100mgx1 &
Κλοπιδογρέλη 75mgx1

Ασπιρίνη 160-300mg x1

*21 ημέρες

10 ημέρες ή
εξιτήριο

1^η

3^η

CT

7^η

CT

14^η

CT

- Ασπιρίνη (50-325mg x1)
- Κλοπιδογρέλη (75mg x1)
- Τριφλουζάλη (600mg x1)
- Ασπιρίνη/διπυριδαμόλη (25mg/200mg x2)

NOAC ή Sintrom

**ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
«ΚΑΡΔΙΟΜΕΤΑΒΟΛΙΚΗ ΙΑΤΡΙΚΗ»**

Πρωτογενής Πρόληψη ΑΕΕ
Δευτερογενής πρόληψη (αντιθρομβωτική αγωγή)

Σας ευχαριστώ πολύ για την προσοχή σας!