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 2019
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
- Postmenopausal 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

Conditions:
- Hypertensive disorders of pregnancy (chronic hypertension, gestational hypertension, preeclampsia, eclampsia, HELLP syndrome)
- Gestational diabetes mellitus
- IUGR (intrauterine growth retardation)
- Preterm birth (idiopathic/spontaneous)
- Placental abruption
- Obesity/excessive pregnancy weight gain/post-partum weight retention
- Sleep disorders; moderate-to-severe obstructive sleep apnea
- Maternal age older than 40 years

Cardiovascular risk screening within 3 months post-partum

Medical History
- Smoking history
- Physical activity
- Breastfeeding
- PMH of hypertension, diabetes, CVD
- First degree family history of CVD, HTN, DM

Physical Examination
- Resting blood pressure and heart rate
- Body mass index and waist circumference

Laboratory testing
- Lipid profile
- Diabetes screening
- Urine protein:creatinine ratio

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).
Hypertensive disorders of pregnancy

Aspirin reduces stroke risk in women with prior hypertensive disorders of pregnancy (HDP)

Study question
Does aspirin or statin use reduce long-term stroke risk in women with prior HDP?

83,749 women aged ≤ 60 years
1995 California Teachers Study
2015

Parameters assessed: HDP History | Aspirin/statin use | All stroke | Stroke at < 60 years

Risk of stroke was increased by...

1.3x overall in women with prior HDP.
1.5x in women aged ≤ 60 years with prior HDP and who did not take aspirin regularly.

No increased risk of stroke...
in women aged ≤ 60 years with prior HDP who took aspirin regularly.

Statin use did not affect stroke risk.

Guidelines estimating 10-year cardiovascular risk including stroke, do not consider HDP history.

HDP history increases long-term stroke risk in women.

Risk estimation guidelines should consider HDP.

Recommend trials exploring aspirin use for stroke prevention in women with prior HDP.

Women with prior HDP have increased long-term stroke risk, which is reduced by aspirin use.

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, Stroke 2014
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

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).
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 nighttime BP pattern.

• Women might derive more benefit from BP control using ambulatory BP measurements as opposed to conventional BP monitoring.
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 dependent edema
## Antihypertensive drugs in pregnancy

### Table 4. Summary of Antihypertensive Drugs Used During Pregnancy

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

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

<table>
<thead>
<tr>
<th>ADA (79,80)</th>
<th>ACC/AHA (3,4,6)</th>
<th>ESC (81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HgA1c</td>
<td>Goal &lt;7.0%</td>
<td>&lt;7.0%</td>
</tr>
<tr>
<td></td>
<td>&lt;7.0%</td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>Goal of &lt;140/90 mm Hg</td>
<td>BP goal of &lt;130/80 mm Hg</td>
</tr>
<tr>
<td></td>
<td>Goal of &lt;130/80 mm Hg if high risk of CVD</td>
<td>Initiate treatment if BP &gt;130/80 mm Hg (specific DM recommendations)</td>
</tr>
<tr>
<td></td>
<td>&lt;7.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;6.5% if achievable without hypoglycemia</td>
<td>Less stringent in elderly patients</td>
</tr>
<tr>
<td>LDL</td>
<td>&lt;40 yrs no ASCVD risk factor—no statin</td>
<td>&gt;40 yrs of age, moderate-intensity statin regardless of 10-yr ASCVD risk</td>
</tr>
<tr>
<td></td>
<td>&lt;40 yrs ASCVD risk factors—high-intensity statin</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>≥40 yrs no ASCVD risk factor—moderate-intensity statin</td>
<td>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 &lt;60 ml/min/1.73 m², retinopathy, neuropathy, or ankle-brachial index (&lt;0.9), it may be reasonable to initiate statin therapy</td>
</tr>
<tr>
<td></td>
<td>≥40 yrs ASCVD risk factor—high-intensity statin</td>
<td>Very high-risk LDL &lt;55 mg/dl or LDL 50% reduction</td>
</tr>
<tr>
<td></td>
<td>&lt;40 yrs of age, moderate-intensity statin regardless of 10-yr ASCVD risk</td>
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<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>DM who are at increased risk of CVD</td>
<td>No specific DM recommendations</td>
</tr>
<tr>
<td></td>
<td>Only in very high risk/high risk</td>
<td></td>
</tr>
</tbody>
</table>

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.
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

Anichini 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
Dyslipidemia

Statins for ASCVD prevention in women

- **Yes**
  - Secondary Prevention
    - Clinical ASCVD
  - Primary hyperlipidemia
    - LDL-C ≥190 mg/dl
  - Diabetes mellitus

- **No**
  - Primary Prevention
    - Age 40-75 years at low risk (<5%)
    - Pregnant
    - Intending to get pregnant in the next 1-2 months

- **Maybe**
  - Primary Prevention
    - Age 40-75 years at borderline risk (5% to <7.5%) with risk enhancers*

* If clinician-patient risk discussion favors statin

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** ↑↑
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/m²,
  - 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 R1

"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 orchard production and transportation, not given any.

Allison Hess, a Geisinger executive, said the Fresh Food Pharmacy 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.

"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 macaroni 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

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Number of events in the intention-to-treat population</th>
<th>Hazard ratio (95% CI); p value</th>
<th>Number of events in the per-protocol population</th>
<th>Hazard ratio (95% CI); p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin (n=6,270)</td>
<td>Placebo (n=6,276)</td>
<td></td>
<td>Aspirin (n=3,970)</td>
</tr>
<tr>
<td>Myocardial infarction, stroke, cardiovascular death, unstable angina, or transient ischaemic attack</td>
<td>269 (4.29%)</td>
<td>281 (4.48%)</td>
<td>0.96 (0.81-1.13); p=0.6038</td>
<td>129 (3.40%)</td>
</tr>
<tr>
<td>Myocardial infarction*</td>
<td>208 (3.32%)</td>
<td>218 (3.47%)</td>
<td>0.95 (0.79-1.15); p=0.6190</td>
<td>103 (2.72%)</td>
</tr>
<tr>
<td>Myocardial infarction*</td>
<td>95 (1.52%)</td>
<td>112 (1.78%)</td>
<td>0.85 (0.64-1.11); p=0.2325</td>
<td>37 (0.98%)</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>88 (1.40%)</td>
<td>98 (1.56%)</td>
<td>0.90 (0.67-1.20); p=0.4562</td>
<td>32 (0.84%)</td>
</tr>
<tr>
<td>Stroke*</td>
<td>75 (1.20%)</td>
<td>67 (1.07%)</td>
<td>1.12 (0.80-1.55); p=0.5077</td>
<td>40 (1.06%)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>38 (0.61%)</td>
<td>39 (0.62%)</td>
<td>0.97 (0.62-1.52); p=0.9010</td>
<td>26 (0.69%)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>20 (0.32%)</td>
<td>20 (0.32%)</td>
<td>1.00 (0.54-1.86); p=0.9979</td>
<td>8 (0.21%)</td>
</tr>
<tr>
<td>Transient ischaemic attack</td>
<td>42 (0.67%)</td>
<td>45 (0.72%)</td>
<td>0.93 (0.61-1.42); p=0.7455</td>
<td>19 (0.50%)</td>
</tr>
<tr>
<td>Any death</td>
<td>160 (2.55%)</td>
<td>161 (2.57%)</td>
<td>0.99 (0.80-1.24); p=0.9459</td>
<td>108 (2.85%)</td>
</tr>
</tbody>
</table>

*Fatal or non-fatal.

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

Gaziano JM, The Lancet 2018
ARRIVE trial

Table with details of patients and HR (95% CI) values for different factors.

- **Sex**
  - Male: 8838 (70%)
  - Female: 3708 (30%)
  - HR: 0.99 (0.82–1.20) 0.4342
  - p value: 0.2681

- **Age**
  - <65 years: 7029 (56%)
  - ≥65 years: 5517 (44%)
  - HR: 0.85 (0.60–1.20)
  - p value: 0.8468

- **Smoking within past 12 months**
  - Yes: 3594 (29%)
  - No: 8952 (71%)
  - HR: 0.98 (0.73–1.32)
  - p value: 1.02 (0.84–1.23)

- **Body-mass index**
  - ≤25: 2689 (21%)
  - >25: 9854 (79%)
  - HR: 0.75 (0.52–1.09)
  - p value: 0.0920

- **Cardiovascular disease risk score quartiles**
  - ≤10.5: 3129 (25%)
  - 10.5 to 15.1: 3129 (25%)
  - 15.1 to 21.6: 3129 (25%)
  - >21.6: 3128 (25%)
  - HR: 0.58 (0.35–0.97)
  - p value: 1.18 (0.91–1.52)

- **Overall**
  - 12546 (100%)
  - HR: 0.96 (0.81–1.13)
  - p value: 0.0920
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, ESJ 2022
"I am Woman"
Stoke affects me, Stroke affects everyone.

- 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