ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
«ΚΑΡΔΙΟΜΕΤΑΒΟΛΙΚΗ ΙΑΤΡΙΚΗ»

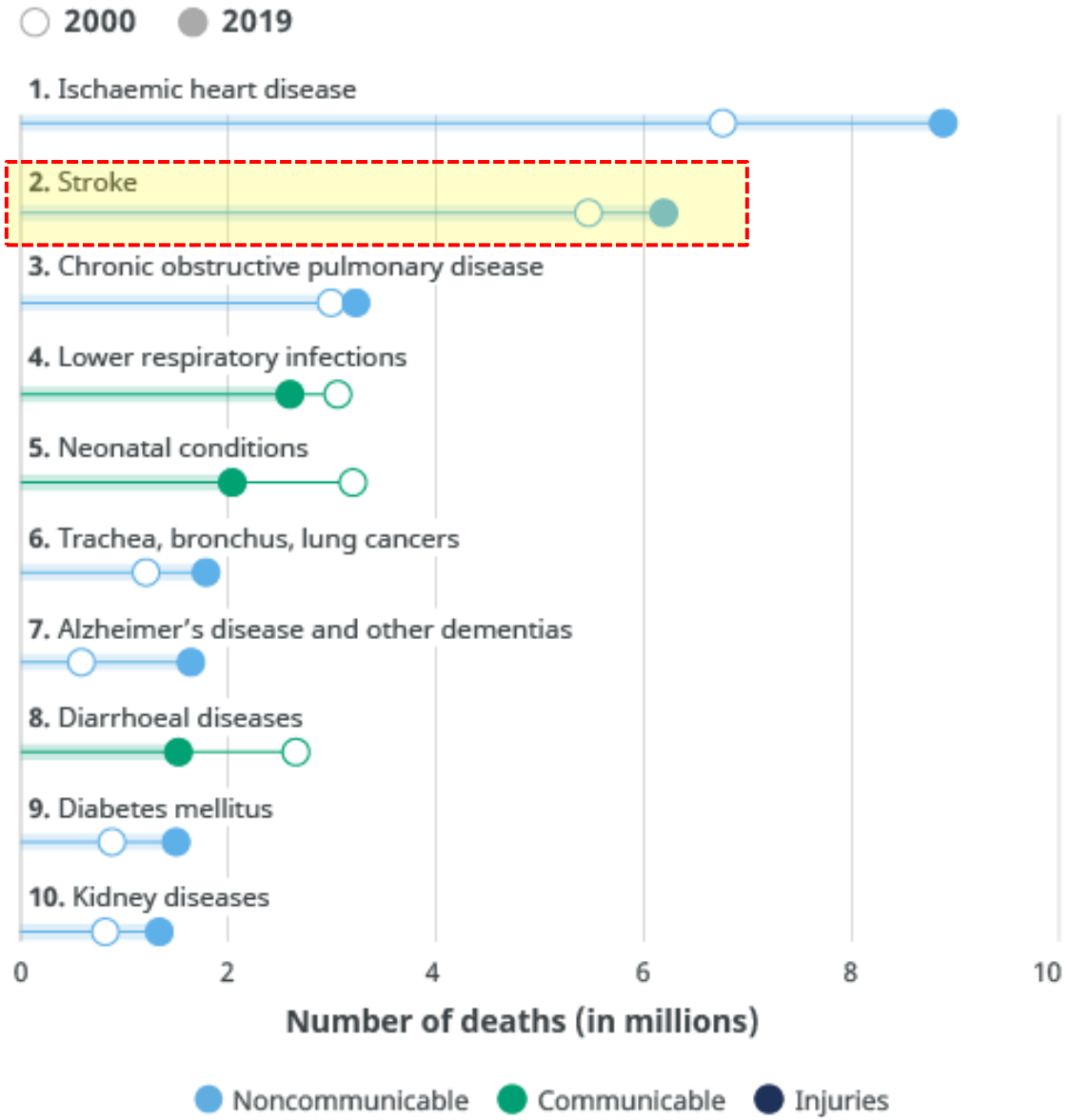
Πρωτογενής Πρόληψη ΑΕΕ

Κακαλέτσης Νικόλαος

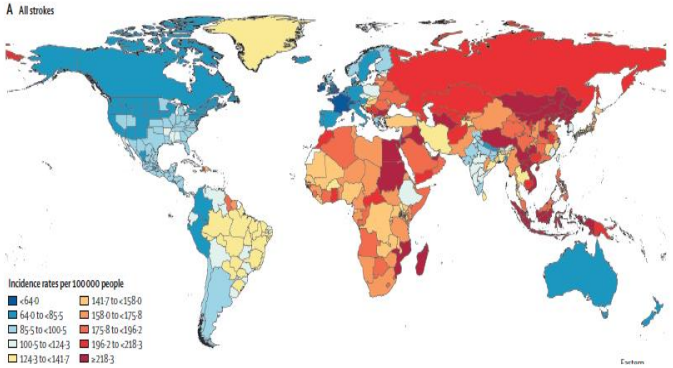
Παθολόγος
Επιμελητής Β’, Β’ Παθολογική Κλινική, Γ.Ν.Θ. Ιπποκράτειο
Μεταδιδακτορικός Ερευνητής Ιατρικής Σχολής Α.Π.Θ.

18 Απριλίου 2024

Leading causes of death globally



Source: WHO Global Health Estimates.



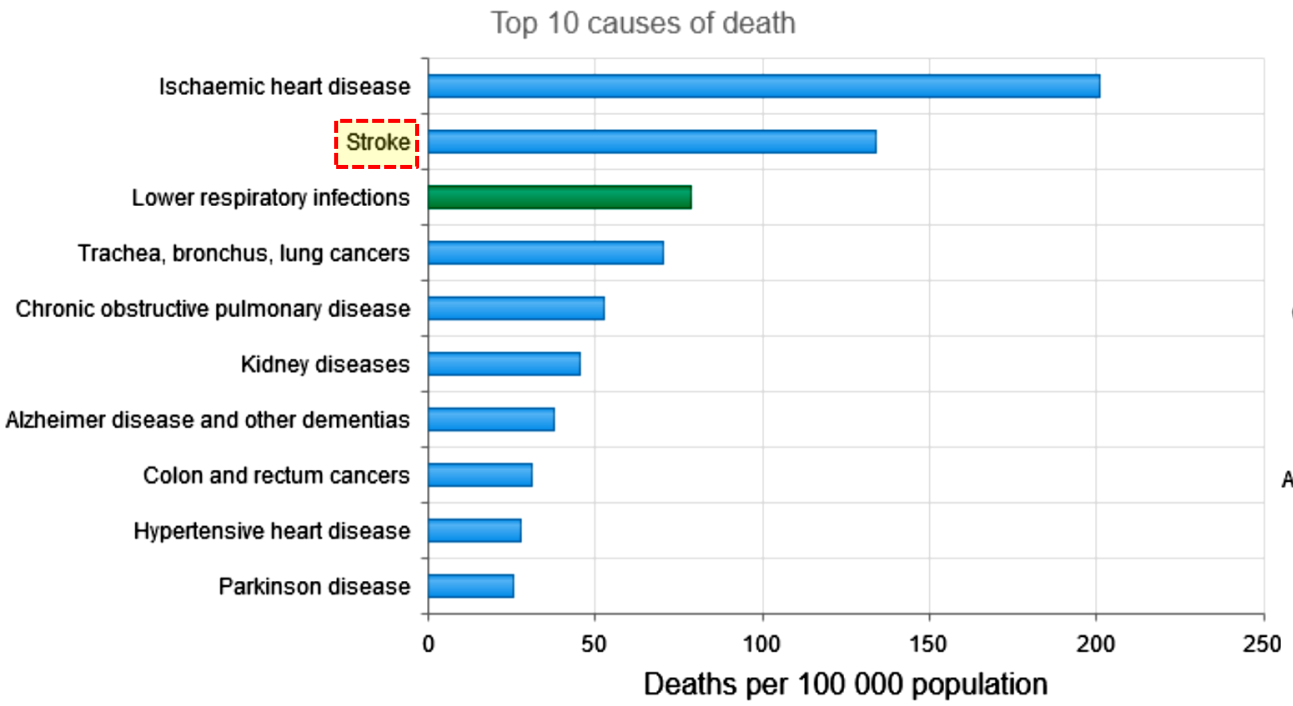
World Health Organization

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

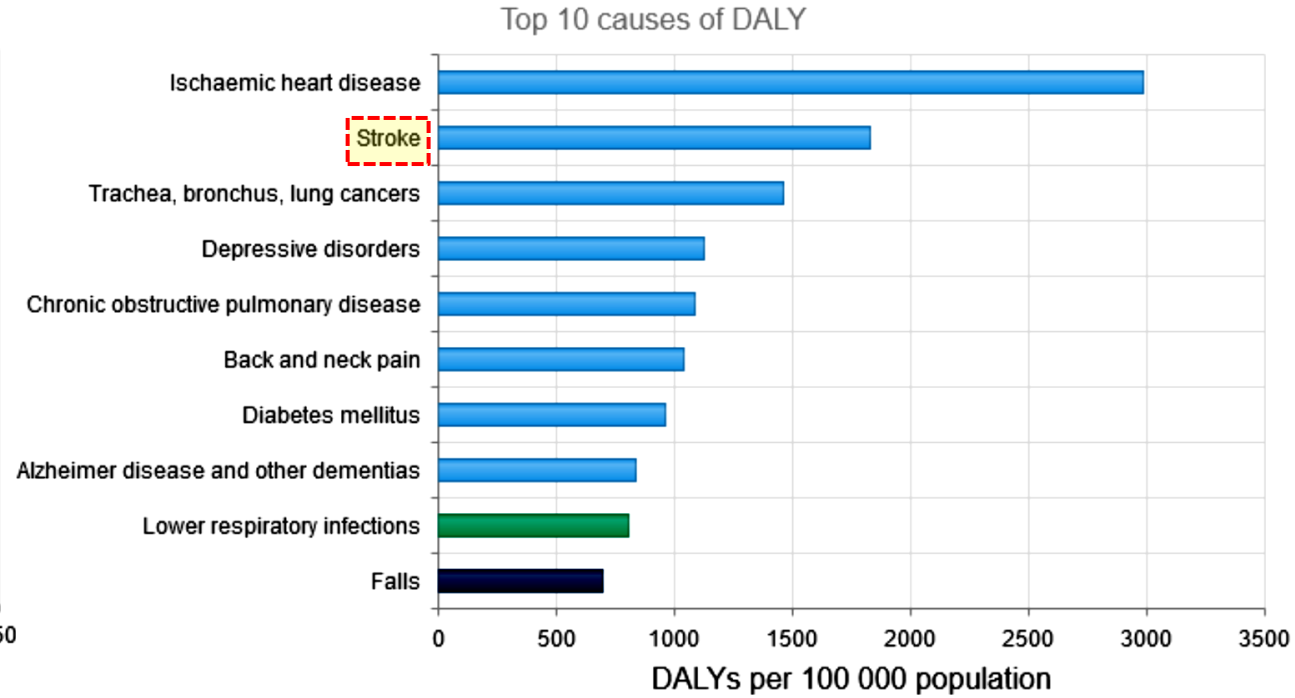
1. Neonatal conditions
2. Ischaemic heart disease
3. Stroke
4. Lower respiratory infections
5. Diarrhoeal diseases
6. Road injury
7. Chronic obstructive pulmonary disease
8. Diabetes mellitus
9. Tuberculosis
10. Congenital anomalies

https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates

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)



https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates

Ischemic stroke is an etiologically heterogeneous syndrome

Stroke due to Small Vessel Disease (SVD)

ISCHEMIC STROKE

Non-SVD, non-embolic Stroke

Embolic Stroke

Non-thrombosis-mediated embolism

Σηπτικό έμβολο - ενδοκαρδίτιδα

Non-thrombotic cardiogenic embolism

Κολπική Μαρμαρυγή

Μεταλλική Βαλβίδα

Valvular Disease

Chamber embolism

Cardiogenic embolism

Ραγείσα αθηροσκληρωτική πλάκα στη καρωτίδα

Διαχωρισμός στη καρωτίδα

Atherosclerotic

Non-Atherosclerotic

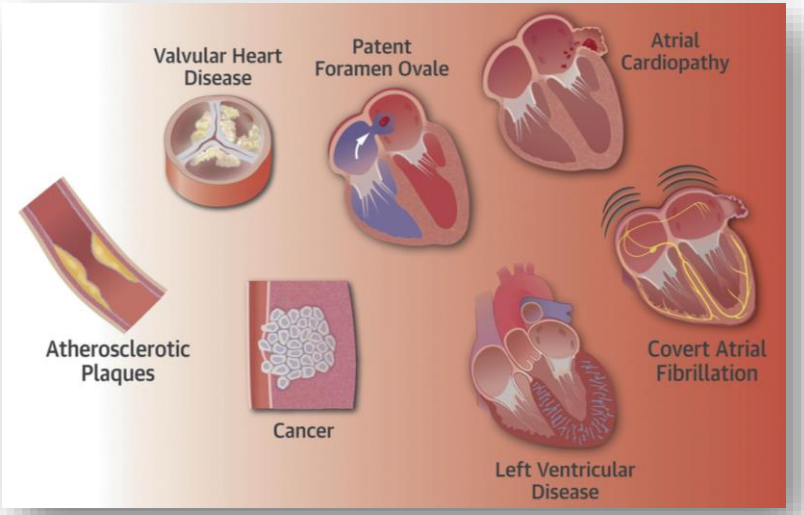
Arteriogenic embolism

Paradoxical embolism

ΕΒΦΘ κάτω άκρου και PFO

Thrombosis-mediated embolism

Ntaios G, Hart RG. Embolic stroke. Circulation. 2017;136:2403e2405.

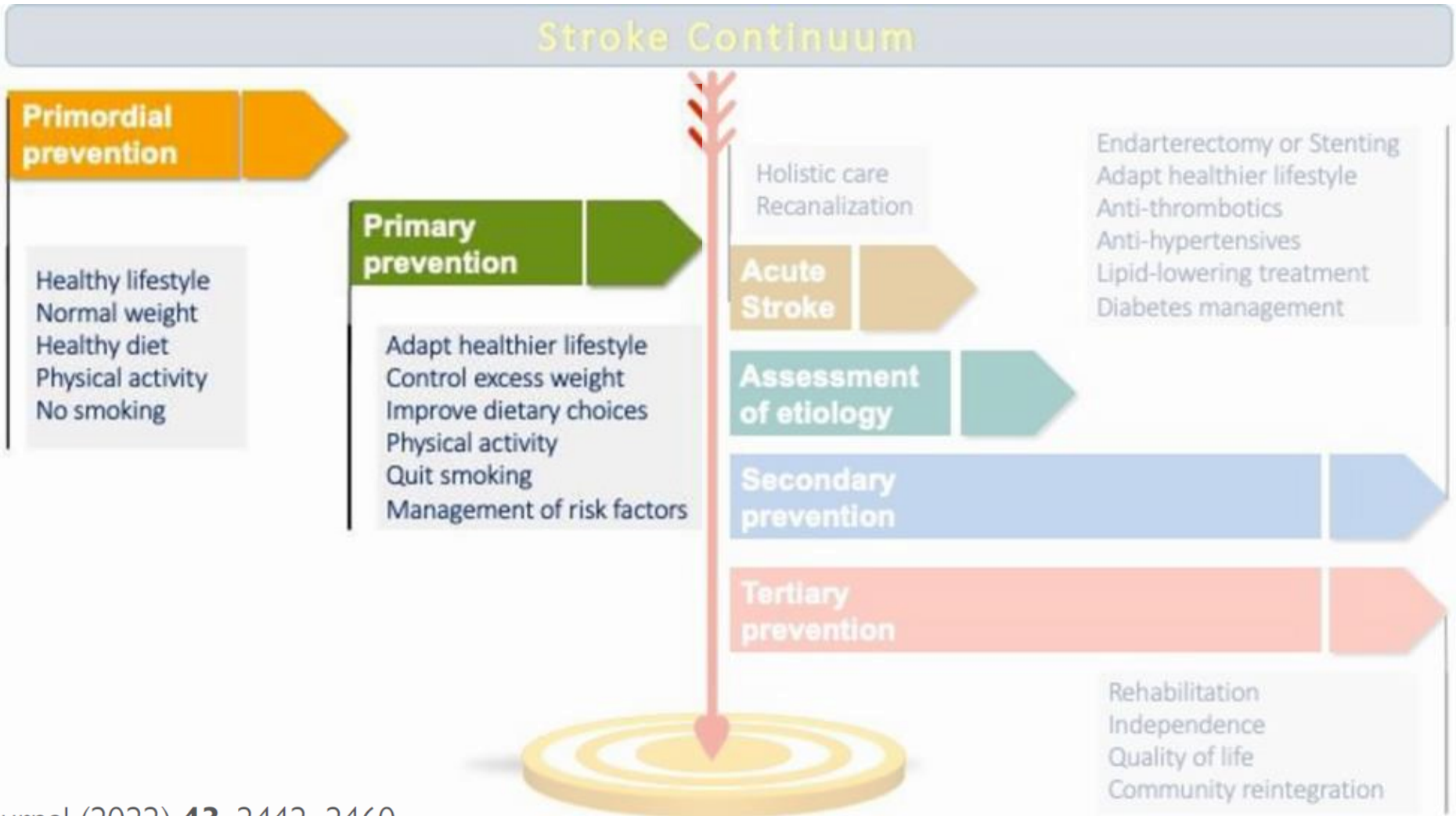


Ntaios G. Embolic Stroke of Undetermined Source: JACC Review Topic of the Week. J Am Coll Cardiol. 2020 Jan 28;75(3):333-340.

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 Lenarczyk[3], Giuseppe Boriani [5], Wolfram Doehner [6], Laura A. Benjamin[7], Marc Fisher[8], Deborah Lowe[9], Ralph L. Sacco[10], Renate Schnabel[11], Caroline Watkins[12], George Ntaios [13], and Tatjana Potpara [4,14†]



European Heart Journal (2022) **43**, 2442–2460

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

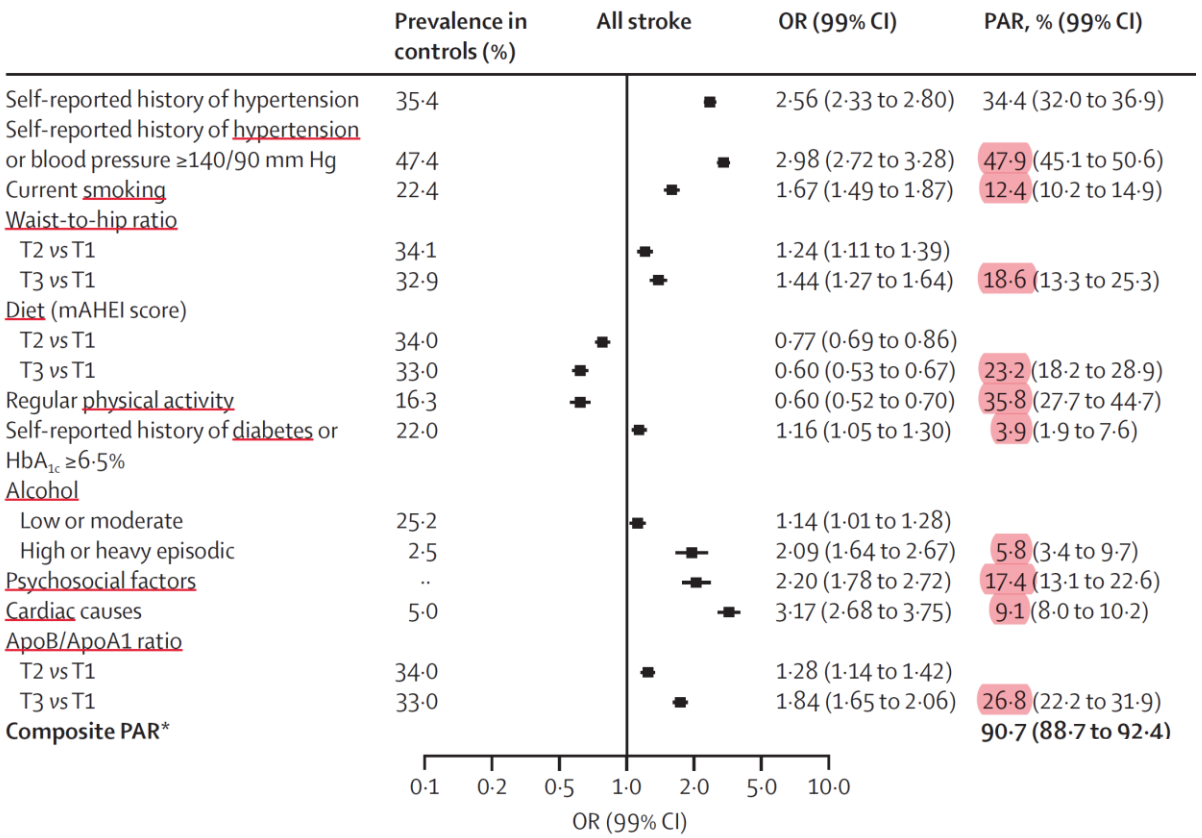


TABLE 1. TEN MODIFIABLE RISK FACTORS CONTRIBUTING TO 90% OF STROKES WORLDWIDE

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.

Lancet 2016 20;388:761-75

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*	

Circ Res. 2017;120:472-495

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.

JACC VOL. 75, NO. 15, 2020
APRIL 21, 2020:1804–18

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

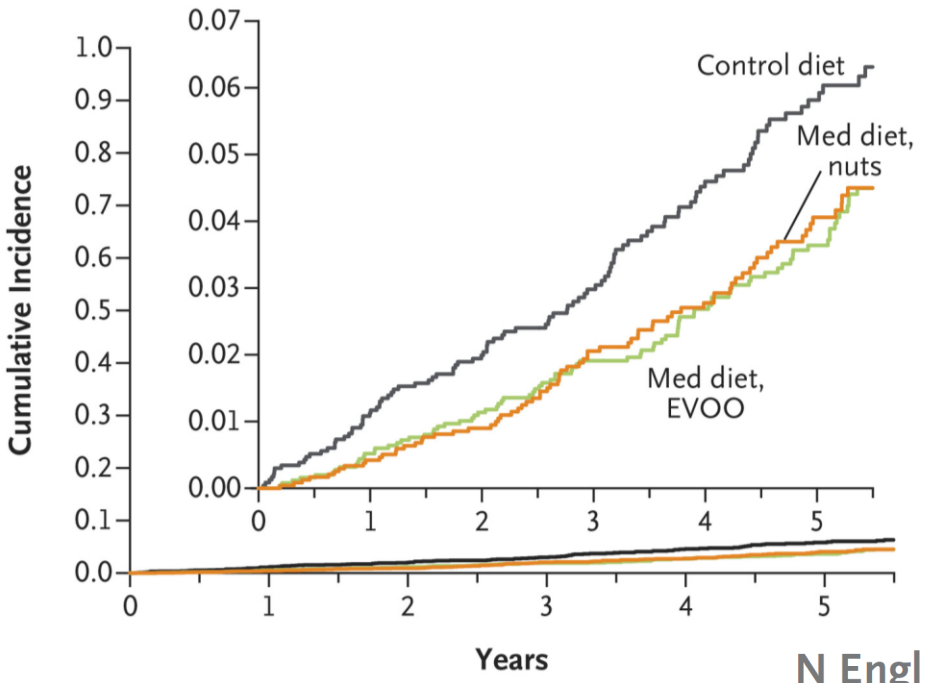
MeDiet + EVOO
N = 2543

MeDiet + Nuts
N = 2454

Control Diet
N = 2450

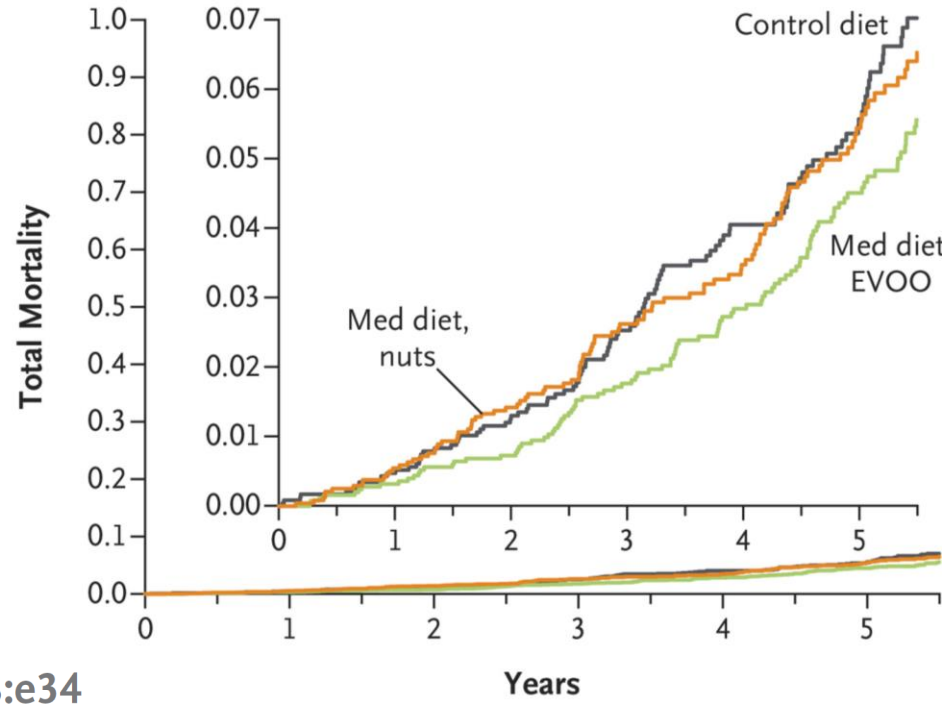
A Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)

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

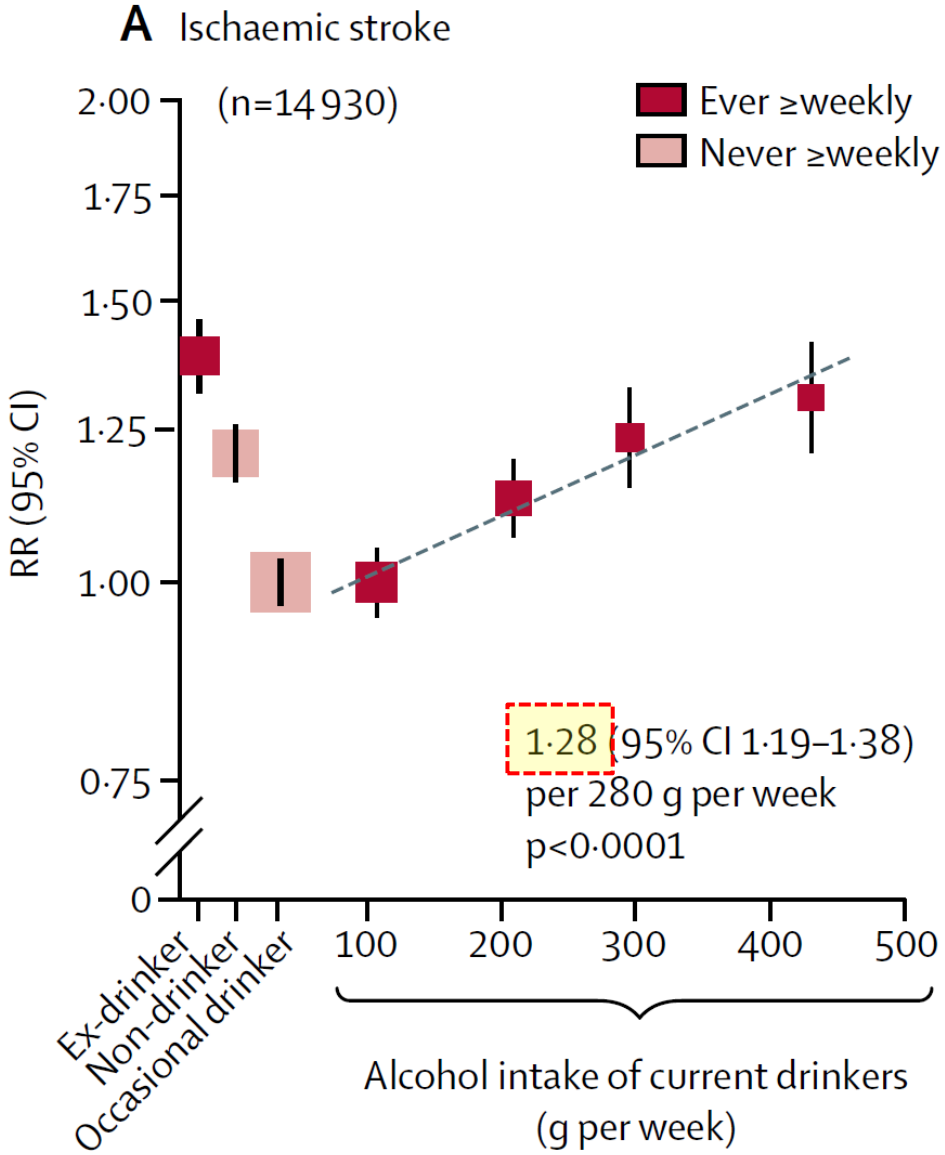
Med diet, EVOO: hazard ratio, 0.90 (95% CI, 0.69–1.18)
Med diet, nuts: hazard ratio, 1.12 (95% CI, 0.86–1.47)



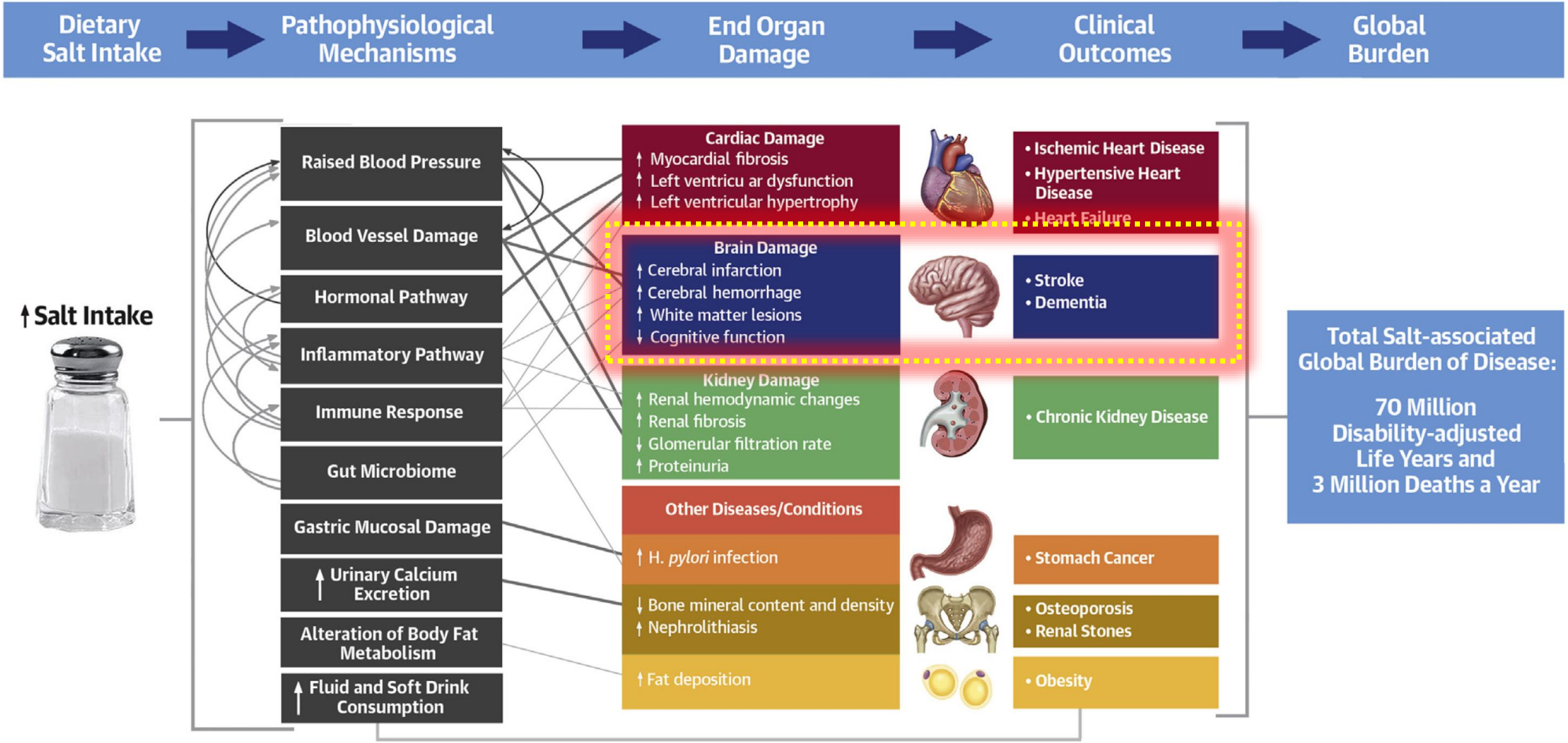
N Engl J Med 2018;378:e34

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



Lancet 2019 4;393:1831-1842



He, F.J. et al. J Am Coll Cardiol. 2020;75(6):632-47.

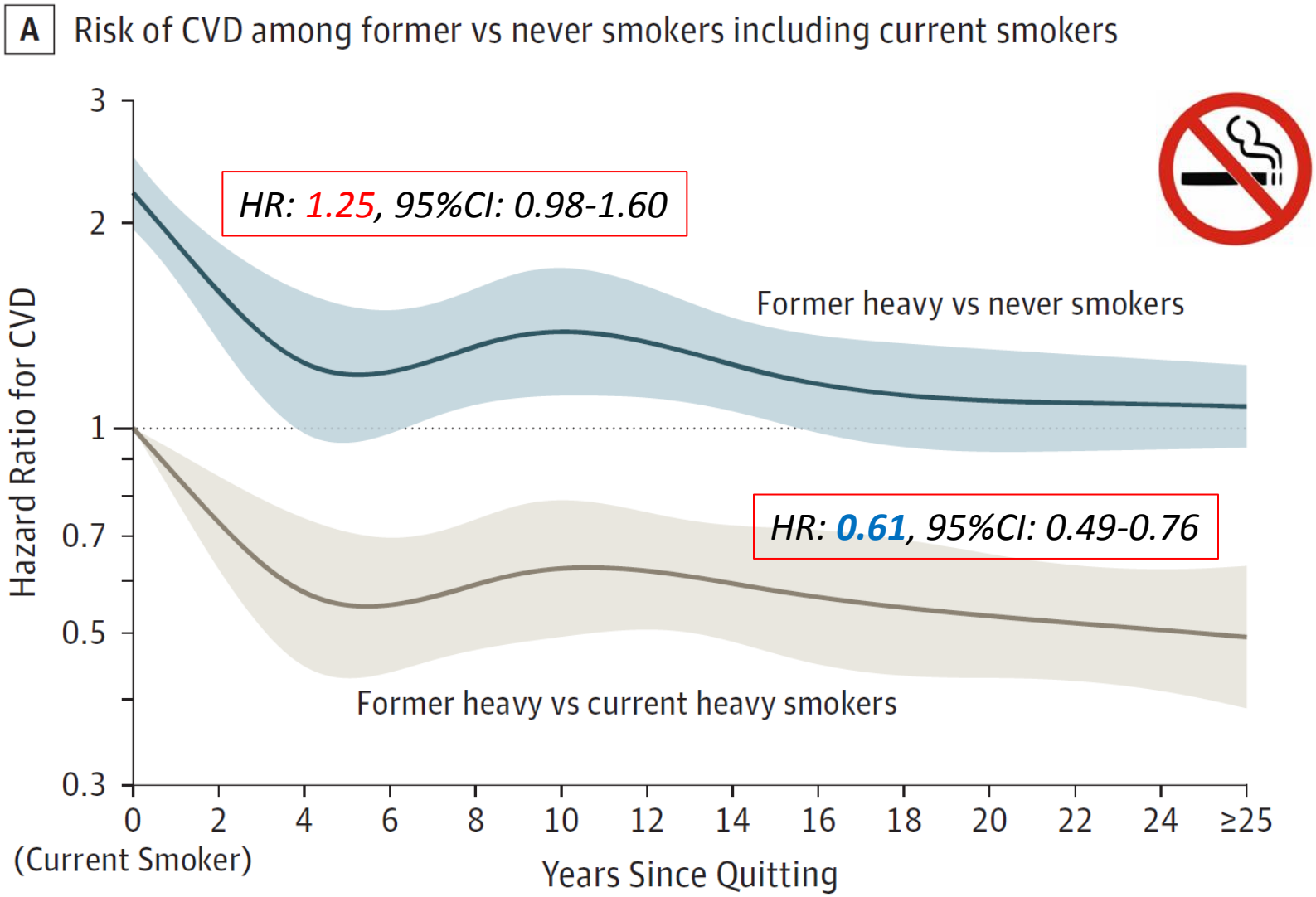
How Far Should Salt Intake Be Reduced?

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

Hypertension. 2003;42:1093-1099

Association of Smoking Cessation With Subsequent Risk of Cardiovascular Disease



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.

JAMA. 2019;322(7):642-650

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

Neurology® 2009;73:1774–1779

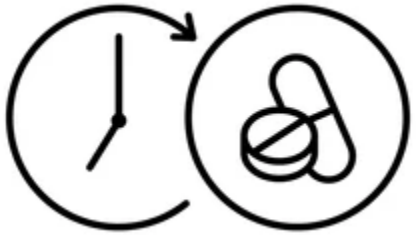
International Journal of Stroke
2021, Vol. 16(6) 738–750

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*	

Circ Res. 2017;120:472-495

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

ESC
European Society of Cardiology

GLOBAL PREVALENCE OF AF

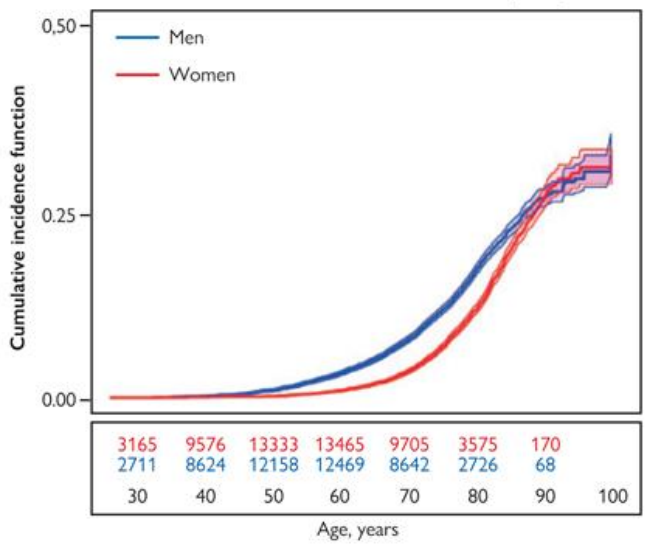
(globally, 43.6 million individuals had prevalent AF/AFL in 2016)

LIFETIME RISK for AF
1 in 3 individuals

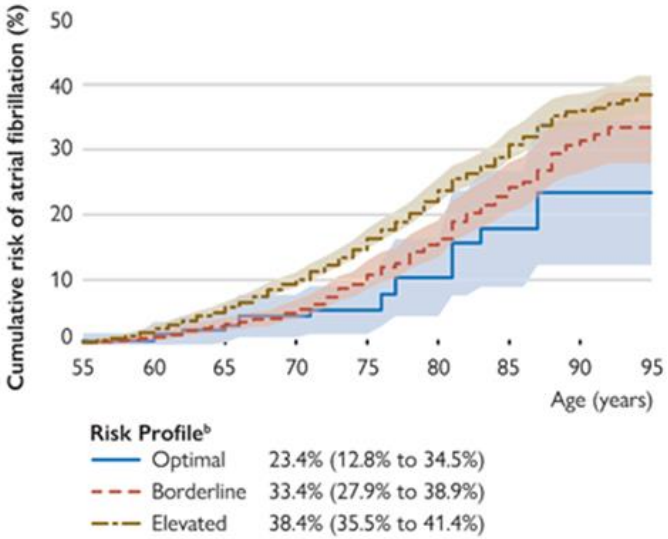
of European ancestry
at index age of 55 years
37.0% (34.3% to 39.6%)

AF is more common in males

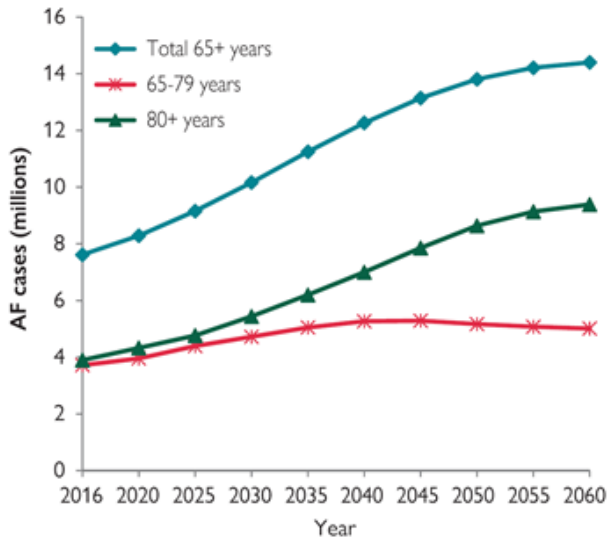
Cumulative incidence curves and 95% CIs
for AF in women and men with death as a competing risk



Lifetime risk of AF increases with increasing risk factor burden[a]

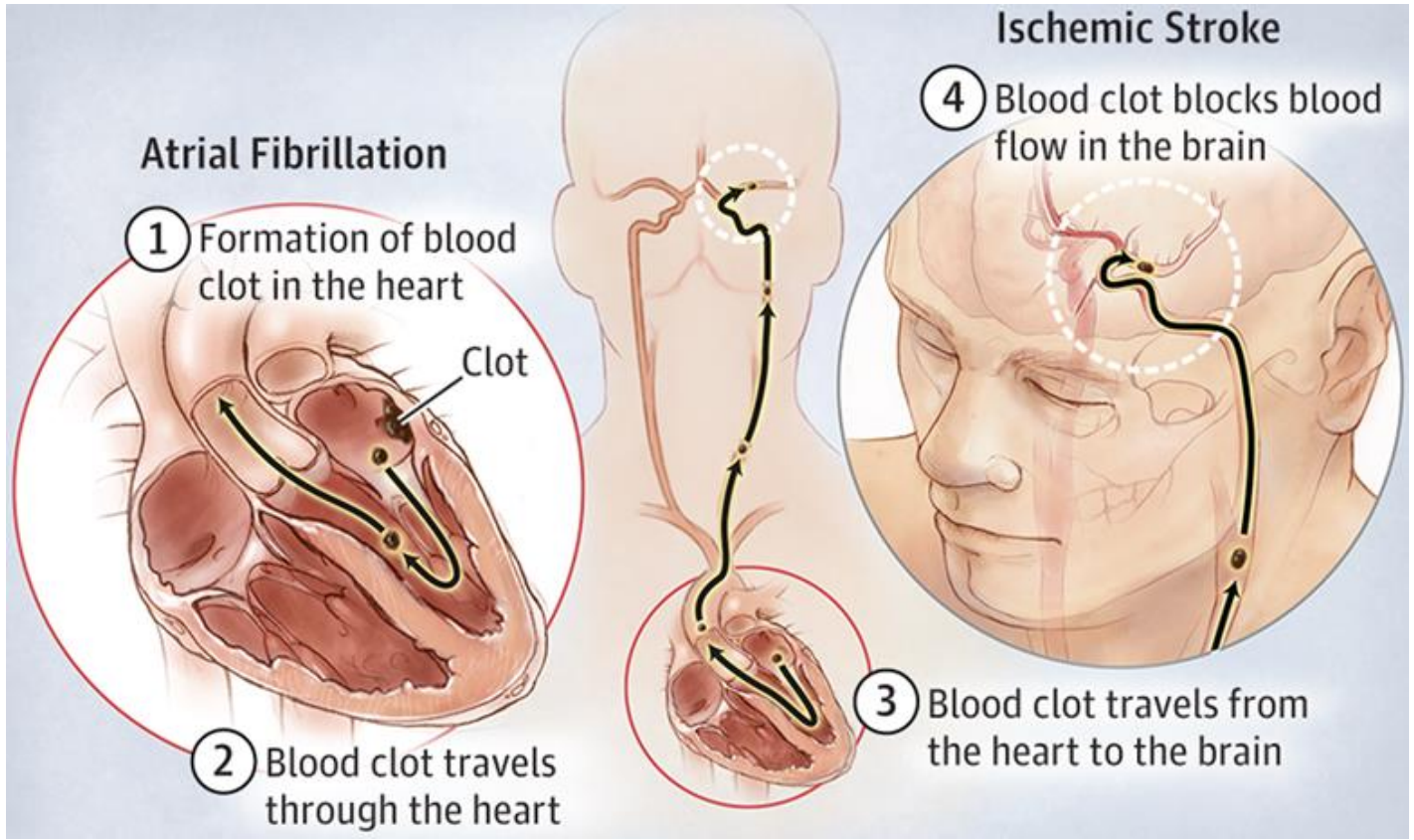


Projected increase in AF prevalence among elderly in EU 2016-2060



European Heart Journal (2020) **42**, 373–498

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



CHA_2DS_2-VASc score Risk factors and definitions		Points awarded
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**

European Heart Journal (2020) **42**, 373–498

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

ESC European Society of Cardiology

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Maximum score		**9**

European Heart Journal (2020) **42**, 373–498

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

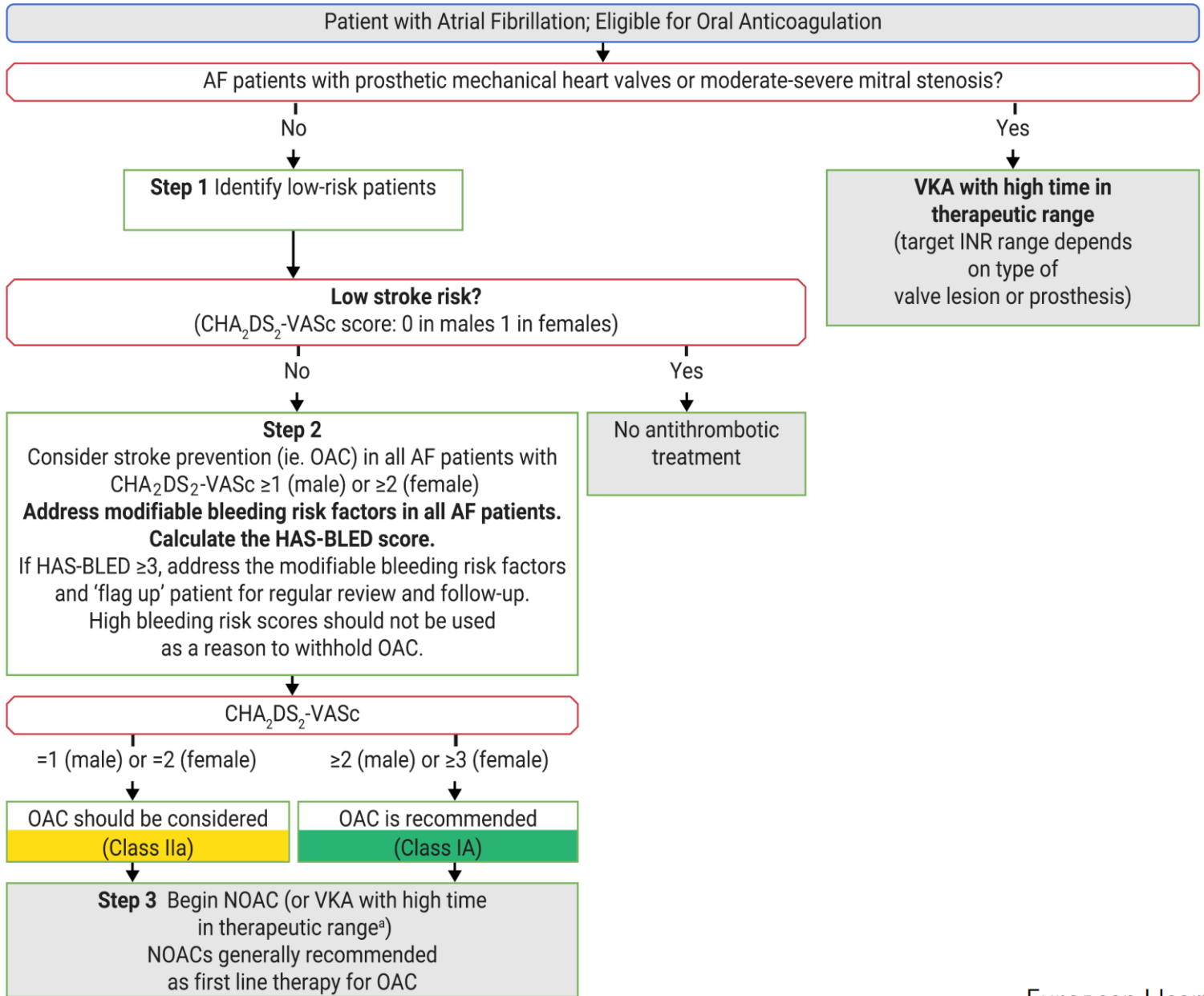
The Euro Heart Survey on Atrial Fibrillation

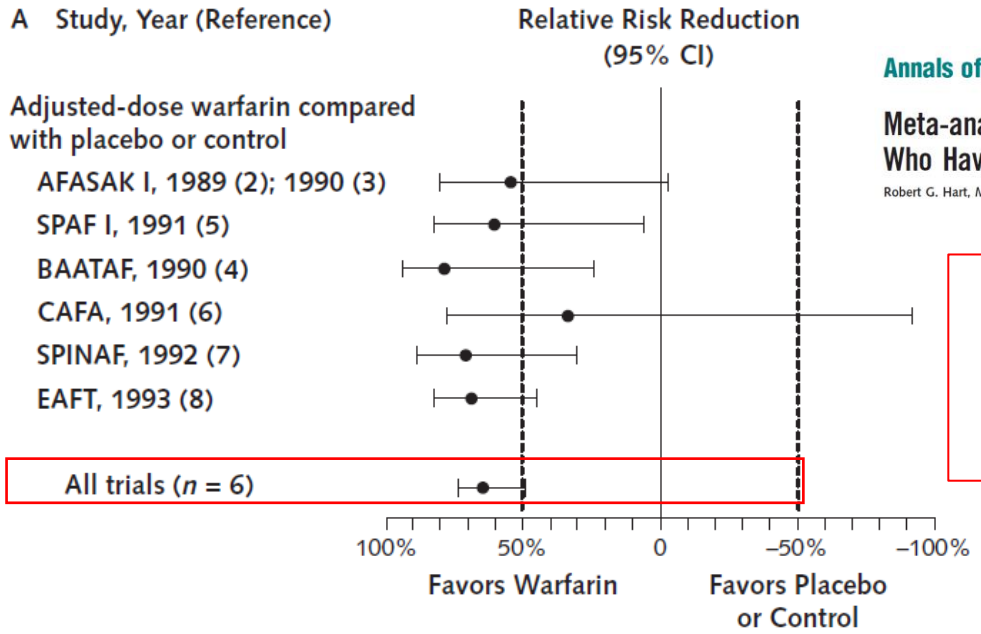
Table 6—Stroke or Other TE at 1 Year Based on the 2009 Birmingham (CHA_2DS_2-VASc) Scoring System

CHA_2DS_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

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



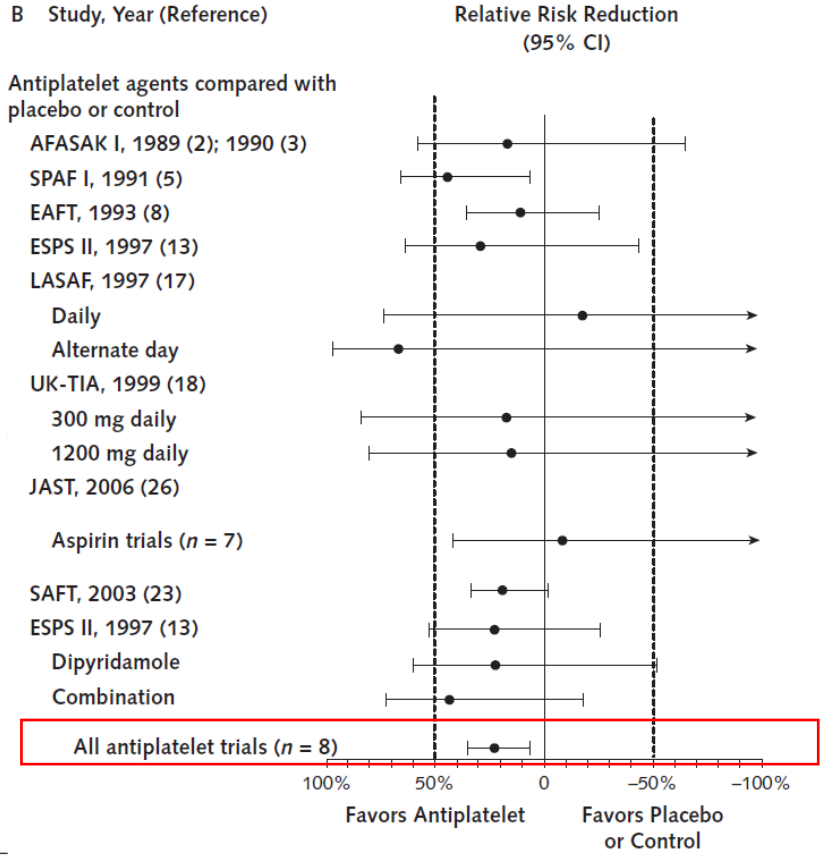


Annals of Internal Medicine | REVIEW

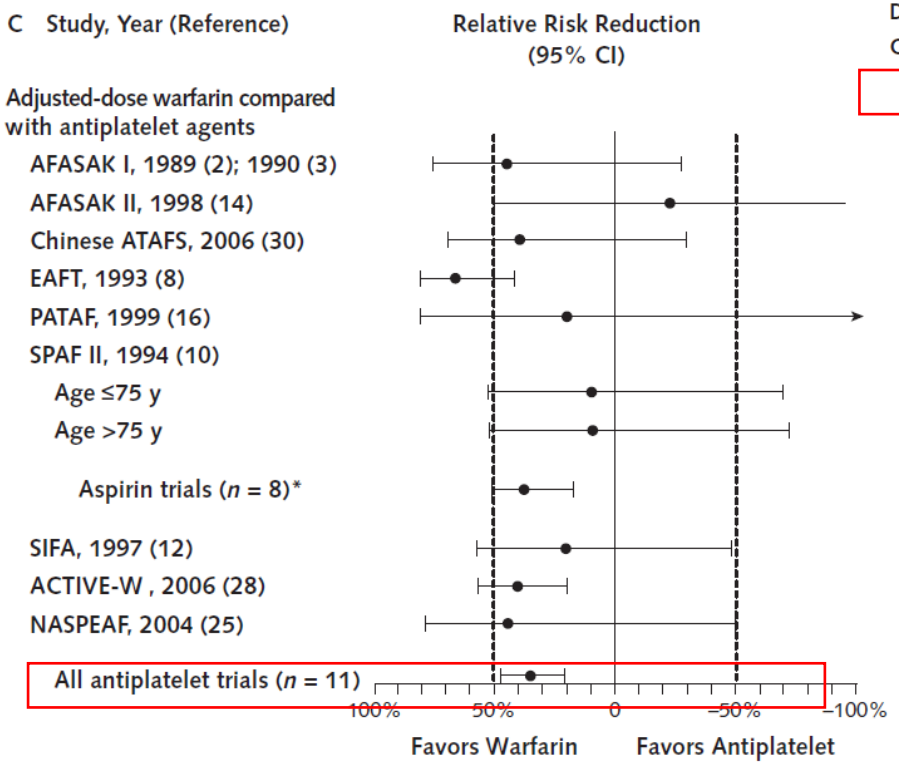
Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation

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.



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



Ann Intern Med. 2007;146:857-867.

ROCKET AF

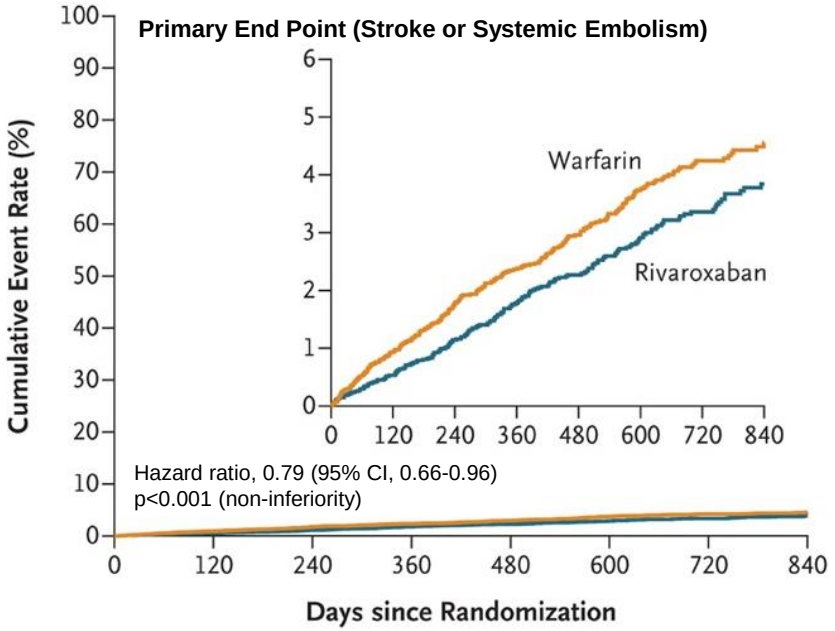
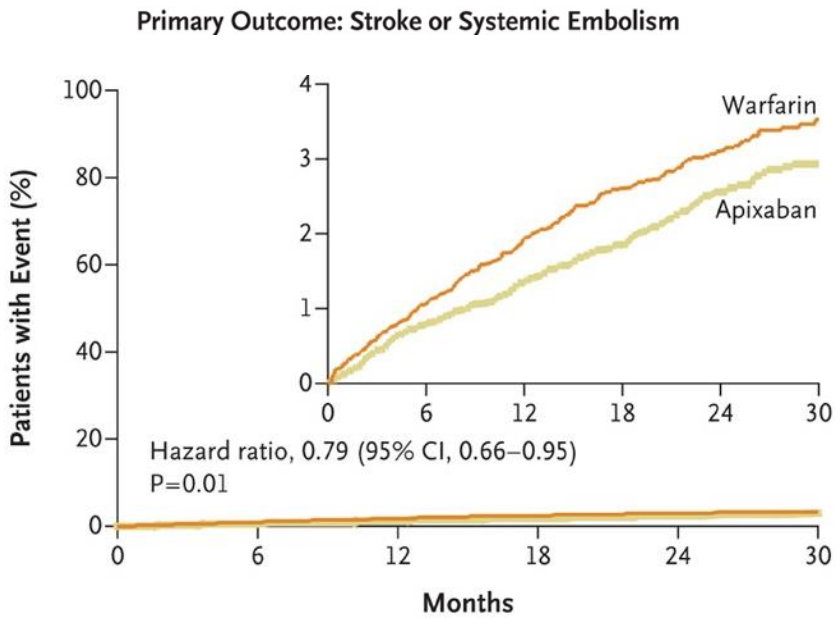


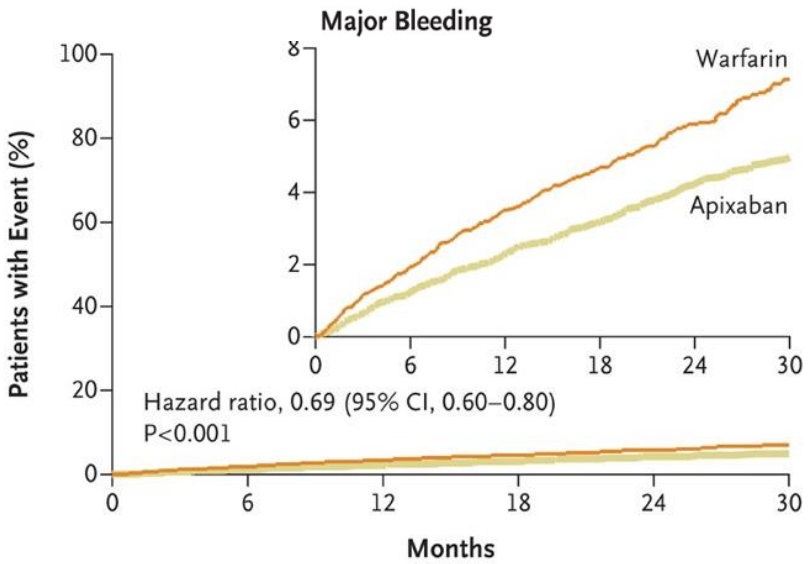
Table 3. Rates of Bleeding Events.*

Variable	Rivaroxaban (N=7111) Events no. (%)	Rivaroxaban (N=7111) Event Rate no./100 patient-yr	Warfarin (N=7125) Events no. (%)	Warfarin (N=7125) Event Rate no./100 patient-yr	Hazard Ratio (95% CI)†	P Value‡
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

N Engl J Med 2011;365:883-91

ARISTOTLE





N Engl J Med 2011;365:981-92

RE-LY

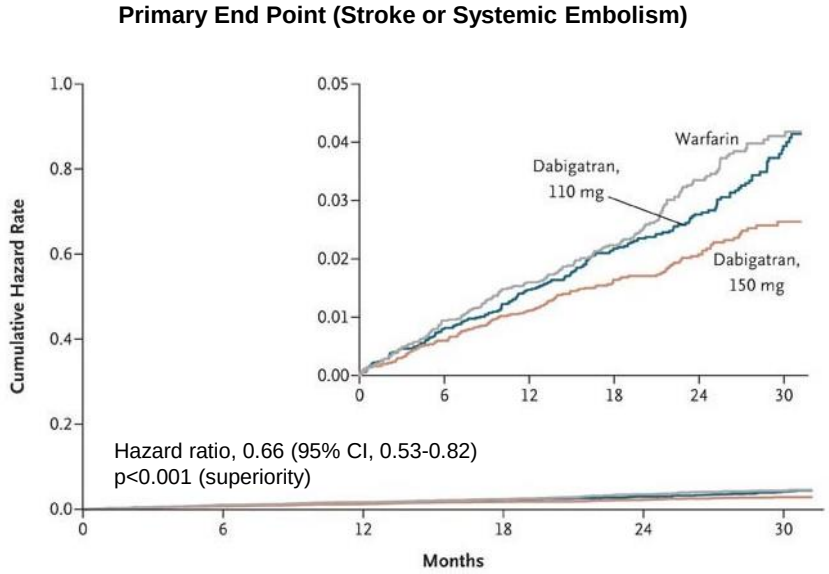


Table 3. Safety Outcomes, According to Treatment Group.*

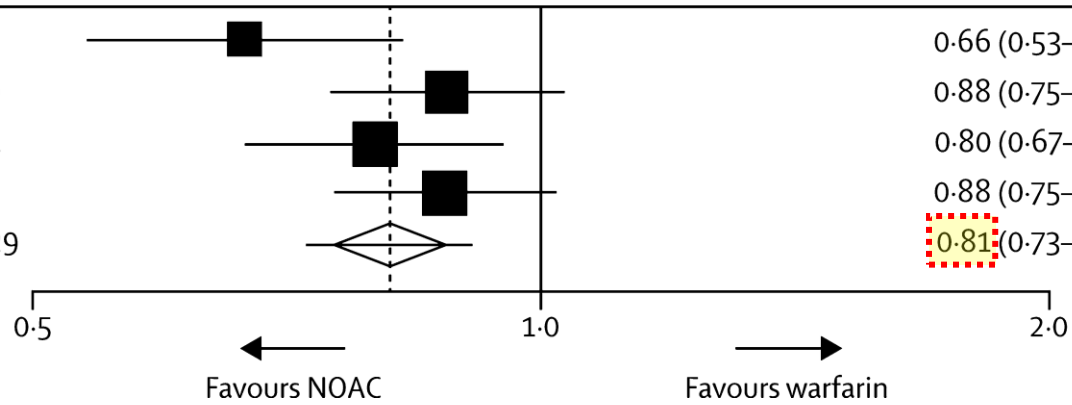
Event	Dabigatran, 110 mg no. of patients	Dabigatran, 110 mg %/yr	Dabigatran, 150 mg no. of patients	Dabigatran, 150 mg %/yr	Warfarin no. of patients	Warfarin %/yr	Dabigatran, 110 mg, vs. Warfarin Relative Risk (95% CI)	Dabigatran, 110 mg, vs. Warfarin P Value	Dabigatran, 150 mg, vs. Warfarin Relative Risk (95% CI)	Dabigatran, 150 mg, vs. Warfarin 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

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

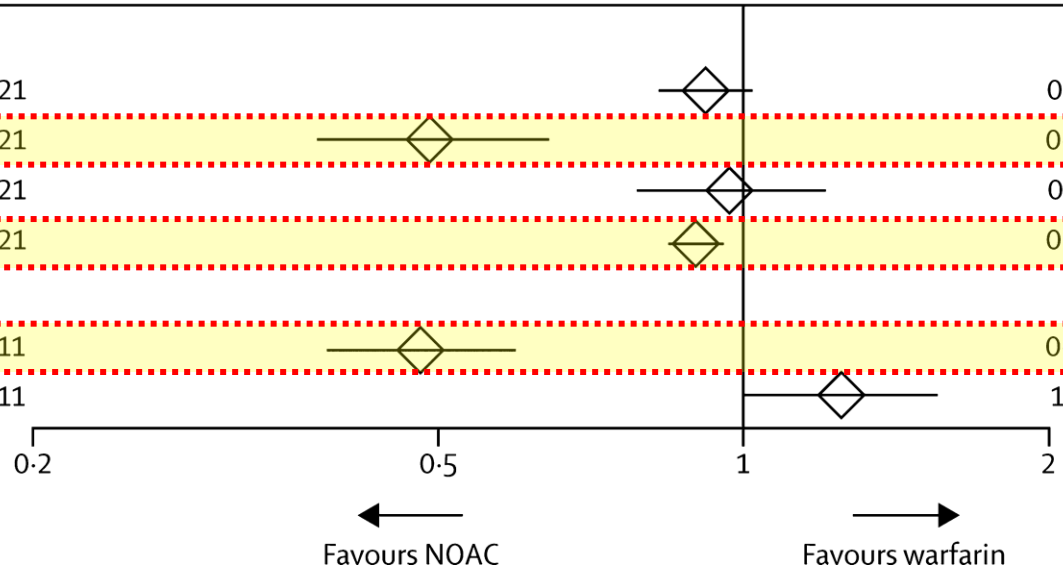
Stroke or systemic embolic events

	NOAC (events)	Warfarin (events)	RR (95% CI)	p
RE-LY[5]*	134/6076	199/6022	0·66 (0·53–0·82)	0·0001
ROCKET AF[6]†	269/7081	306/7090	0·88 (0·75–1·03)	0·12
ARISTOTLE[7]‡	212/9120	265/9081	0·80 (0·67–0·95)	0·012
ENGAGE AF–TIMI 48[8]§	296/7035	337/7036	0·88 (0·75–1·02)	0·10
Combined (random)	911/29 312	1107/29 229	0·81 (0·73–0·91)	<0·0001



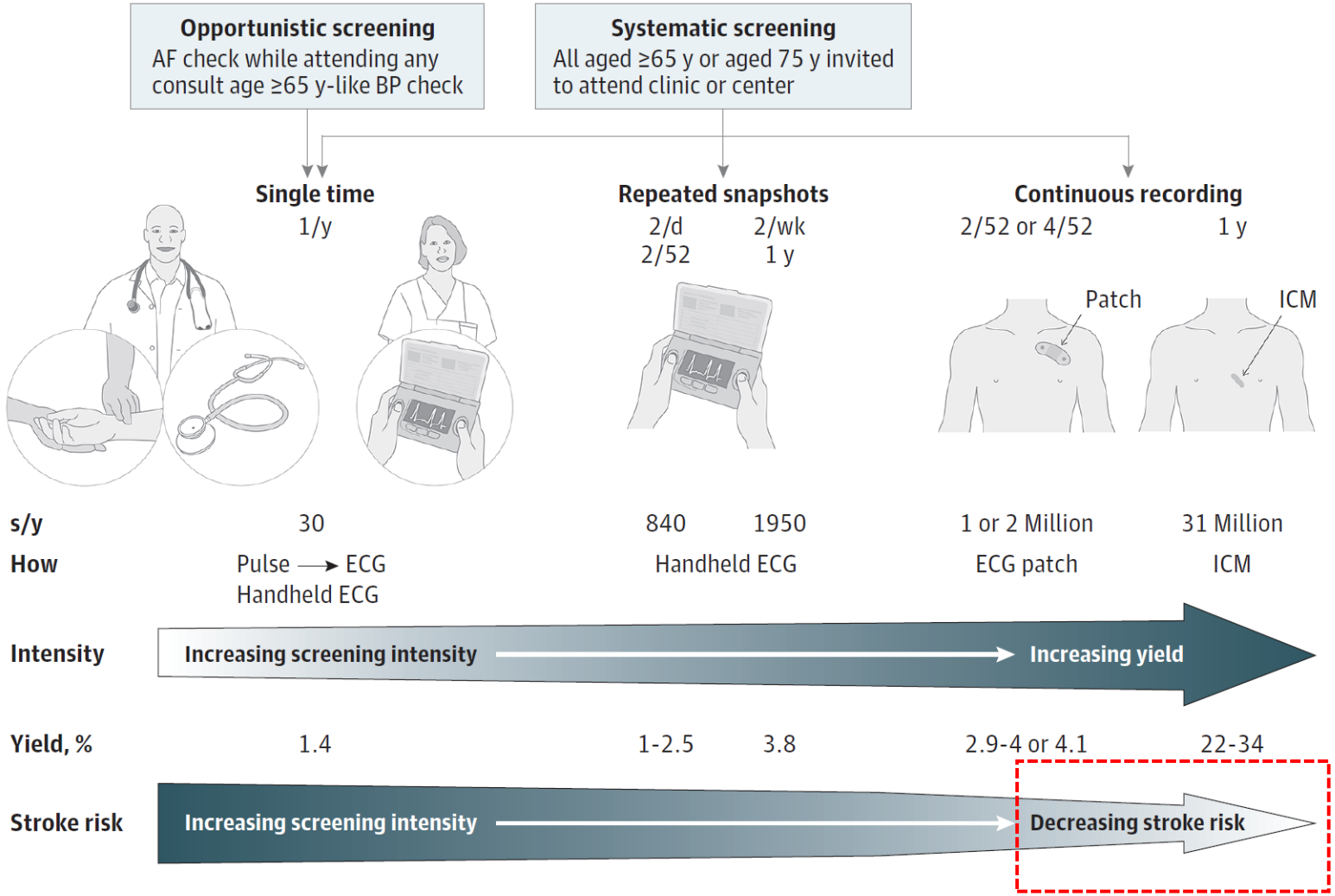
Secondary efficacy and safety outcomes

	Pooled NOAC (events)	Pooled warfarin (events)	RR (95% CI)	p
Efficacy				
Ischaemic stroke	665/29 292	724/29 221	0·92 (0·83–1·02)	0·10
Haemorrhagic stroke	130/29 292	263/29 221	0·49 (0·38–0·64)	<0·0001
Myocardial infarction	413/29 292	432/29 221	0·97 (0·78–1·20)	0·77
All-cause mortality	2022/29 292	2245/29 221	0·90 (0·85–0·95)	0·0003
Safety				
Intracranial haemorrhage	204/29 287	425/29 211	0·48 (0·39–0·59)	<0·0001
Gastrointestinal bleeding	751/29 287	591/29 211	1·25 (1·01–1·55)	0·043



Lancet 2014; 383: 955–62

Opportunistic Electrocardiogram Screening for Atrial Fibrillation to Prevent Stroke



JAMA Cardiol. 2019, 1;4(2):91-92

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

ESC European Society of Cardiology

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_2DS_2-VASc clinical stroke risk score to initially identify patients at 'low stroke risk' (CHA_2DS_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_2DS_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_2DS_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

European Heart Journal (2020) **42**, 373–498

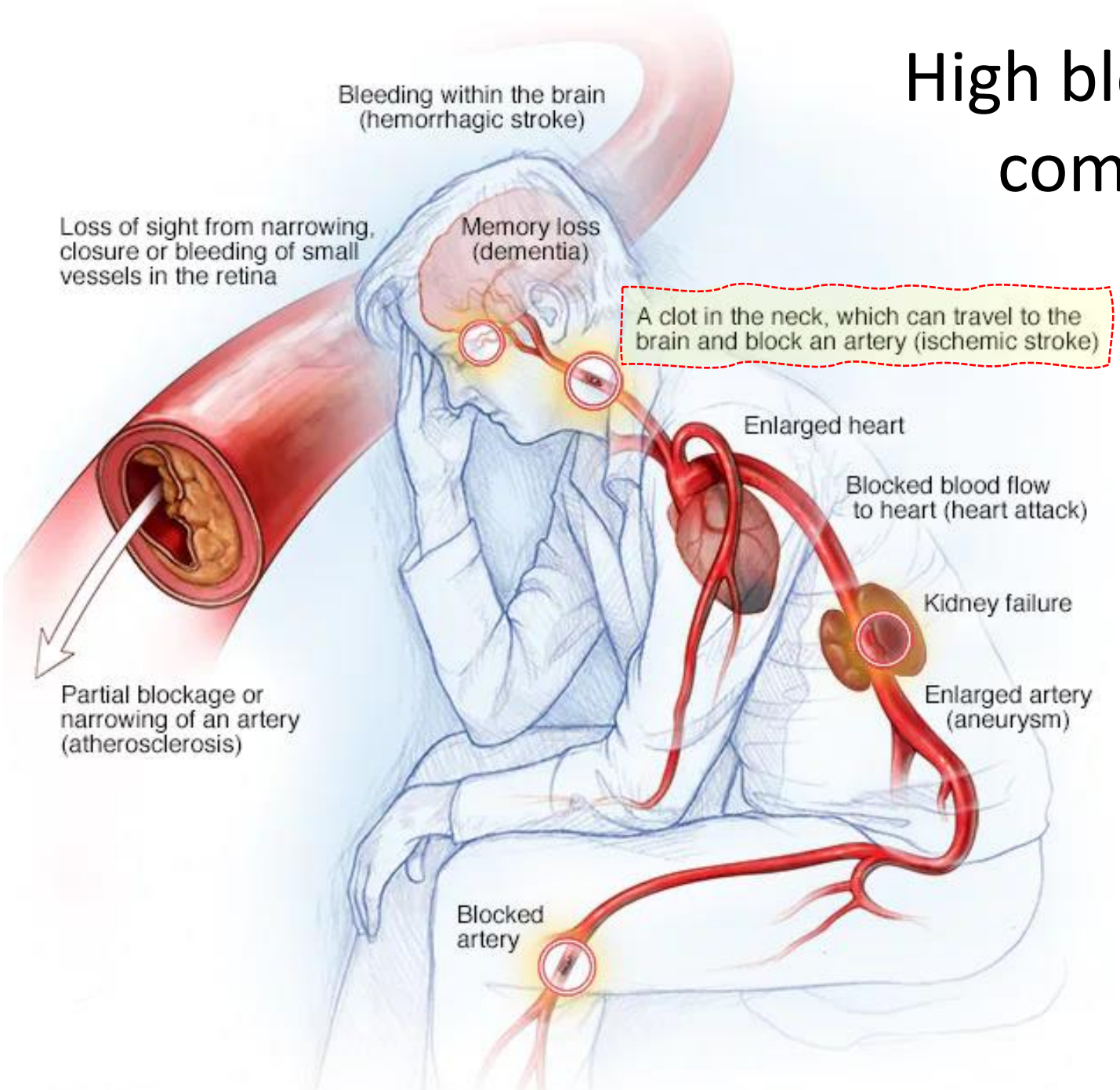
For a formal risk-score-based assessment of bleeding risk, the HAS-BLED score should be considered to help address modifiable bleeding risk factors, and to identify patients at high risk of bleeding (HAS-BLED score ≥3) for early and more frequent clinical review and follow-up.[388,395,404,406]	IIa	B
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≥70%.[414]	I	B
In patients on VKAs with low time in INR therapeutic range (e.g. TTR<70%), recommended options are: • Switching to a NOAC but ensuring good adherence and persistence with therapy[415,416]; or	I	B
• 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*	

Circ Res. 2017;120:472-495

High blood pressure complications



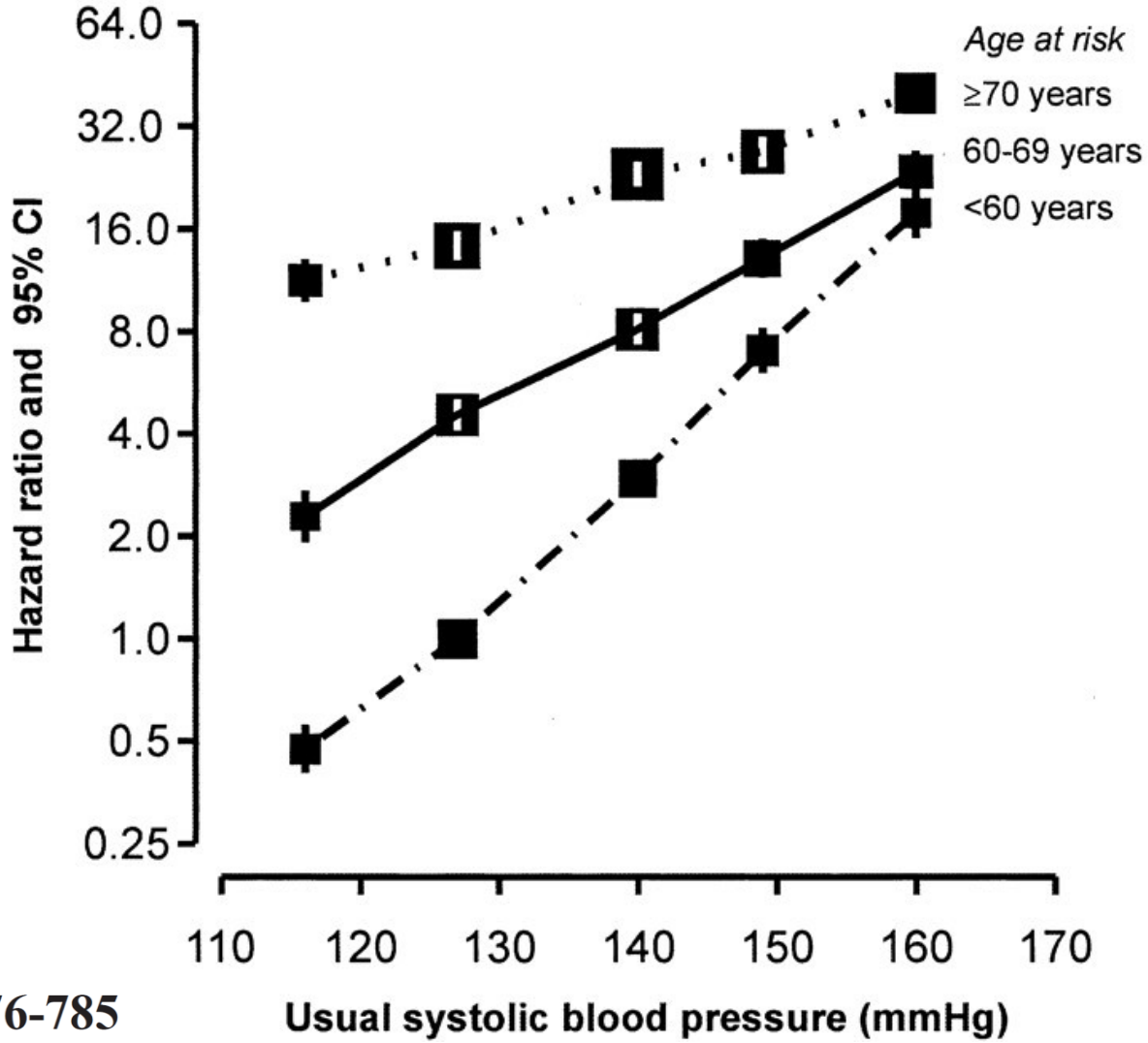
www.mayoclinic.org

Blood Pressure and Stroke

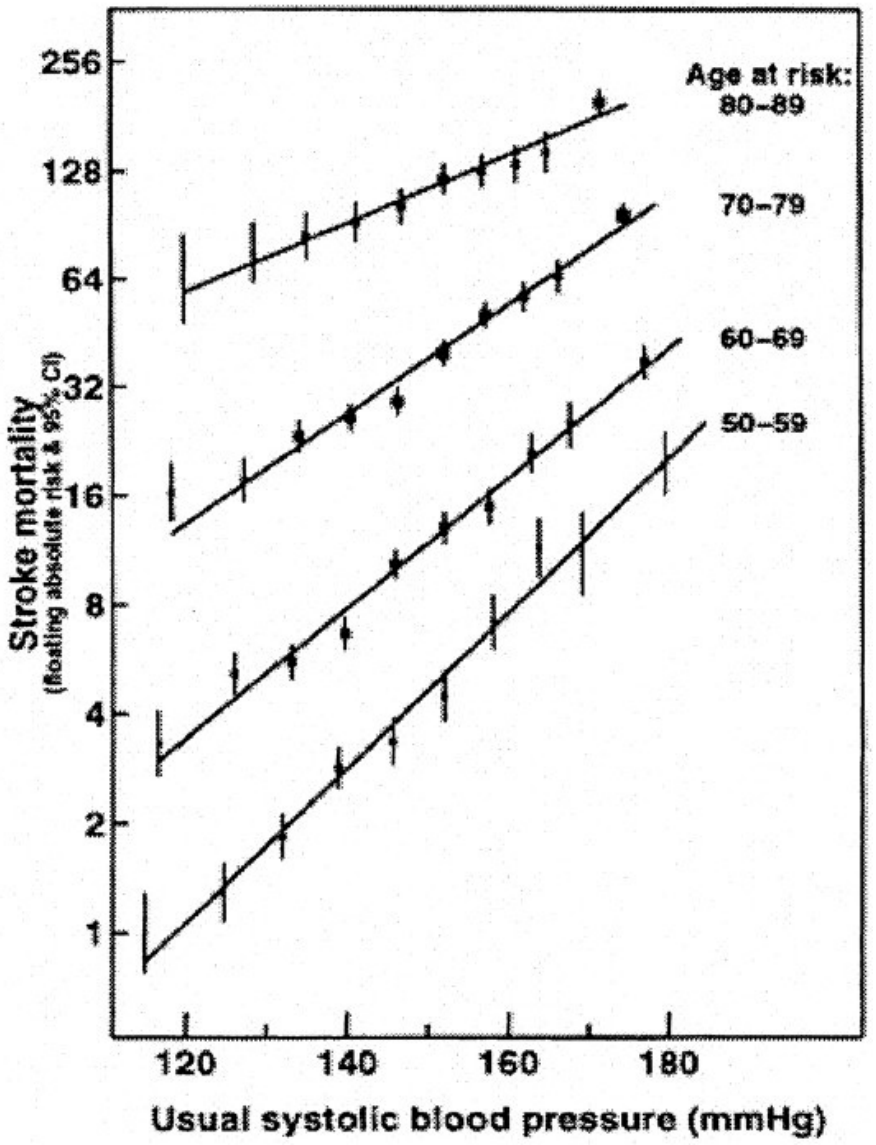
An Overview of Published Reviews

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

Asia Pacific Cohort Studies Collaboration



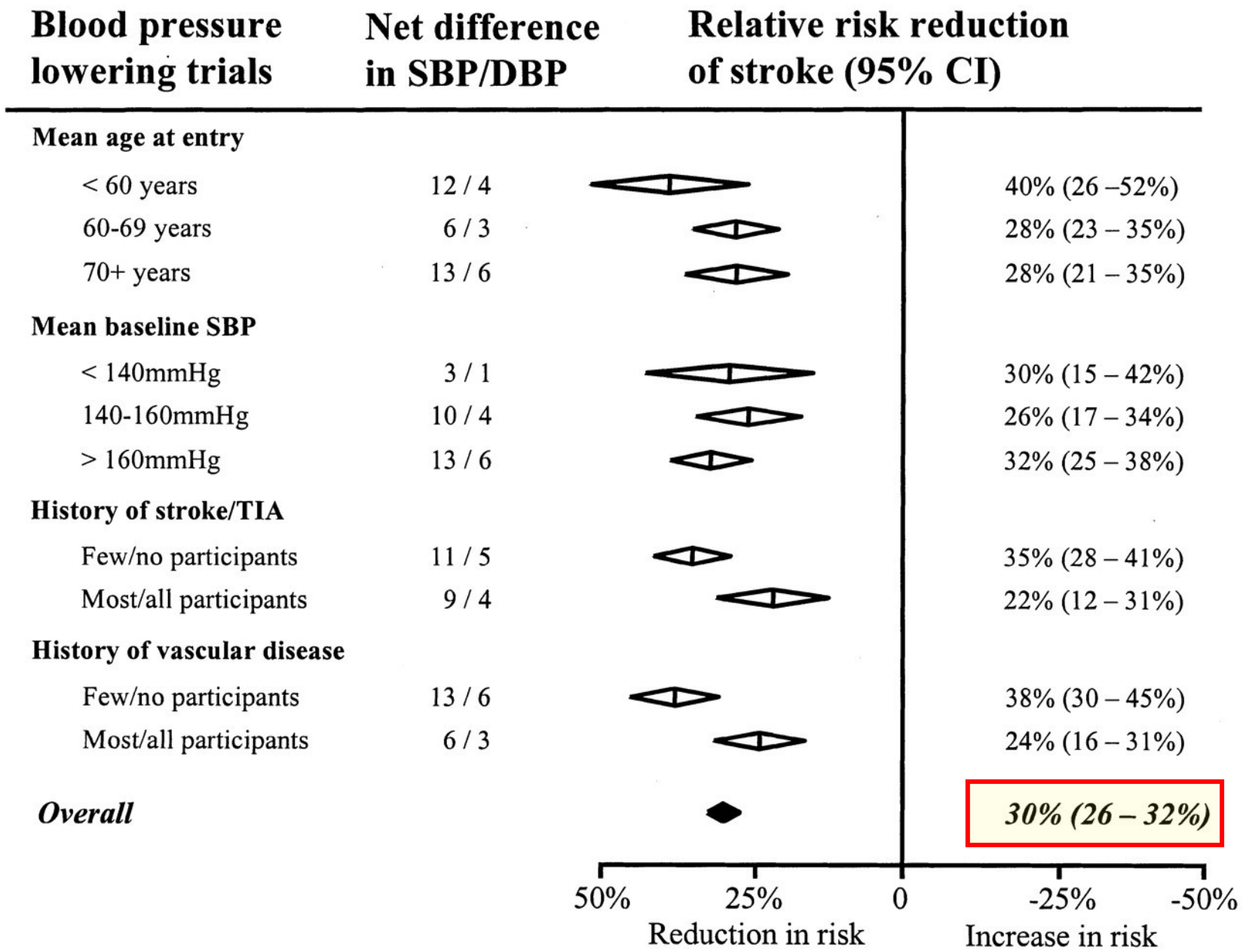
Prospective Studies Collaboration



Stroke. 2004;35:776-785

Blood Pressure and Stroke

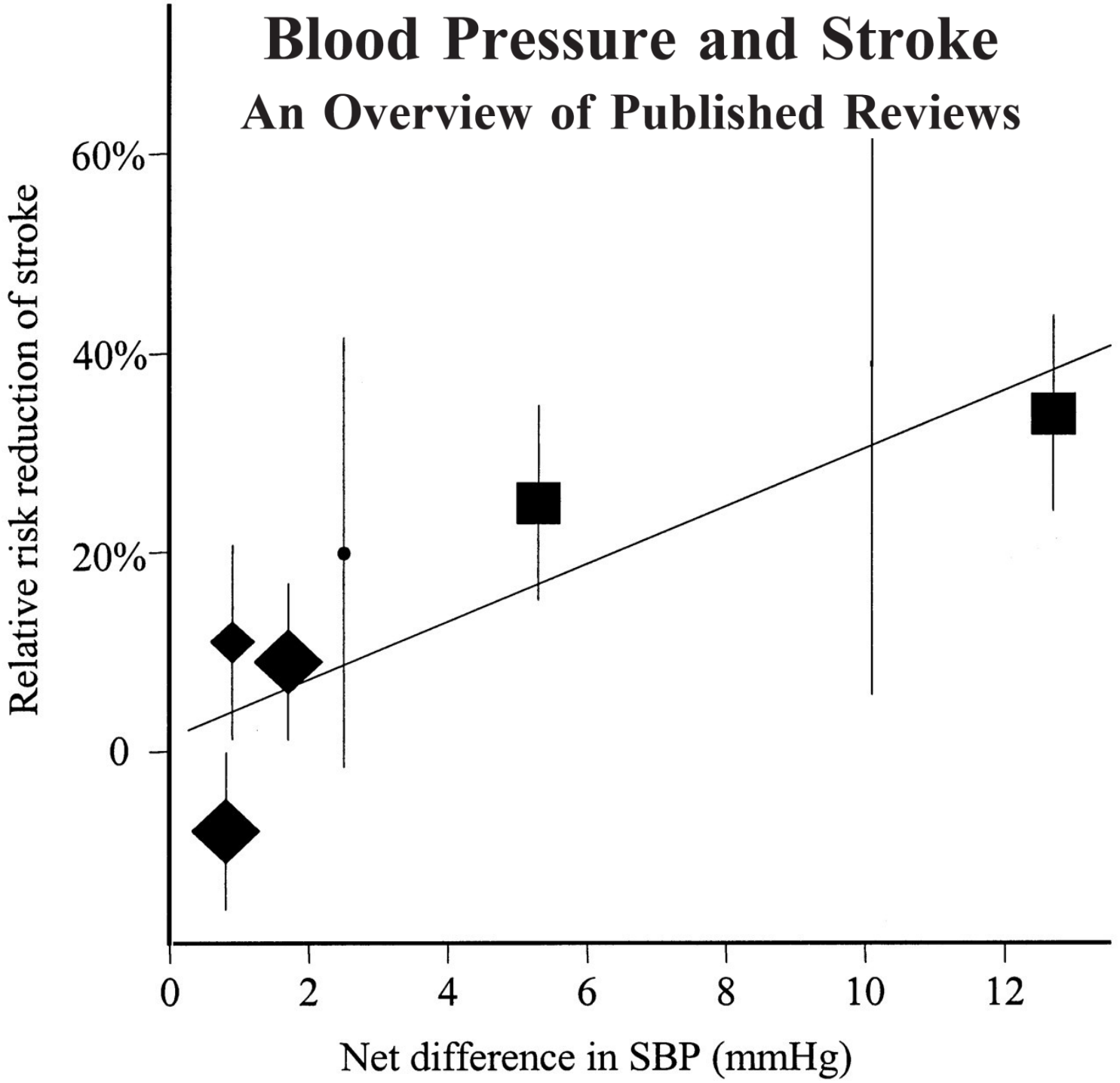
An Overview of Published Reviews



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

Stroke. 2004;35:776-785

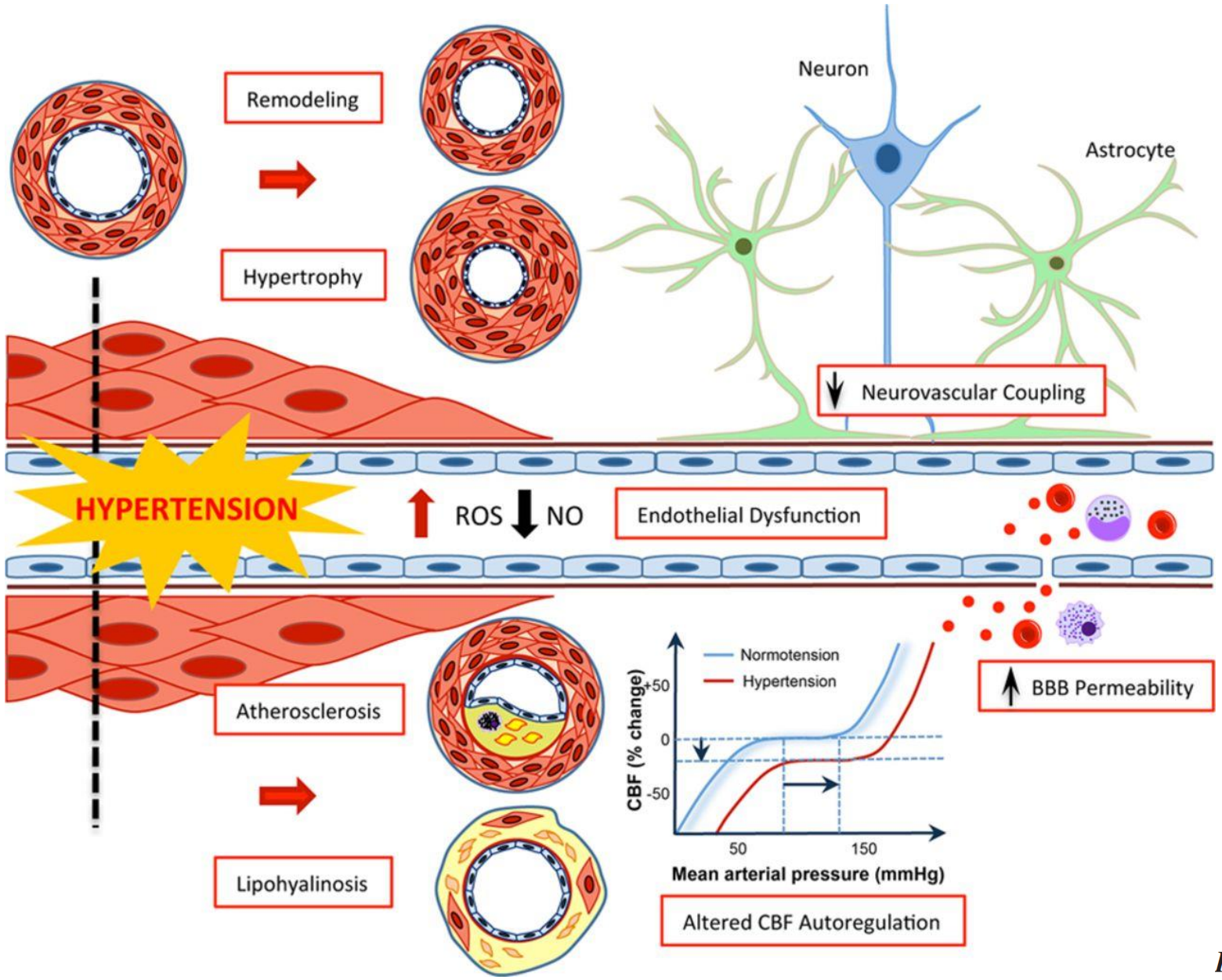
Net **reduction in SBP** and relative risk **reduction in stroke** in RCTs of BP lowering



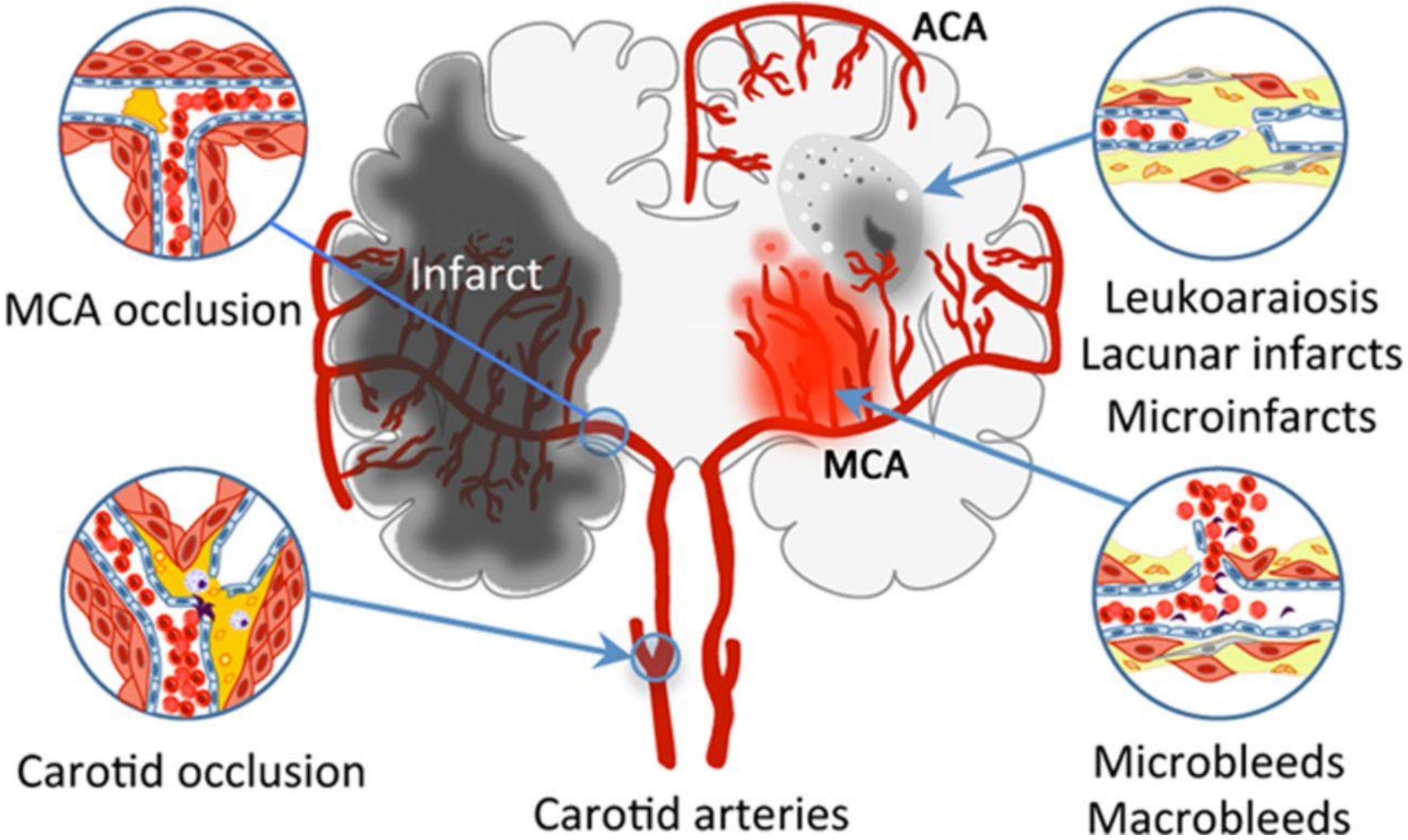
Stroke. 2004;35:776-785

Hypertension

A Harbinger of Stroke and Dementia

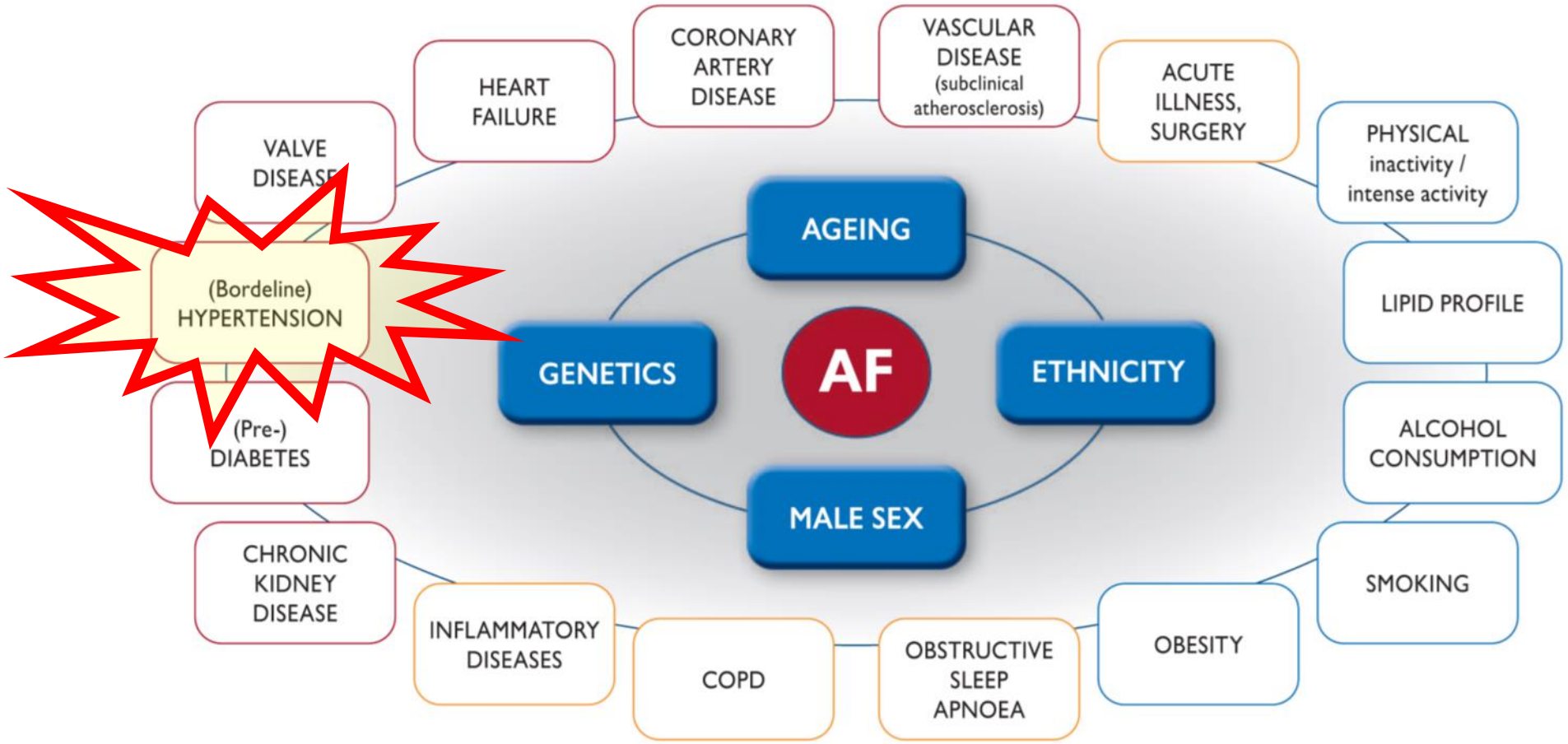


Hypertension. 2013;62:810-817



Hypertension. 2013;62:810-817

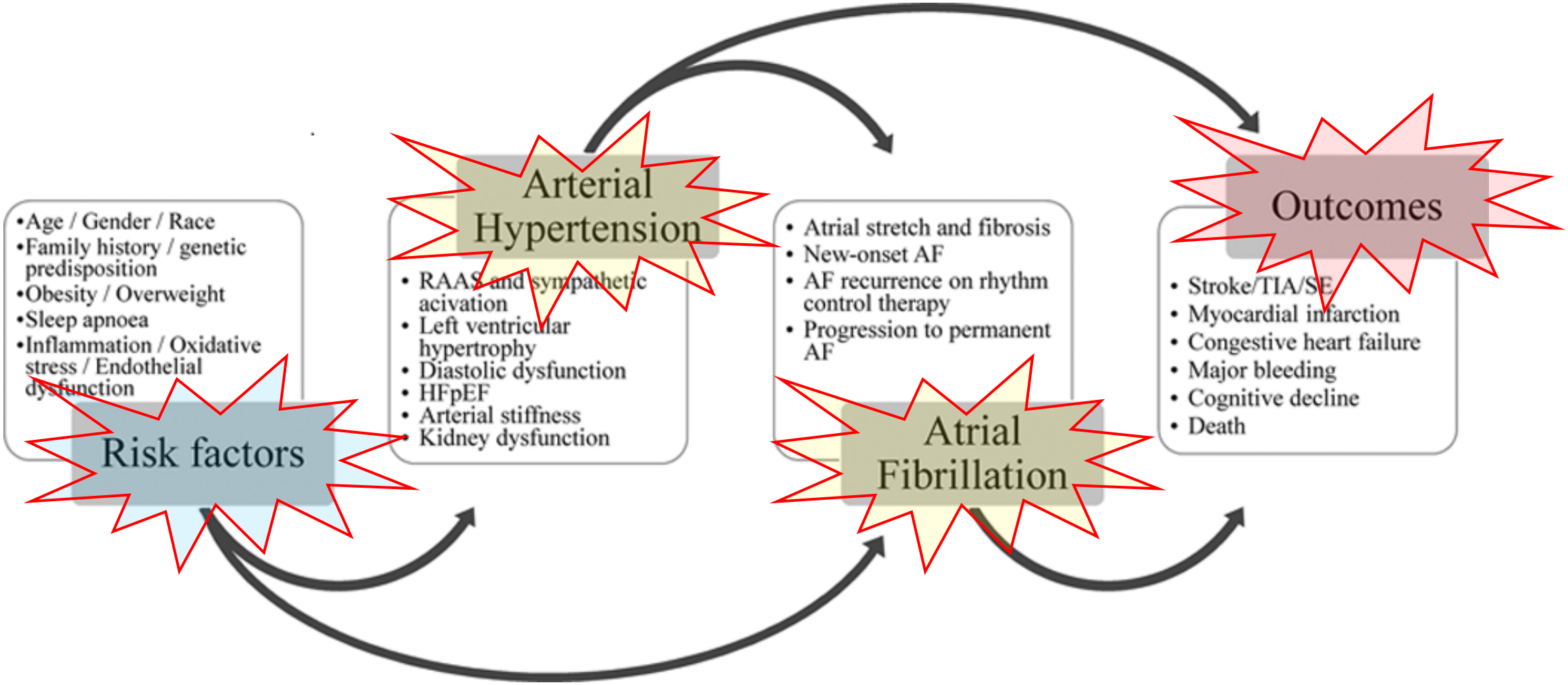
Summary of risk factors for incident AF



*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*

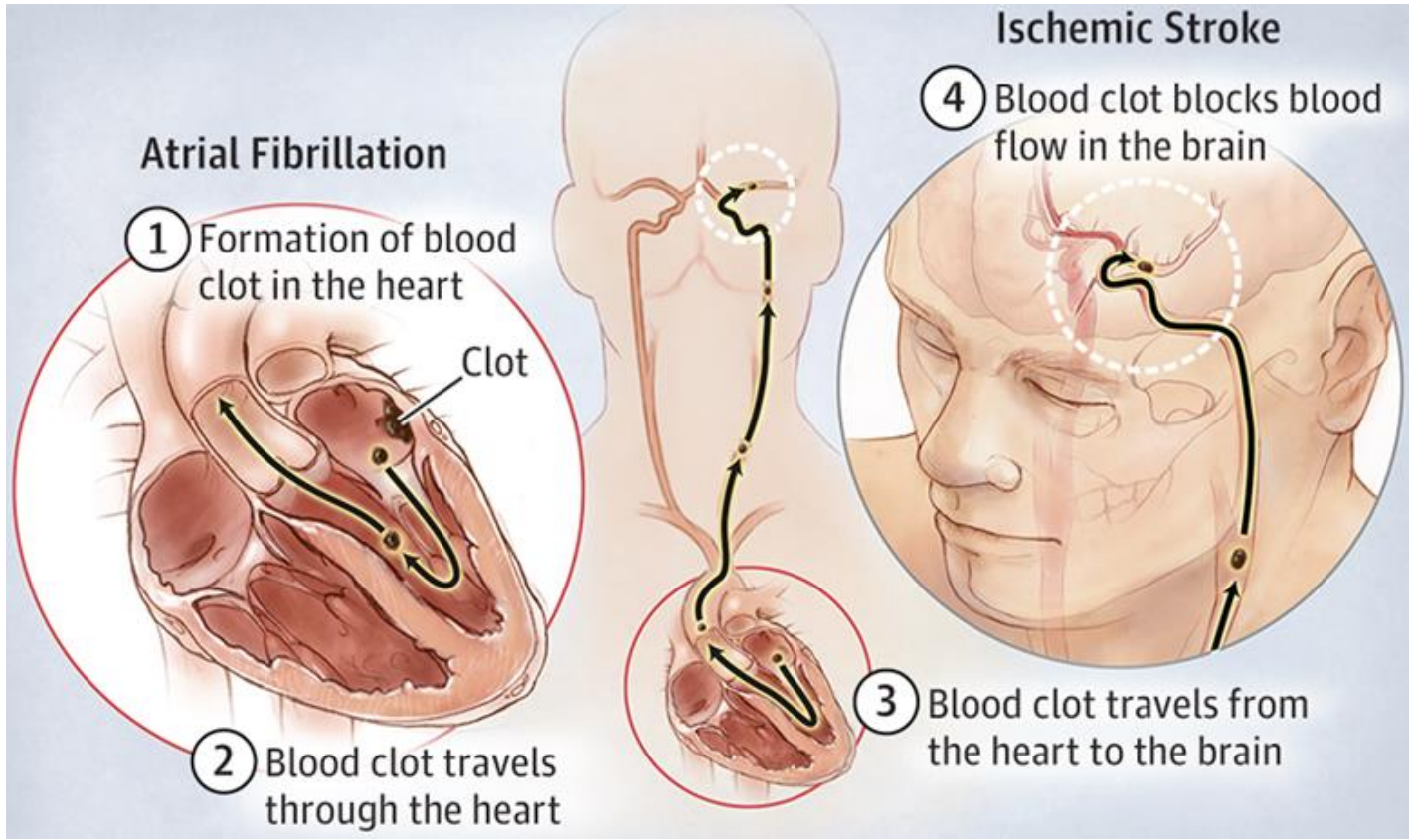
Atrial Fibrillation and Hypertension

Hypertension and atrial fibrillation axis in the cardiovascular disease continuum



Hypertension. 2017;70:854-861

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



CHA_2DS_2-VASc score Risk factors and definitions		Points awarded
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**

European Heart Journal (2020) **42**, 373–498

Ischemic stroke is an etiologically heterogeneous syndrome

Stroke due to Small Vessel Disease (SVD)

ISCHEMIC STROKE

Non-SVD, non-embolic Stroke

Embolic Stroke

Non-thrombosis-mediated embolism

Non-thrombotic cardiogenic embolism

Valvular Disease

Chamber embolism

Cardiogenic embolism

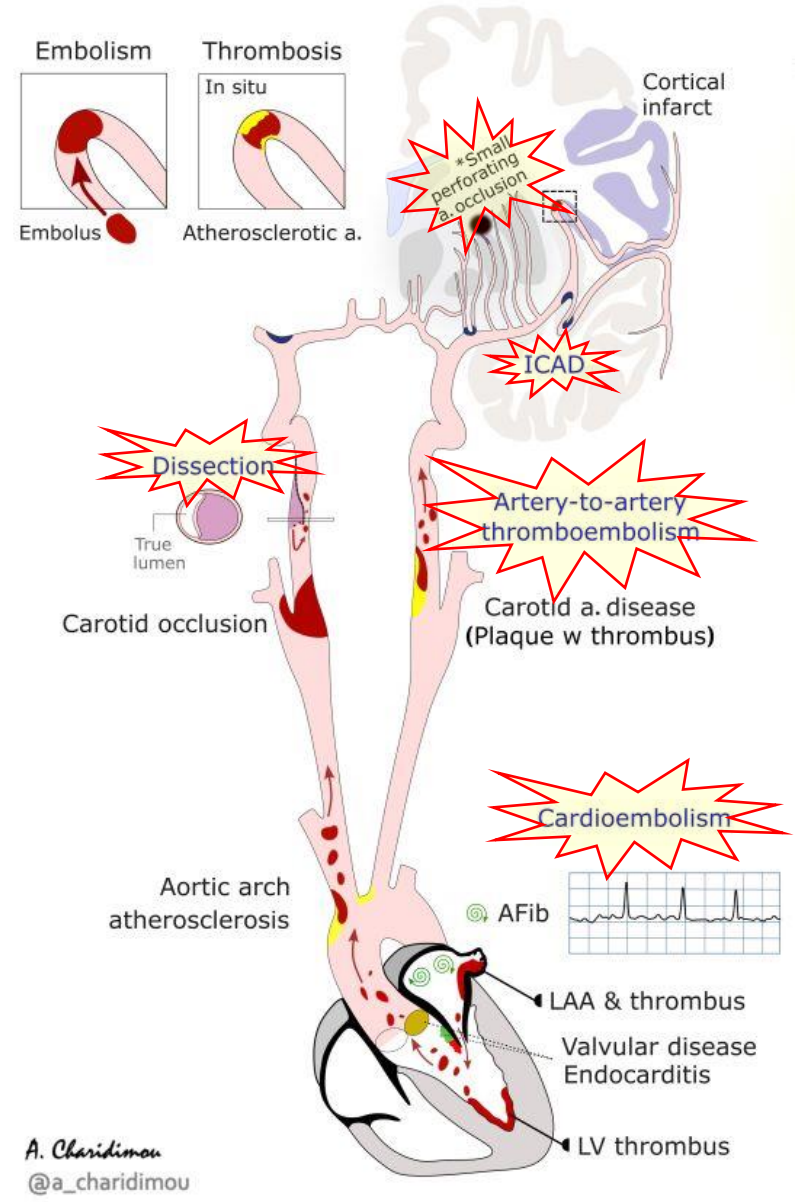
Atherosclerotic

Non-Atherosclerotic

Arteriogenic embolism

Paradoxical embolism

Thrombosis-mediated embolism



Ntaios G, Hart RG. Embolic stroke. Circulation. 2017;136:2403e2405.

ESC European Society of Cardiology

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.

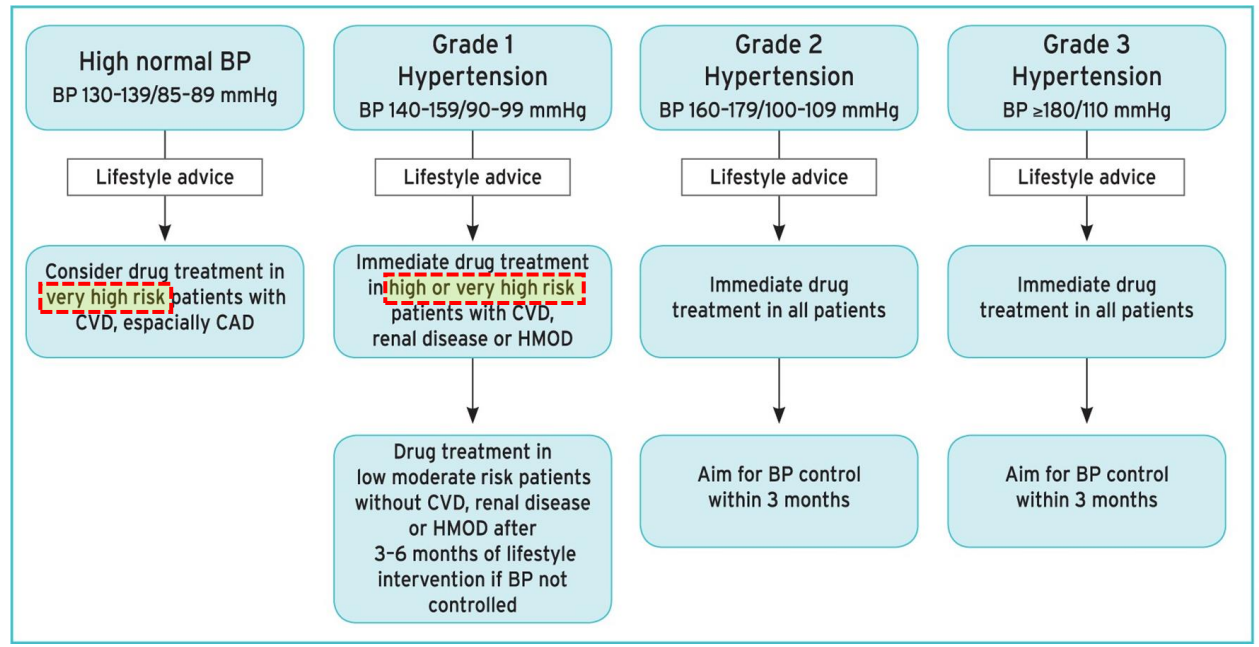
[a]Treatment may be considered in these very high-risk patients with high–normal SBP (i.e. SBP 130–140 mmHg).

European Heart Journal (2018) **39**, 3021–3104

2018 ESC/ESH Guidelines for the management of arterial hypertension

ESC European Society of Cardiology

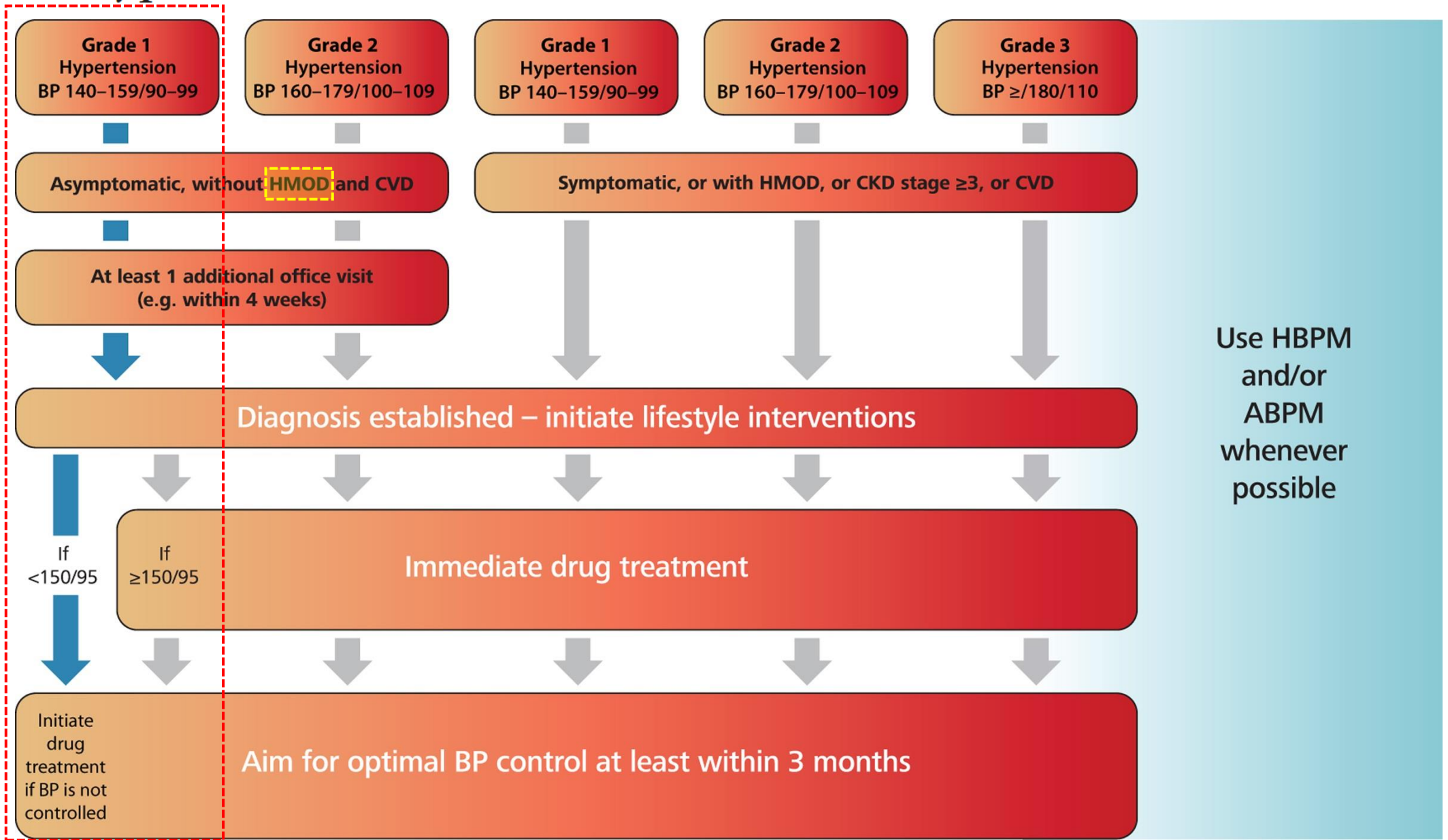
Very high risk	**People with any of the following:**
	Documented CVD, either clinical or unequivocal on imaging. • **Clinical CVD** includes acute myocardial infarction, acute coronary syndrome, coronary or other arterial revascularization, stroke, TIA, aortic aneurysm, and PAD • **Unequivocal documented CVD on imaging** includes significant plaque (i.e. ≥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 m^2) • **A calculated 10 year SCORE of ≥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 ≥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 m^2)
	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%**



European Heart Journal (2018) **39**, 3021–3104

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*	

Circ Res. 2017;120:472-495

Diabetes and Cardiovascular Disease

JAMA, May 11, 1979—Vol 241, No. 19

The Framingham Study

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

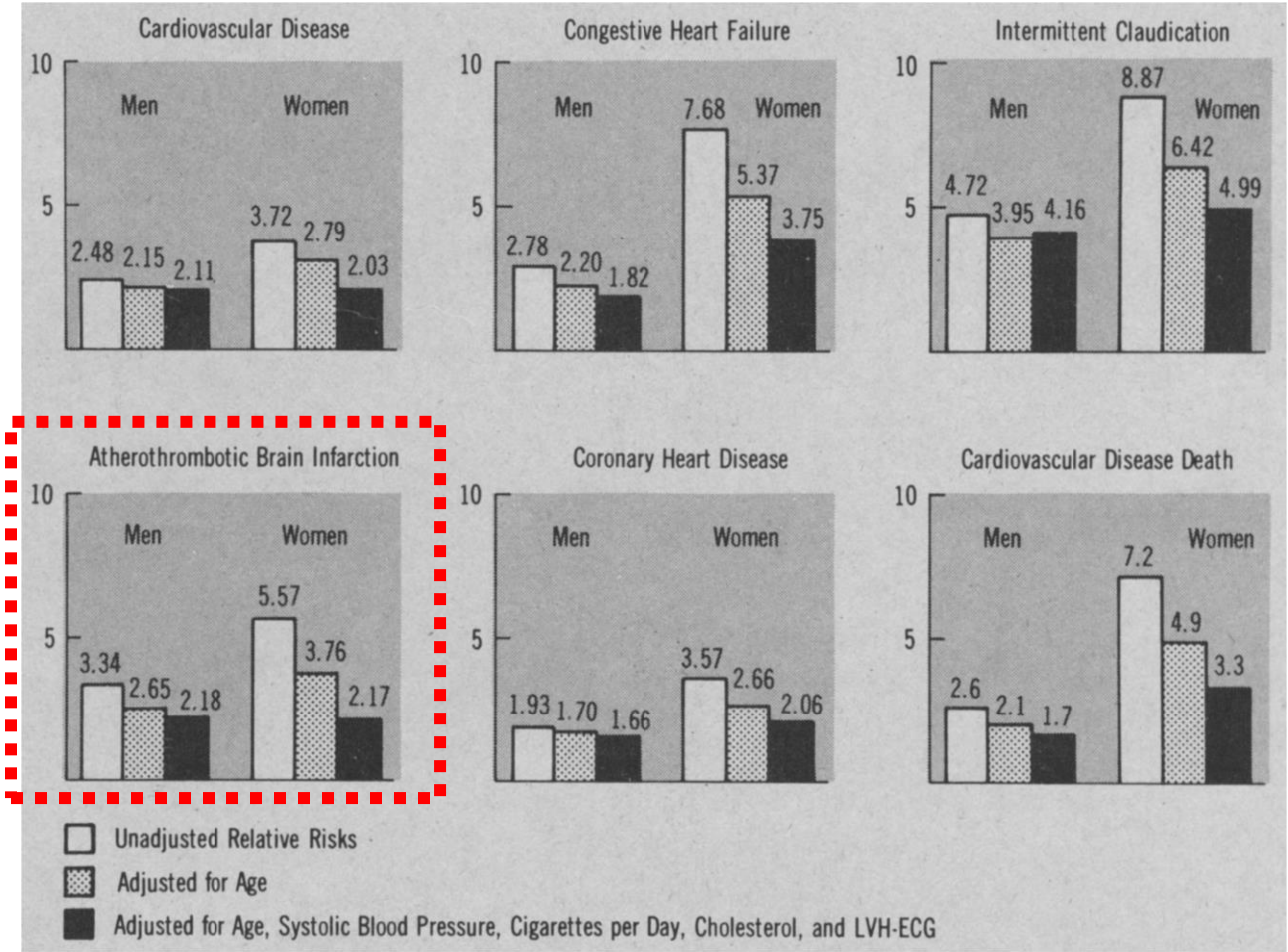
*Framingham cohort including men and women aged 45 to 74 years

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.

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



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)*

		Diabetes using fasting glucose ≥140 mg/dl			Diabetes using fasting glucose ≥126 mg/dl		
Model and adjustment variables	Events (*n*)	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

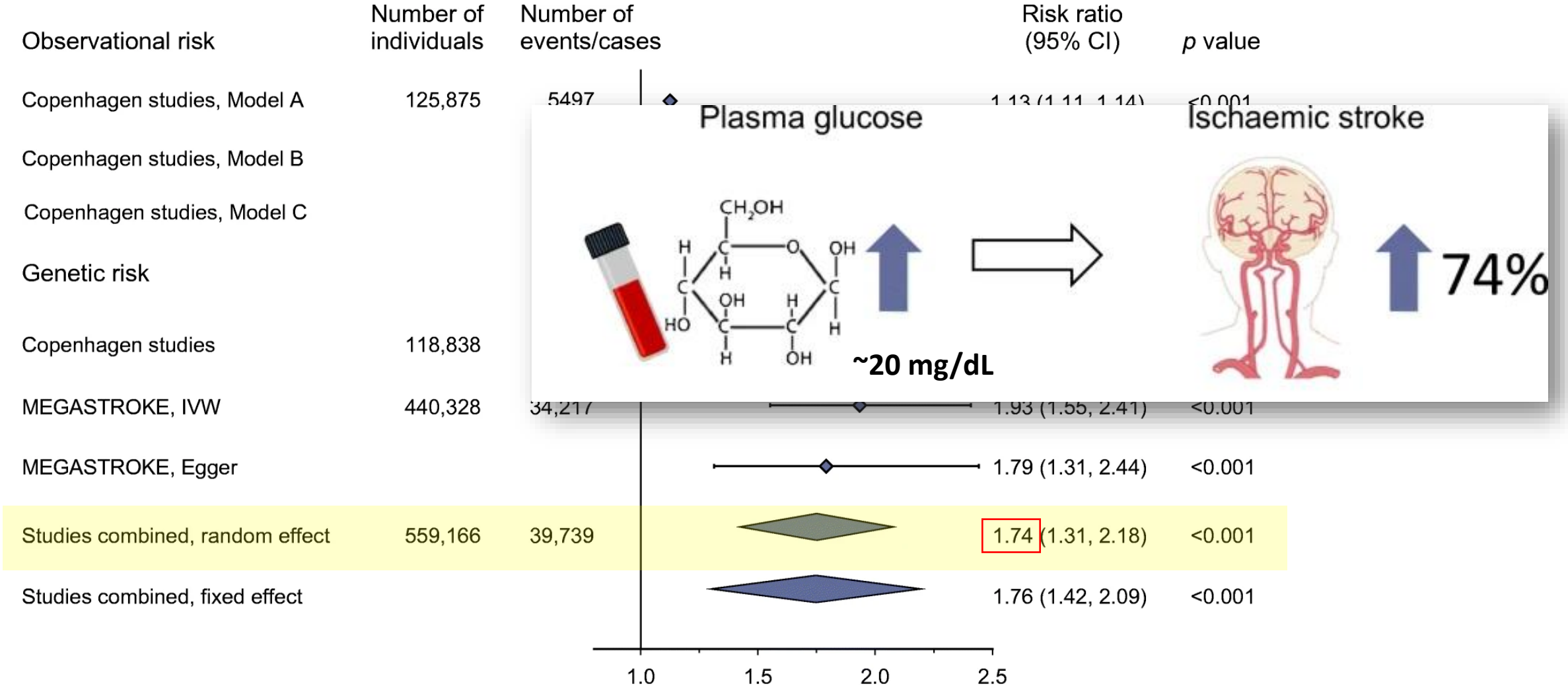
Also included as diabetes: nonfasting glucose ≥200 mg/dl, physician diagnosis of diabetes, or use of hypoglycemic medication. †The reference group is subjects without diabetes. RR, relative risk.

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

Diabetes Care 22:1077–1083, 1999

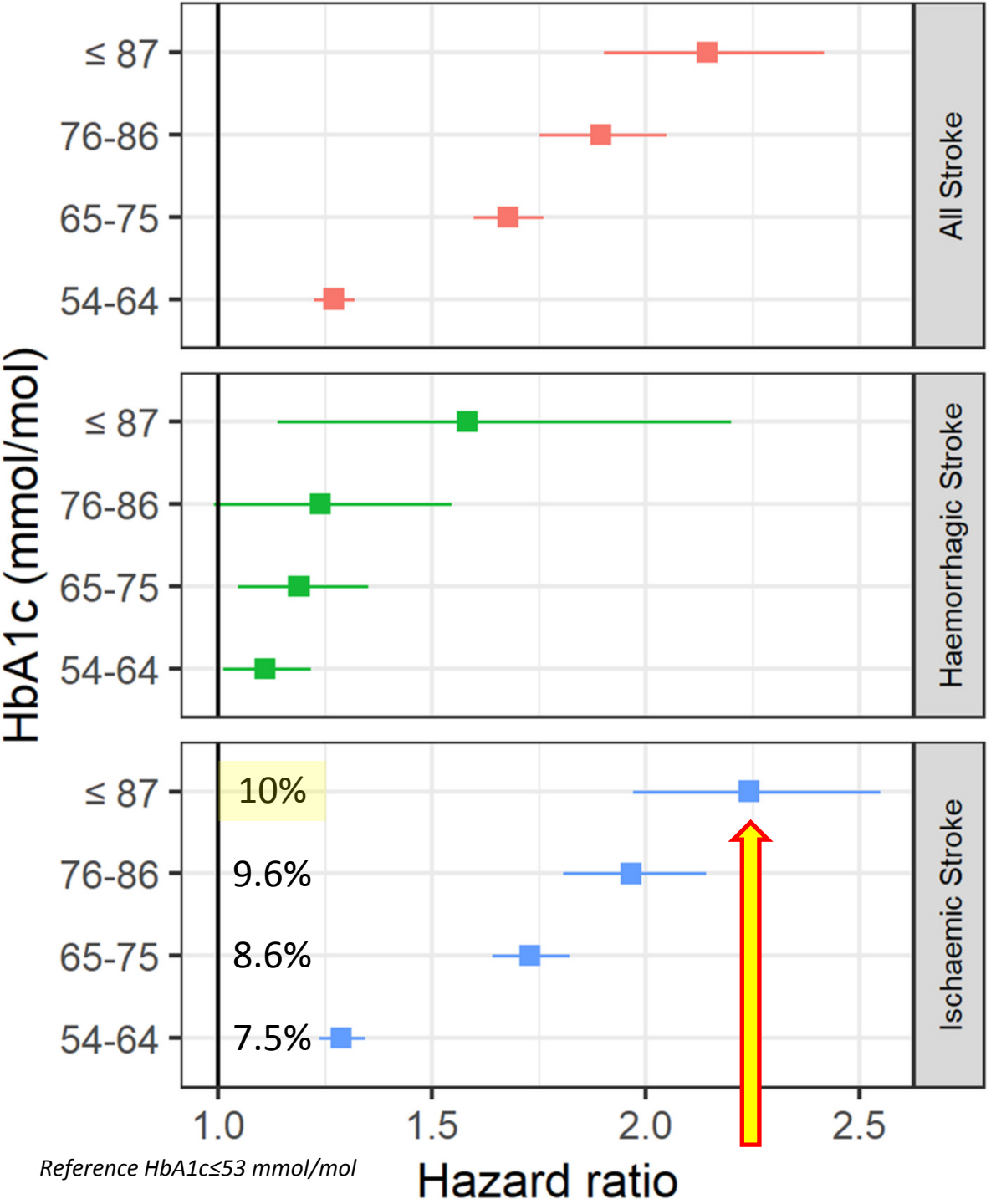
Impact of high glucose levels and glucose lowering on risk of ischaemic stroke: a Mendelian randomisation study and meta-analysis

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



Diabetologia (2021) 64:1492–1503

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



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

Diabetes Obes Metab. 2020;22:182–190

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	Macrovascular
Retinopathy	Ischaemic heart disease
Nephropathy	Stroke
Neuropathy	Peripheral vascular disease

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

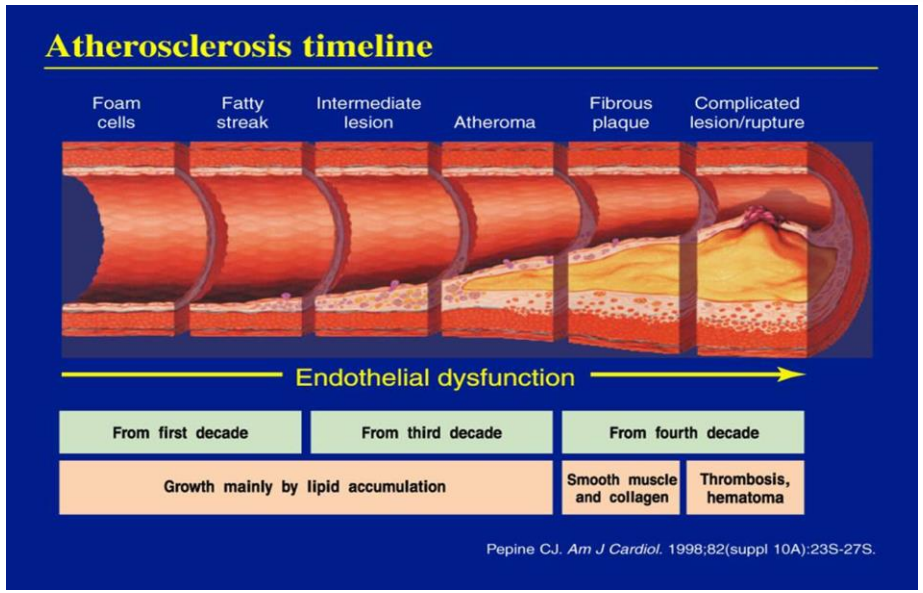
Etiology	Nondiabetic, n = 3,118	Diabetic, n = 572	*p*	Total, n = 3,690
Large-artery disease, n (%)	966 (31)	240 (42)	<0.0001	1,206 (33)
Small-vessel disease, n (%)	468 (15)	160 (28)		628 (17)
Cardiogenic embolism, n (%)	716 (23)	80 (14)		796 (21)
Other, n (%)	531 (17)	63 (11)		594 (16)
Undetermined,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

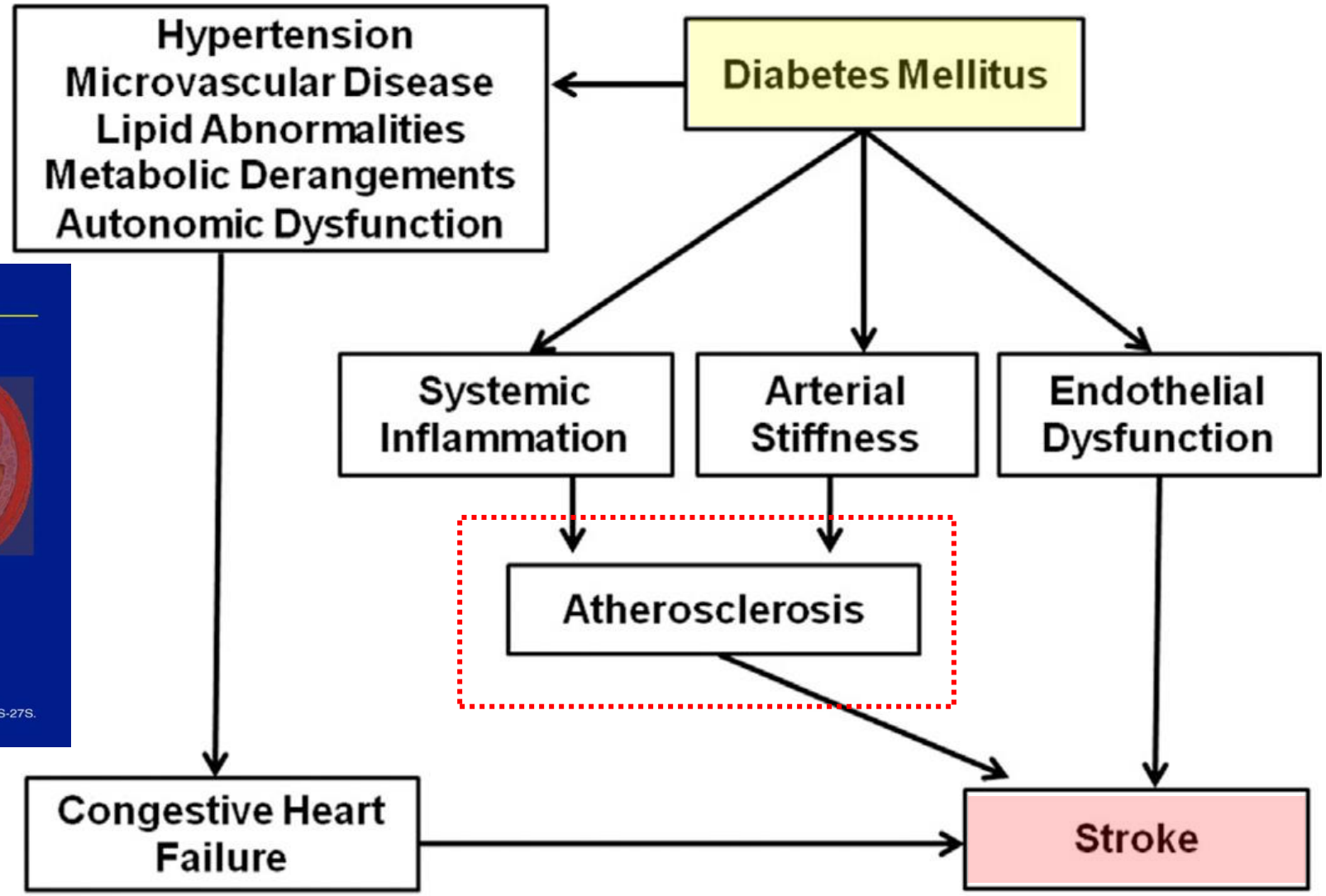
Table 5 *Variables associated with small-vessel and large-artery disease and subgroup analysis according to hypertension and age (multiple logistic regression analysis)**

	Small-vessel disease		Large-artery disease	
Variable	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

NEUROLOGY 2004;62:1558–1562

Diabetes and Stroke: Epidemiology, Pathophysiology, Pharmaceuticals and Outcomes

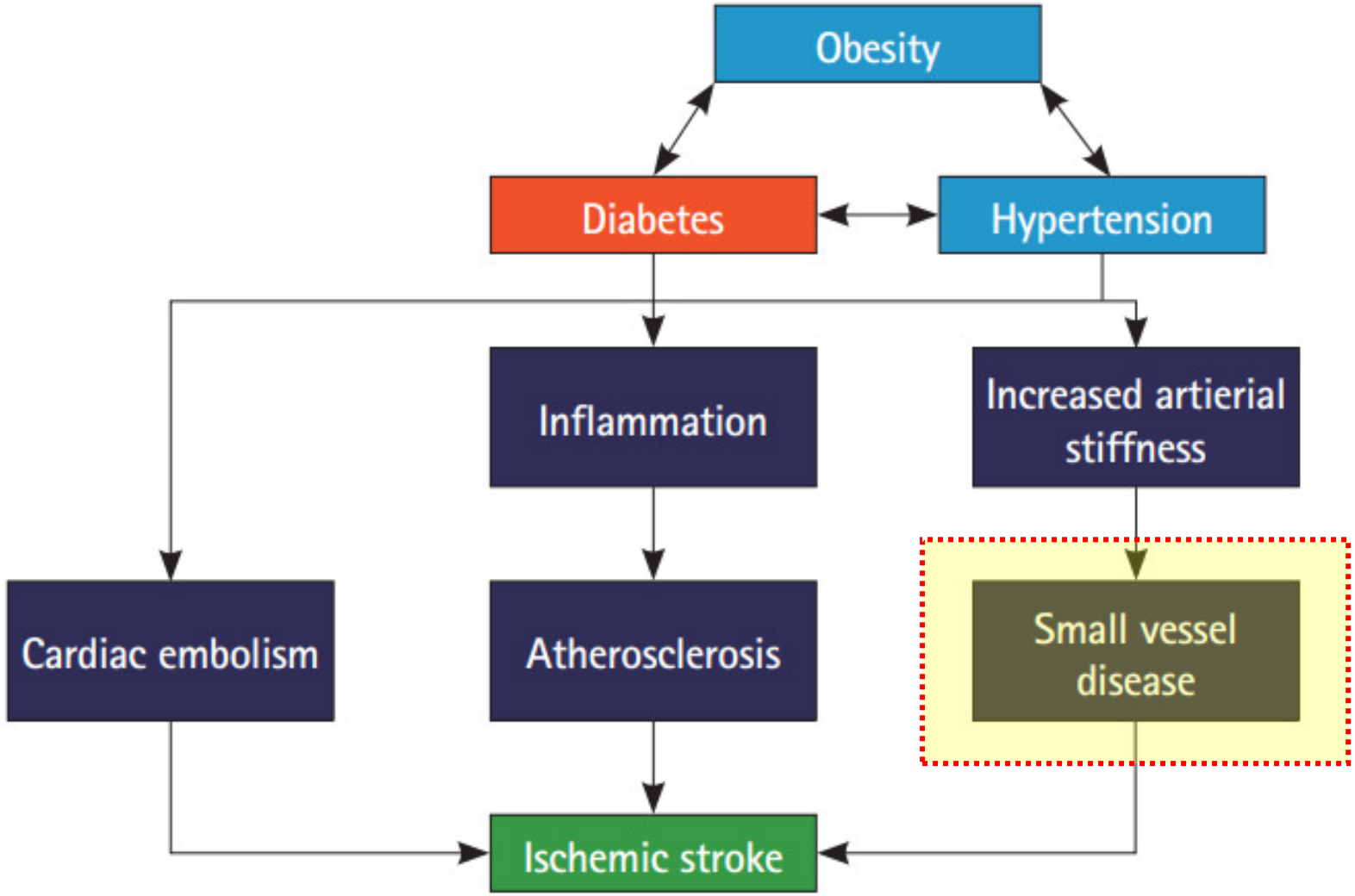




Possible mechanisms of stroke in individuals with diabetes

Am J Med Sci. 2016 April ; 351(4): 380–386

Diabetes and Stroke: What Are the Connections?



Journal of Stroke 2023;25(1):26-38

Risk factors for lacunar infarction syndromes

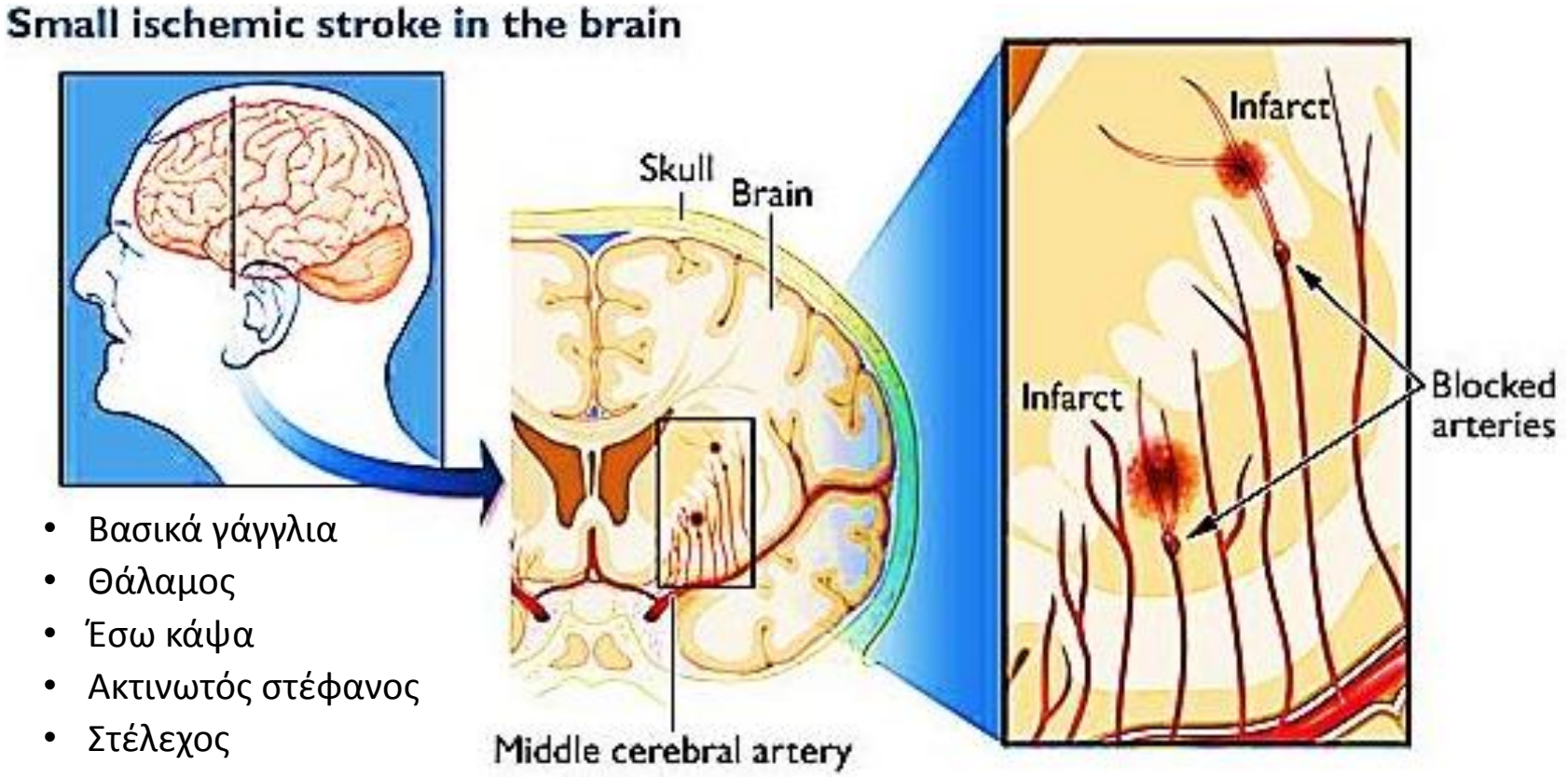
Table 2. Risk of lacunar infarction associated with the examined risk factors estimated by conditional logistic regression

Risk factors	Cases No.	Cases (%)	Controls No.	Controls (%)	Univariate analysis OR	Univariate analysis (95% CI)	Multivariate analysis OR	Multivariate analysis (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)

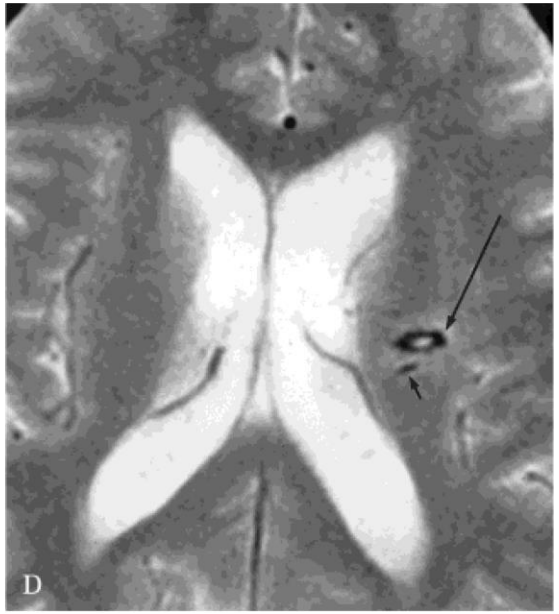
NEUROLOGY 1995;45:1483-1487

Νόσος Μικρών Αγγείων
Κενοχωριώδη → Lacunar

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

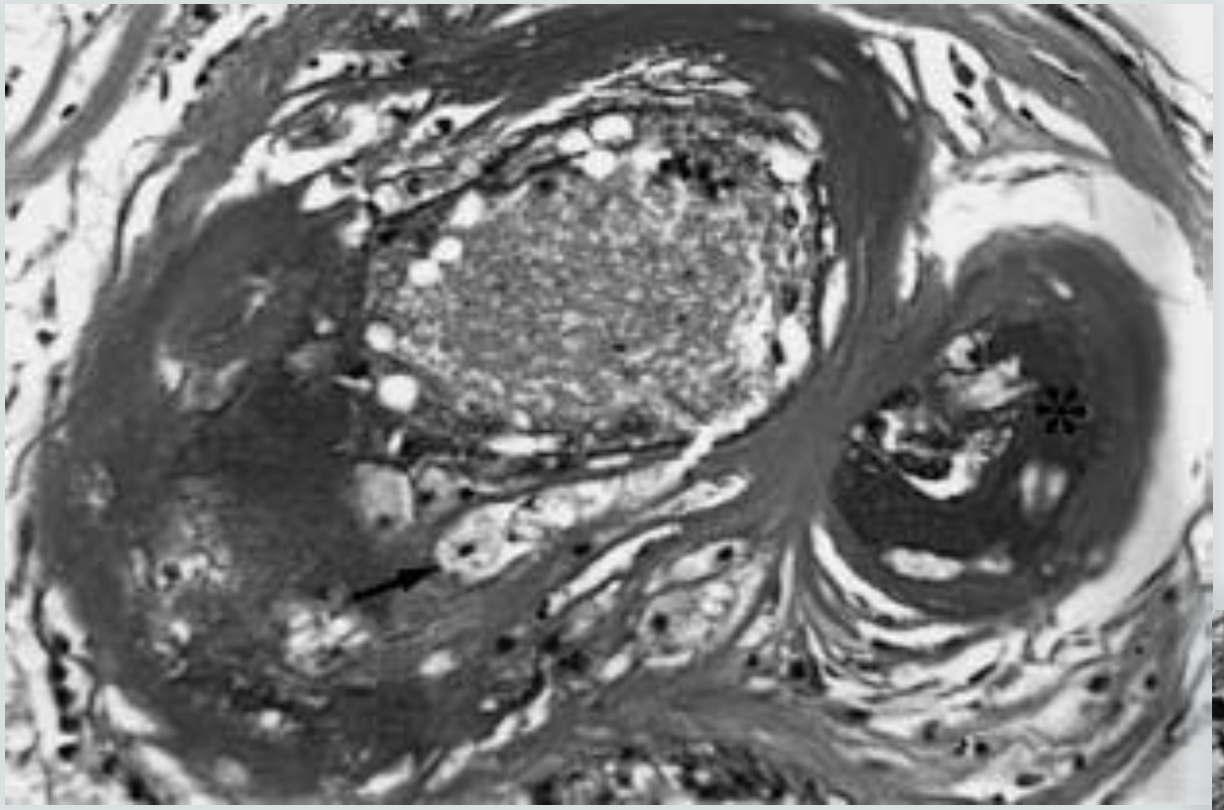


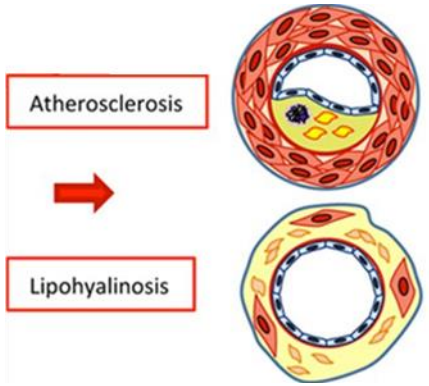
- Βασικά γάγγλια
- Θάλαμος
- Έσω κάψα
- Ακτινωτός στέφανος
- Στέλεχος

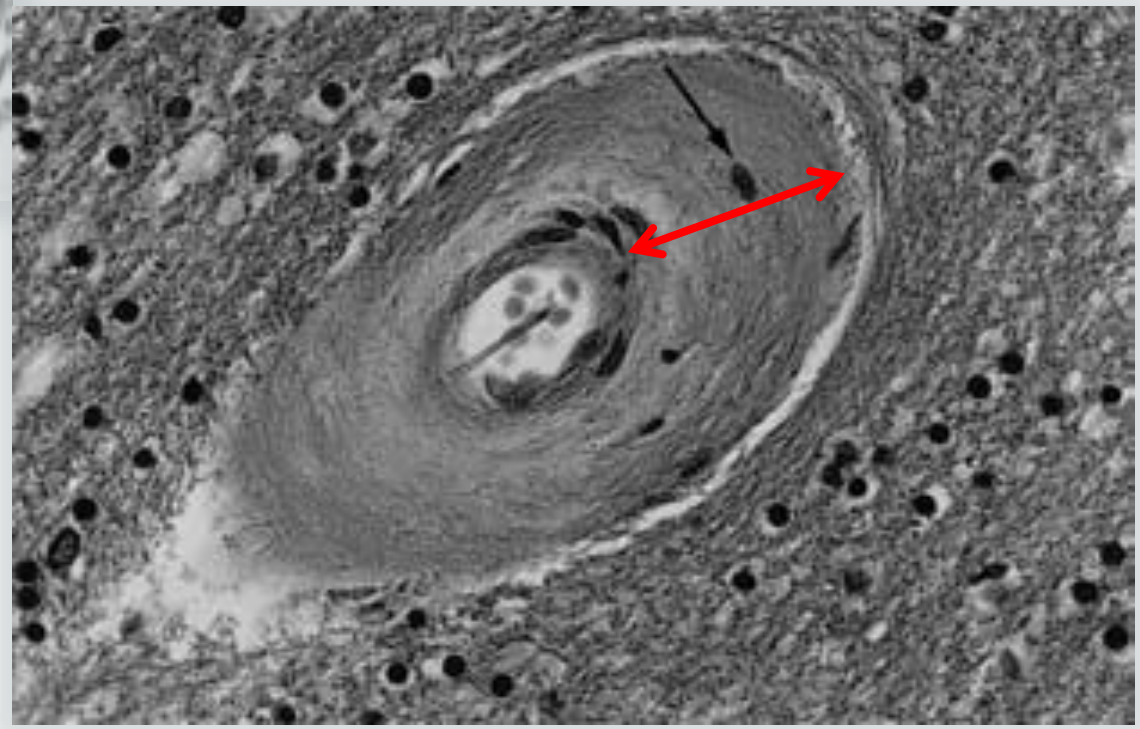


Ann Neurol 2001;50:208–215

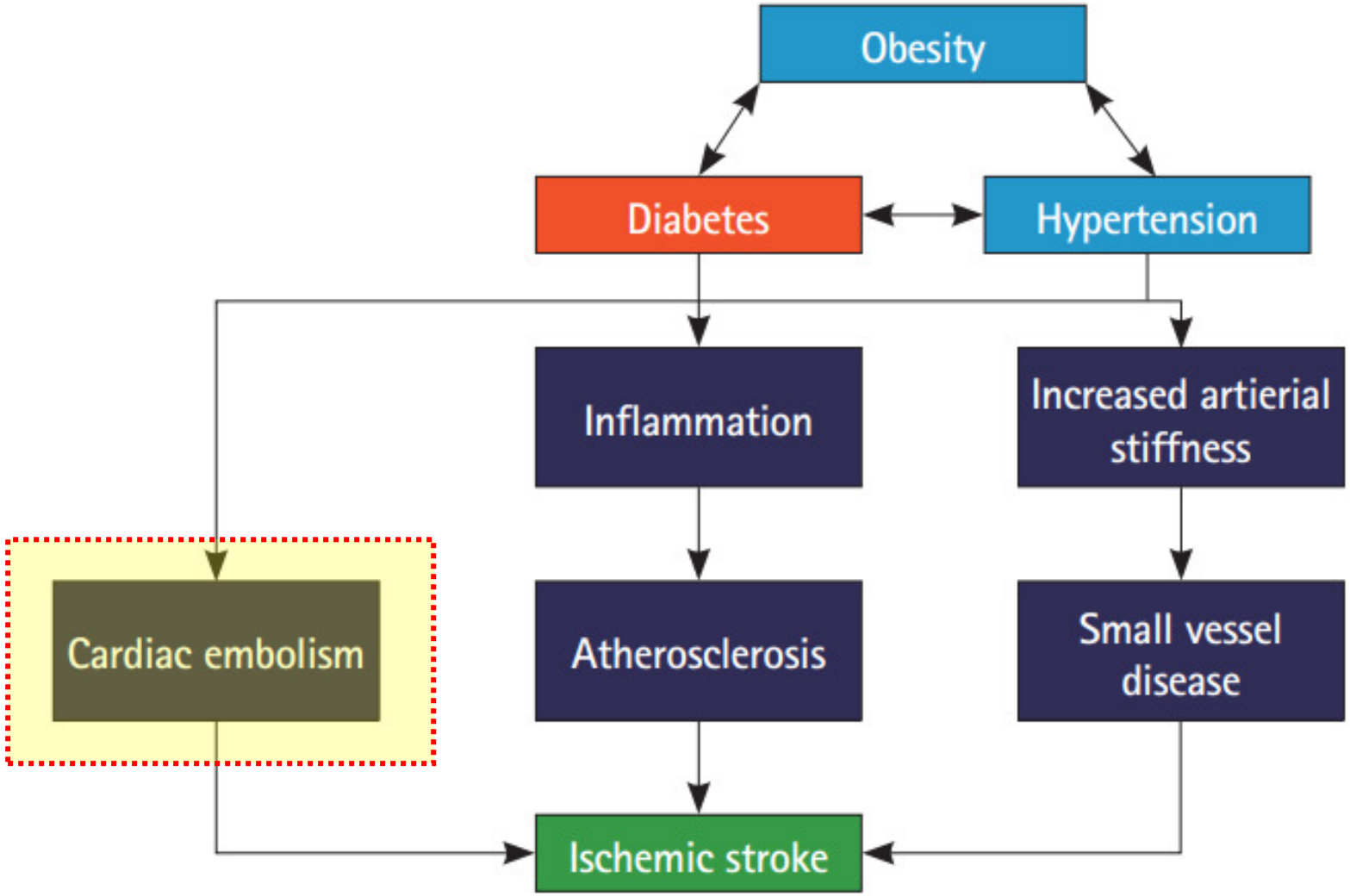
Brainin & Heiss, Textbook of Stroke Medicine, 2010




Atherosclerosis
Lipohyalinosis



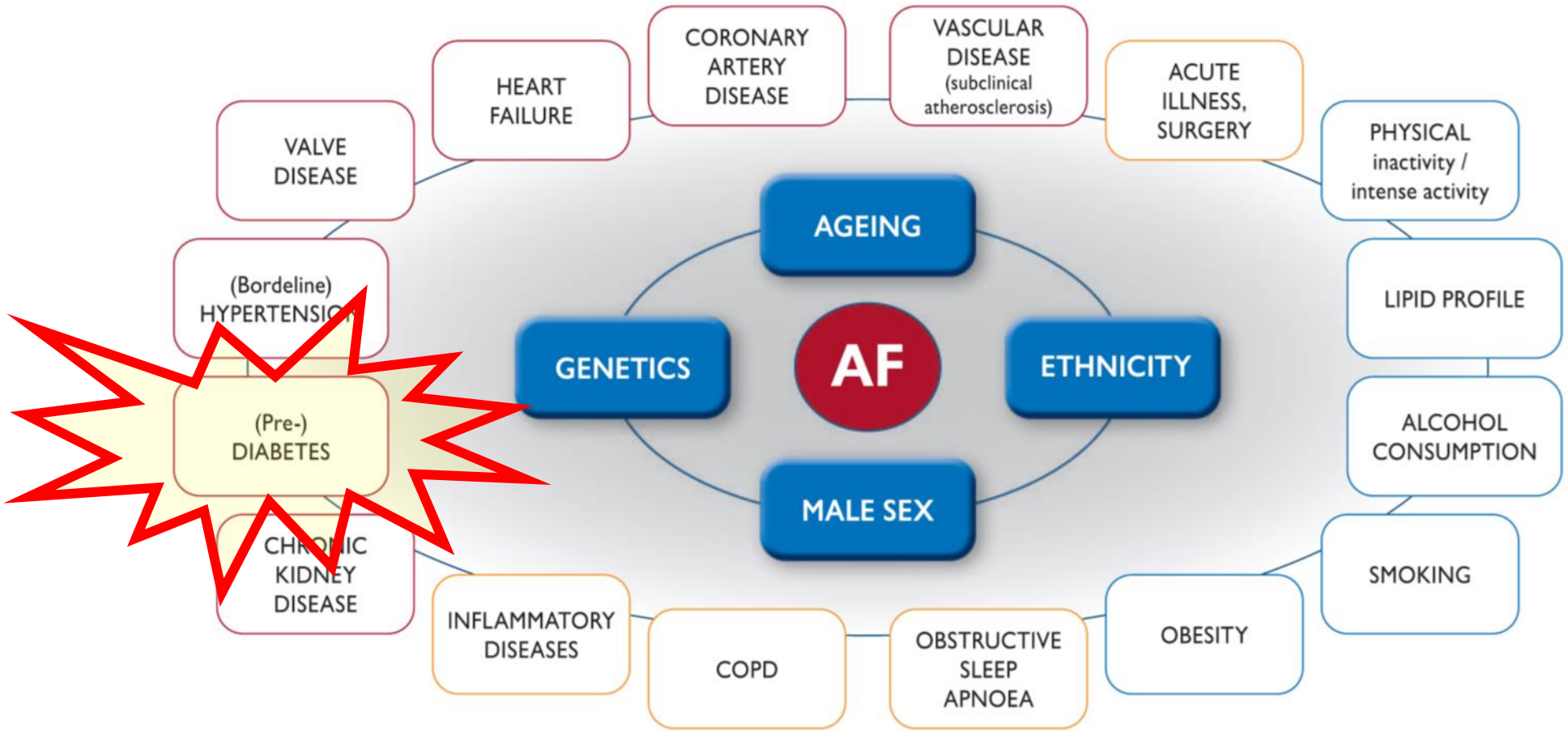
Diabetes and Stroke: What Are the Connections?



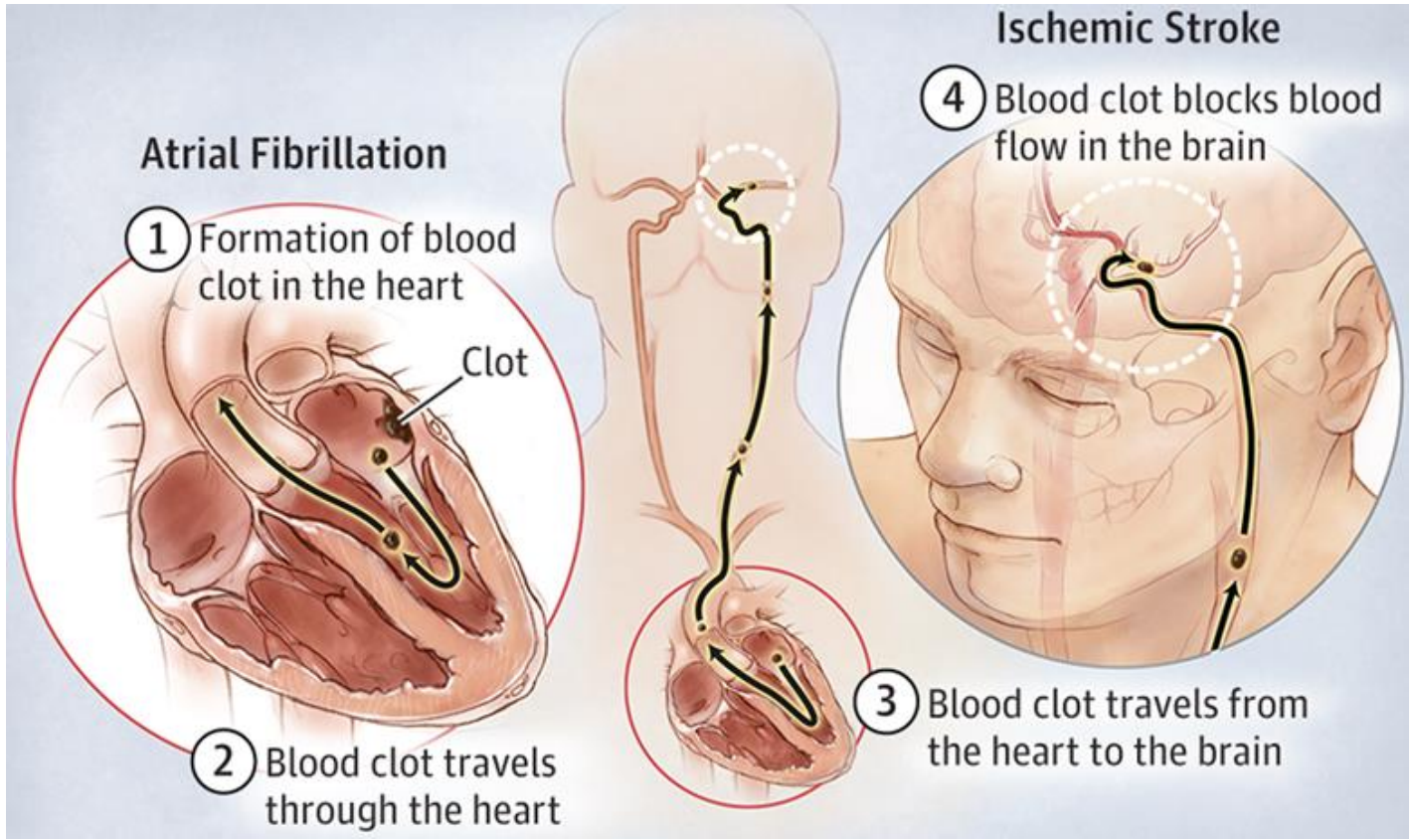
Journal of Stroke 2023;25(1):26-38

ESC European Society of Cardiology

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_2DS_2-VASc score Risk factors and definitions		Points awarded
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**

European Heart Journal (2020) **42**, 373–498

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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 ≥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

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 m^2 irrespective of albuminuria; or eGFR 45–59 mL/min/1.73 m^2 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]

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

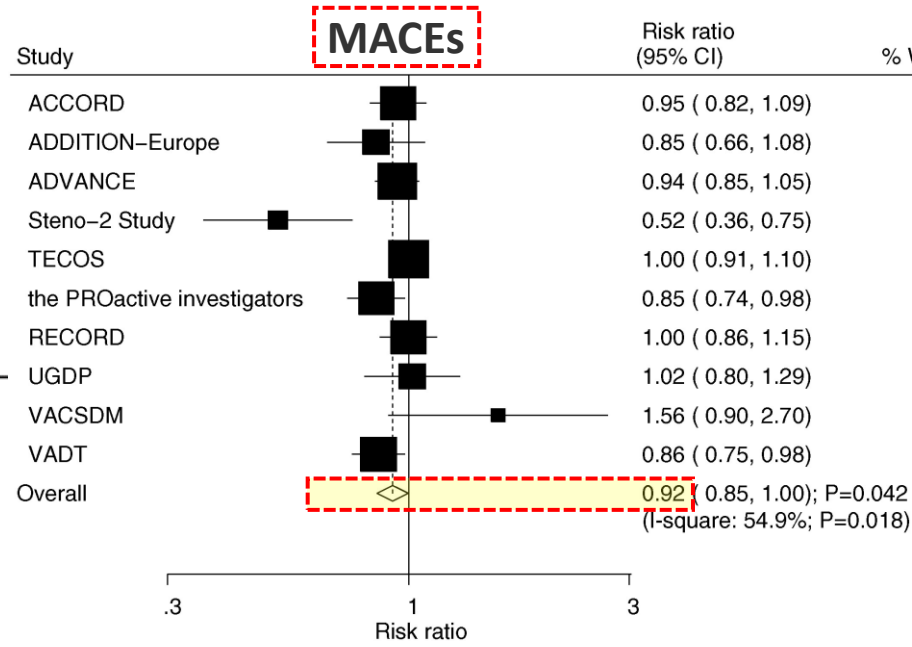
European Heart Journal (2023) **44**, 4043–4140

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

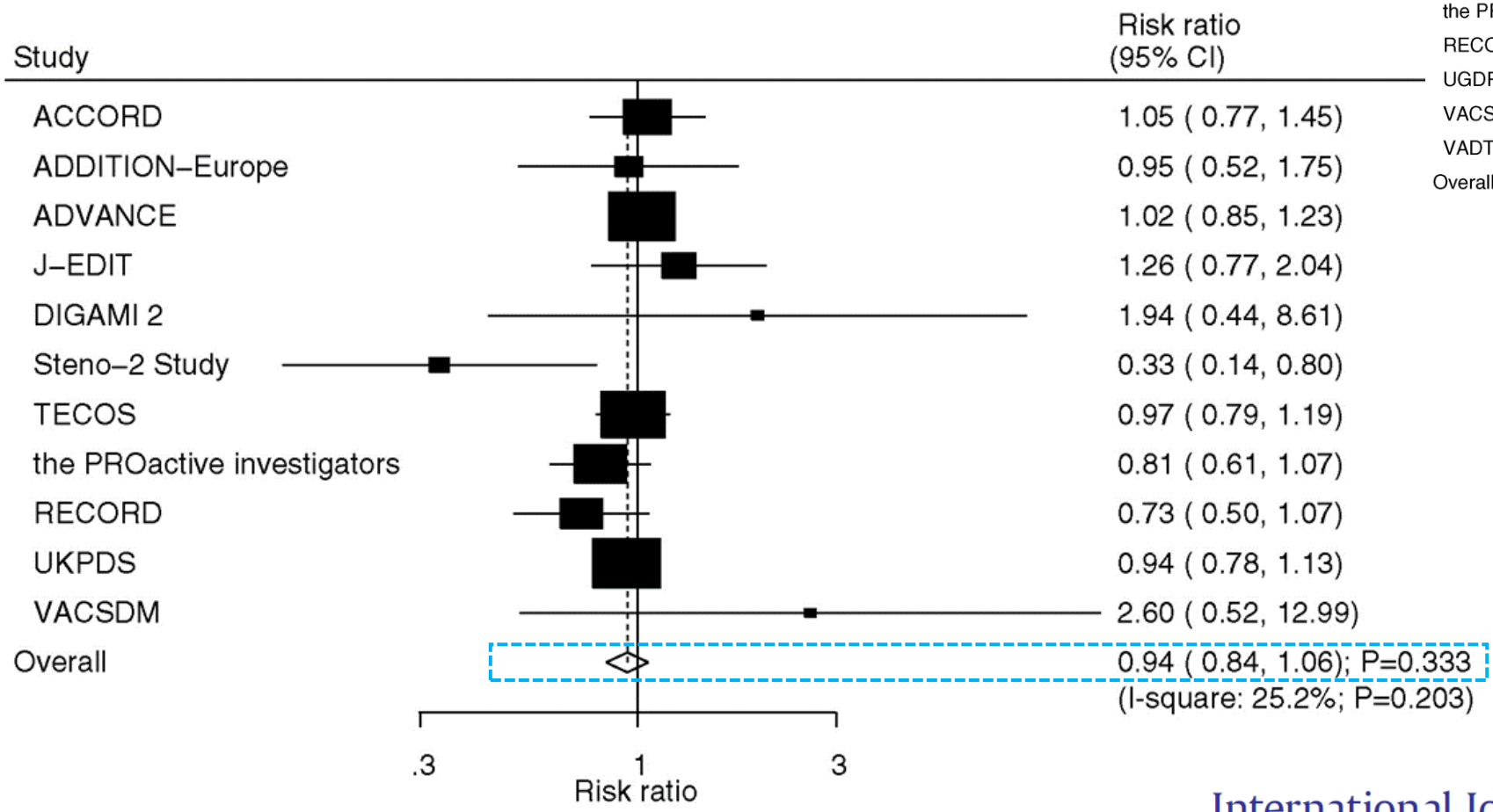
Recommendations	Class[a]	Level[b]
It is recommended to apply tight glucose control, targeting a near-normal HbA1c (<7.0% or <53 mmol/mol), to decrease microvascular complications in individuals with DM.[145–149]	I	A
It is recommended that HbA1c targets are individualized according to the duration of 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

European Heart Journal (2020) **41**, 255–323

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

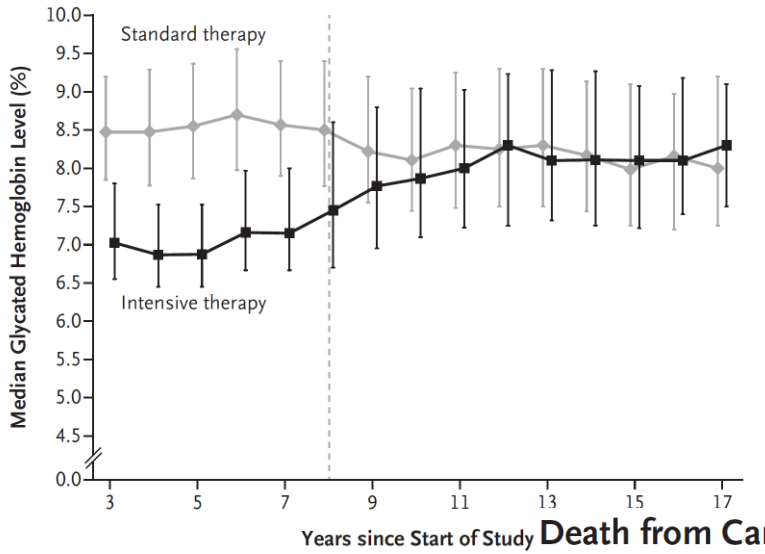
T2DM patients who received intensive glucose lowering therapy are associated with a reduced risk of MACEs and MI, whereas it has **no significant effect** on the risk of total mortality, cardiac death, stroke, and congestive heart failure.

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

International Journal of Cardiology 218 (2016) 50–58

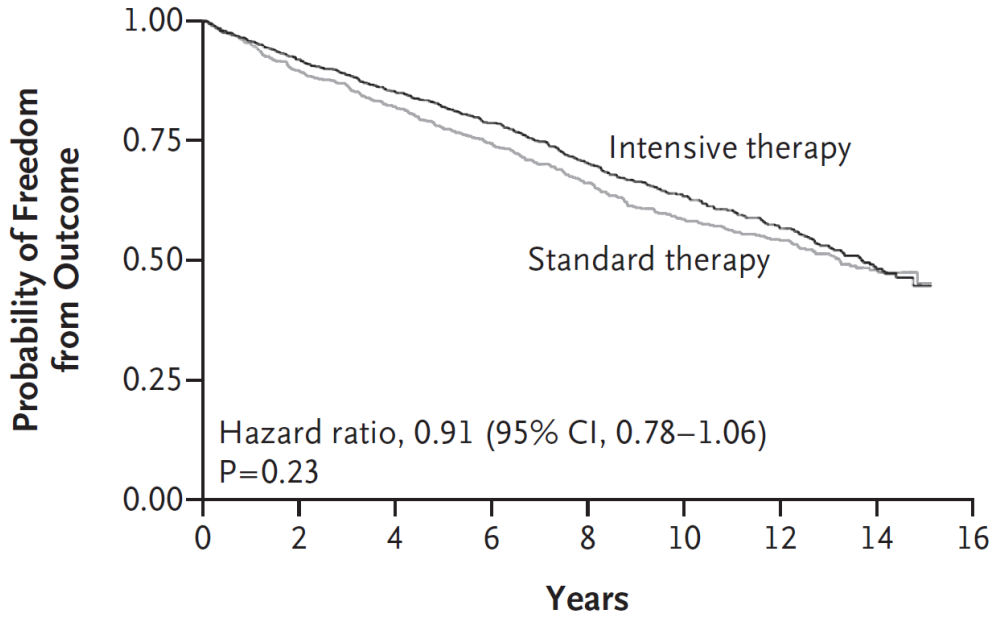
VADT

Intensive Glucose Control in Patients with Type 2 Diabetes — 15-Year Follow-up

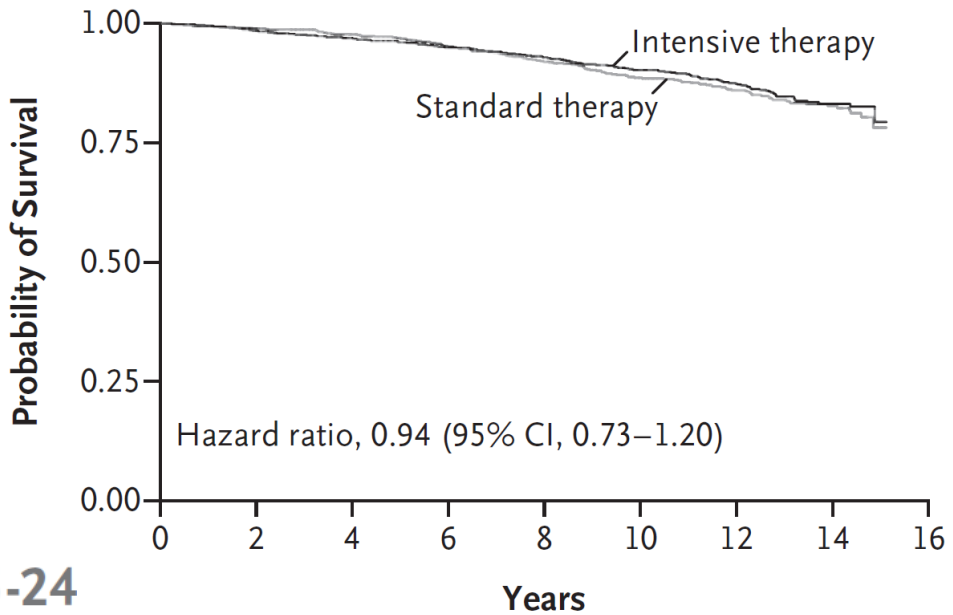


A median of 5.6 years of intensive as compared with standard glucose lowering in 1791 military veterans with type 2 diabetes resulted in a **risk of major cardiovascular events** that was significantly lower (by **17%**) after a total of 10 years of combined intervention and observational follow-up

Primary Outcome



Death from Cardiovascular Causes



Conclusions

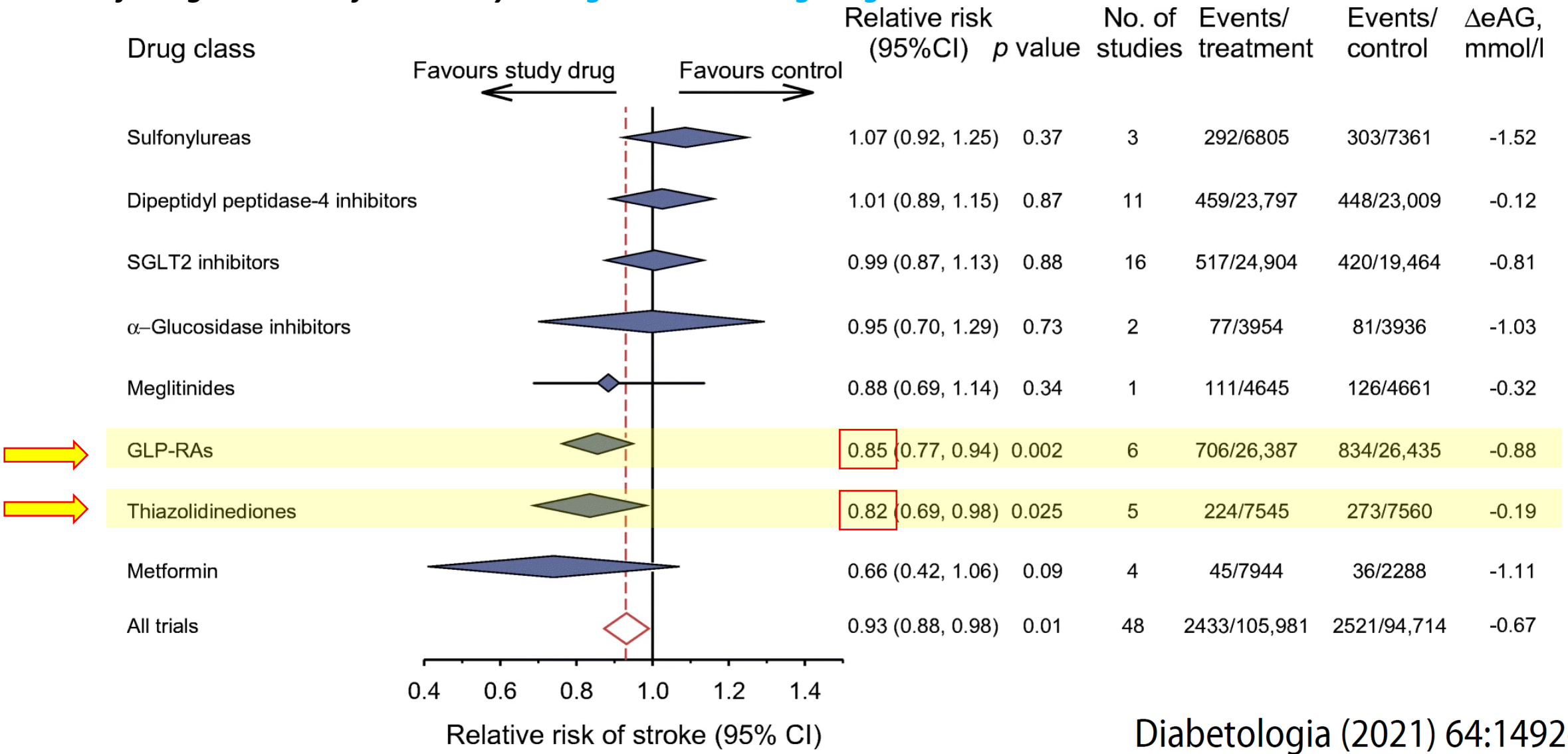
Participants with type 2 diabetes who had been randomly assigned to intensive glucose control for 5.6 years had a lower risk of cardiovascular events than those who received standard therapy *only during the prolonged period in which the glycated hemoglobin curves were separated*.

There was no evidence of a legacy effect or a mortality benefit with intensive glucose control.

N Engl J Med 2019;380:2215-24

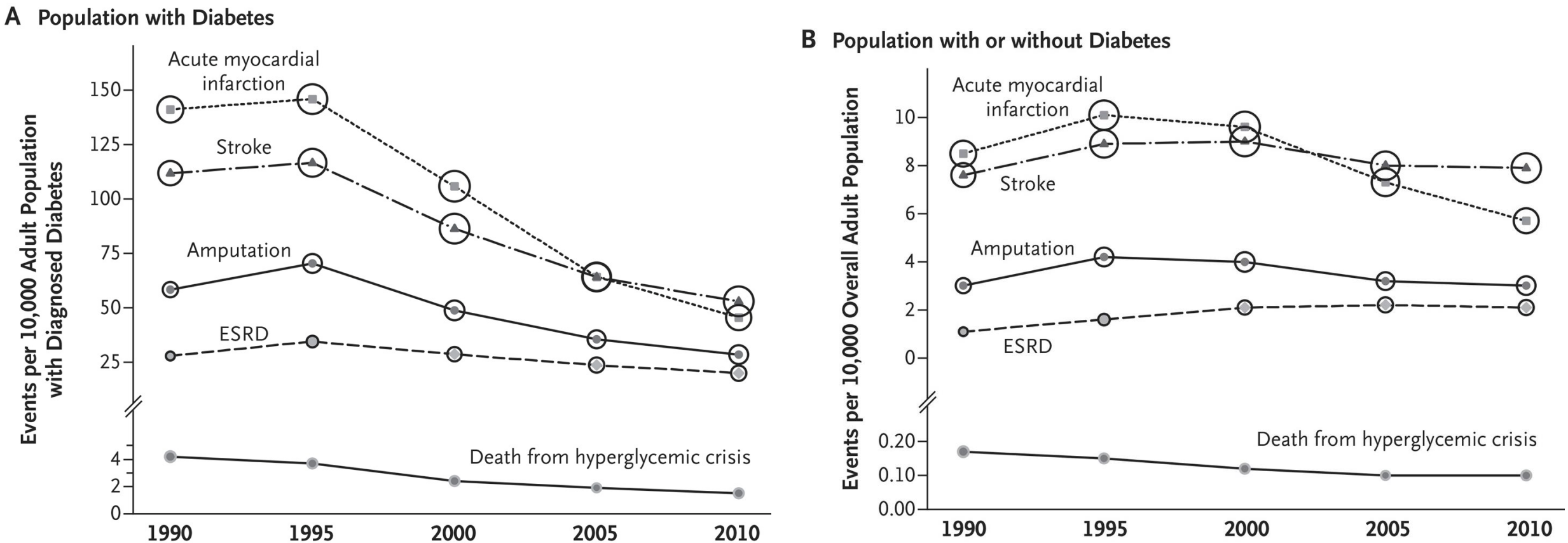
Impact of high glucose levels and glucose lowering on risk of ischaemic stroke: a Mendelian randomisation study and meta-analysis

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



Diabetologia (2021) 64:1492–1503

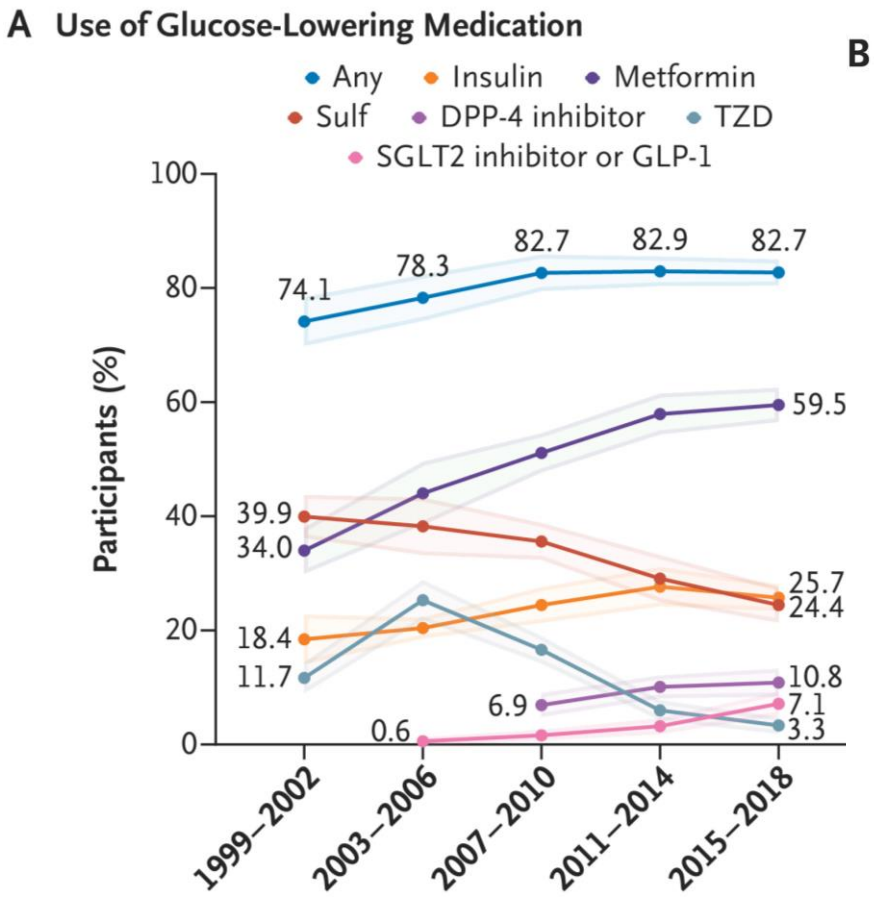
Changes in Diabetes-Related Complications in the United States, 1990–2010

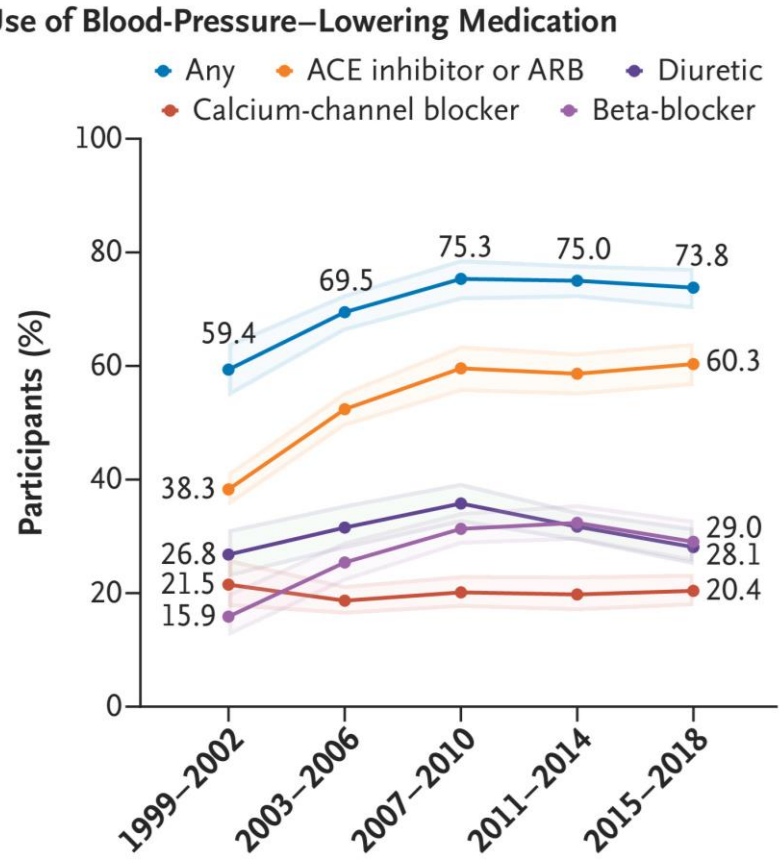


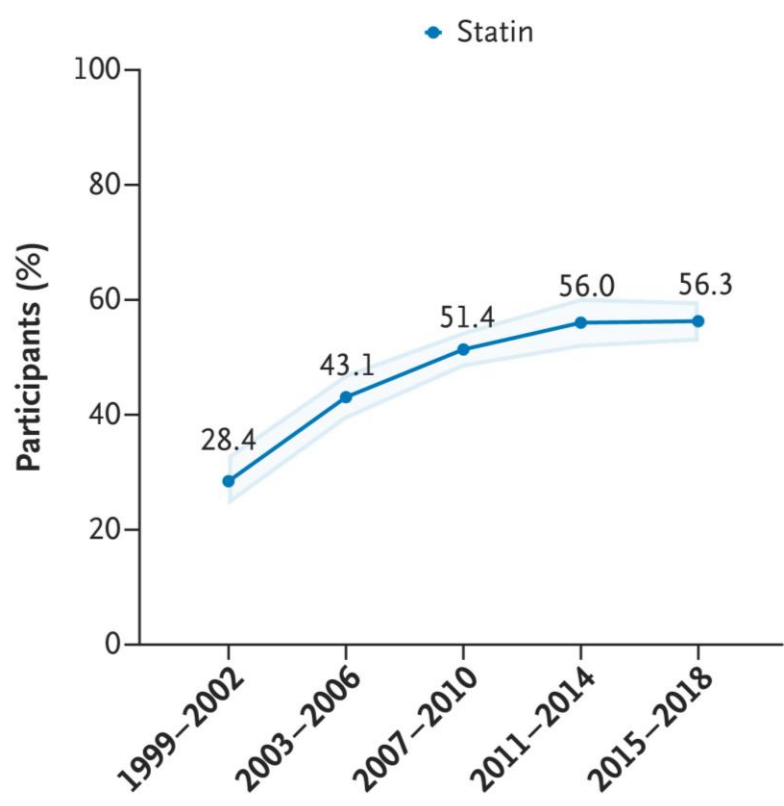
Rates of diabetes-related complications have declined substantially in the past two decades, but a large burden of disease persists because of the continued increase in the prevalence of diabetes

N Engl J Med 2014;370:1514-23

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







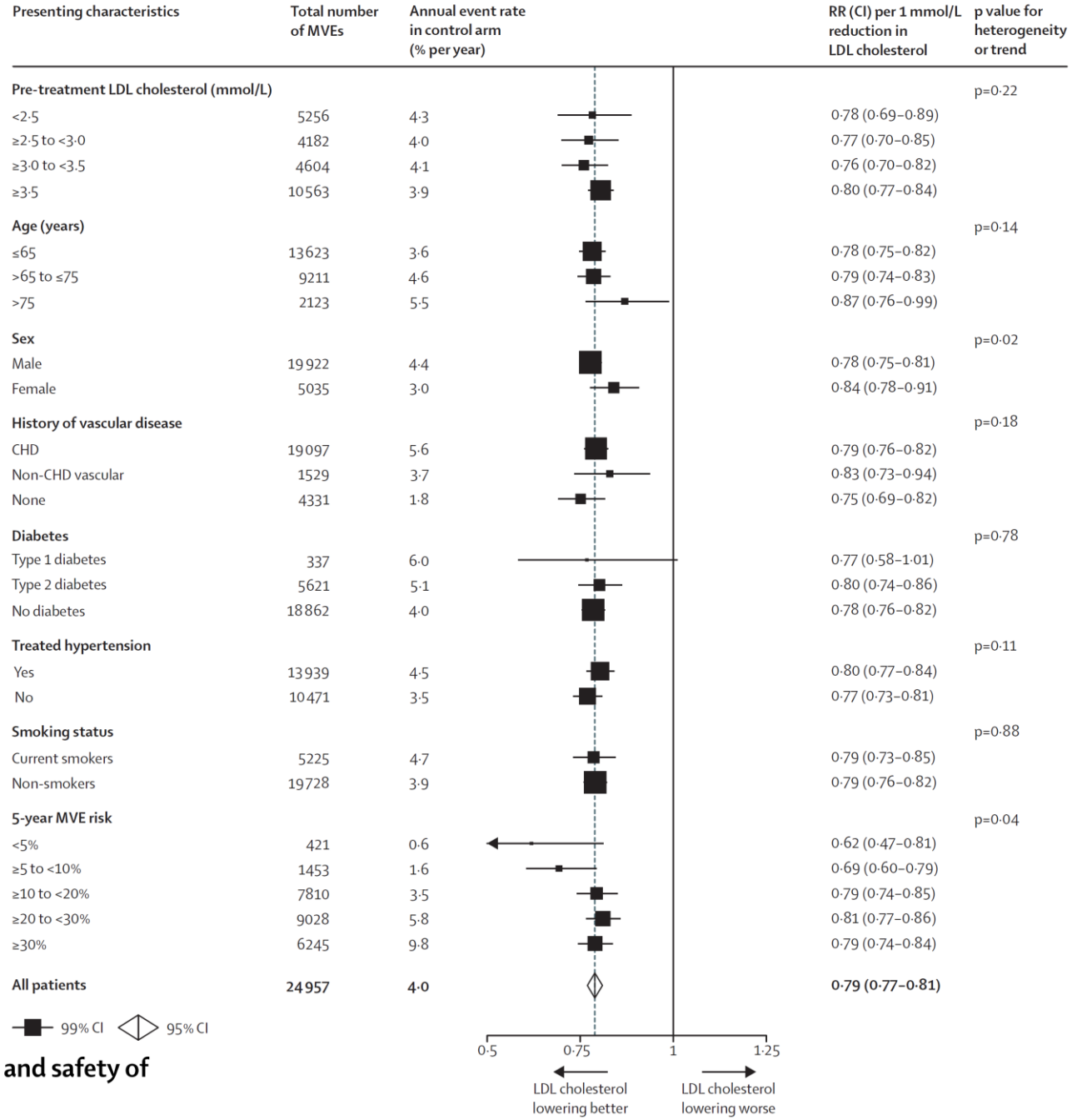
N Engl J Med 2021;384:2219-28

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*	

Circ Res. 2017;120:472-495

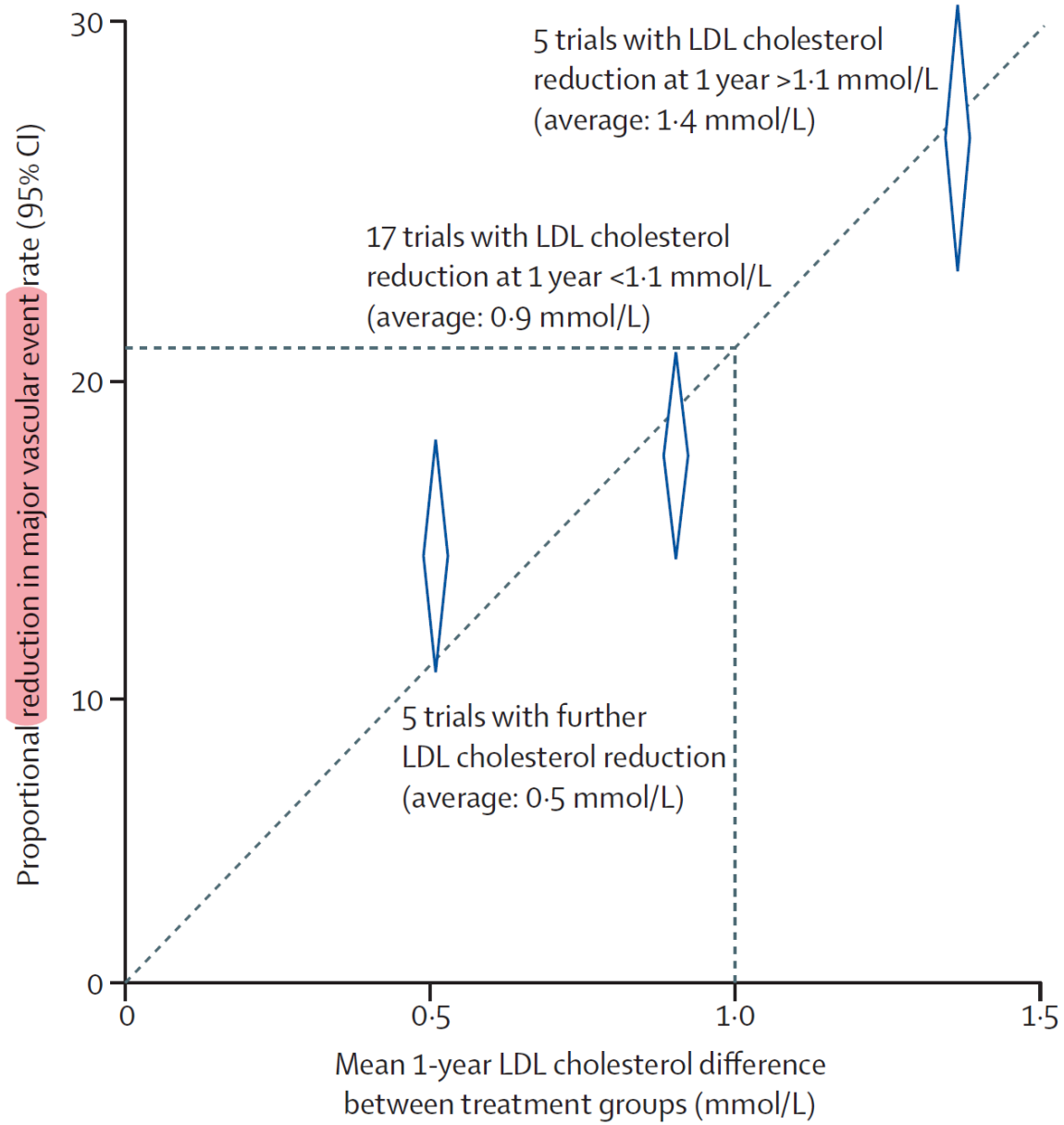
Figure 1: **Similar proportional reductions in risks of major vascular events per mmol/L LDL cholesterol reduction in randomised trials of statin therapy among people with different presenting characteristics**



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

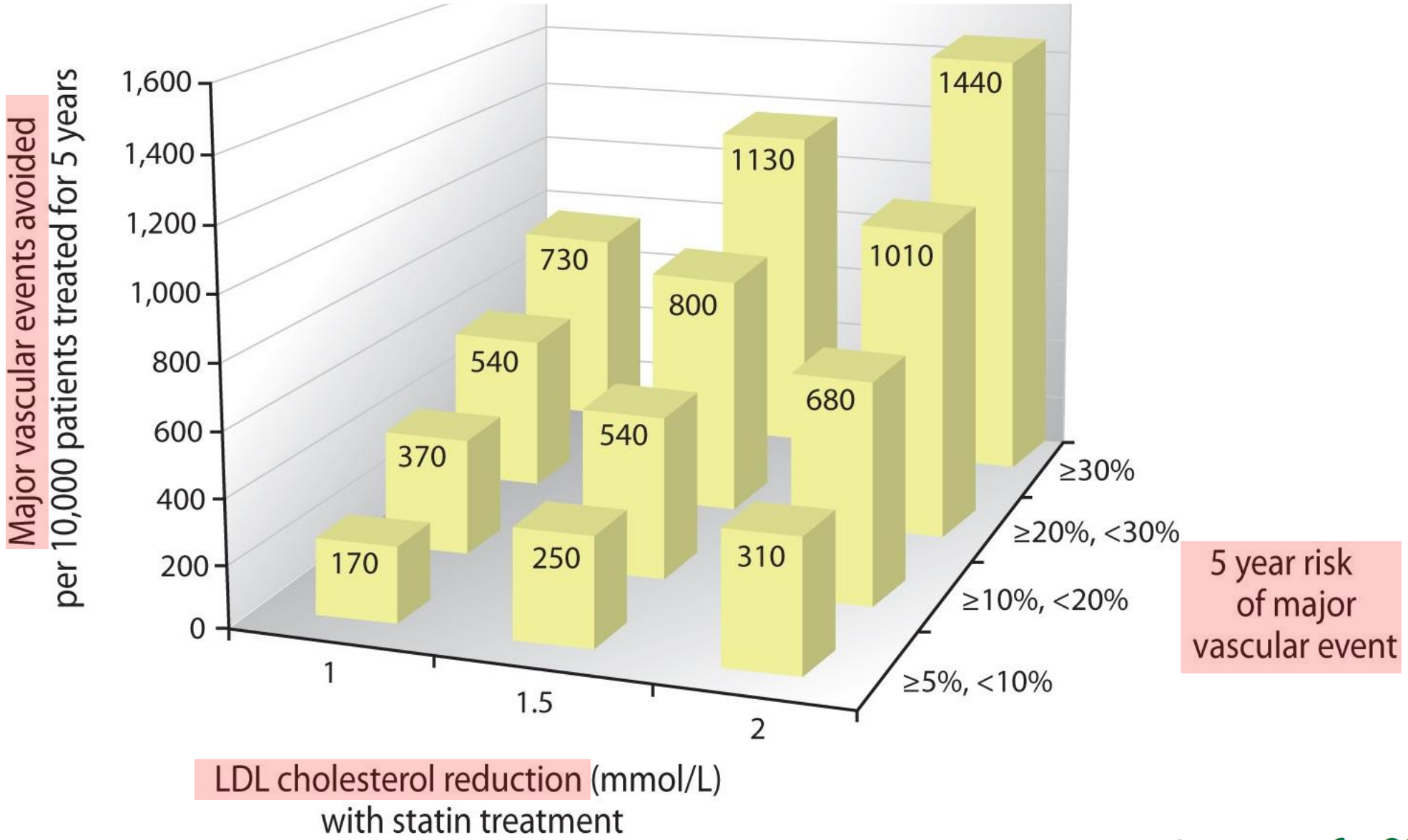
Lancet 2016; 388: 2532–61

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



Lancet 2016; 388: 2532–61

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



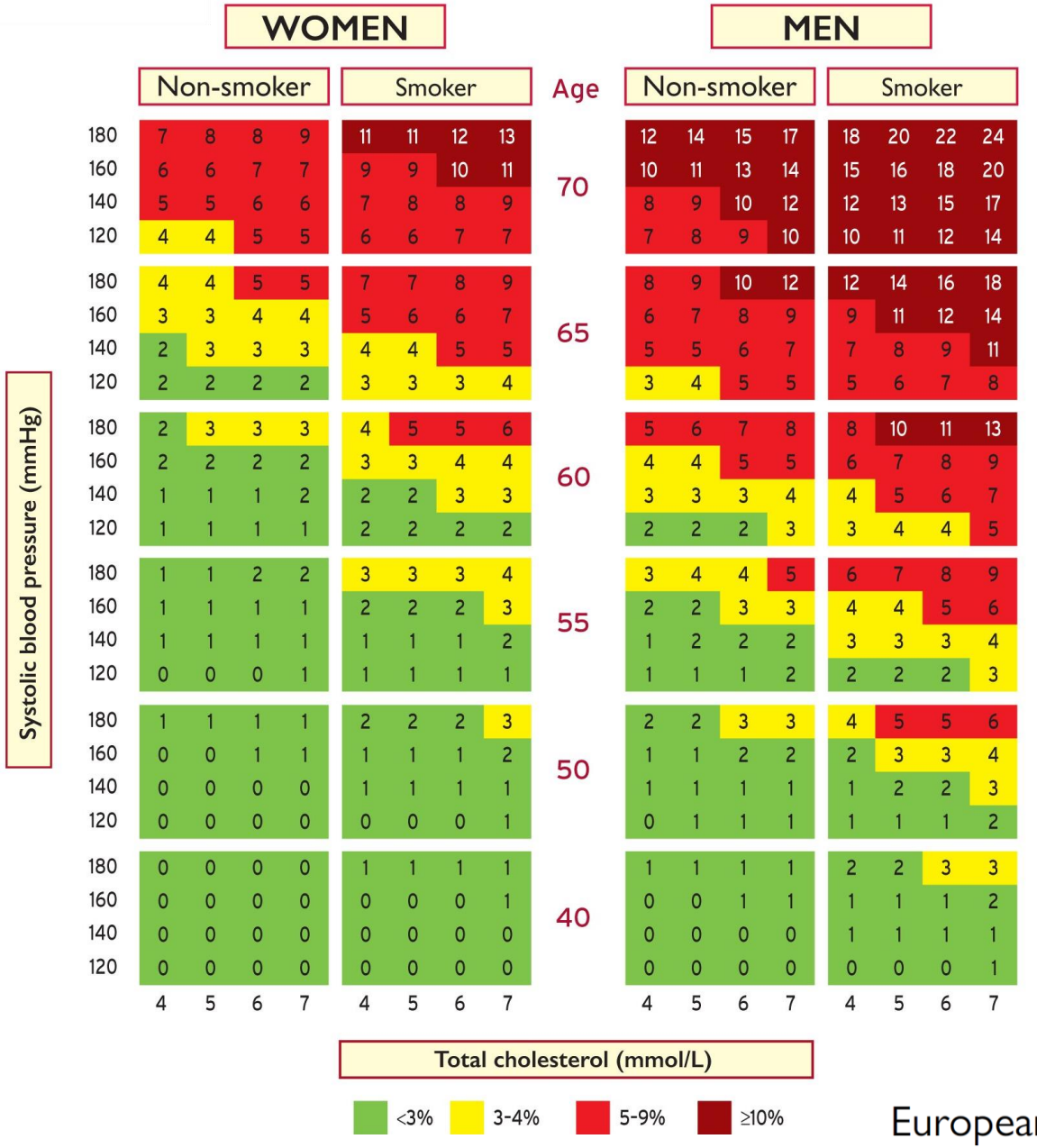
Lancet 2016; 388: 2532–61

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

SCORE Cardiovascular Risk Chart

10-year risk of fatal CVD

Low-risk regions of Europe



ESC European Society of Cardiology

European Heart Journal (2020) **41**, 111–188

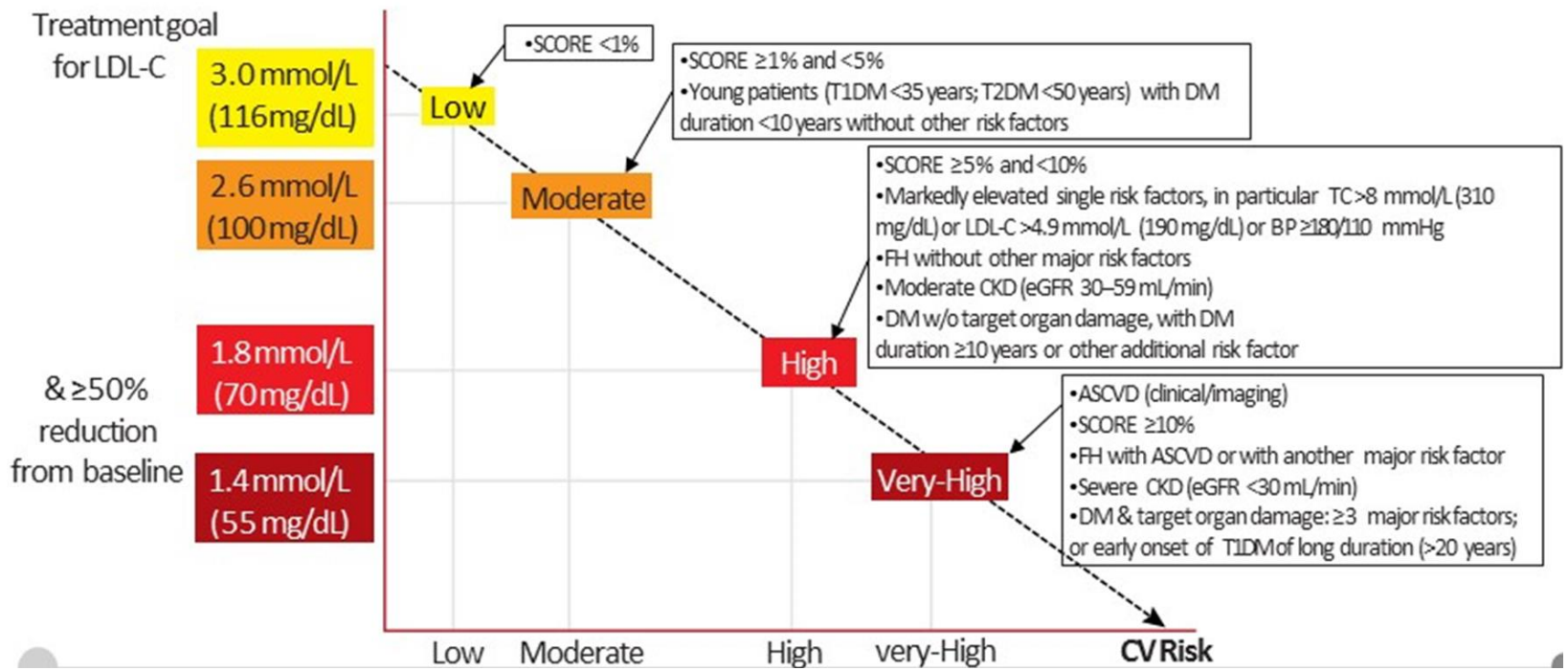
ESC
European Society of Cardiology

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

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 m^2). 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 m^2). 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.

© ESC 2019

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



European Heart Journal (2020) **41**, 111–188

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

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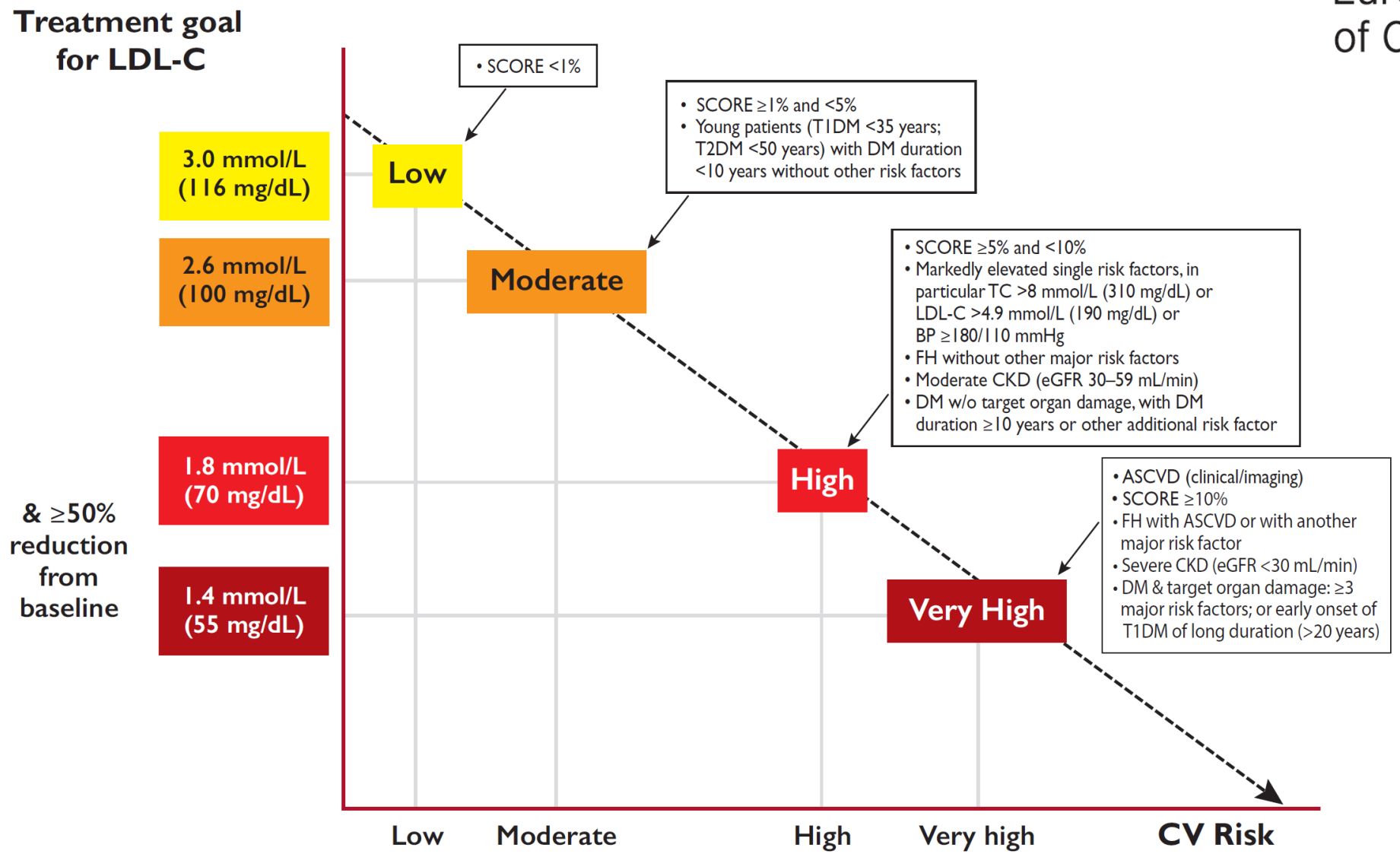

European Heart Journal (2020) **41**, 111–188

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

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LDL-C	**Very-high risk in primary or secondary prevention:** A therapeutic regimen that achieves ≥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 ≥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.

European Heart Journal (2020) **41**, 111–188

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

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	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	IIa/A	IIa/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	IIa/A	IIa/A	IIa/A	IIa/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]	IIa/A	IIa/A	IIa/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]	IIa/B	IIa/A	I/A	I/A	I/A	I/A

European Heart Journal (2020) **41**, 111–188

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

EAS ESC European Society of Cardiology

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

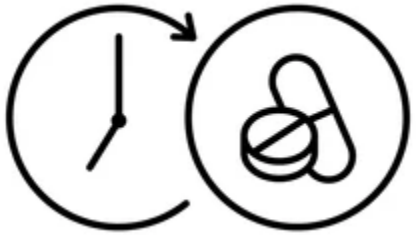
International Journal of Stroke
2021, Vol. 16(6) 738–750

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*

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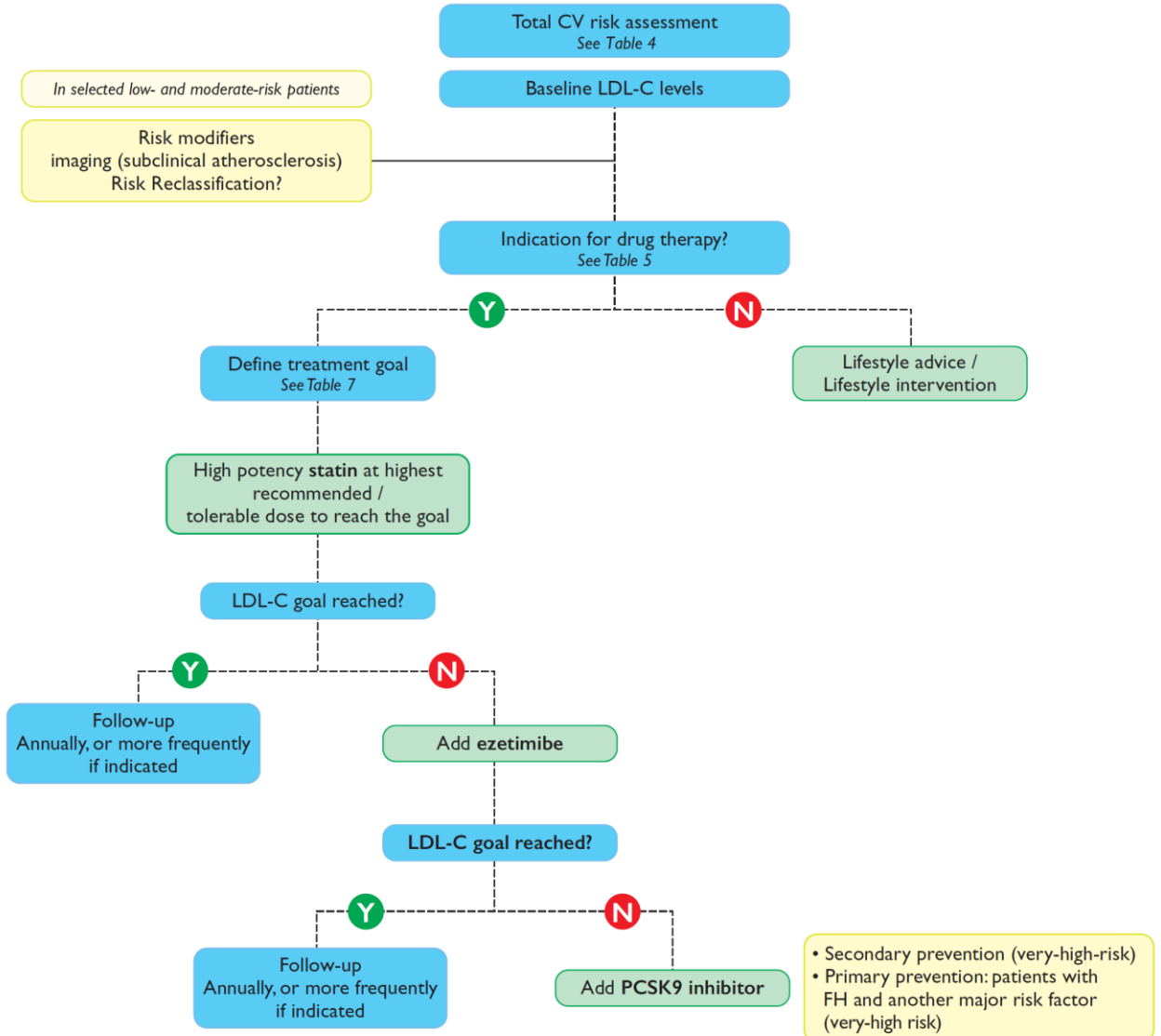


European Heart Journal (2020) **41**, 111–188

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.

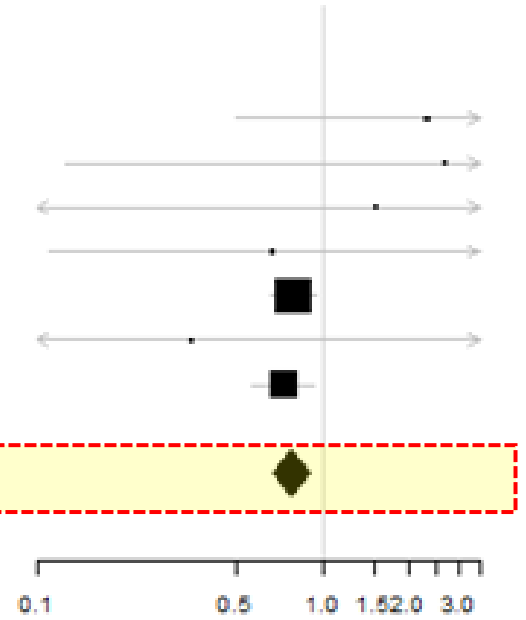
Table 3: **Average relative reductions in LDL cholesterol concentrations with different doses of commonly used statins**[160,163]

Lancet 2016; 388: 2532–61

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

Effect of monoclonal antibody therapy on **stroke**

	mAbs		placebo		
Study	**Events**	**N**	**Events**	**N**	**OR**
ODYSSEY LONG TERM	9	1550	2	788	2.30
ODYSSEY COMBO I	2	207	0	107	2.63
ODYSSEY FHI	1	322	0	163	1.53
GLAGOV	2	484	3	484	0.66
FOURIER	207	13784	262	13780	0.78
ODYSSEY-KT	0	97	1	102	0.34
ODYSSEY OUTCOMES	111	9462	152	9462	0.72
Summary	**332**	**25906**	**420**	**24886**	**0.77 (0.67, 0.89)**
Test for heterogeneity	**p-value=0.77**				



Pharmacological Research 143 (2019) 143–150

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

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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%

European Heart Journal (2020) **41**, 111–188

Monitor for statin-related adverse effects

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

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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

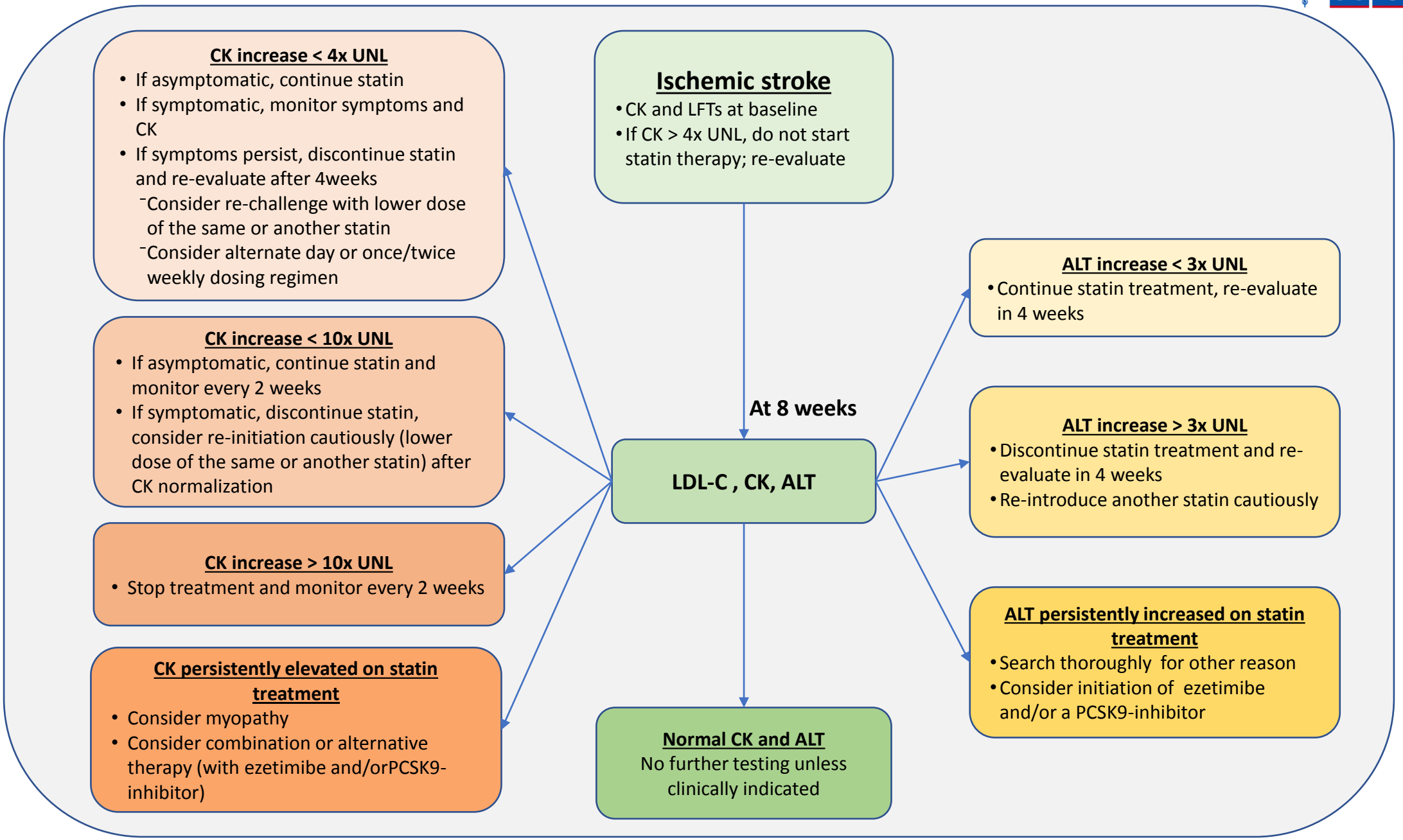
European Heart Journal (2020) **41**, 111–188

International Journal of Stroke
2021, Vol. 16(6) 738–750

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).



International Journal of Stroke
2021, Vol. 16(6) 738-750

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

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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

European Heart Journal (2020) **41**, 111–188

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

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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).

European Heart Journal (2020) **41**, 111–188

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*	

Circ Res. 2017;120:472-495

Primary and Secondary Prevention of Ischemic Stroke and Cerebral Hemorrhage

JACC Focus Seminar

ASYMPTOMATIC CAROTID STENOSIS

JACC VOL. 75, NO. 15, 2020
APRIL 21, 2020:1804–18

Management Strategies for Asymptomatic Carotid Stenosis

A Systematic Review and Meta-analysis

Figure 1. Forest plot of ipsilateral stroke (including any stroke within 30 days) in RCTs of CAS versus CEA.

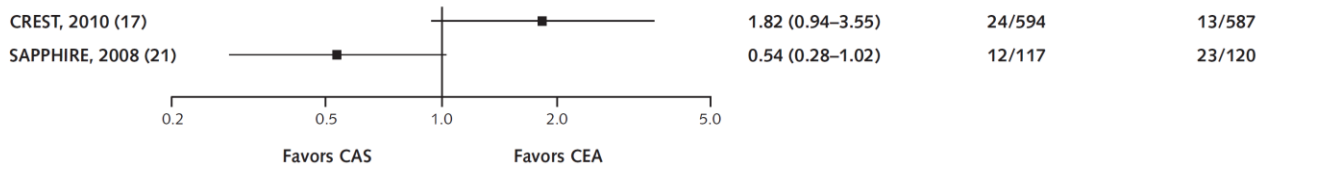
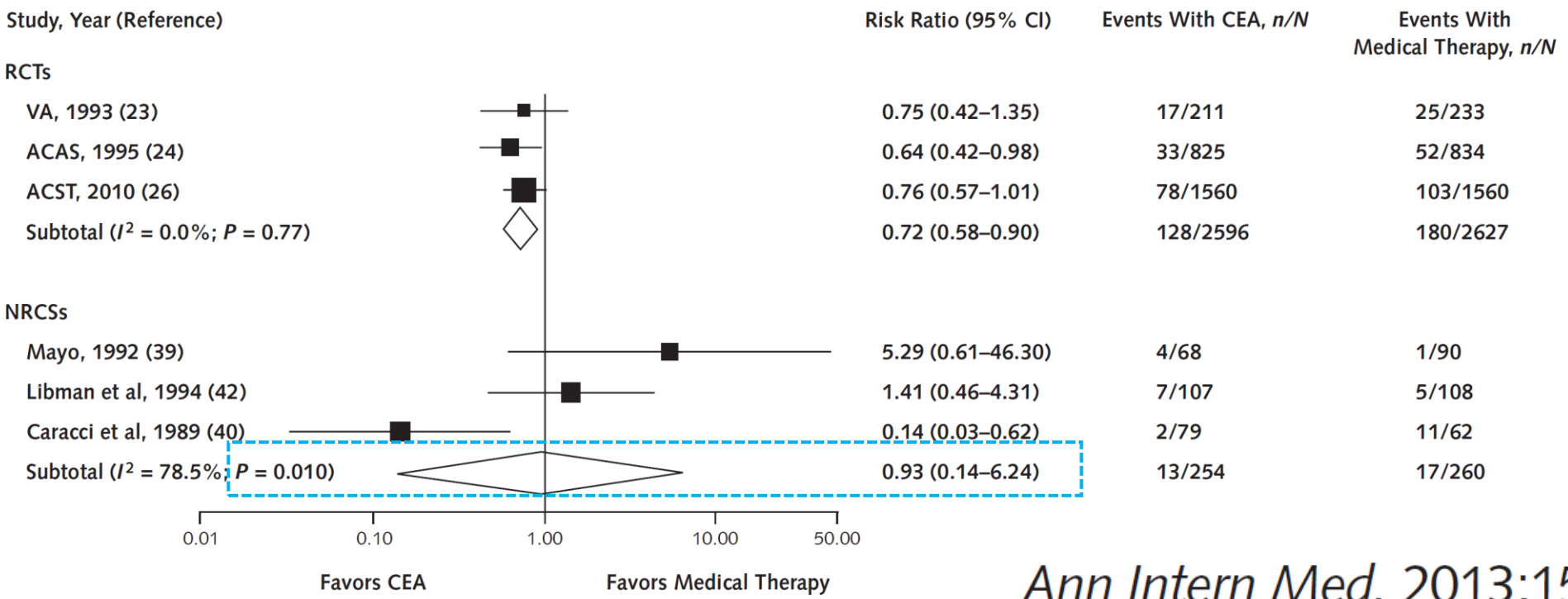


Figure 2. Meta-analysis of ipsilateral stroke (including any stroke within 30 days) in RCTs and NRCSs of CEA versus medical therapy.



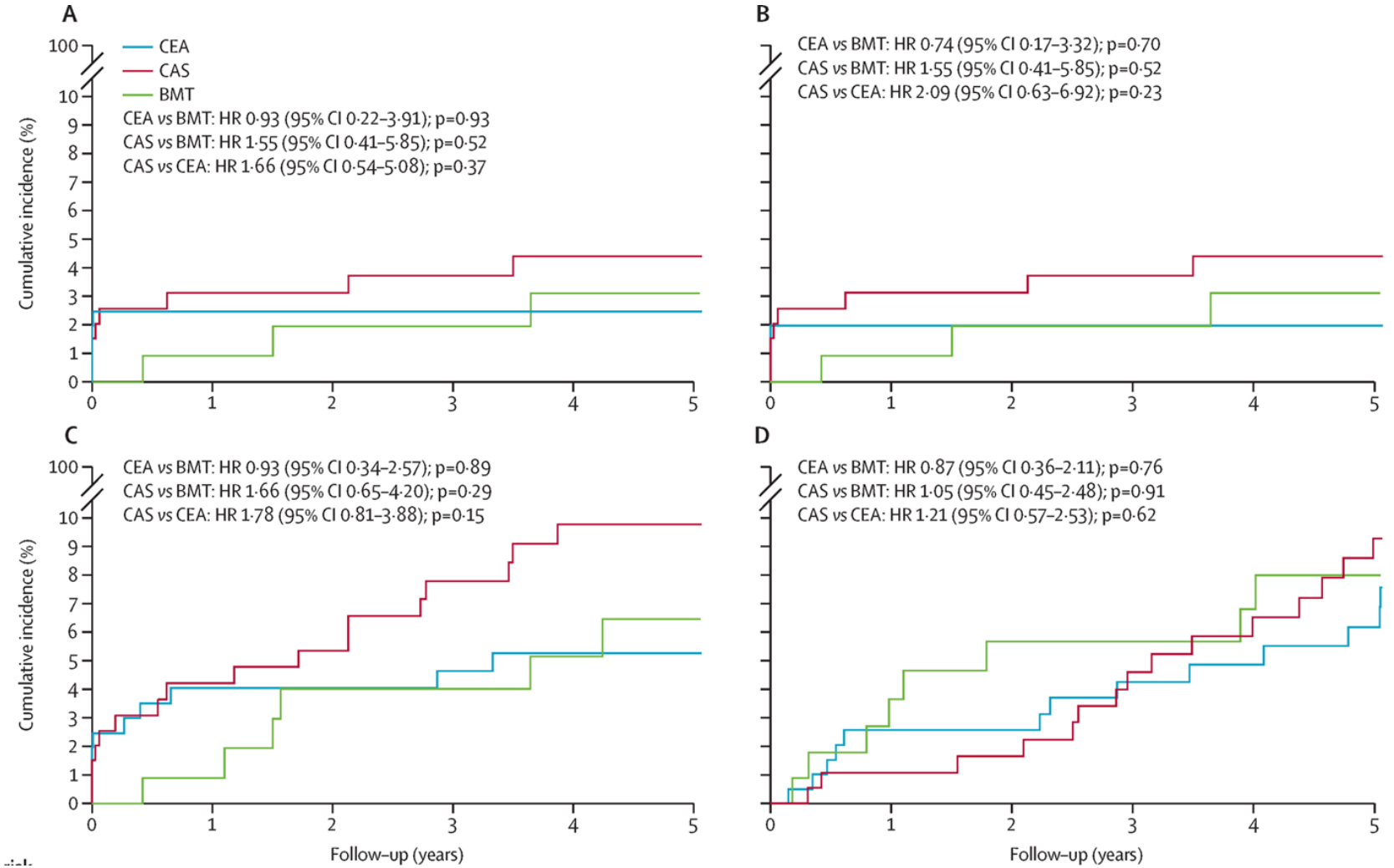
Ann Intern Med. 2013;158:676-685

Carotid endarterectomy or stenting or best medical treatment alone for moderate-to-severe asymptomatic carotid artery stenosis: 5-year results of a multicentre, randomised controlled trial

SPACE-2

Interpretation

CEA plus BMT or CAS plus BMT were ***not found*** to be superior to BMT alone regarding risk of any stroke or death within 30 days or ipsilateral stroke during the 5-year observation period. Because of the small sample size, results should be interpreted with caution.



Lancet Neurol 2022; 21: 877–88

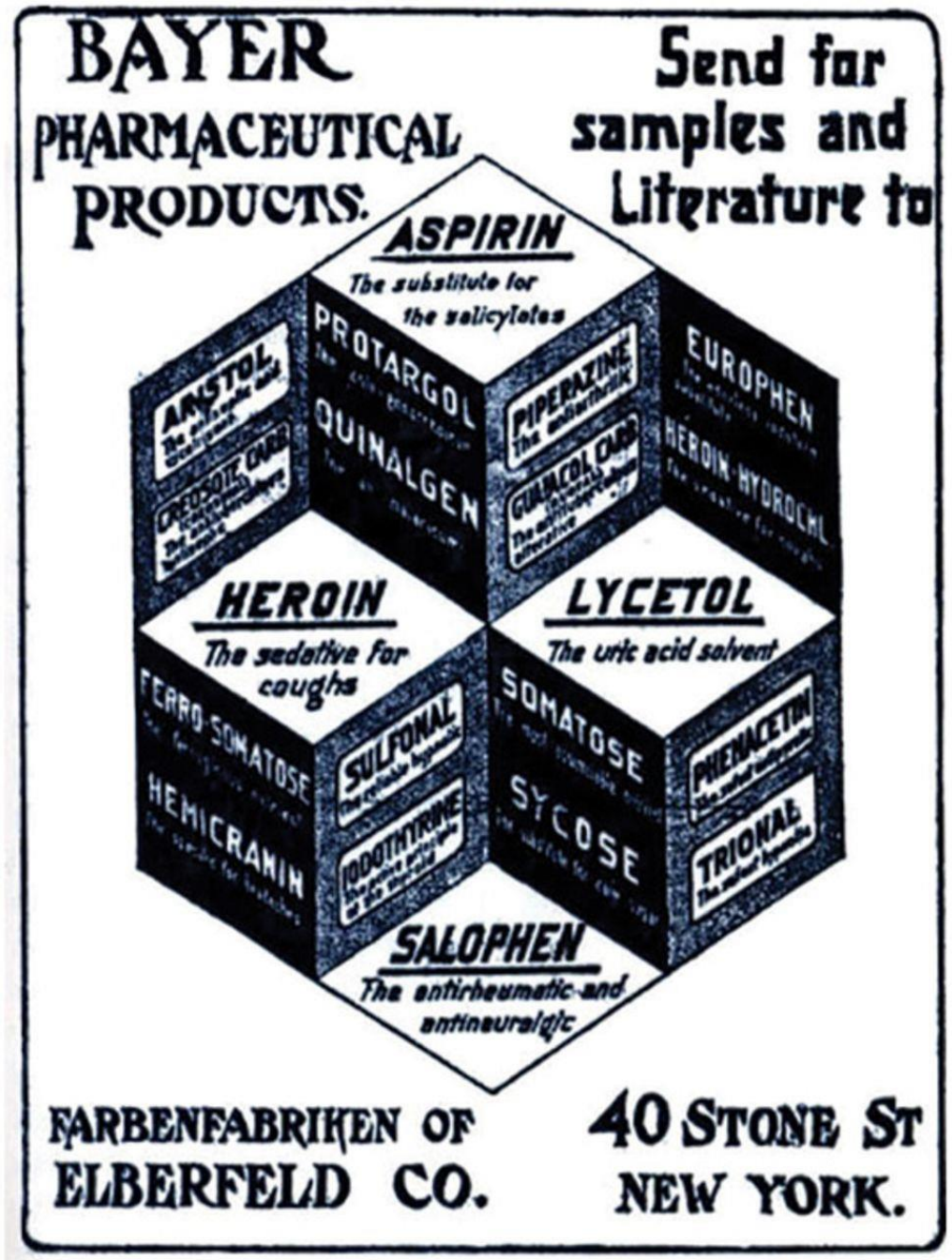
Primary and Secondary Prevention of Ischemic Stroke and Cerebral Hemorrhage

JACC Focus Seminar

ANTITHROMBOTIC THERAPY

JACC VOL. 75, NO. 15, 2020
APRIL 21, 2020:1804–18

Aspirin:
4,000 years and still learning



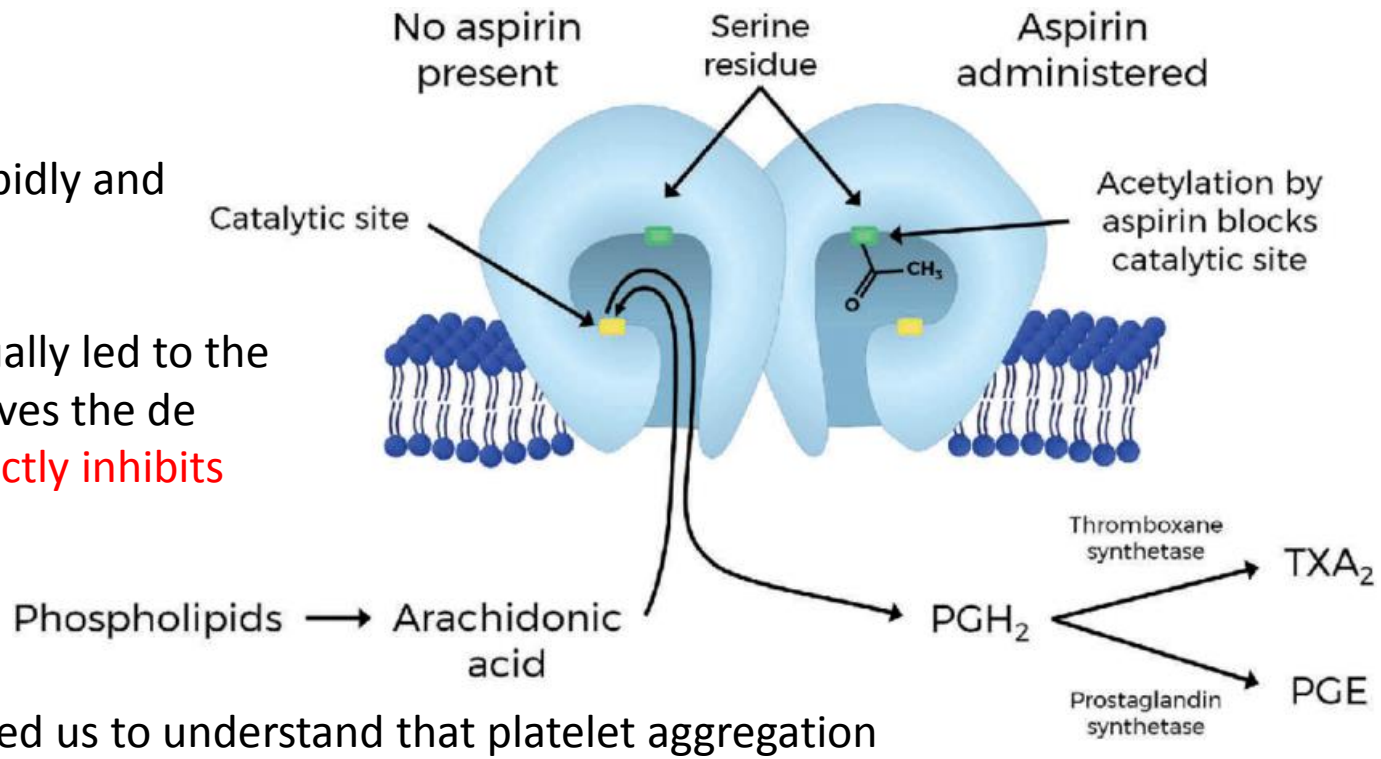
Aspirin: 4,000 years and still learning

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.

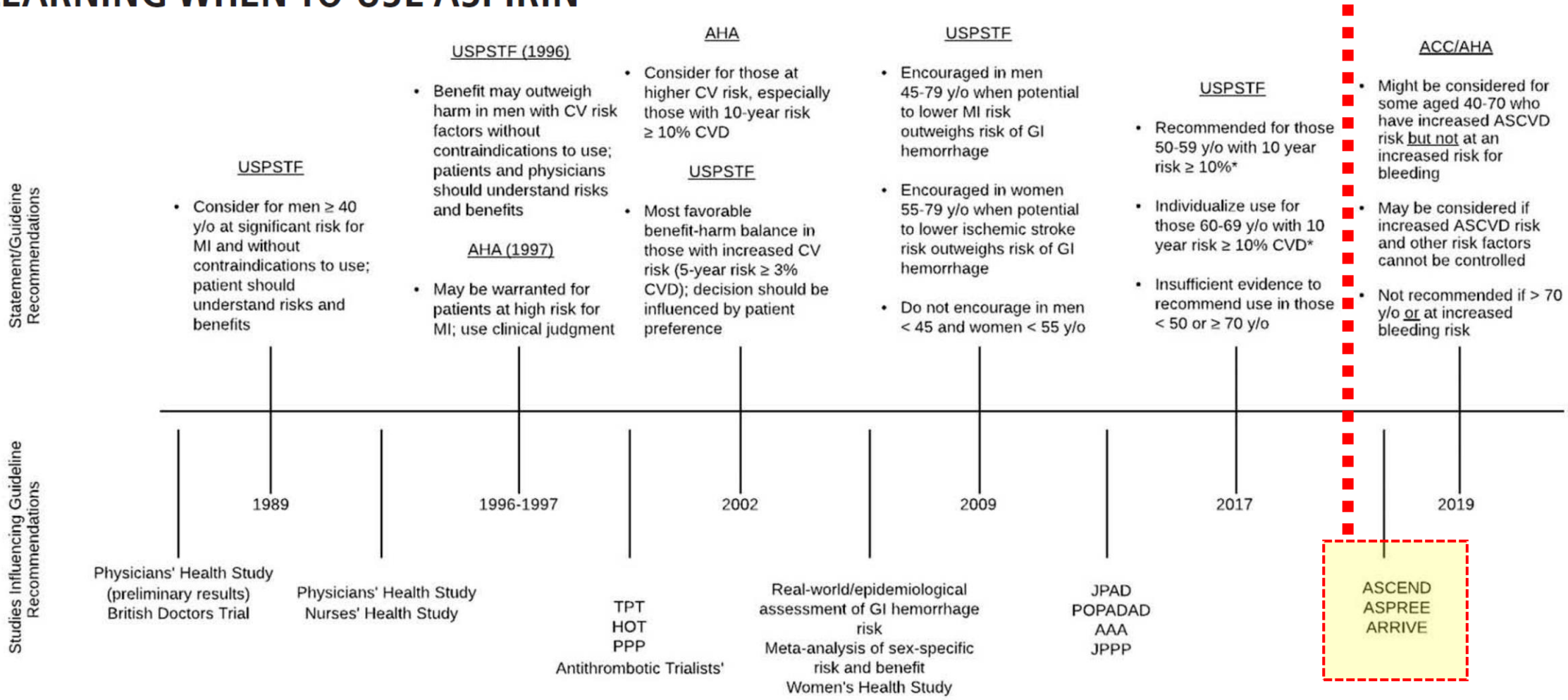


- Further work connecting these lines of investigation led us to understand that platelet aggregation is enhanced by the prostaglandin derivative thromboxane A2, produced by cy-clooxygenase-1, and that aspirin irreversibly inhibits this enzyme by acetylation.

Expert Rev Cardiovasc Ther. 2019 Aug;17(8):561-573

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

LEARNING WHEN TO USE ASPIRIN



Expert Rev Cardiovasc Ther. 2019 Aug;17(8):561-573

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	Hypertension	CV death, MI, stroke	Yes
TPT[35]	1998	5085	75 mg/d	NR	6.7 y	CV risk factors	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	Polycythemia vera	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	PAD	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

Circulation. 2016;134:1579–1594

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.

Circulation. 2016;134:1579–1594

Guidelines for the Primary Prevention of Stroke

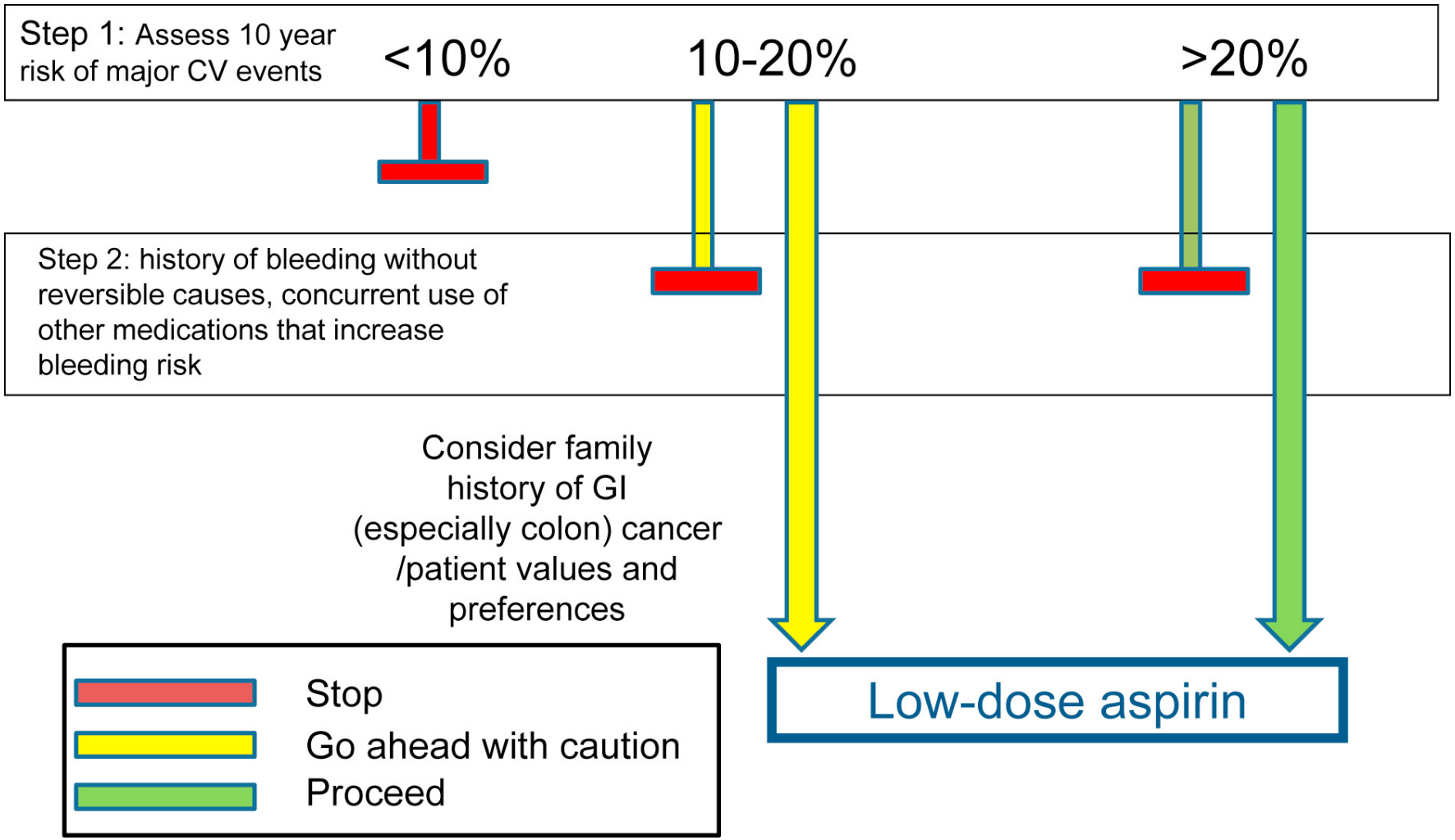
A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

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 (*Class I; Level of Evidence A*).	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 (*Class IIb; Level of Evidence B*).	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 (*Class IIa; Level of Evidence A*).	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}) (*Class IIb; Level of Evidence C*). This recommendation does not apply to severe 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 (*Class IIb; Level of Evidence B*).	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 (*Class III; Level of Evidence C*).	New recommendation

Aspirin Therapy in Primary Cardiovascular Disease Prevention

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

J Am Coll Cardiol 2014;64:319–27



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.

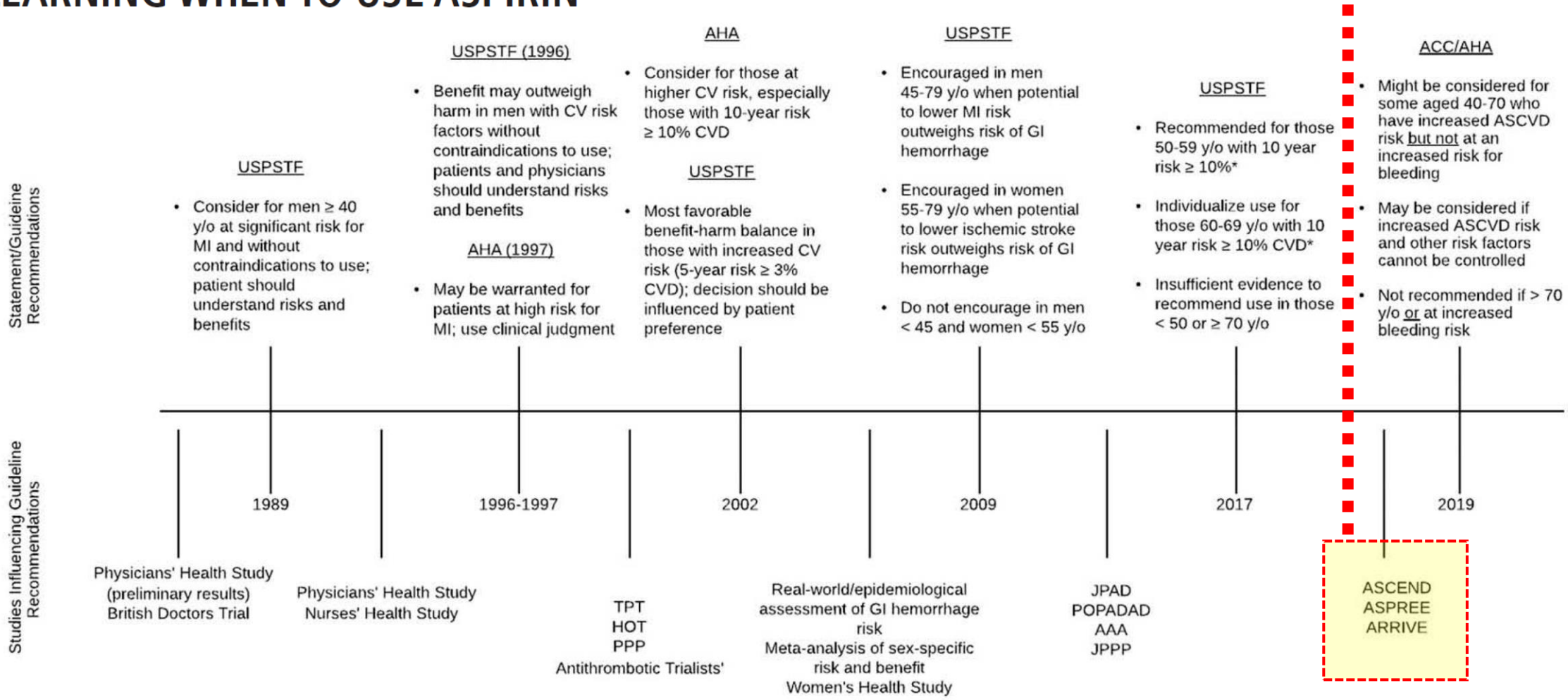
Age (years)	10-year CVD risk	Family history of CRC		No family history of CRC	
		HBR	no HBR	HBR	no HBR
<50	<5%	No ASA	No ASA	No ASA	No ASA
<50	5–10%	No ASA	Initiate ASA	No ASA	Clinical judgment
50–59	5–10%	No ASA	Initiate ASA	No ASA	Clinical judgment
50–59	10–20%	Clinical judgment	Initiate ASA	No ASA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

Circulation. 2016;134:1579–1594

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

LEARNING WHEN TO USE ASPIRIN

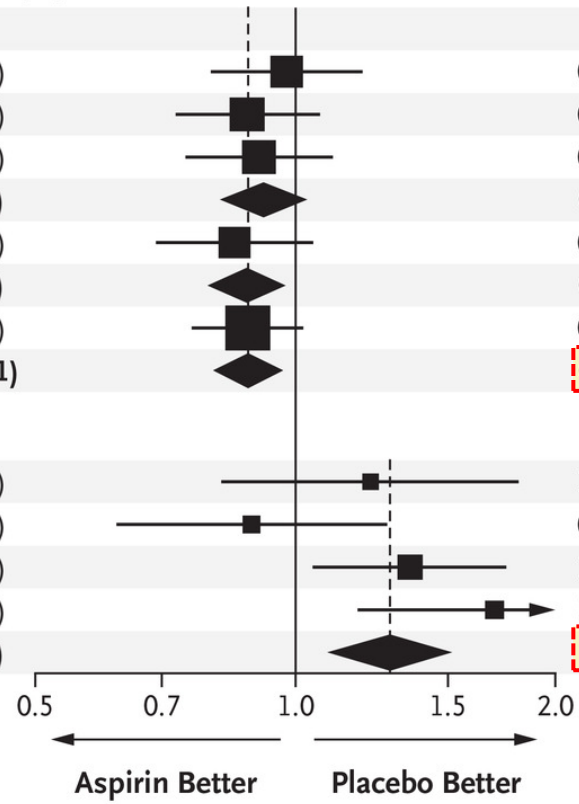


Expert Rev Cardiovasc Ther. 2019 Aug;17(8):561-573

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

ASCEND

Type of Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of participants with event (%)			
Vascular Outcomes				
Nonfatal myocardial infarction	191 (2.5)	195 (2.5)	0.98 (0.80–1.19)	
Nonfatal presumed ischemic stroke	202 (2.6)	229 (3.0)	0.88 (0.73–1.06)	
Vascular death excluding intracranial hemorrhage	197 (2.5)	217 (2.8)	0.91 (0.75–1.10)	
Any serious vascular event excluding TIA	**542 (7.0)**	**587 (7.6)**	**0.92 (0.82–1.03)**	
TIA	168 (2.2)	197 (2.5)	0.85 (0.69–1.04)	
Any serious vascular event including TIA	**658 (8.5)**	**743 (9.6)**	**0.88 (0.79–0.97)**	**0.01**
Any arterial revascularization	340 (4.4)	384 (5.0)	0.88 (0.76–1.02)	
Any serious vascular event or revascularization	**833 (10.8)**	**936 (12.1)**	**0.88 (0.80–0.97)**	
Major Bleeding				
Intracranial hemorrhage	55 (0.7)	45 (0.6)	1.22 (0.82–1.81)	
Sight-threatening bleeding in eye	57 (0.7)	64 (0.8)	0.89 (0.62–1.27)	
Serious gastrointestinal bleeding	137 (1.8)	101 (1.3)	1.36 (1.05–1.75)	
Other major bleeding	74 (1.0)	43 (0.6)	1.70 (1.18–2.44)	
Any major bleeding	**314 (4.1)**	**245 (3.2)**	**1.29 (1.09–1.52)**	**0.003**



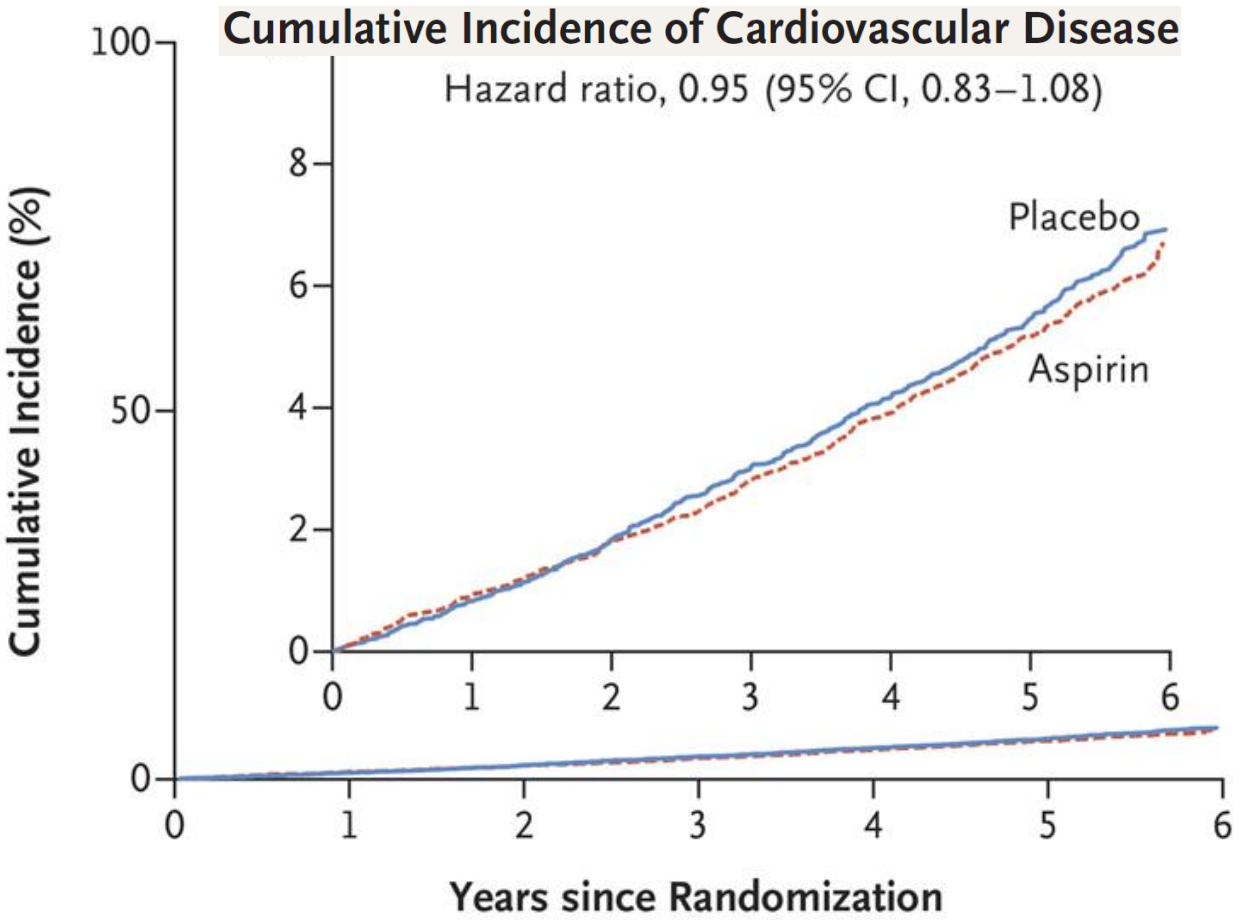
N Engl J Med 2018;379:1529-39

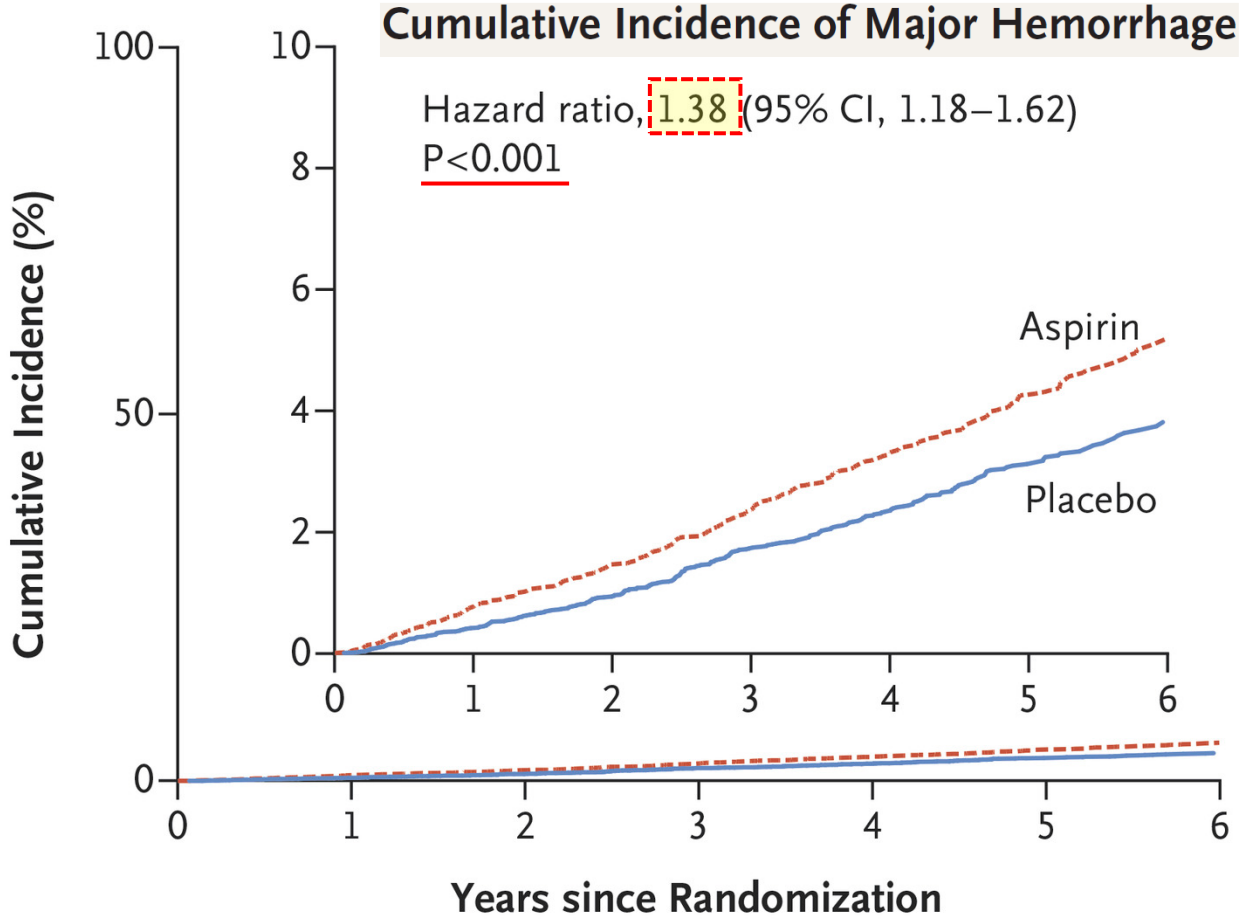
Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly

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.

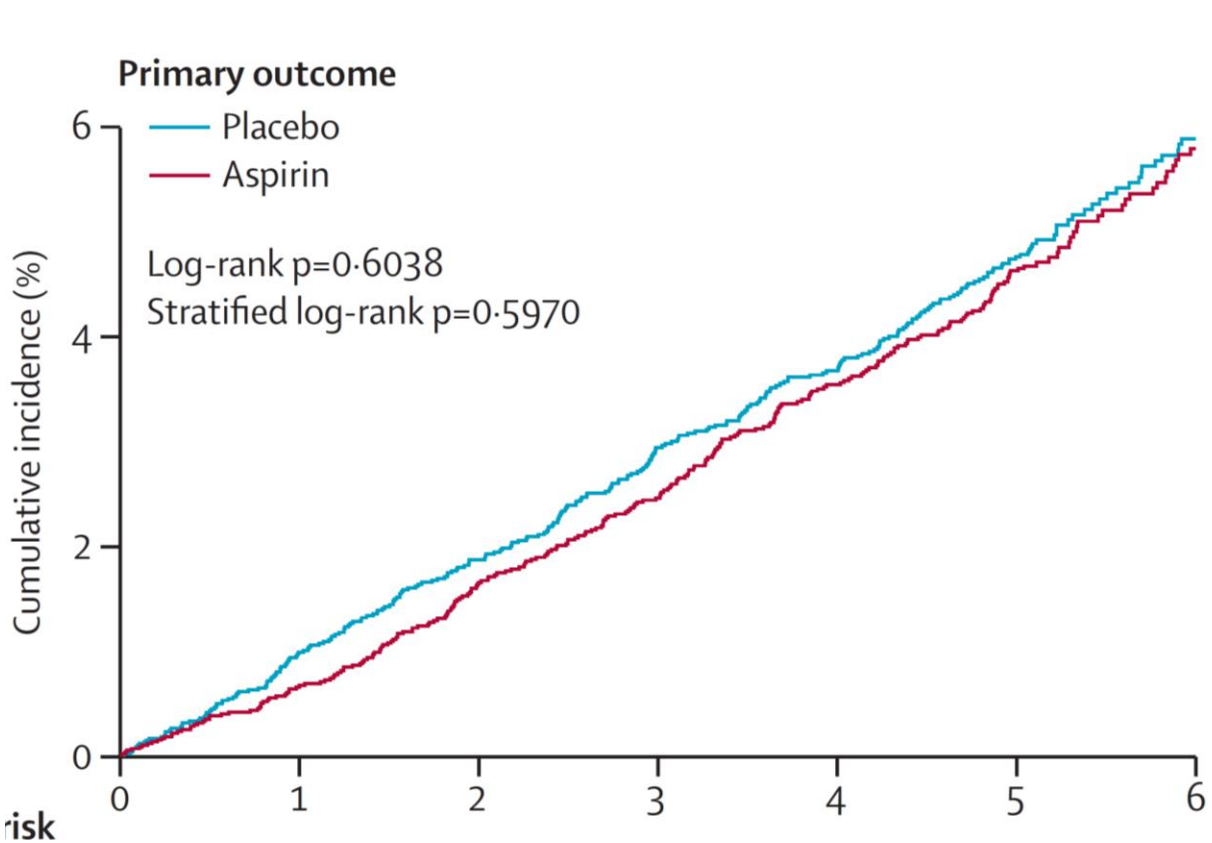


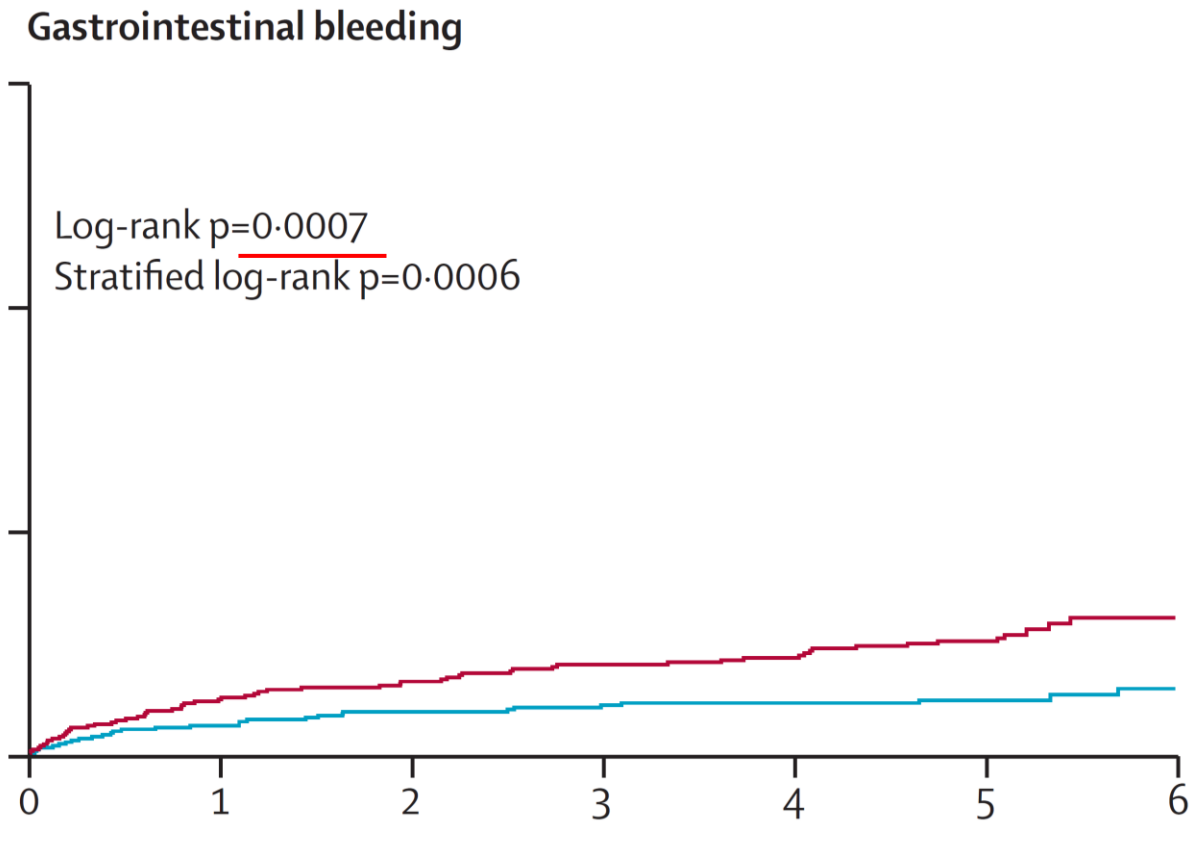


N Engl J Med 2018;379:1509-18

ARRIVE

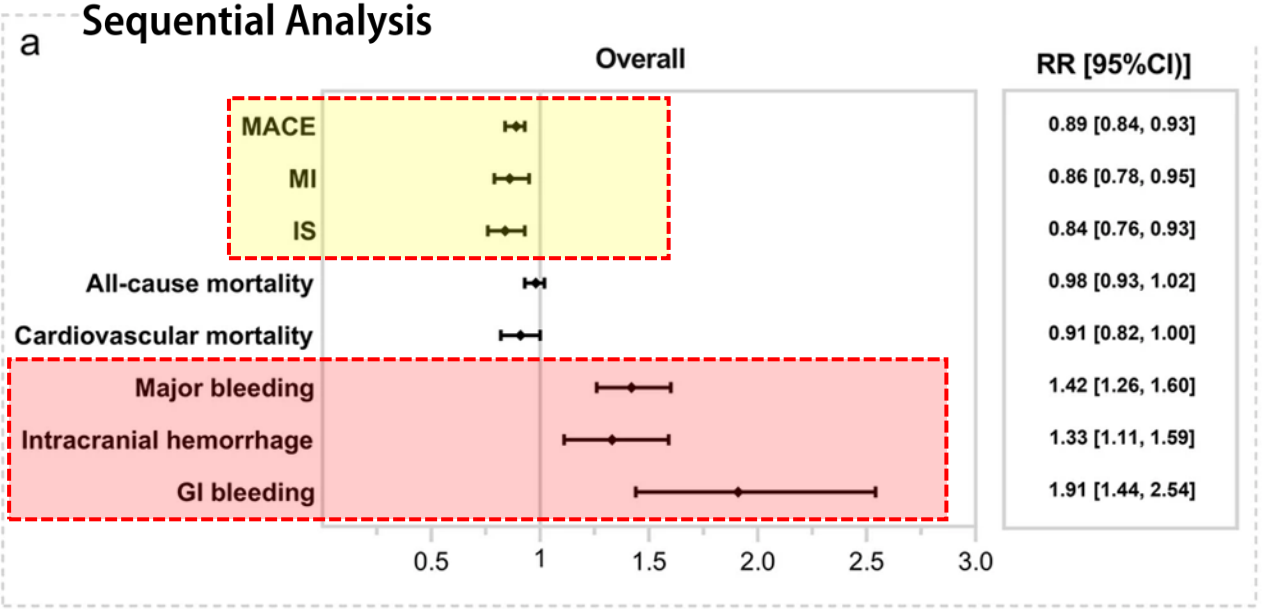
Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial

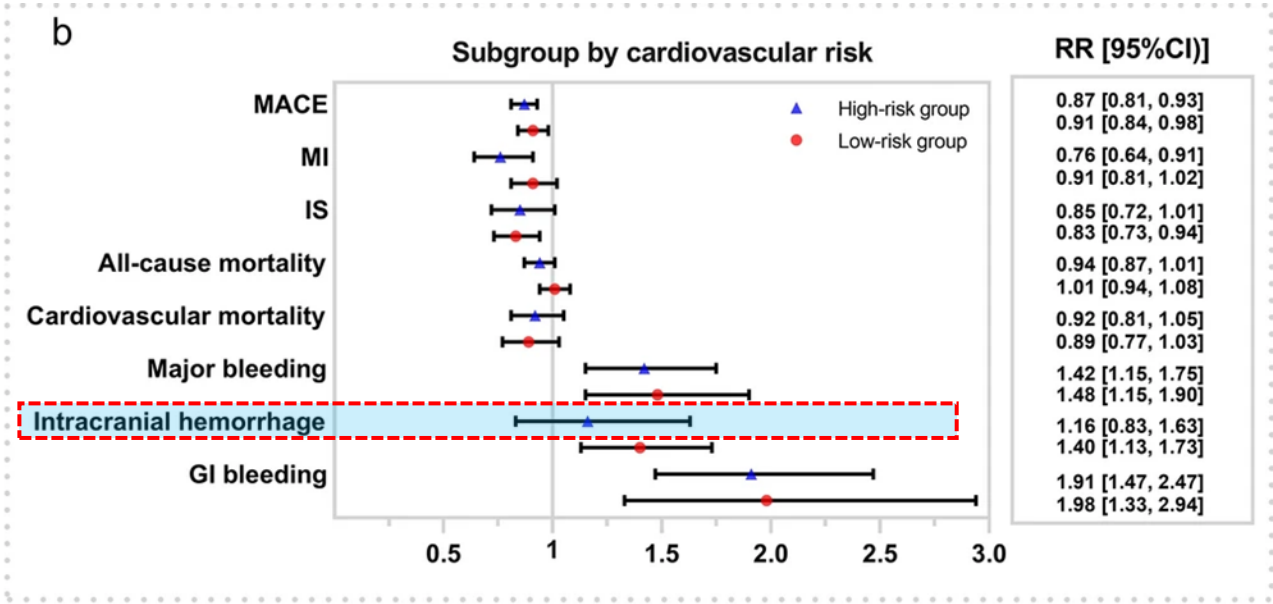


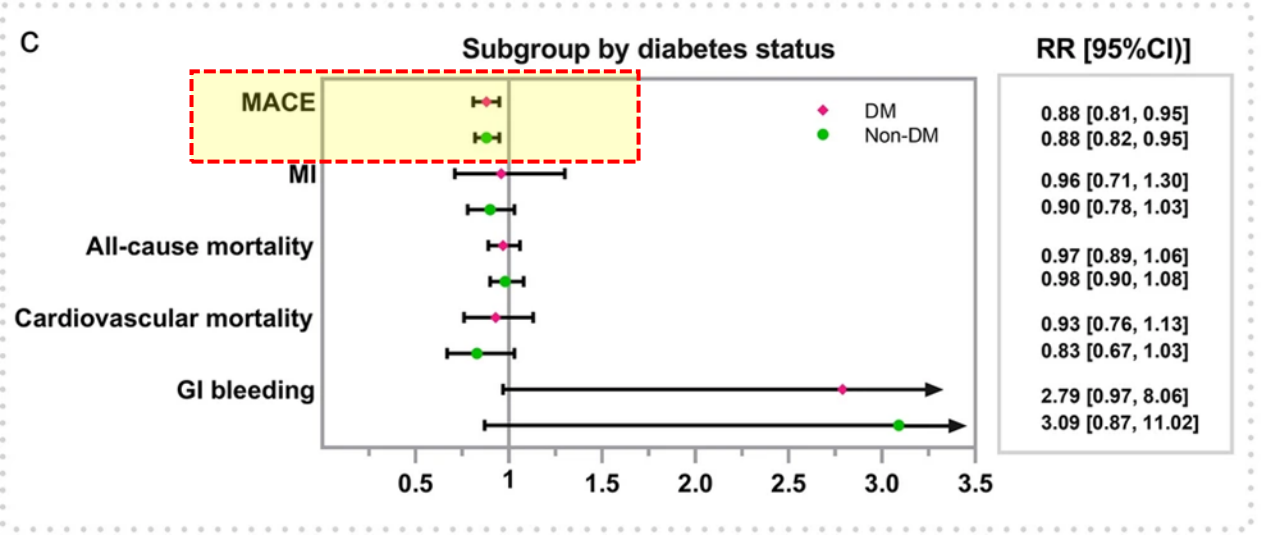


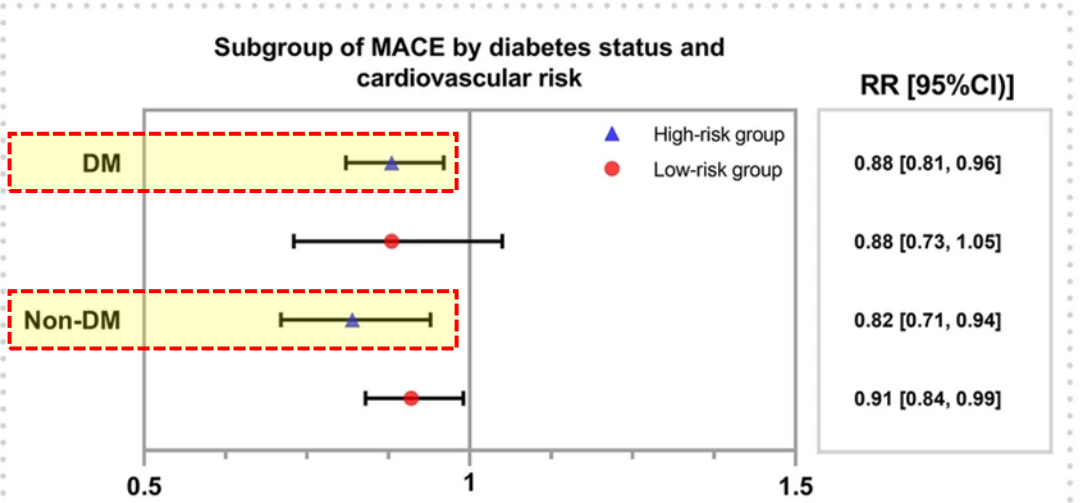
Lancet 2018; 392: 1036–46

Benefits and Risks Associated with Low-Dose Aspirin Use for the Primary Prevention of Cardiovascular Disease: A Systematic Review and Meta-Analysis of Randomized Control Trials and Trial Sequential Analysis

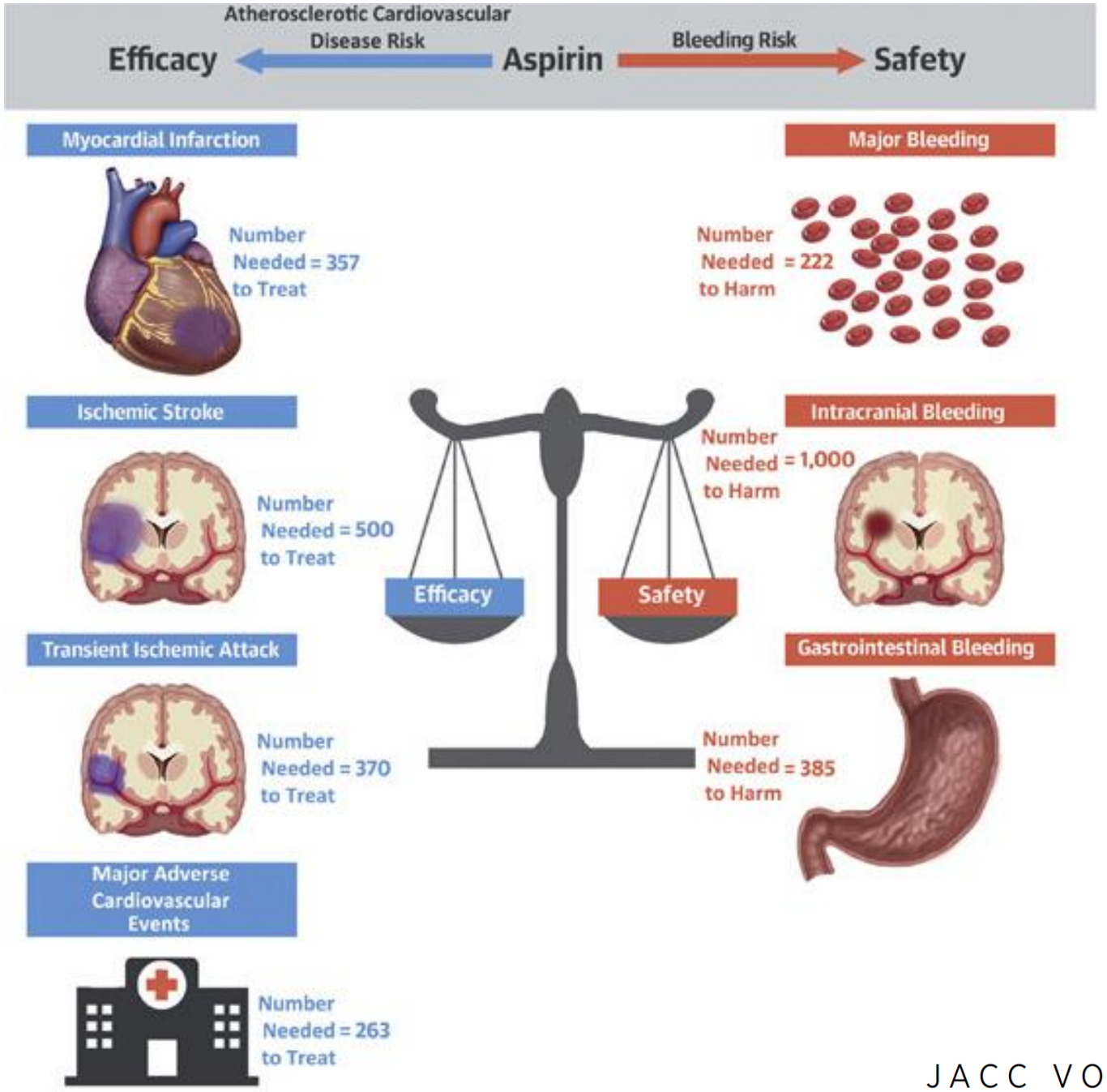








Aspirin for Primary Prevention of Cardiovascular Events



2021 ESC Guidelines on cardiovascular disease prevention in clinical practice

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

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

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.[S4.6-1–S4.6-8]
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.[S4.6-9]
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.[S4.6-10]

Circulation. 2019;140:e596–e646

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

ANTIPLATELET AGENTS

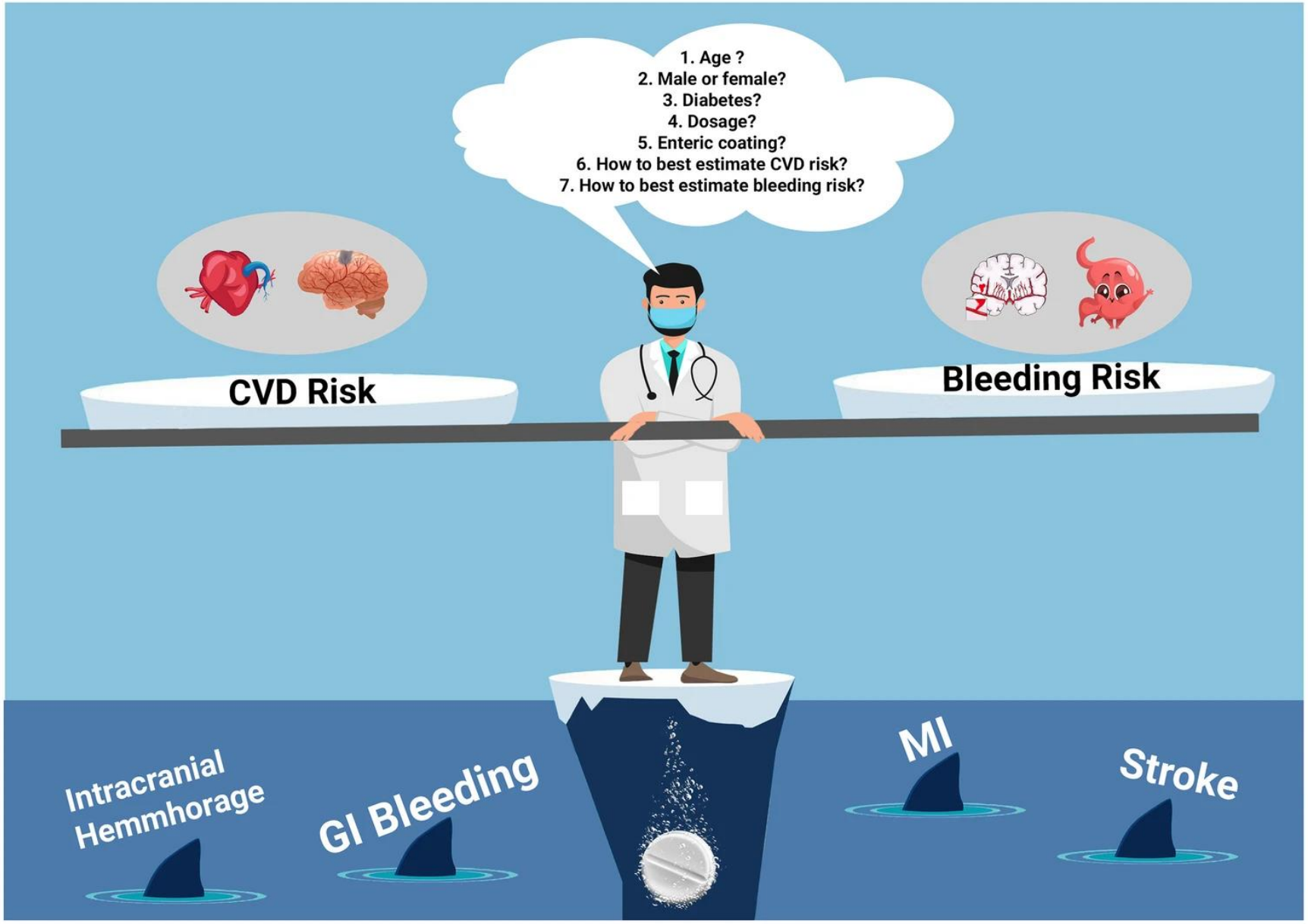
Recommendations

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 Dimitriadis[1] · Emilia Lazarou[1] · Panagiotis Tsioufis[1] · Stergios Soulaidopoulos[1] · Konstantinos Tsioufis[1]



Current Cardiology Reports (2022) 24:1139–1147

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

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Risk-Enhancing Factors
Family history of premature ASCVD (males, age <55 y; females, age <65 y)
Primary hypercholesterolemia (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L]; non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])*
Metabolic syndrome (increased waist circumference [by ethnically appropriate cutpoints], elevated triglycerides [>150 mg/dL, nonfasting], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 mg/dL in women] are factors; a tally of 3 makes the diagnosis)
Chronic kidney disease (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)
Chronic inflammatory conditions, such as psoriasis, RA, lupus, or HIV/AIDS
History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk, such as preeclampsia
High-risk race/ethnicity (eg, South Asian ancestry)
Lipids/biomarkers: associated with increased ASCVD risk
Persistently elevated* primary hypertriglyceridemia (≥175 mg/dL, nonfasting)
If measured:
Elevated high-sensitivity C-reactive protein (≥2.0 mg/L)
Elevated Lp(a): A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a).
Elevated apoB (≥130 mg/dL): A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor
ABI (<0.9)

Circulation. 2019;140:e596–e646

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

Circulation. 2023;147:e93–e621

Primary and Secondary Prevention of Ischemic Stroke and Cerebral Hemorrhage

JACC Focus Seminar

JACC VOL. 75, NO. 15, 2020
APRIL 21, 2020:1804–18

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 (6-13)	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

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Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
«ΚΑΡΔΙΟΜΕΤΑΒΟΛΙΚΗ ΙΑΤΡΙΚΗ»

Πρωτογενής Πρόληψη ΑΕΕ

Σας ευχαριστώ πολύ για την προσοχή σας!