

Treatment and Prevention of Stroke in Women: Across the Lifespan



MAY 25, 2021

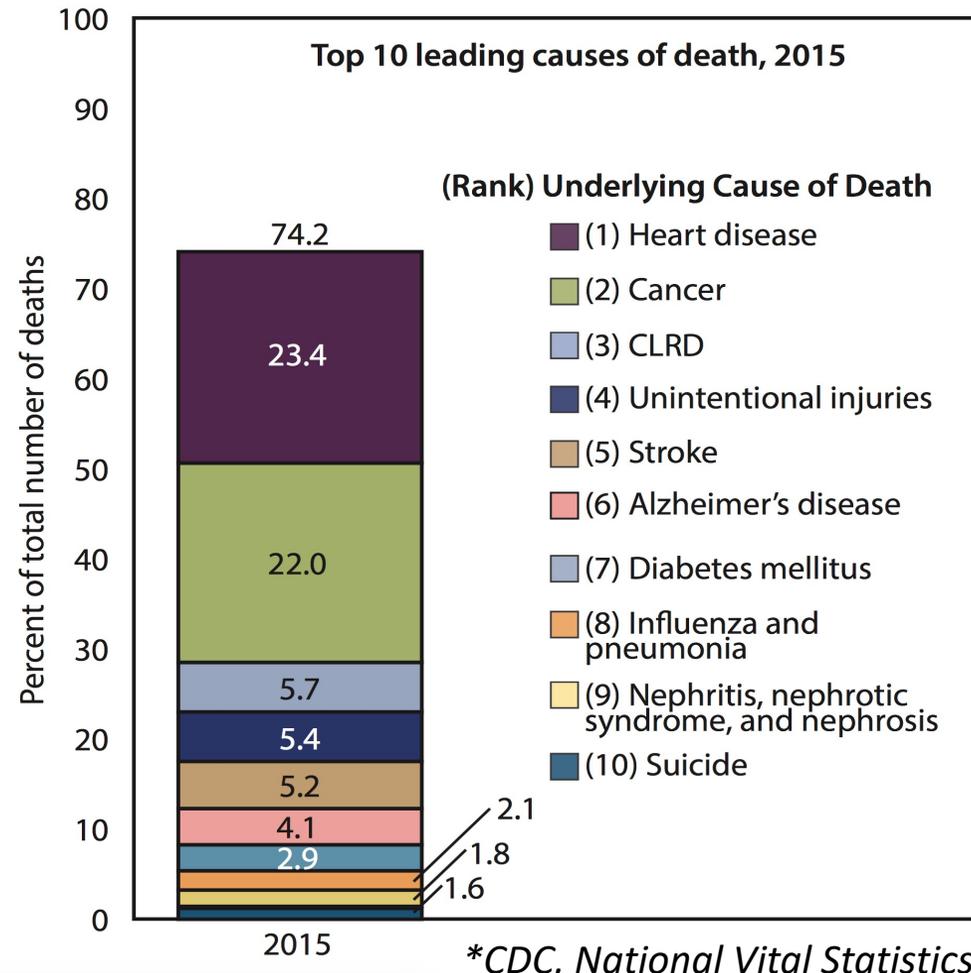
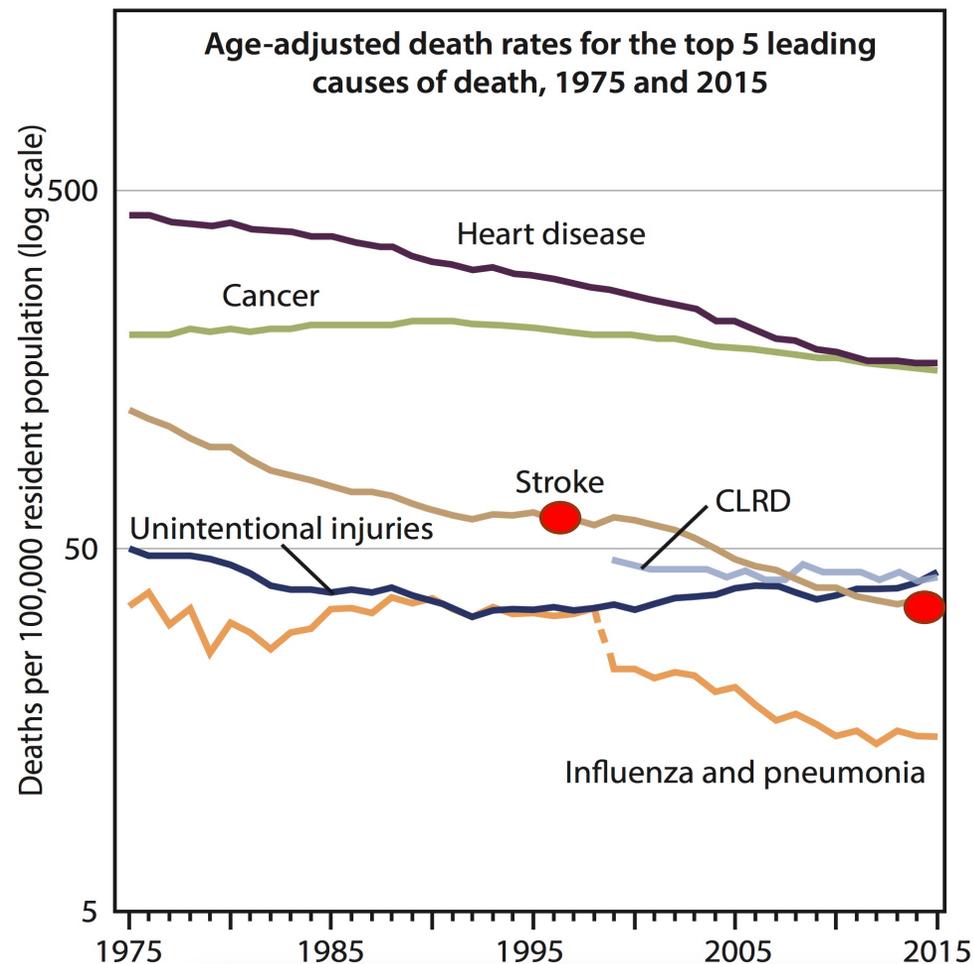
CHRISTINA MIJALSKI SELLS, MD, MPH

CLINICAL ASSISTANT PROFESSOR

STANFORD UNIVERSITY MEDICAL CENTER

Stroke and public health impact

Figure 8. Leading causes of death in 1975 and 2015: United States, 1975–2015



Epidemiology

Stroke is a major public health burden.

- Stroke is a preventable cause of substantial morbidity and mortality worldwide and in the United States.

The Centers for Disease Control and Prevention list stroke as the 5th leading cause of death.

Cause of death*	Number of deaths
Heart disease	611,105
Cancer	584,881
Chronic lower respiratory diseases	149,205
Accidents (unintentional injuries)	130,557
Stroke (cerebrovascular diseases)	128,978

**Data from the CDC for 2013 (<http://www.cdc.gov/>)*

Epidemiology

The risk of stroke varies by age, gender, and ethnic group.

Men are more likely to have a stroke than women.

- Over the age of 75, women are more likely to have a stroke than men.

Among ethnic groups, American Indian, Alaska natives, and African Americans have the highest prevalence of stroke.

Ethnic group*	Prevalence (%)
American Indian/Alaska natives	4.6
Non-Hispanic blacks	4.0
Non-Hispanic whites	2.5
Hispanics of any race	2.3
Hispanics of any race	1.3

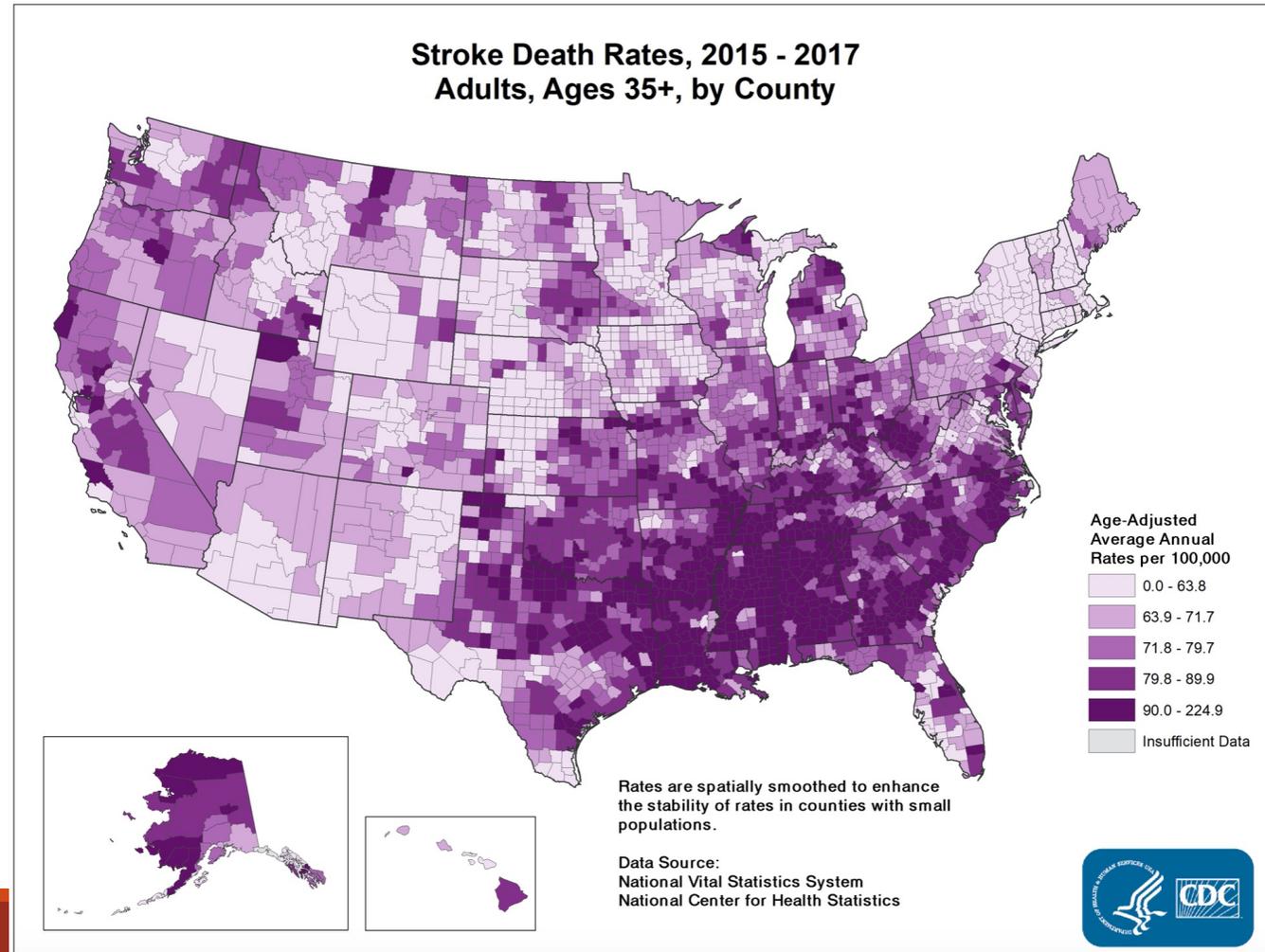
**Heart Disease and Stroke Statistics-2016 Update: A Report From the AHA*

Epidemiology

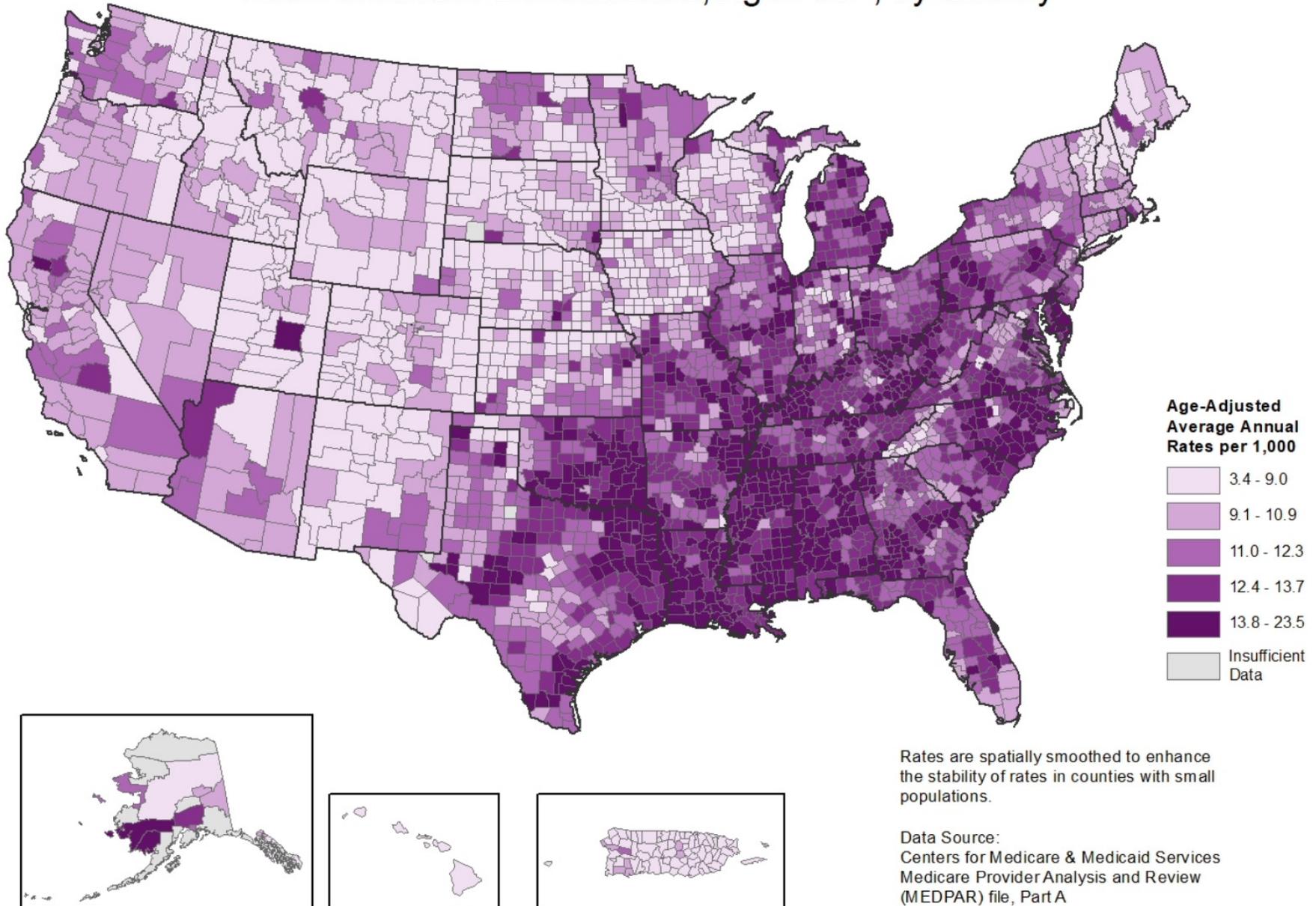
Stroke due to ischemia comprises about 68% of all strokes globally and 80% of strokes in the United States.

In the U.S., stroke is more common in the southern states.

- Behavioral and lifestyle factors
- Socioeconomic status
- Access to care



Stroke Hospitalization Rates, 2015-2017 Adult Medicare Beneficiaries, Ages 65+, by County

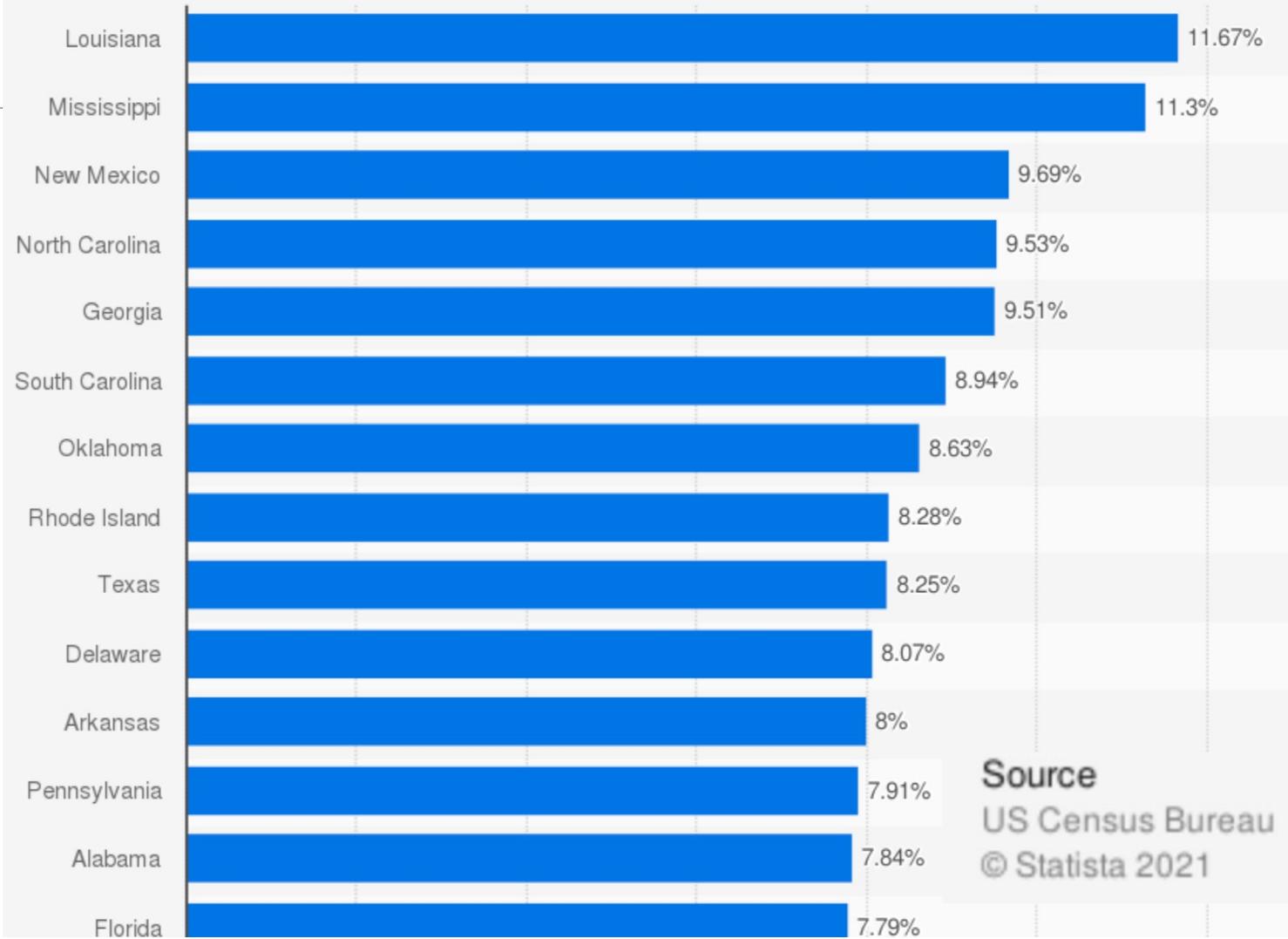


Epidemiology

A similar distribution is also shown in the percentage of households by state that are led by a single mother

- Inequitable burden on women in these states that affects women's health
- SES
- Access to care

Percentage of households led by a single mother with children under age 18 living in the household in the U.S. in 2018, by state*



Source
US Census Bureau
© Statista 2021

BE FAST BOB

B E F A S T

Know the signs of stroke

Balance

Face

Eyes

Arms

Speech

Time

Balance

Sudden loss of balance.

Eyes

*Sudden loss of vision
in one or both eyes.*

Face

Does the face look uneven?

Arms

*Does one arm drift down?
Ask them to raise
both arms.*

Speech

*Does their speech sound
strange? Ask them to
repeat a phrase.*

Time

*Time is brain.
Every second brain cells
die during a stroke.*



Classification of stroke by subtype

The mechanisms and pathophysiology of stroke are best considered in the context of specific stroke subtypes.

There are two primary categories of stroke, and these vary by country and region. In the United states:

- **80% of strokes are ischemic**
- **20% of strokes are hemorrhagic**

There are 5 major categories of ischemic stroke largely based on etiology (TOAST classification)

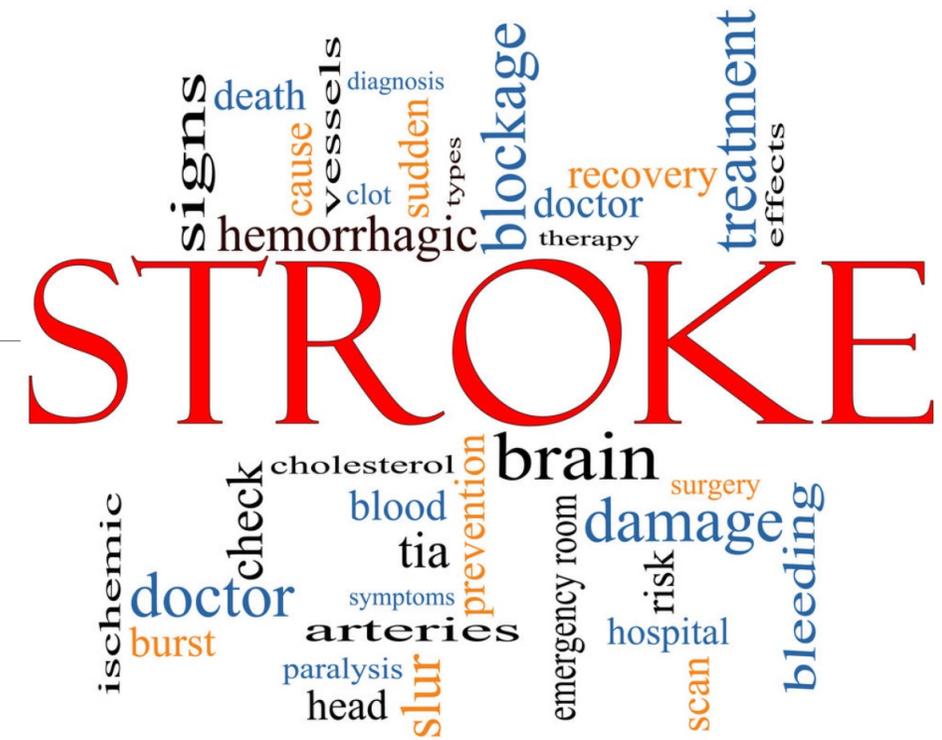
- Implications for diagnostic work-up and treatment

Stroke subtypes

The 5 TOAST categories of ischemic stroke:

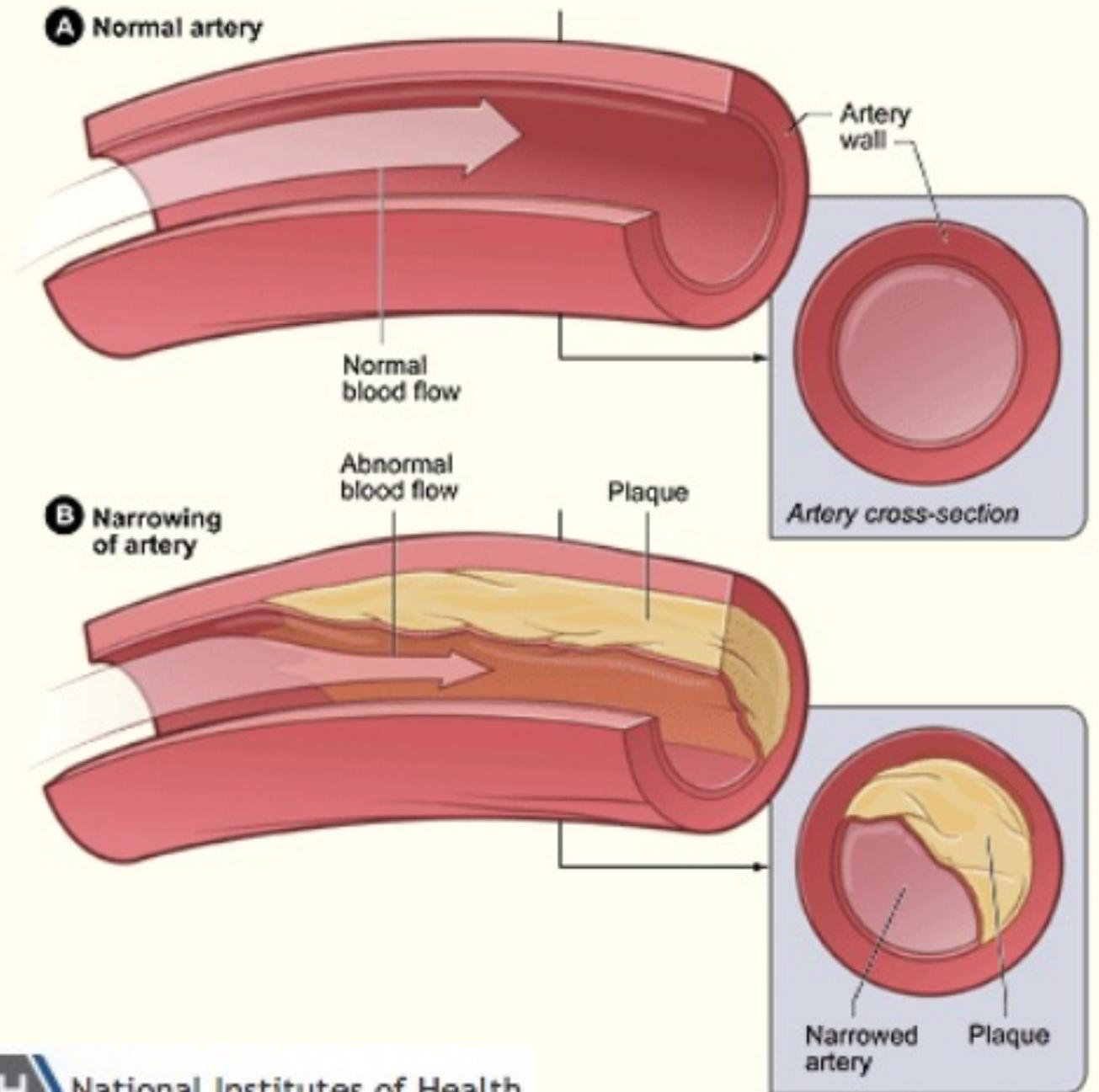
- 1) Cardioembolic
- 2) Lacunar strokes, small vessel disease
- 3) Large artery atherosclerosis, atheroembolic
- 4) Stroke of “other” etiology
- 5) Stroke of undetermined etiology

Each classification has associated characteristic risk factors, clinical presentation and radiographic findings.



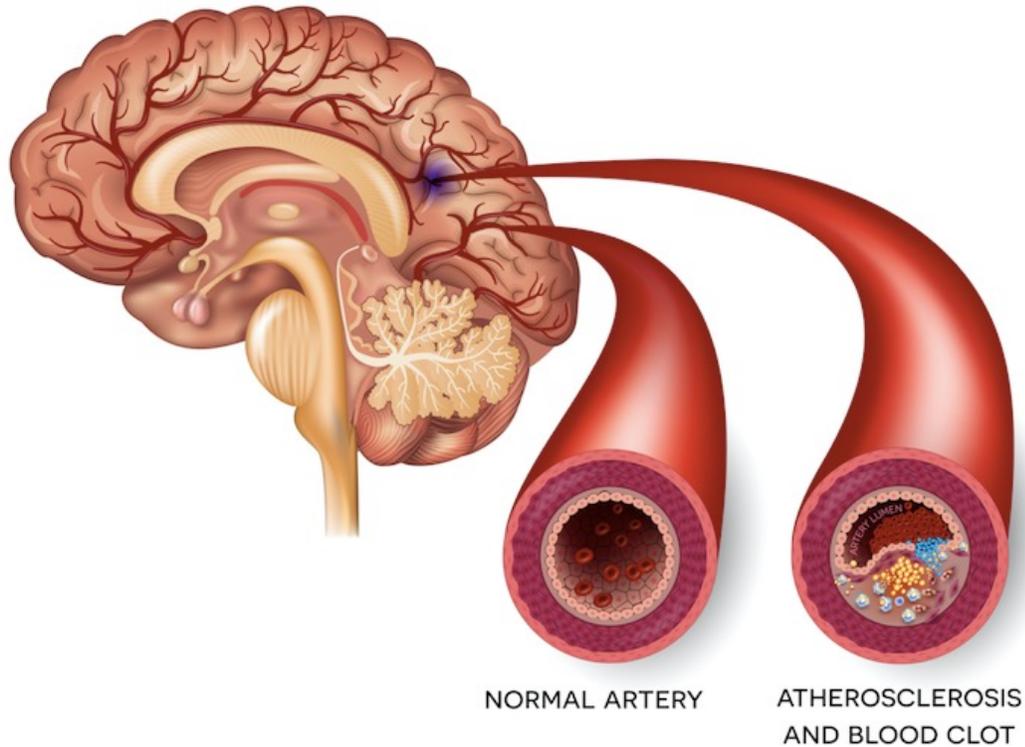
Atherosclerosis

- A gradual narrowing of the arteries from the build-up of fat, cholesterol, calcium and other debris that limits the flow of blood and oxygen.
- Affects medium and large arteries, usually at branching points.

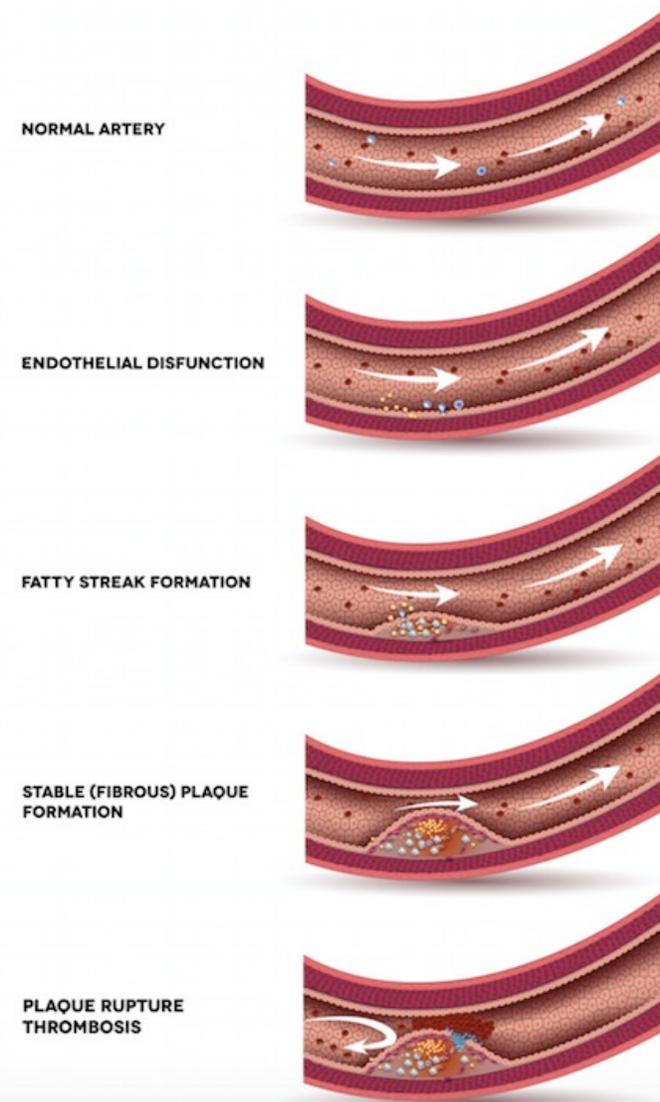


Intracranial atherosclerosis

NORMAL CEREBRAL ARTERY AND ARTERY WITH ATHEROSCLEROSIS, BLOOD CLOT



ATHEROSCLEROSIS



Cardioembolic

High-risk sources of cardioembolism:

- Atrial fibrillation
- Myocardial infarction
- Prosthetic valves
- Endocarditis
- Cardiomyopathy

Coronary heart disease

Angina (dull/heavy to sharp chest pain or discomfort)
Pain in neck, jaw, throat, upper abdomen or back

Heart attack

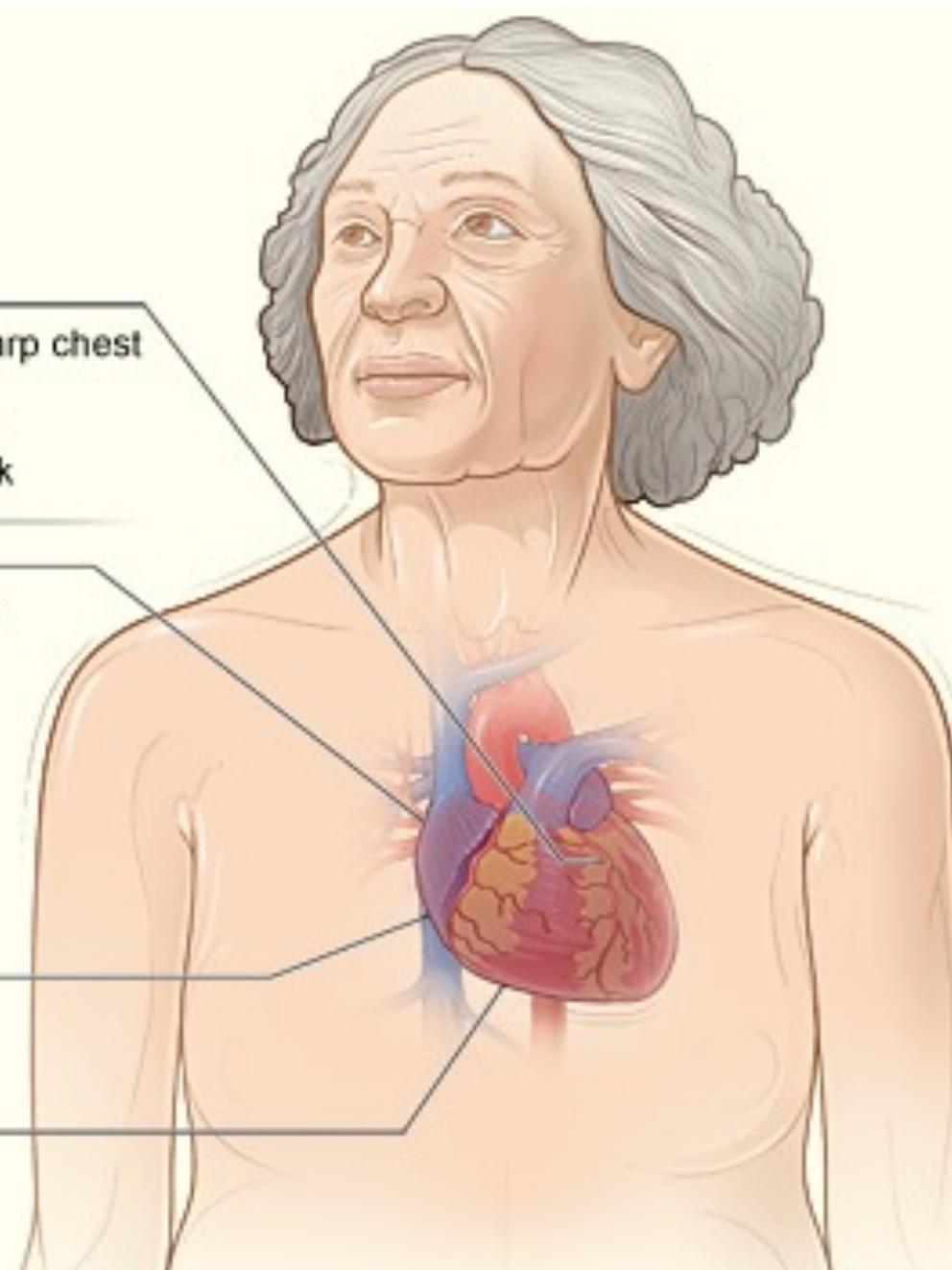
Chest pain or discomfort
Upper back or neck pain
Indigestion
Heartburn
Nausea and vomiting
Extreme fatigue
Upper body discomfort
Shortness of breath

Arrhythmia

Fluttering feelings (palpitations)

Heart failure

Shortness of breath
Fatigue
Swelling in feet, ankles, legs, and abdomen.



Cardioembolic

Recent myocardial infarction (MI) can facilitate the formation of a cardiac thrombus due to endothelial damage.

- The dysfunction of the ventricular wall can lead to stagnation of blood and thrombus formation.

Strokes due to MI are most likely to occur within 5 days.

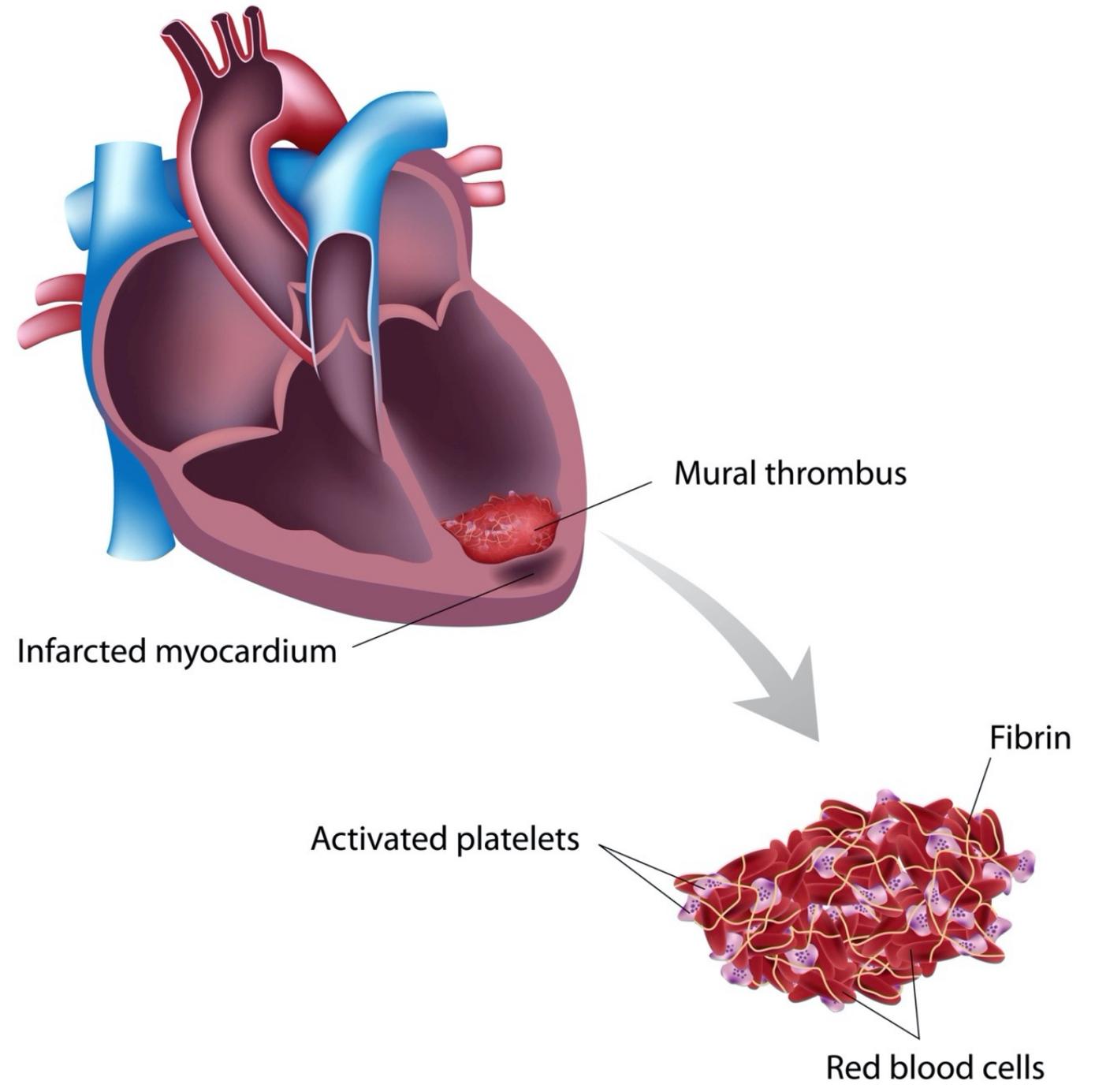
Additional risk factors for MI associated stroke include:

- Atrial fibrillation
- ST elevation on ECG
- History of prior stroke

(G.S. Silva et al., Acute Ischemic Stroke, Springer-Verlag Berlin Heidelberg 2011).

(Moore et al. Ischemic Stroke After Acute Myocardial Infarction. Stroke. 1997; 28: 762-767).

Cardioembolic



Common risk factors for ischemic stroke

Underlying conditions that increase risk of ischemic stroke:

- 1) Hypertension
- 2) Dyslipidemia
- 3) Diabetes
- 4) Heart disease
- 5) *Family and genetic risk factors

Common behaviors that increase risk of ischemic stroke:

- 1) Alcohol use
- 3) Tobacco use
- 3) Physical inactivity
- 4) Unhealthy diet

Gender differences in stroke

Reproductive factors strongly affect stroke risk and incidence in women across the lifespan

- Hormonal influences, pregnancy, and hormonal contraception and hormonal replacement therapy after menopause

Presenting symptoms of stroke vary between women and men

- Affects timely recognition, diagnosis and treatment

Stroke outcomes are influenced by age, pre-stroke functional status, and comorbidities

- Severity
- Functional status
- Mortality

Epidemiology

Pediatric stroke (infant to 18 years)

Incidence of stroke in infants and children:

- 0.6 to 7.9/100,000 children per year
- American Indian, Alaska natives, and African Americans have the highest prevalence of stroke
- Pediatric ischemic stroke is more common in boys than in girls, unknown cause

Risk factors and cause of stroke:

- Congenital and acquired heart problems
- hematologic conditions
- Vasculopathies (dissection, traumatic and spontaneous)
- Metabolic disorders
- Drug ingestion

Patent Foramen Ovale

Patent foramen ovale (PFO) is a persistent shunt in the heart that allows blood from the right atrium to flow to the left atrium.

In up to about 27% of the population this shunt does not close from fetal circulation and may be considered a normal variant.

- Blood clots in the venous circulation may cross into the left side of the heart and cause stroke

Recent published trials in 2017 (**RESPECT**, **REDUCE**, and **CLOSE**) showed a lower rate of stroke with closure and antiplatelet therapy.

- Benefit was realized in longer-term term follow-up
- Improved characterization of high risk PFOs

(G.S. Silva et al., Acute Ischemic Stroke, Springer-Verlag Berlin Heidelberg 2011).

Epidemiology

Sex and age influence stroke diagnoses in the United States

- 20-59 years: Similar prevalence of stroke between men and women
- 60-79 years: Higher prevalence of stroke among men
- 80 years and older: Higher prevalence of stroke among women

Race and ethnicity are significant predictors of stroke incidence and outcomes within gender groups

- Socioeconomic status

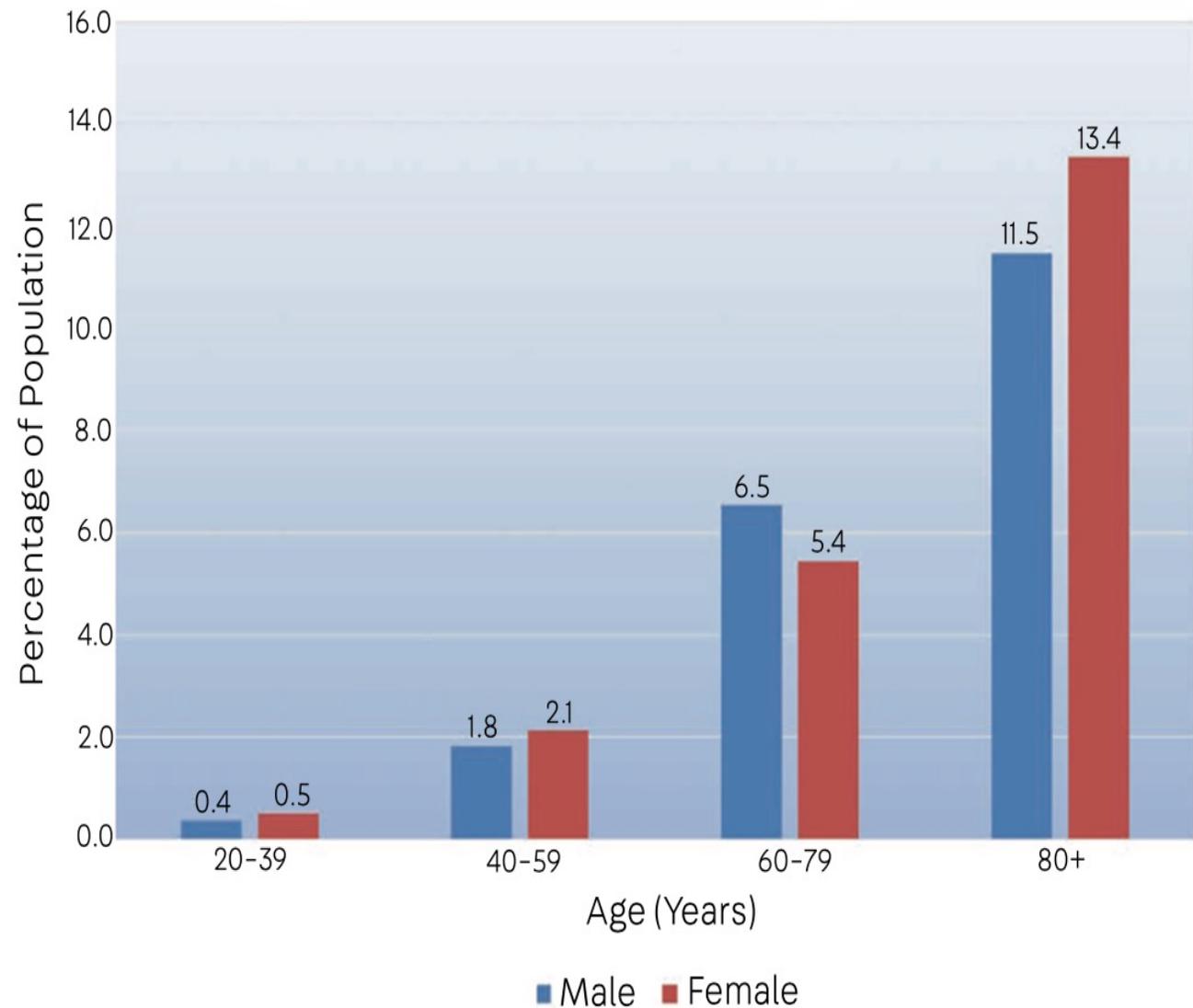


FIGURE 7-1

Prevalence of stroke by age and sex.

Reprinted with permission from Benjamin EJ, et al, *Circulation*.² © 2019 American Heart Association, Inc.

Presentation and risk factor identification

Presenting signs and symptoms of stroke vary between women and men

- Affects timely recognition, diagnosis and treatment

Circumstances at presentation:

- Women are more often older, live alone, have increased comorbidities (age effect).*

Disease:

- Women are more likely than men to have cardioembolic stroke, more severe disease.

Preventive therapy:

- Women with atrial fibrillation are less likely to be treated with anticoagulation vs. men.

Women	Men
Generalized weakness	Paresthesia
Mental status changes: Disorientation, Memory deficits, and confusion	Ataxia
Fatigue	Double vision
Headache	Nystagmus
Pain	Dysarthria

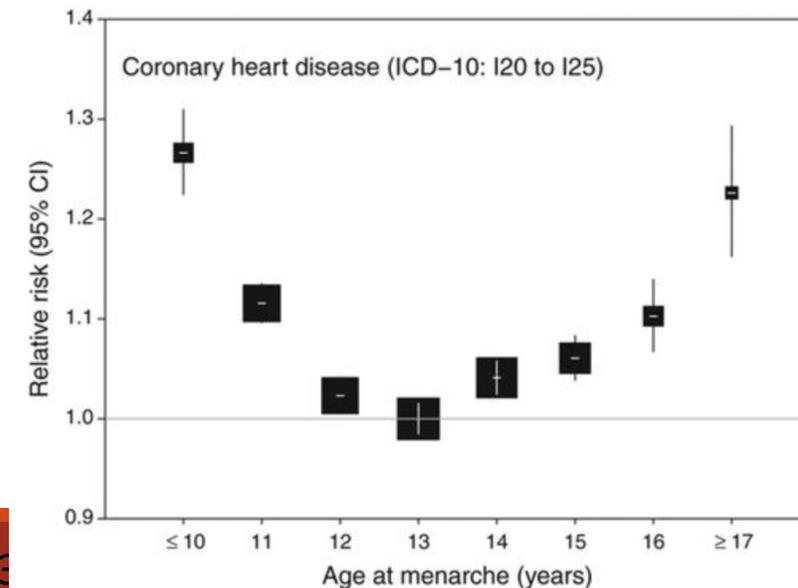
Age at menarche

There is a U-shaped curve between age at onset of menarche and incidence of stroke:

- Large UK study, women between 60 and 64 years of age ⁴
- Onset at 10 years or younger increases future risk of stroke by about 25%
- Onset at 17 years and older also increases relative lifetime risk
- Strongest trend in coronary heart disease
- Hypertensive disease has a similar trend

Associations:

- Lower SES is associated with earlier onset of menarche
- Childhood obesity: SES, increased and longer duration of exposure to estradiol, earlier onset of puberty ^{5, 6}



Contraception and HRT

There is up to two-times increased risk of stroke in women taking ESTROGEN-containing oral contraceptives ⁷

- Dose-dependent relationship to estrogen, 1.7-2.0 x greater risk vs. non-users
- Should be avoided in women with history of any stroke (including pregnancy)
- Physiologic levels of estrogen can decrease activity of pro-inflammatory pathways
 - Decreases clot formation and endothelial damage



Hormone
Replacement
Therapy

Contraception and HRT

There is **NO** evidence of increased risk of stroke or MI in women using **PROGESTIN-ONLY-containing contraceptives** ⁸

- OCPs
- Injectables
- Implantable/intrauterine devices
- *Patches – *may* increase risk of VTE but not arterial clots



Hormone
Replacement
Therapy

Pregnancy

Risk of stroke increases 3-times during pregnancy and the postpartum period, approximately 30/100,000⁹

- Ischemic stroke, hemorrhagic stroke, cerebral venous sinus thrombosis
- Risk factors: Age >35, eclampsia/pre-eclampsia, smoking, C-section

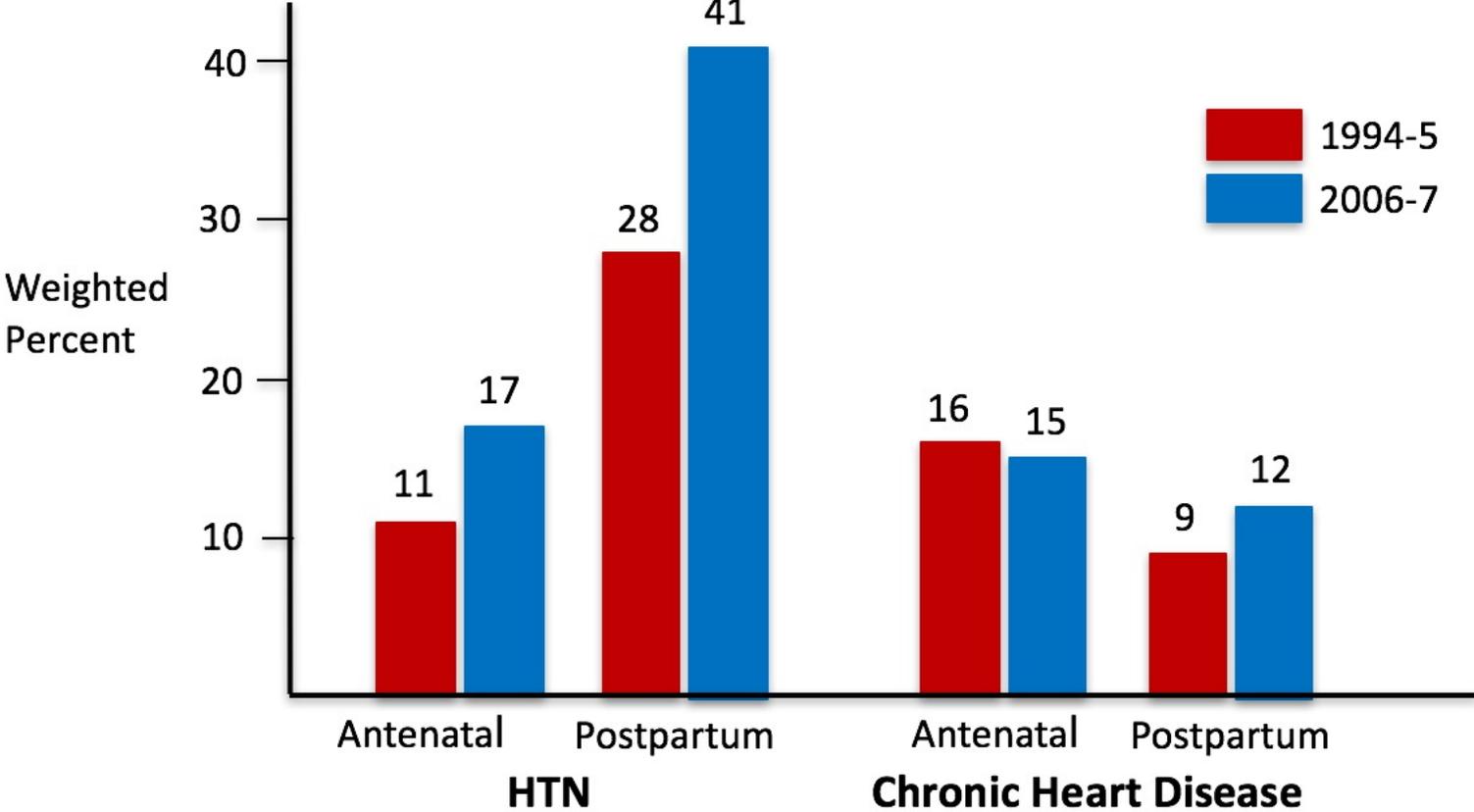
Hemodynamic and vascular changes¹⁰

- Fluid retention, venous stasis, decreased vascular resistance, increased CO and HR
- Collagen/elastin changes: compliance, endothelial dysfunction, vessel wall permeability

Physical changes

- Structural compression: IVC, aorta, uterine arteries and veins

Increase in Rate of Stroke Follows Increases in Rates of HTN and Chronic Heart Disease



ARTICLE

CLASS OF EVIDENCE

Stroke in Pregnancy and Puerperium

Validated Incidence Trends With Risk Factor Analysis in Finland 1987–2016

Liisa Karjalainen, MD, Minna Tikkanen, MD, PhD, Kirsi Rantanen, MD, MSc, Karoliina Aarnio, MD, PhD, Aino Korhonen, BcM, Anna Saaros, BcM, Hannele Laivuori, MD, PhD, Mika Gissler, PhD, and Petra Ijäs, MD, PhD, MSc

Correspondence

Dr. Karjalainen
liisa.karjalainen@helsinki.fi

Neurology[®] 2021;96:e2564–e2575. doi:10.1212/WNL.0000000000011990

Increases in Pregnancy-Associated Stroke

Recent study in Finland (published April 2021): Rate of pregnancy-associated stroke increased over 3 decades.

- 30-year review (1987-2016) – retrospective population-based cohort, case-control
- Pregnancy Associated Stroke (PAS) – Ischemic stroke, hemorrhagic stroke, SAH, CVST during pregnancy or puerperium
- Calculated Pregnancy Associated Stroke (PAS) per 5-year age groups, and per number of deliveries
- Associated with maternal age, smoking after 12 weeks' gestation, migraine, and hypertensive disorders during pregnancy.

Figure 2 Incidence of PAS and Its Subtypes by 5-Year Time Intervals During 1987 to 2016

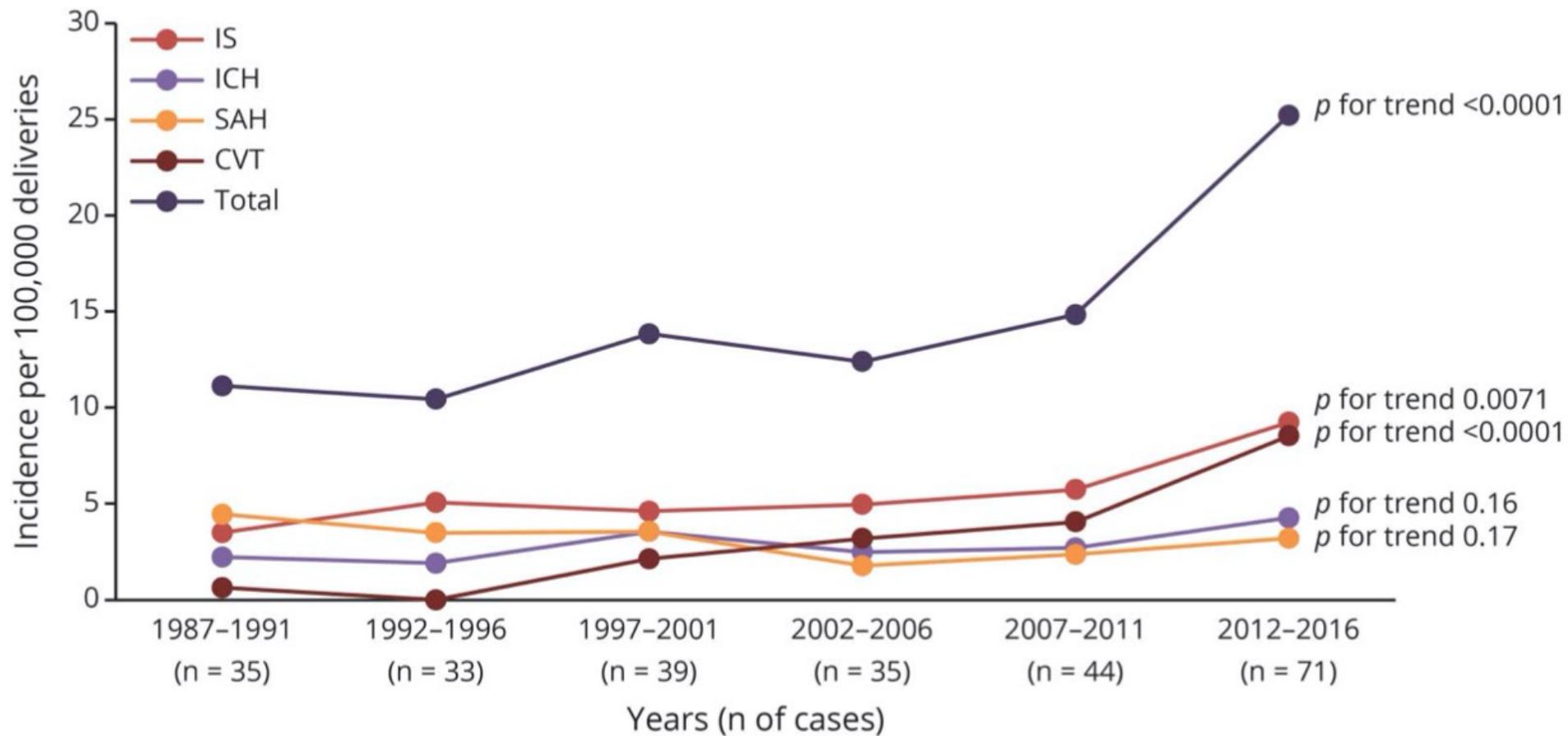
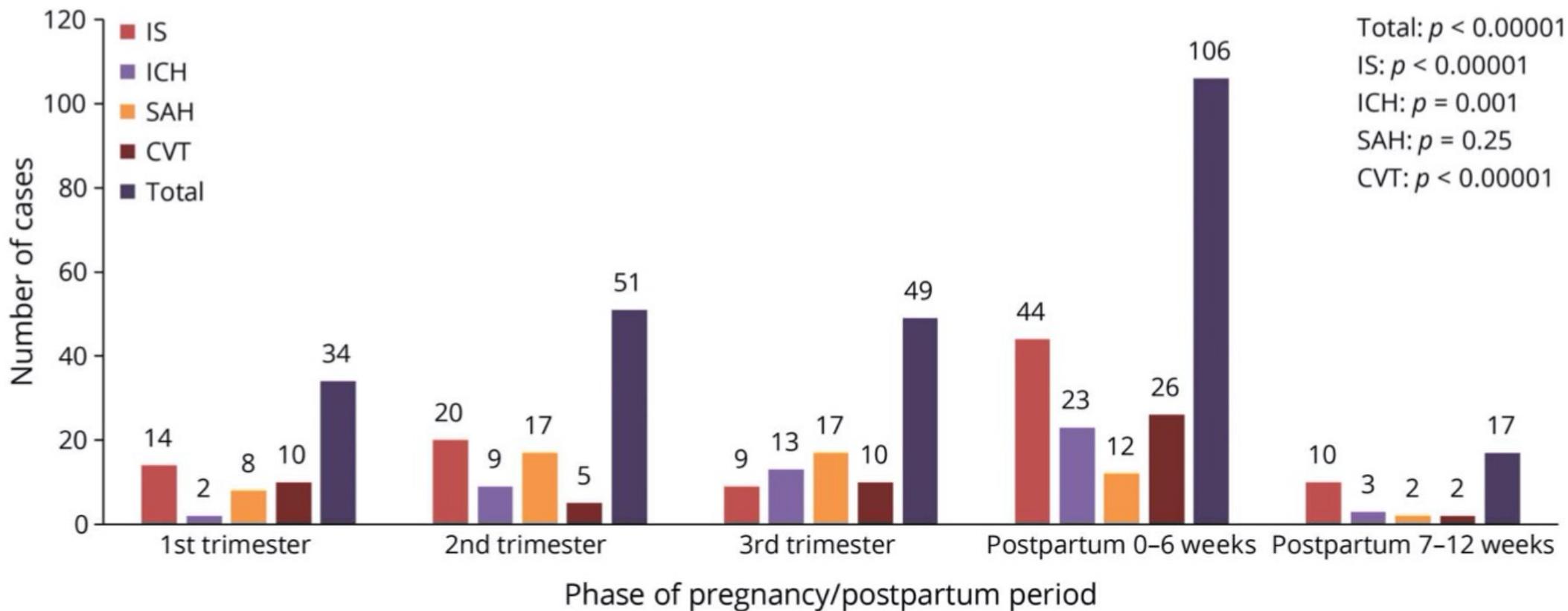


Figure 4 Distribution of PAS and Its Subtypes Across Pregnancy Trimesters and Postpartum Period



Increases in Pregnancy-Associated Stroke

Data:

- Incidence increased from 11.1/100,000 deliveries to 25.2 between 1987 and 2016
- Incidence increased by age from 9.8/100,00 (20-24) to 29.9/100,00 (>40)
- 5-fold higher risk in early post-partum
- Most important risk factors: Smoking after 12 weeks gestation, **Migraine**, Hypertensive disorders

Conclusion:

- **PAS incidence is increasing**
- **Need for careful pregnancy surveillance and risk factor management, particularly in older expectant mothers and extending to puerperium.**

Pregnancy and coagulation

Alterations in the coagulation cascade ^{10, 11}

- Hypercoagulable state, greatest risk during late third trimester and puerperium (~16 weeks)
 - Acute blood loss, physiologic Protein S deficiency, Fe deficiency anemia, dehydration
- Increases in procoagulant factors, decreases in coagulation inhibitors, Increased thrombin generation and fibrinolysis, increased platelet consumption



Hypercoagulable state

Increases in procoagulant factors

- Increase in factors I, VII, VIII, IX, X, XII, and XIII
- No change in factors II, V, XI

Decreases in coagulation inhibitors

- Decreased AT III
- Decreased protein S
- Functional protein C resistance

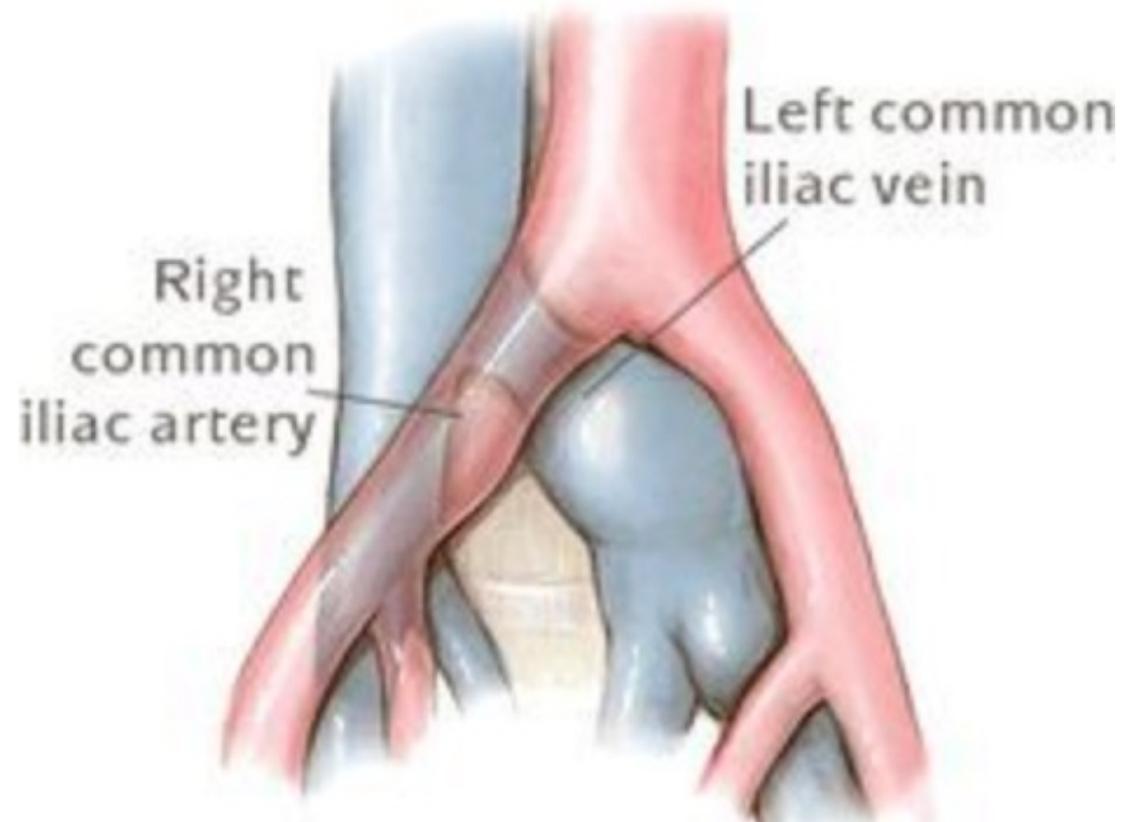
Thrombin generation and fibrinolysis

- Increased thrombin generation
- Increased fibrinogen and fibrinolysis
- Platelet consumption

Physical changes

Mass effect and vascular changes

- Compression of the IVC and iliac vessels
 - **May Thurner Syndrome**
- Compression of the aorta
- Compression of uterine arteries and veins
- Decreased venous compliance



Physiological changes

Hemodynamic changes

- Sodium and water retention from increased renin activity
- Increased levels of prostacyclin lead to decrease in systemic vascular resistance and drop in systolic and diastolic blood pressures
- Venous stasis
- Increased RBC mass
- Mild hemodilutional anemia due to increase in plasma volume
- Increased cardiac output, stroke volume, heart rate by 30–50 %

Physiological changes

Vascular and Connective Tissue Changes

- Reduced collagen and elastin content in arterial wall structure leading to increased arterial stiffness
- Endothelial Dysfunction
- Increased vessel wall permeability → vasogenic edema
- Decreased venous compliance/capacitance → venous stasis

ORIGINAL ARTICLE

Risk of a Thrombotic Event after the 6-Week Postpartum Period

Hooman Kamel, M.D., Babak B. Navi, M.D., Nandita Sriram, B.S.,
Dominic A. Hovsepian, B.S., Richard B. Devereux, M.D.,
and Mitchell S.V. Elkind, M.D.

Thrombosis risk in the puerperium (Kamel)

1,687,930 Californian women hospitalizations for delivery from Jan 2005 - June 2010

Thrombotic events: Stroke, MI, VTE

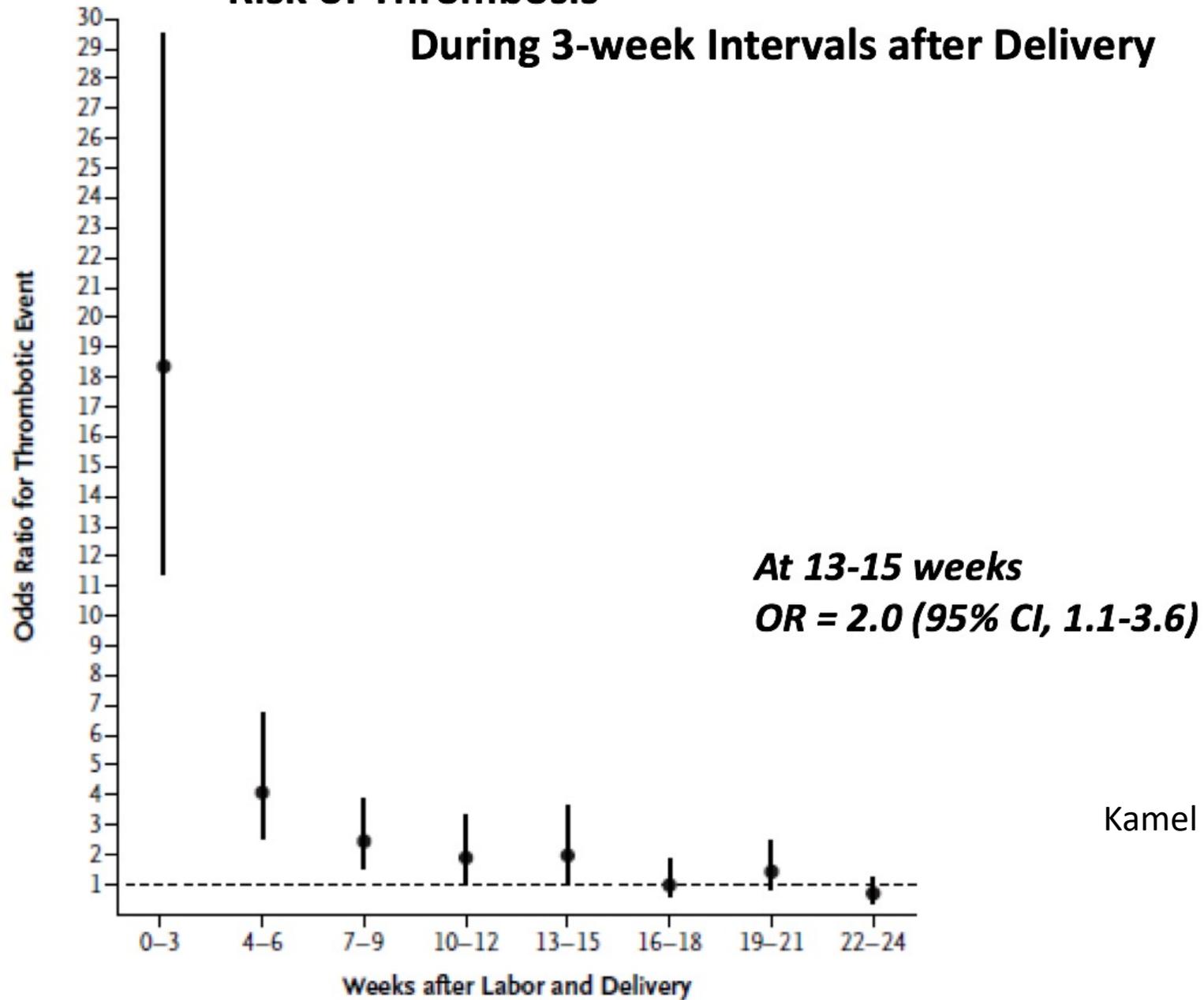
Risk factors:

- Older, White or African American v. Hispanic or Asian
- no private insurance

Other risk factors for thrombosis:

- Age > 35 years
- Eclampsia
- Primary hypercoagulable state
- Smoking
- Cesarean delivery

Risk of Thrombosis During 3-week Intervals after Delivery



Kamel NEJM 2014;370:1307

Risk of stroke based on time after delivery

<i>Time after Delivery</i>	<i>Case Period</i> <i>Rate per 100,000 deliveries</i>	<i>Crossover Period</i>	<i>Absolute Risk Difference</i>	<i>Odds Ratio (95% CI)</i>
Weeks 0-6	7.1	0.8	6.2	8.5 (4.9 - 14.8)
Weeks 7-12	0.9	0.5	0.4	1.7 (0.7 - 3.8)
Weeks 13-18	0.5	0.5	0	1.0 (0.4 - 2.5)
Weeks 19-24	0.9	0.9	0.1	1.1 (0.5 - 2.2)

Risk of thrombotic event based on time after delivery (odds ratios)

<i>Time after Delivery</i>	<i>Stroke</i>	<i>MI</i>	<i>VTE</i>	<i>Composite</i>	<i>All</i>
Weeks 0-6	8.5	13.0	12.1	10.8	22.8
Weeks 7-12	1.7	4.0	2.2	2.2	2.1
Weeks 13-18	1.0	1.0	1.6	1.4	1.0
Weeks 19-24	1.1	2.5	0.9	1.0	0.9

Risk of thrombotic event based on time after delivery (odds ratios)

<i>Time after Delivery</i>	<i>Stroke</i>	<i>MI</i>	<i>VTE</i>	<i>Composite</i>	<i>All</i>
Weeks 0-6	8.5	13.0	12.1	10.8	22.8
Weeks 7-12	1.7	4.0	2.2	2.2	2.1
Weeks 13-18	1.0	1.0	1.6	1.4	1.0
Weeks 19-24	1.1	2.5	0.9	1.0	0.9

Thrombotic events during pregnancy

***Clear increase in risk for at least 12 weeks;
though small after 6 weeks...***

Relative risk of stroke during pregnancy

<i>Stroke Type</i>	<i>Relative Risk of Stroke during Pregnancy</i>	<i>Relative Risk of Stroke during the Puerperium (6 wk)</i>
Cerebral infarction	0.7	8.7
Cerebral hemorrhage	2.5	28.5

Rare Causes of Stroke in Pregnancy

Choriocarcinoma

- Malignant transformation of trophoblasts
- Molar pregnancy; term, abortion, ectopic
- Early metastases to lungs, brain, liver, vagina
- Vascular invasion causing thrombosis and hemorrhage

Amniotic Fluid Embolism

- Dyspnea
- Hypotension
- Cardiorespiratory collapse
- DIC
- Neurologic deficits

Risks

- Difficult labor
- Multiparity
- Greater gestational age
- Advanced maternal age

Air Embolism

- C-section
- Vaginal insufflation

Sheehan Syndrome

- Anterior pituitary hypertrophy
- Limited blood supply
- Hemorrhage and hypotension

Pregnancy complications and sequelae

Pregnancy-related stroke is increasing, along with HTN and CVD

- 83% increase in stroke between 1993 and 2007, most postpartum

Hypertensive disorders of pregnancy (Pre-eclampsia, eclampsia, and gestational hypertension):

- Associated with ischemic and hemorrhagic stroke, vasculopathies (RCVS, PRES)
- Increased risk of premature birth, maternal morbidity, mortality (increased 29%)¹²
- Increased future risk of HTN, stroke, CHF, CAD, cardiovascular death

Rare causes of stroke:

- CVST, amniotic fluid embolism, air emboli, choriocarcinoma, Sheehan syndrome

Pregnancy complications and sequelae

Treatment of ischemic stroke:

- Risk of withholding therapies
- TPA and endovascular therapy may (should) be considered in pregnancy¹³

Secondary prevention:

- Comprehensive work-up, testing, cardiac screening (blood tests, imaging, consultations)
- Identification and control of risk factors
- Diagnosis and treatment of underlying disease
- Antithrombotic therapy

Conclusions for PAS

- **Strokes are uncommon complications of pregnancy.**
- **Most ischemic strokes, CVTs, and PEE-associated ICH occur during the early postpartum period, the time of greatest risk.**
- **Pregnancy and the puerperium are a hypercoagulable state.**
- **Preeclampsia-eclampsia is a major contributor underlying pregnancy-related stroke, both ischemic and hemorrhagic.**
- **Most patients with arterial and venous thrombotic events have identifiable predisposing conditions**
- **Pregnant women should receive full evaluations, with precautions for unique risks, and the full range of available therapies to minimize risk of long-term disability.**

Menopause and HRT

Younger age at menopause is associated with increased ischemic stroke risk:

- Average age is 51, onset before age 40 carries an increased risk of coronary heart disease, all cardiovascular disease and ischemic stroke ¹⁴ (Reproductive lifespan effect)

Estrogen deficiency decreases regulation of the inflammatory response ¹⁵

- Physiologic levels of estrogen can decrease activity of pro-inflammatory pathways
- Estrogen has a protective effect on blood vessels, lost after menopause



Menopause and HRT

Vasomotor symptoms are associated with increase risk of CVD and stroke ¹⁵

- 82% of women: Hot flashes and night sweats
- Associated with CVD: HTN, HLD and autonomic system affection sleep, anxiety, mood

HRT for vasomotor symptoms may increase risk of thromboembolism ¹⁶

- HRT initiated >10 years after menopause increases risk of thromboembolic disease
- HRT initiated <10 years has little to no risk
- Should be avoided if history of cardiovascular or cerebrovascular event or high risk
- Transdermal is safer than oral, underused

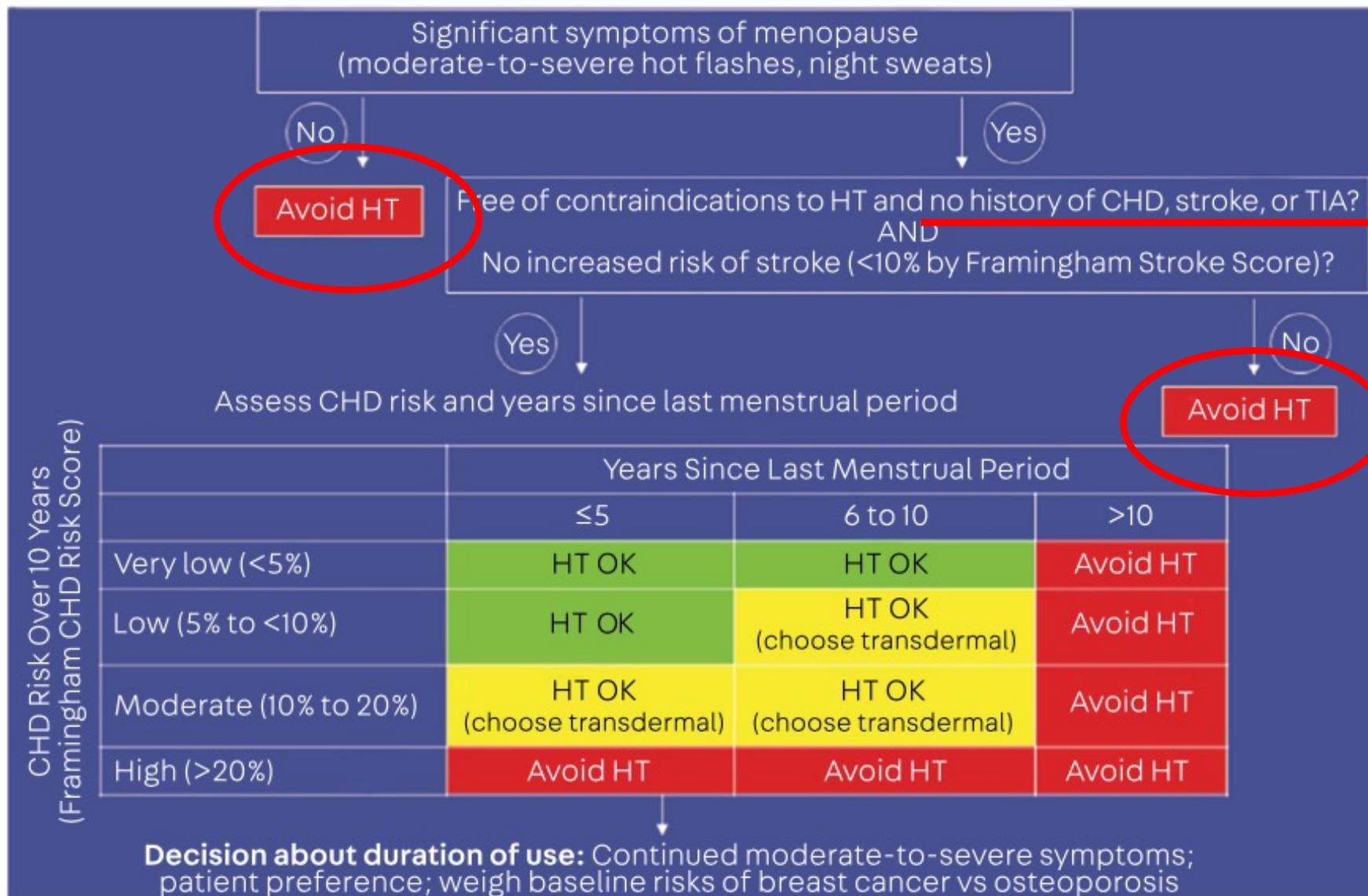


FIGURE 7-4

Flowchart for identifying appropriate women for postmenopausal hormone therapy (HT).

16

CHD = coronary heart disease; TIA = transient ischemic attack.

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Treatment and prevention of stroke

Presenting symptoms of stroke vary between women and men

- Affects timely recognition, diagnosis, and treatment
- Delays in acute stroke care

More strokes occur in women older than 80 years of age

- More women are excluded from receiving IV thrombolysis based on age criteria than men despite data-supported benefit in this age group.¹⁷
- Women obtain the SAME benefit from endovascular therapy as men¹⁸
- Revascularization is more important than age in outcome after thrombectomy.

Women are under-represented in stroke trials, about 40% of study population.^{19, 20}

- May lead to withholding beneficial therapies

Treatment and prevention of stroke

Recognition of disparities including signs and symptoms of stroke, risk factors, hormonal effects across the lifespan and additional inclusion in research will improve outcomes of stroke in women

Women's Heart Health

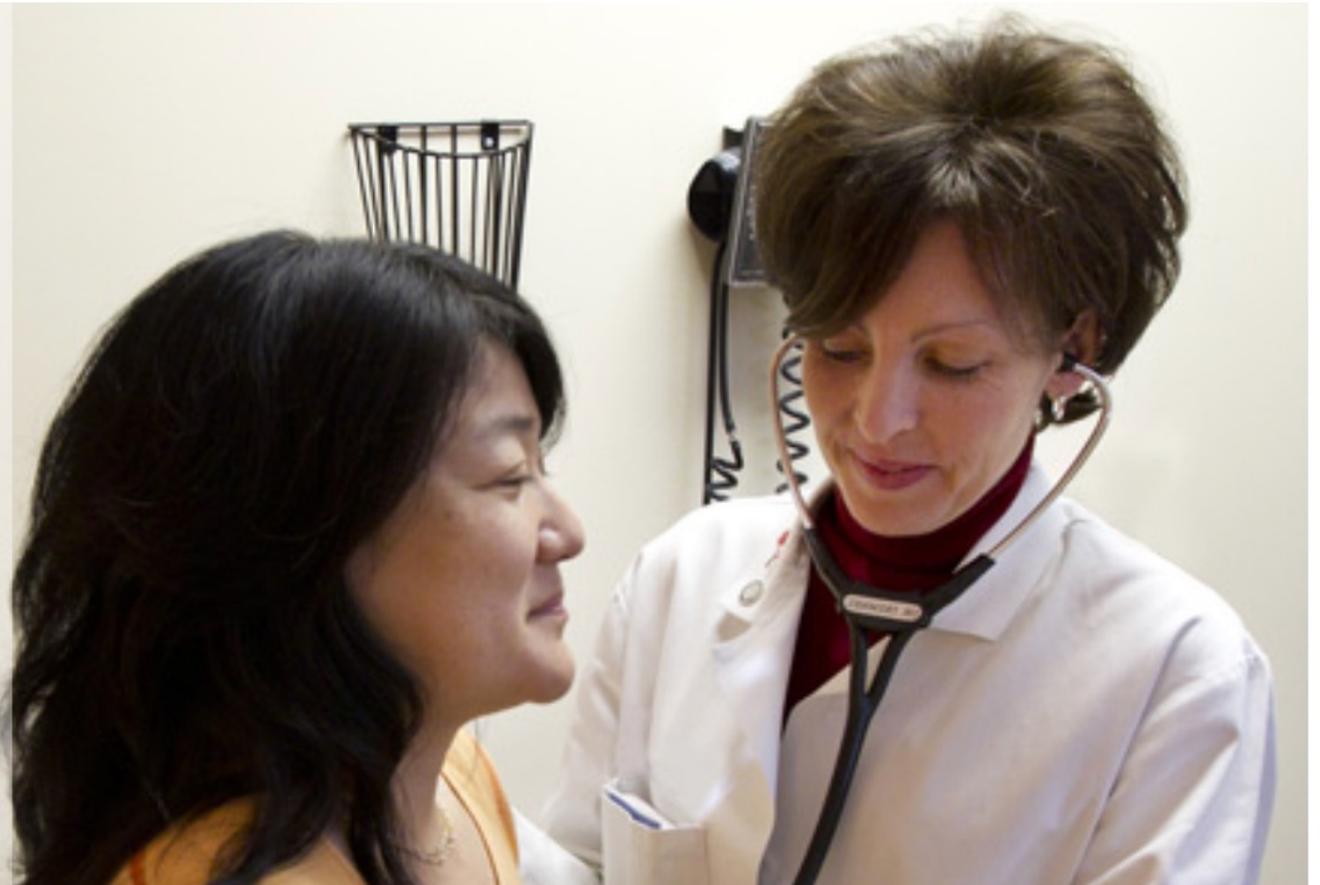
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Discussion and questions – thank you!



Additional slides

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