Prevention of stroke in women

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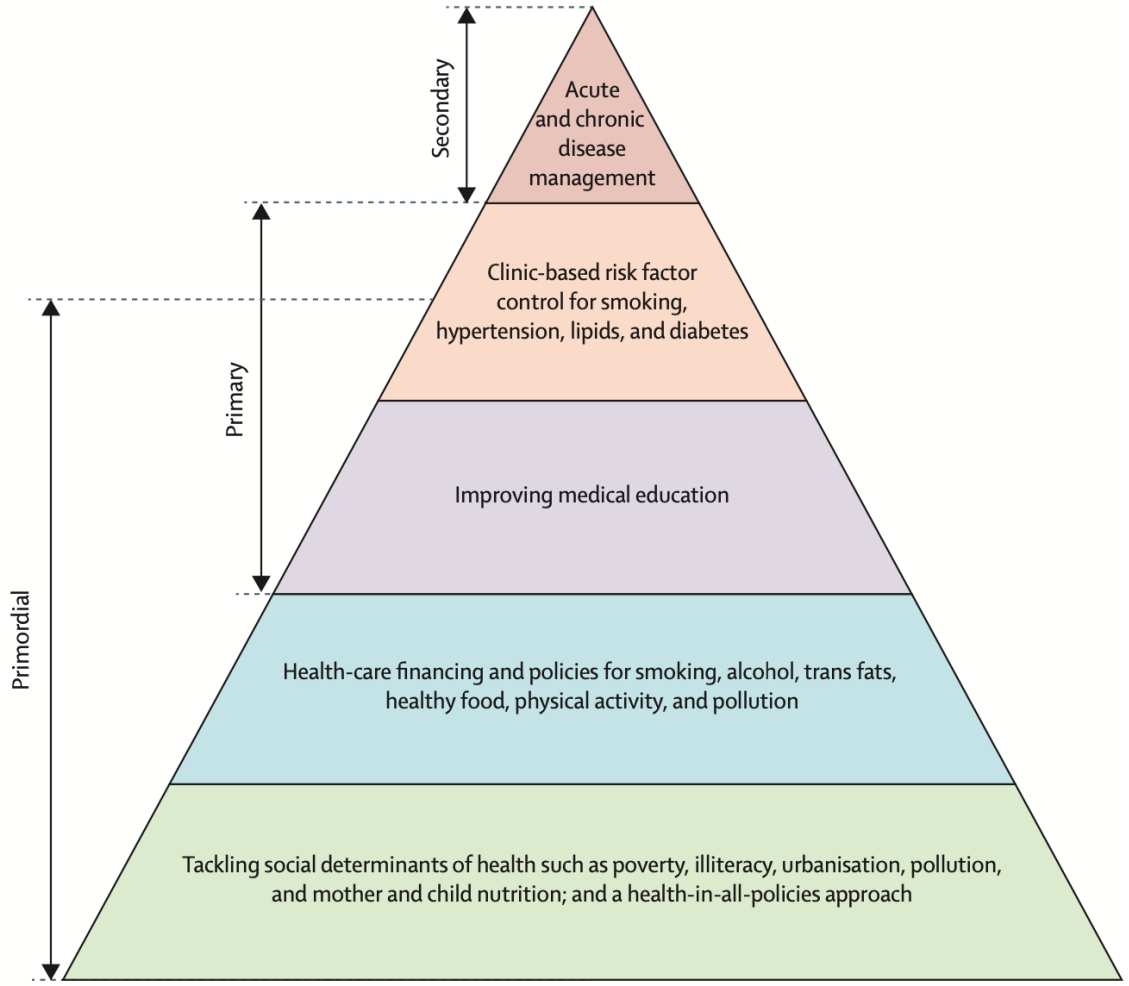
Stroke prevention in women

- Women have a 20% lifetime risk of stroke
- The majority of stroke-related deaths occur in women
- Reducing the burden of stroke in women through primary and secondary prevention should be a goal of public health

Prevention

- Individual level
- Populational level



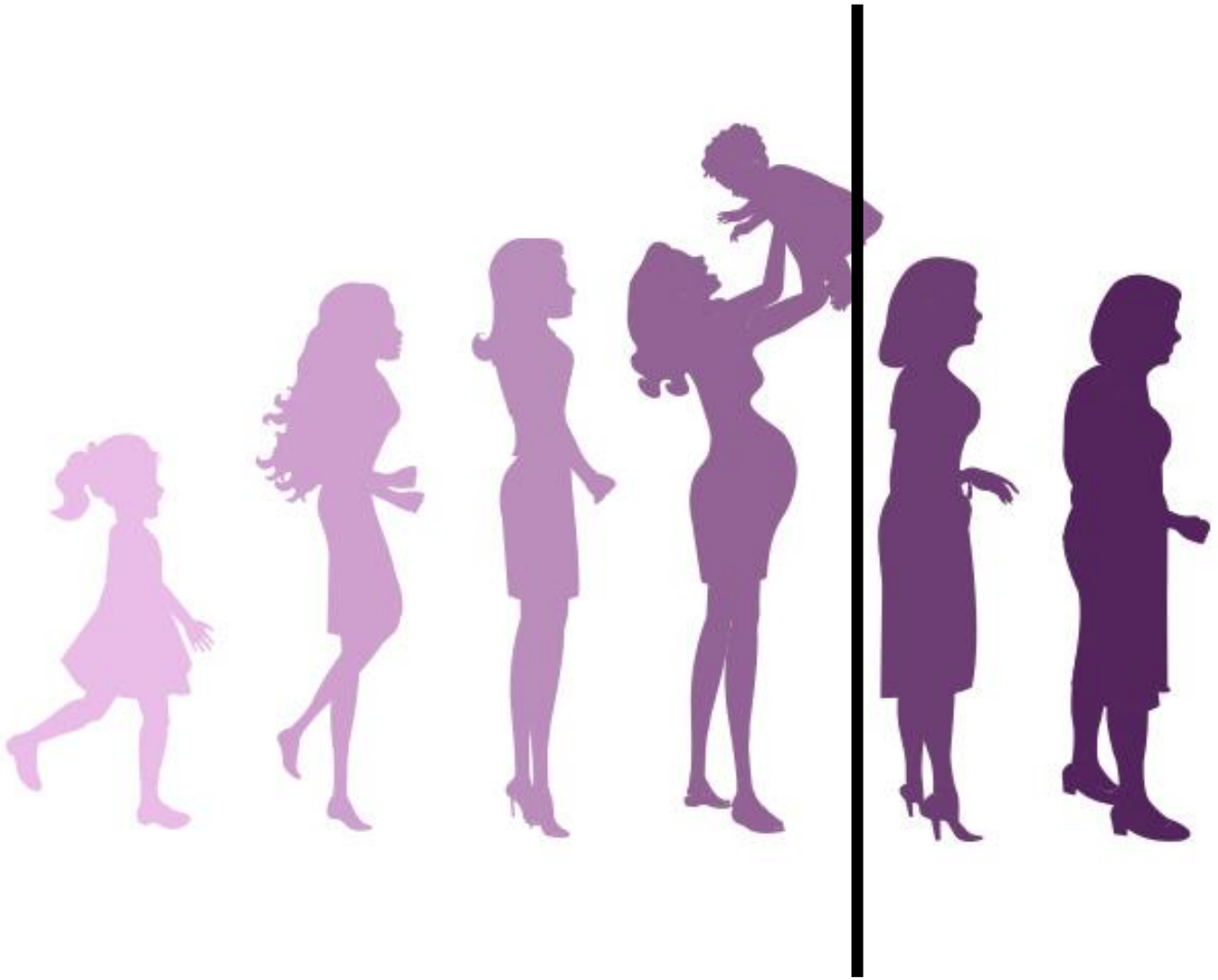
Gupta Ret al, Lancet

Individual level

Vascular risk factors control

Antithrombotic treatment

Stroke prevention in women



Stroke risk factors in women

Women-specific

- Pregnancy
- Preeclampsia
- Gestational diabetes
- Oral contraceptive use
- Postmenopaussal hormonal use

Stronger or more prevalent in women

- Migraine with aura
- Atrial fibrillation
- Diabetes mellitus
- Hypertension
- Psychosocial stress

Similar prevalence to men , unknown impact

- Physical inactivity
- Age
- Prior CV disease
- Diet
- Smoking
- Obesity
- Metabolic syndrome

Bushnell et al, Stroke 2014

Evidence based prevention ?

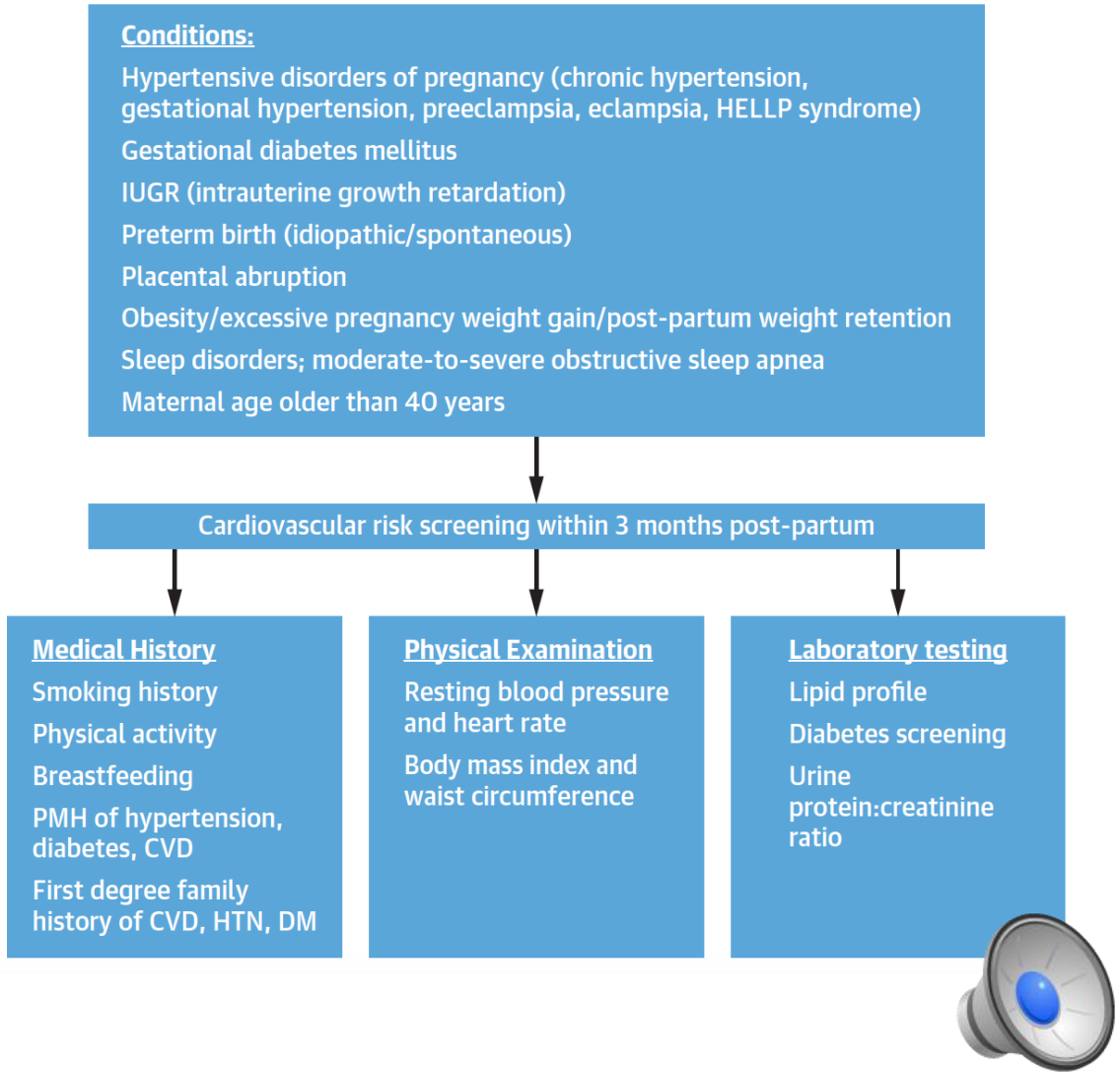
- Most data used to develop specific evidence based-guidelines for primary stroke prevention in women were derived from coronary heart disease studies

- Stroke was secondary outcome

- Women underrepresented in stroke prevention trial cohorts

Women-specific

Adverse pregnancy outcomes



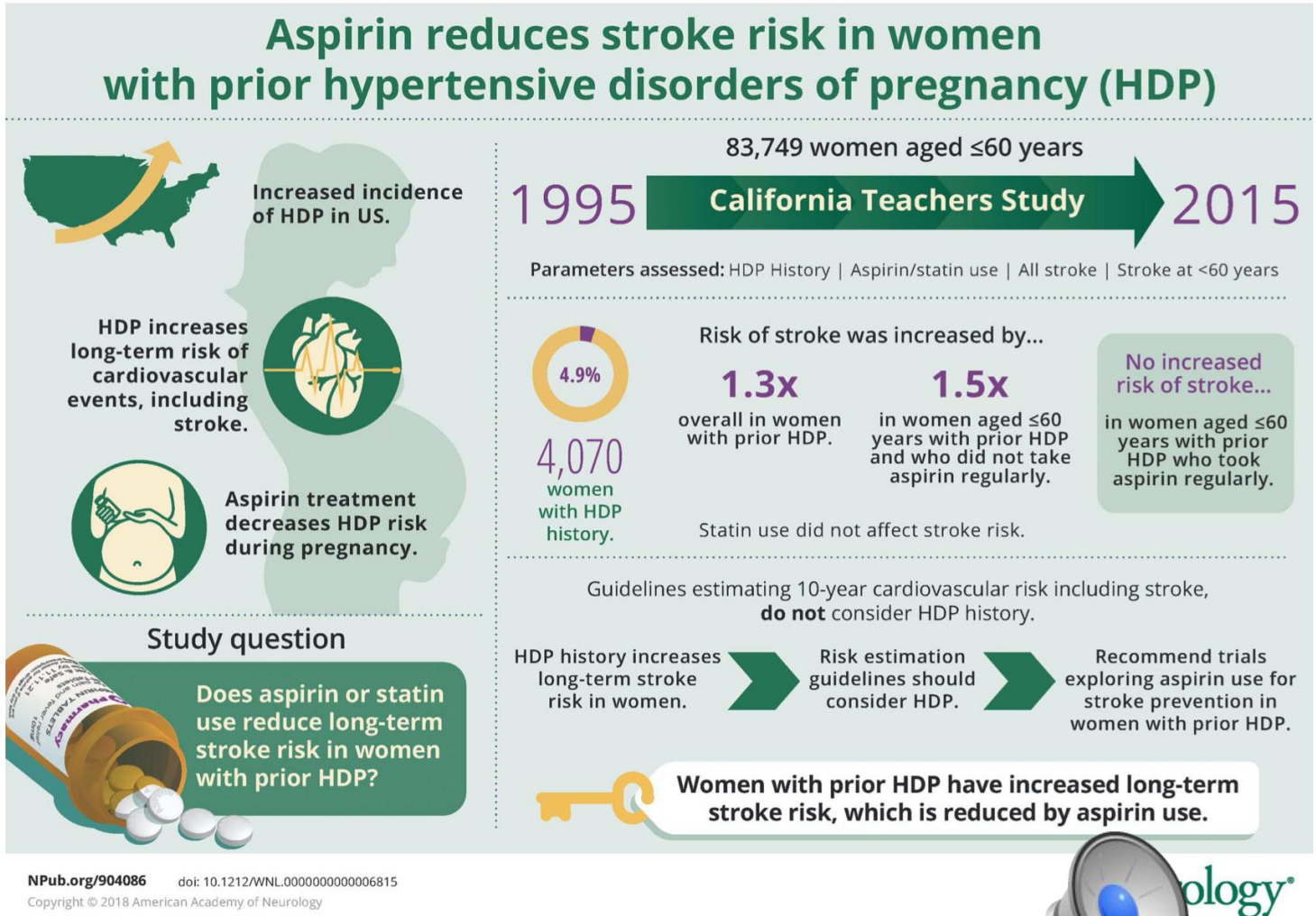
Cho et al, JACC 2020

Pre-eclampsia

- Doubles the risk of stroke in later life
- Consider evaluating all women starting 6 months to 1 year post partum, as well as those who are past childbearing age, for a history of preeclampsia/ eclampsia and document their history of preeclampsia/eclampsia as a risk factor
- Evaluate and treat for cardiovascular risk factors including hypertension, obesity, smoking, and dyslipidemia (Class IIa; Level of Evidence C).

Bushnell et al, Stro

Hypertensive disorders of pregnancy



Miller EC et al, Neurology 2019

Oral Contraceptives

- OCs may be harmful in women with additional risk factors (eg, cigarette smoking, prior thromboembolic events) (Class III; Level of Evidence
- Among OC users, aggressive therapy of stroke risk factors may be reasonable (Class IIb; Level of Evidence C).
- Routine screening for prothrombotic mutations before initiation of hormonal contraception is not useful (Class III; Level of Evidence A).
- Measurement of BP before initiation of hormonal contraception is recommended (Class I; Level of Evidence B)

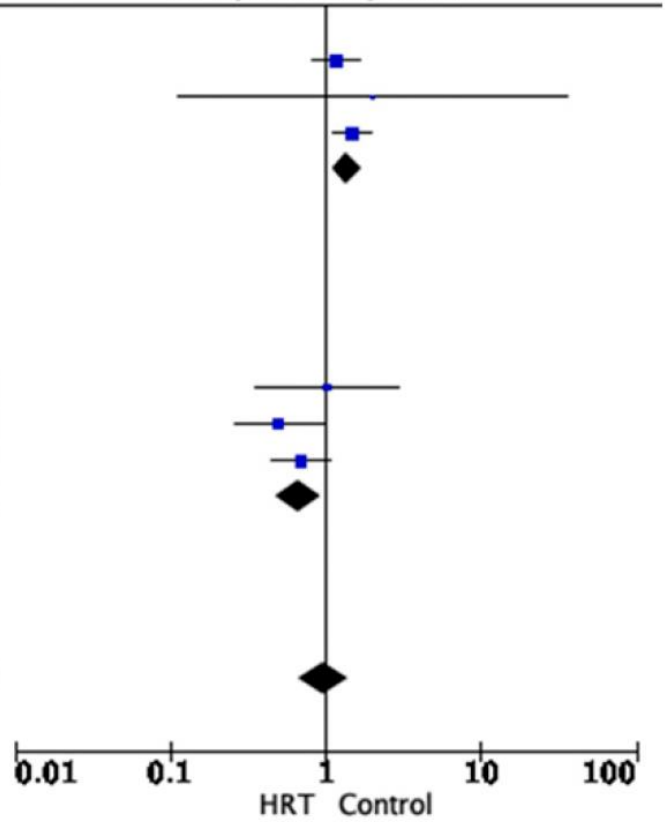
Bushnell et al, St[illegible]

Postmenopausal hormone use

- Menopause is associated with increased stroke risk.
- 10 years after menopause, stroke risk doubles
- Related to loss of endogenous estrogen at menopause.

Postmenopausal hormone use

Study or Subgroup	HRT Events	HRT Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.4.1 HRT						
HERS 2002	69	1380	59	1383	24.5%	1.18 [0.83, 1.69]
SMART 2015	6	8036	0	1241	1.7%	2.01 [0.11, 35.70]
WHI 2003	125	8506	81	8102	26.7%	1.48 [1.11, 1.96]
Subtotal (95% CI)		17922		10726	52.9%	1.36 [1.09, 1.69]
Total events	200		140			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.00$, $df = 2$ ($P = 0.61$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.73$ ($P = 0.006$)						
1.4.2 Receptor modulator						
Christiansen 2010 R-Modu	10	1849	5	942	8.9%	1.02 [0.35, 2.99]
de Villiers 2011 R-Modul	26	3758	13	943	15.9%	0.50 [0.26, 0.97]
PEARL 2010 R-Modul	50	5704	36	2852	22.3%	0.69 [0.45, 1.06]
Subtotal (95% CI)		11311		4737	47.1%	0.66 [0.47, 0.93]
Total events	86		54			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.35$, $df = 2$ ($P = 0.51$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.37$ ($P = 0.02$)						
Total (95% CI)		29233		15463	100.0%	0.97 [0.66, 1.41]
Total events	286		194			
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 14.41$, $df = 5$ ($P = 0.01$); $I^2 = 65\%$						
Test for overall effect: $Z = 0.18$ ($P = 0.86$)						
Test for subgroup differences: $Chi^2 = 12.03$, $df = 1$ ($P = 0.0005$), $I^2 = 91.7\%$						



Kremer C et al, EJS 2021

Postmenopausal HT:

- HT should not be used for primary prevention of stroke in postmenopausal women
  (Class III; Level of Evidence A).

- In postmenopausal women, we suggest against the use of HRT to reduce the risk of ischaemic stroke.
- Quality of evidence: Very low
- Strength of recommendation: Weak against intervention ↓

Bushnell et al, Stroke 2014; Kremer C

Stronger or more prevalent in women

Stronger or more prevalent in women

- Migraine with aura
- Hypertension
- Atrial fibrillation

Migraine With Aura

- Treatments to reduce migraine frequency might be reasonable, although evidence is lacking (Class IIb; Level of Evidence C).

- It is reasonable to strongly recommend smoking cessation in women with migraine headaches with aura (Class IIa; Level of Evidence B).

Bushnell et al, Stroke 2014

Hypertension

- Is the most common modifiable risk factor for stroke in both men and women
- Has the highest population-attributable
- Women may have a higher risk of first stroke with hypertension.

Hypertension

- Post-menopausal women are more likely to experience a nondipping nightime BP pattern.

- Women might derive more benefit from BP control using ambulatory BP measurements as opposed to conventional BP monitoring

Cho et al, JACC 2020

Hypertension

- Meta-analysis of 31 large, randomized BP trials, treatment of hypertension in women aged >55 years was associated with a 38% risk reduction in fatal and nonfatal cerebrovascular events (95% CI, 27%–47%).
- Women benefit significantly from these interventions as men
- The type of medication used to lower the BP may be less relevant than the achievement of target BP goals

Hypertension

- Currently, no evidence that there are differences in the response to BP medications between the sexes;

- However, in large-scale reviews that examined the efficacy of antihypertensives there is no mention that sex-specific efficacy end points were evaluated

Adherence to antihypertensives

- Side-effects tend to more frequent in women than men.

  - Diuretic-induced disturbances of electrolyte concentration

  - Angiotensin-converting enzyme inhibitor–induced cough

  - Calcium channel blocker related dependent edema

Antihypertensive drugs in pregnancy

Table 4. Summary of Antihypertensive Drugs Used During Pregnancy

Category	Maternal Side Effects	Teratogenicity or Fetal-Neonatal Adverse Effects	Class/Level of Evidence (see Table 2)
Centrally acting α2-adrenergic agonist (eg, methyldopa)	Sedation, elevated LFTs, depression	No	IIa/C
Diuretics (thiazide)	Hypokalemia	No	III/B
β-Blockers (atenolol)	Headache	Associated with fetal growth restriction	III/B
β-Blockers (pindolol, metoprolol)	Headache	Possible fetal growth restriction, neonatal bradycardia	IIa/B
Calcium channel blockers (eg, nifedipine)	Headache; possible interaction with magnesium sulfate; may interfere with labor	No	I/A
Combined α-β blockers (labetalol)	May provoke asthma exacerbation	Possible neonatal bradycardia	IIa/B
Hydralazine	Reflex tachycardia, delayed hypotension	Neonatal thrombocytopenia, fetal bradycardia	III/B
ACE inhibitors, angiotensin receptor blockers, renin inhibitors		Skeletal and cardiovascular abnormalities, renal dysgenesis, pulmonary hypoplasia	III/C

ACE indicates angiotensin-converting enzyme; and LFTs, liver function tests.
Modified from Umans et al[120a] with permission from Elsevier, Copyright © 2009.

Bushnell et al, Stroke 2014

Secondary prevention

Evidence-based recommendation
In people with previous ischaemic stroke or TIA, we suggest aiming for a blood pressure target of <130/80 mmHg to reduce the risk of recurrent stroke.

Quality of evidence: **Moderate** ⊕⊕⊕
Strength of recommendation: **Weak for intervention** ↑?

Dawson J et al,

Diabetes

	ADA (79,80)	ACC/AHA (3,4,6)	ESC (81)
HgA1c	Goal <7.0%	<7.0%	<7.0% <6.5% if achievable without hypoglycemia Less stringent in elderly patients
HTN	Goal of <140/90 mm Hg Goal of <130/80 mm Hg if high risk of CVD	BP goal of <130/80 mm Hg Initiate treatment if BP >130/80 mm Hg (specific DM recommendations)	SBP target 130 mm Hg <130 mm Hg if tolerated but not <120 mm Hg In older patients (age >65 yrs) SBP goal 130–139 mm Hg DBP goal <80 mm Hg but not <70 mm Hg
LDL	<40 yrs no ASCVD risk factor—no statin <40 yrs ASCVD risk factors—high-intensity statin ≥40 yrs no ASCVD risk factor—moderate-intensity statin ≥40 yrs ASCVD risk factor—high-intensity statin	>40 yrs of age, moderate-intensity statin regardless of 10-yr ASCVD risk DM patients with multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more Age 20 to 39 yrs of age with DM that is either of long duration (≥10 yrs of type 2 diabetes mellitus, ≥20 yrs of type 1 diabetes mellitus), albuminuria (≥30 μg of albumin/mg creatinine), estimated glomerular filtration rate <60 ml/min/1.73 m^2, retinopathy, neuropathy, or ankle-brachial index (<0.9), it may be reasonable to initiate statin therapy	Very high-risk LDL <55 mg/dl or LDL 50% reduction High risk <70 mg/dl or LDL 50% reduction Moderate risk <100 mg/dl
Aspirin	DM who are at increased risk of CVD	No specific DM recommendations	Only in very high risk/high risk

Cho et al, JACC 2020

Secondary prevention

Evidence-based recommendation

–

Quality of evidence: –
Strength of recommendation: –

Expert consensus statement

In people with ischaemic stroke or TIA and diabetes mellitus, we support aiming for an HbA1c level of <53 mmol/mol (7%, 154 mg/dl) to reduce risk of microvascular and macrovascular complications. However, this target may need to be individualised based on duration of diabetes, age and comorbidities.

In adult people with ischaemic stroke or TIA there is continued uncertainty over the role of intensive control of glycated haemoglobin level (HbA1c) compared to less intensive HbA1c control.

Dawson J et al,

Diabetes

- Glucagon-like peptide-1 receptor agonists have better glycemic control among men than women; however, women had more weight loss
- Thiazolidinediones appear to have better glycemic reduction in obese women, whereas nonobese men responded better with sulfonylureas

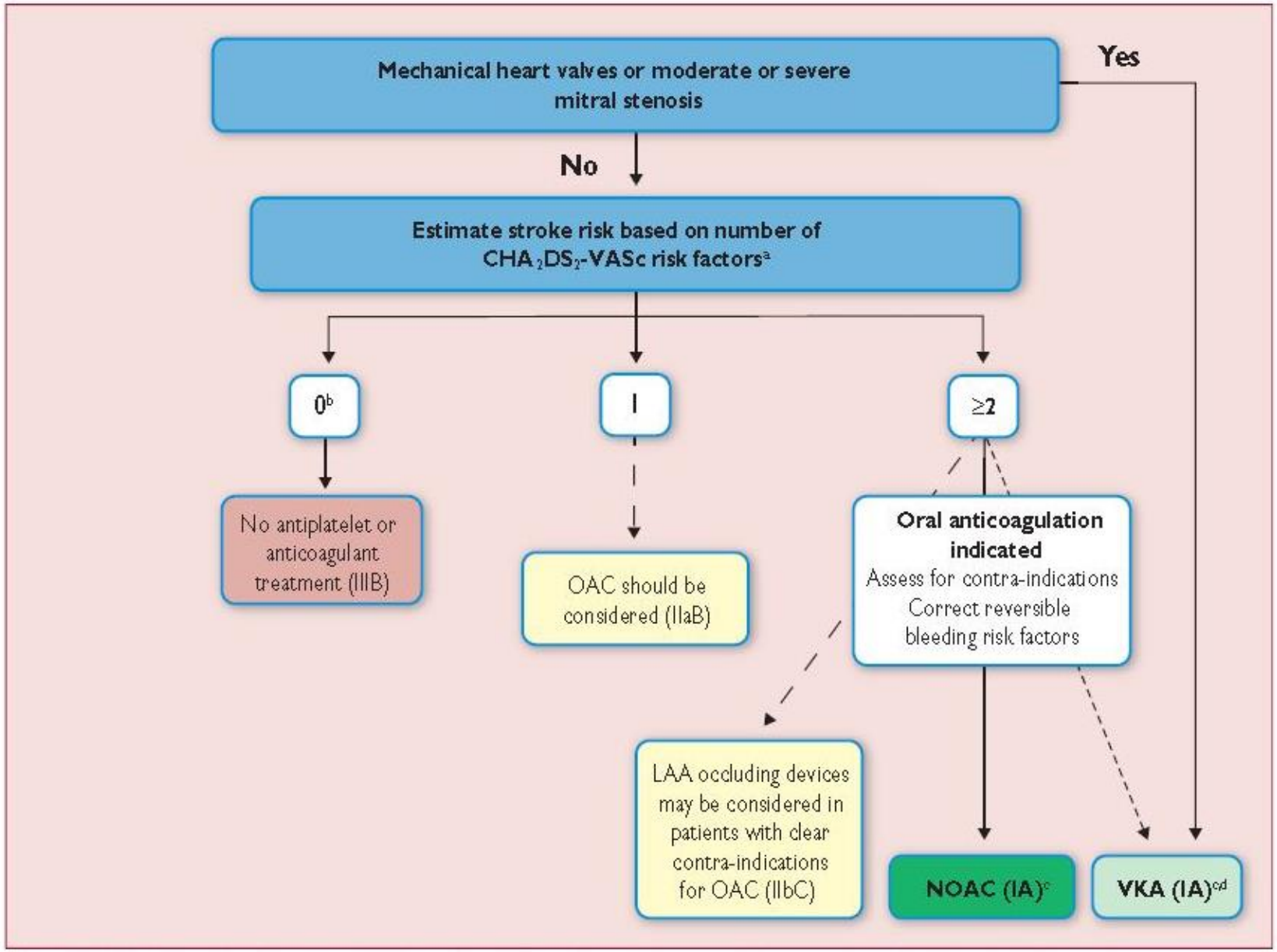
ni et al, DMSO 2013; Dennis JM 2018

Atrial fibrillation

- Considering the increased prevalence of AF with age and the higher risk of stroke in elderly women with AF, active screening (in particular of women >75 years of age) in primary care settings using pulse taking followed by an ECG as appropriate is recommended *(Class I; Level of Evidence B*).

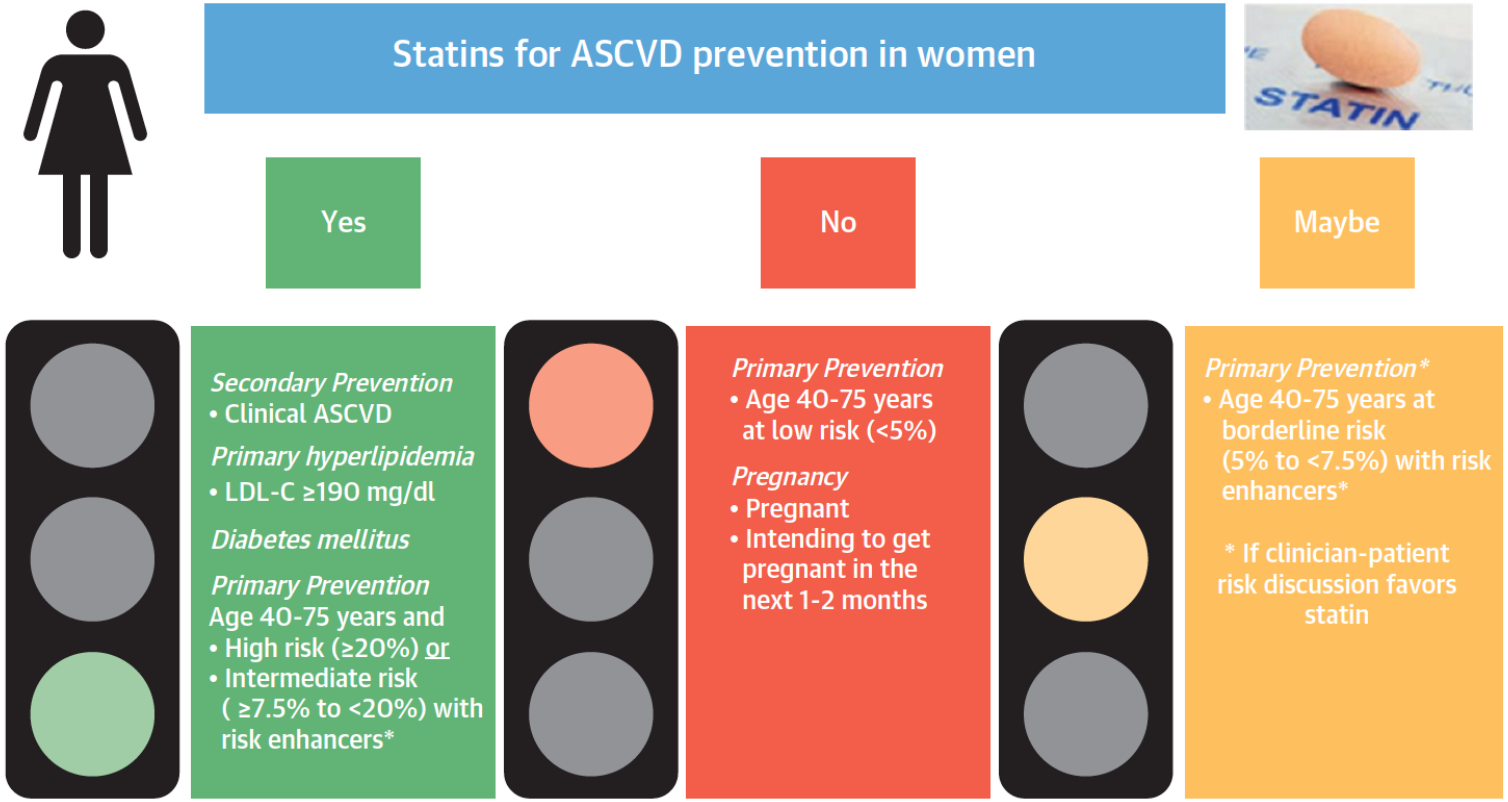
- Oral anticoagulation in women aged ≤65 years with AF alone (no other risk factors; women with CHADS2=0 or CHA2DS2-VASc=1) is not recommended (Class III; Level of Evidence

Bushnell et al, Stroke 2014


Mechanical heart valves or moderate or severe mitral stenosis
Yes
No
Estimate stroke risk based on number of CHA2DS2-VASc risk factors[a]
0[b]
1
≥2
No antiplatelet or anticoagulant treatment (IIIB)
OAC should be considered (IIaB)
Oral anticoagulation indicated
Assess for contra-indications
Correct reversible bleeding risk factors
LAA occluding devices may be considered in patients with clear contra-indications for OAC (IIbC)
NOAC (IA)[c]
VKA (IA)[cd]

ESC 201

Dyslipidemia



Cho et al, JACC 2020

Secondary prevention

Evidence-based recommendation
In people with ischaemic stroke or TIA, we recommend aiming for an LDL cholesterol level of <1.8 mmol/l (70 mg/dl) to reduce the risk of major cardiovascular events.

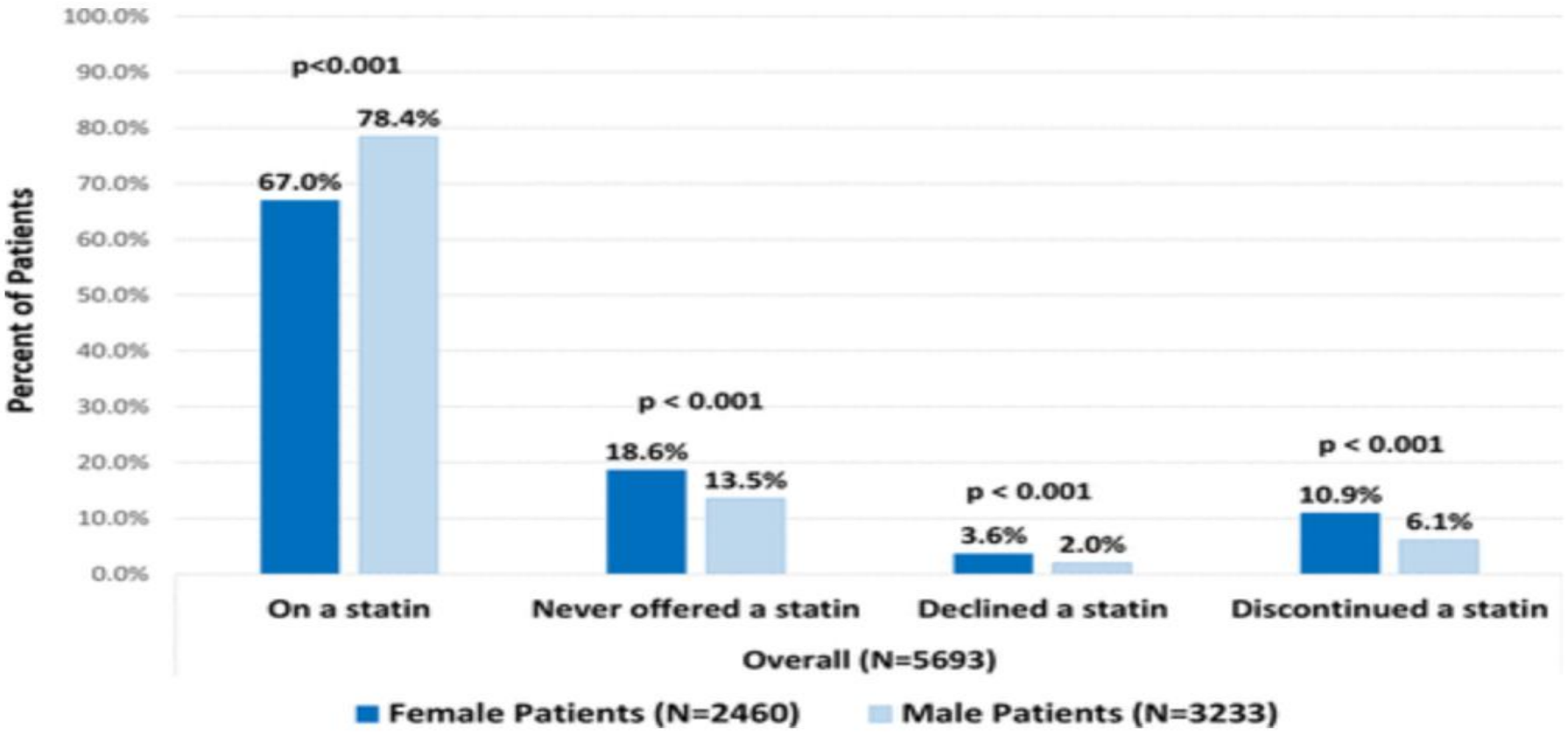
Quality of evidence: **Moderate** ⊕⊕⊕
Strength of recommendation: **Strong for intervention** ↑↑

Evidence-based recommendation
In people with previous ischaemic stroke or TIA we recommend use of a HMGCoA reductase inhibitor to reduce the risk of recurrent ischaemic stroke.

Quality of evidence: **High** ⊕⊕⊕⊕
Strength of recommendation: **Strong for intervention** ↑↑

Dawson J et al,

Dyslipidemia



Nanna NG et al, Circulation:CQO 2019

Similar prevalence in women and men

Obesity, Metabolic Syndrome, and Lifestyle Factors

- In the Women's Health Study, a healthy lifestyle profile was defined as:
  - never smoking
  - alcohol consumption between 4 and 10.5 drinks per week
  - exercise more than four times per week
  - BMI less than 22 kg/m^2,
  - Diet high in cereal fiber, folate, and omega-3 fatty acids, with a high ratio of polyunsaturated to saturated fat, and low in trans-fat and glycemic load

- Women with the highest scores on this scale had a 55% lower risk of stroke than women with the lowest scores (HR 0.45; 95% CI, 0.24–0.83)

Lifestyle Factors

All women, regardless of risk, should be counseled on class I lifestyle recommendations

- smoking cessation
- heart-healthy eating patterns
- regular physical activity
- weight management

Bushnell et al, Stroke 2014

In D.C., doctors are writing prescriptions for broccoli alongside beta blockers

FOOD FROM **B1**

"I was trying to manage my patients' diabetes and high blood pressure, but when they were telling me they were eating Top Ramen, doughnuts and bagels because it keeps them full, all I could say was 'That's too bad, here's some more drugs,' " said Rita Nguyen of the San Francisco Department of Public Health, who now oversees an expanding produce prescription program at six clinics.

In the nation's capital, the Produce Rx program started last month and provides 500 Medicaid patients $20 weekly vouchers for produce at the Giant in Ward 8 through the end of the year.

Ward 8 is the poorest, sickest part of the city and has the highest rates of death for diabetes and heart disease. It's also a food desert, and the Giant is the only full-service grocery store.

The Produce Rx program, which includes the costs of

PHOTOS BY MICHAEL S. WILLIAMSON/THE WASHINGTON POST

not given any.

Allison Hess, a Geisinger executive, said the Fresh Food Farmacy costs about $3,500 per family annually, and drops in blood sugar would result in greater savings from less medication.

"It's kind of a no-brainer," Hess said. "We are going to either pay for this medical expense or pay for this food and education that's going to be more of a lifelong benefit."

The District's approach differs still. Instead of a new pantry or offering food at the doctor's office, the city is nudging residents to buy fruits and vegetables at a grocery store that is already part of their weekly routines.

City health officials said that earlier efforts to connect residents in food deserts to produce at corner stores ran into trouble because the retailers couldn't always find enough customers. The Produce Rx program builds on a more limited subsidy program that already exists at farmers markets.

offer $25 consultations, a fee offset by $25 in vouchers for products. The Ward 8 Giant does not charge for consultations with nutritionists and is the only store in the supermarket chain with an in-store wellness center. It offers diabetes management classes and one-on-one coaching.

"When they tell you to eat healthy, what does that mean to you?" Griffith asked Price from behind her desk in the store's wellness center on a recent afternoon.

Price winced.

"Leaving everything that I love and sticking to the greens," she replied.

Griffith offered a more optimistic answer.

"Maybe you can learn to love new things," she said. "We want to be in the middle and mindful of the things we are eating and how to eat foods that make us happy."

Over the next hour, they talked about what Price likes to eat (pasta and mac and cheese)

ASPIRIN ?

- Aspirin therapy (75–325 mg/d) is reasonable in women with diabetes mellitus unless contraindicated (Class IIa; Level of Evidence B).

- If a high-risk (ie, 10-year predicted CVD risk ≥10%) woman has an indication for aspirin but is intolerant of aspirin therapy, clopidogrel should be substituted (Class I; Level of Evidence B)

Bushnell et al, Stroke 2014

ASPIRIN for primary prevention ?

- Aspirin therapy can be useful in women ≥65 years of age if BP is controlled and the benefit for IS and MI prevention is likely to outweigh the risk of gastrointestinal bleeding and hemorrhagic stroke (Class IIa; Level of Evidence B)

Bushnell et al, Stroke 2014

ARRIVE trial

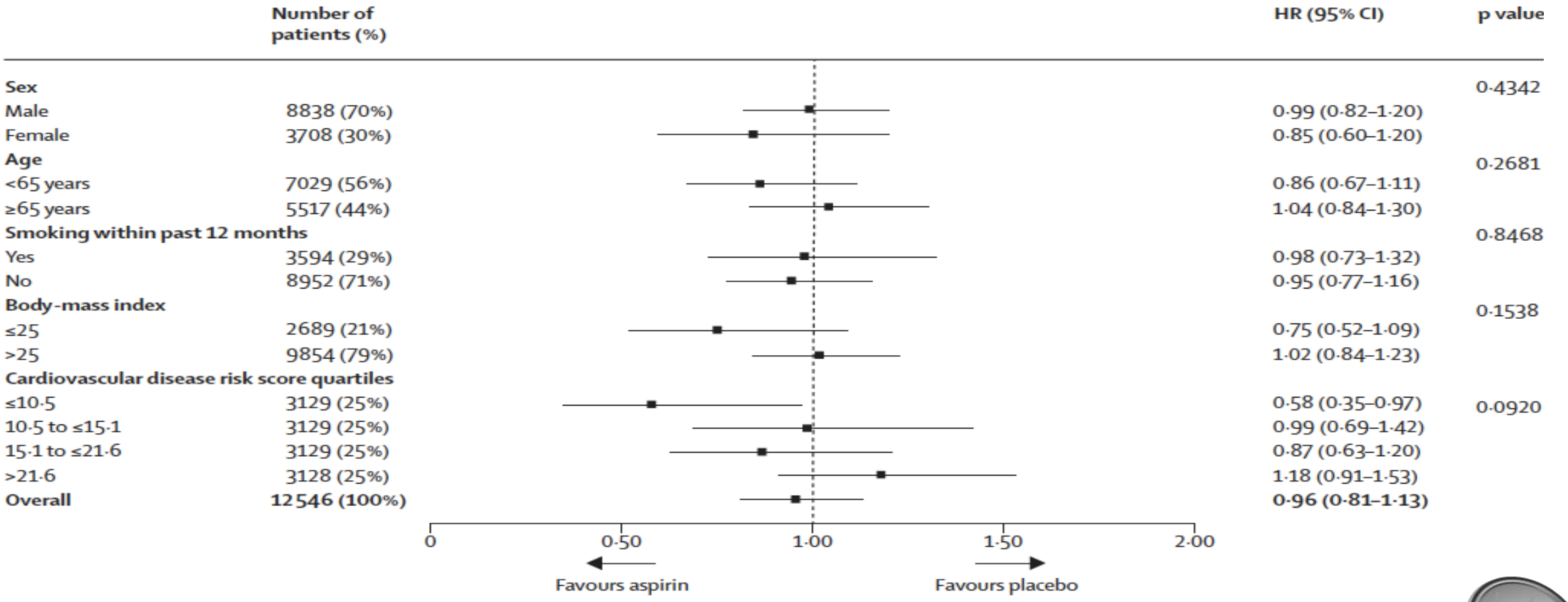
	Number of events in the intention-to-treat population			Number of events in the per-protocol population		
	Aspirin (n=6270)	Placebo (n=6276)	Hazard ratio (95% CI); p value	Aspirin (n=3790)	Placebo (n=3912)	Hazard ratio (95% CI); p value
Myocardial infarction, stroke, cardiovascular death, unstable angina, or transient ischaemic attack	269 (4·29%)	281 (4·48%)	0·96 (0·81–1·13); p=0·6038	129 (3·40%)	164 (4·19%)	0·81 (0·64–1·02); p=0·0756
Myocardial infarction, stroke, or cardiovascular death	208 (3·32%)	218 (3·47%)	0·95 (0·79–1·15); p=0·6190	103 (2·72%)	135 (3·45%)	0·79 (0·61–1·02); p=0·0661
Myocardial infarction*	95 (1·52%)	112 (1·78%)	0·85 (0·64–1·11); p=0·2325	37 (0·98%)	72 (1·84%)	0·53 (0·36–0·79); p=0·0014
Non-fatal myocardial infarction	88 (1·40%)	98 (1·56%)	0·90 (0·67–1·20); p=0·4562	32 (0·84%)	60 (1·53%)	0·55 (0·36–0·84); p=0·0056
Stroke*	75 (1·20%)	67 (1·07%)	1·12 (0·80–1·55); p=0·5072	40 (1·06%)	37 (0·95%)	1·12 (0·71–1·75); p=0·6291
Cardiovascular death	38 (0·61%)	39 (0·62%)	0·97 (0·62–1·52); p=0·9010	26 (0·69%)	26 (0·66%)	1·03 (0·60–1·77); p=0·9161
Unstable angina	20 (0·32%)	20 (0·32%)	1·00 (0·54–1·86); p=0·9979	8 (0·21%)	11 (0·28%)	0·75 (0·30–1·87); p=0·5380
Transient ischaemic attack	42 (0·67%)	45 (0·72%)	0·93 (0·61–1·42); p=0·7455	19 (0·50%)	19 (0·49%)	1·03 (0·55–1·95); p=0·9181
Any death	160 (2·55%)	161 (2·57%)	0·99 (0·80–1·24); p=0·9459	108 (2·85%)	101 (2·58%)	1·10 (0·84–1·45); p=0·4796

*Fatal or non-fatal.

Table 2: **Efficacy endpoints in the intention-to-treat and per-protocol populations**

Gaziano JM, The Lancet 2018

ARRIVE trial



Gaziano JM, The Lancet 2018

Secondary stroke prevention

Evidence-based recommendation

In people with previous ischaemic stroke or TIA, we recommend long-term use of antiplatelet therapy to reduce the risk of recurrent stroke.

Quality of evidence: **Moderate** ⊕⊕⊕

Strength of recommendation: **Strong for intervention** ↑↑

Dawson J et al,

Education

World Stroke Campaign

"I am Woman"

Stroke affects me, Stroke affects everyone.

World Stroke Organization

- 1 in 5 women will have a stroke in their lifetime, compared to 1 in 6 men.
- 60% of people who die from stroke will be women.
- Around 50% of all strokes could be prevented.

Take home messages

- Primary prevention is as essential component in the fight to reduce burden of stroke in women
- Need to monitor risk factors
- Promote healthy lifestyle
- Future studies should report data separately for men and women, stratify by age when examining sex differences in disease rates