



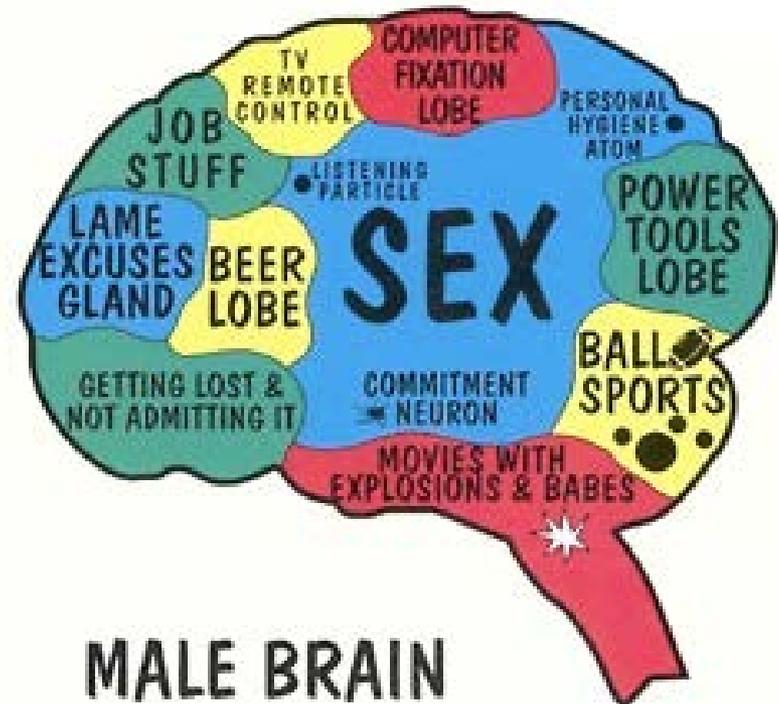
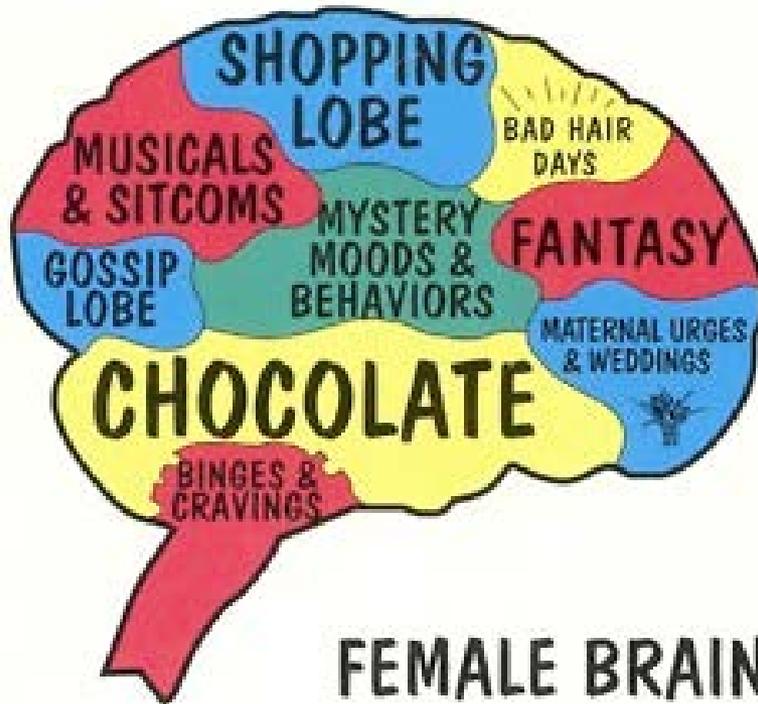
Women and Stroke



Jamelah A. Morton ARNP, ACNP-
BC, CCRN, CNRN

Disclosures

- “I have no relevant commercial relationships to disclose.”



Topics for Discussion

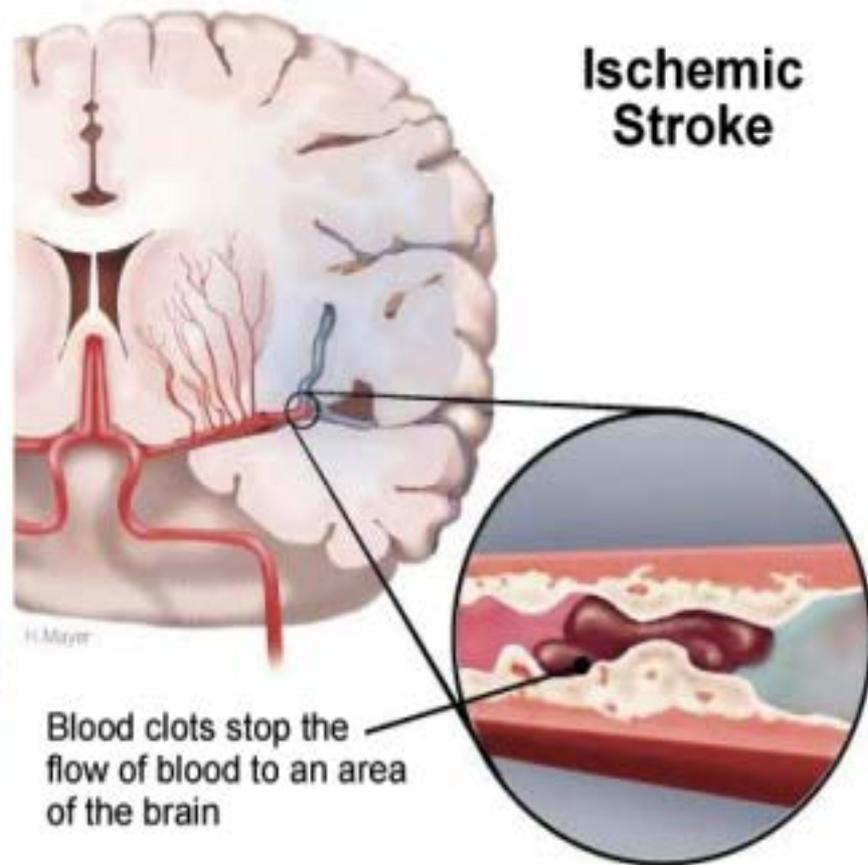
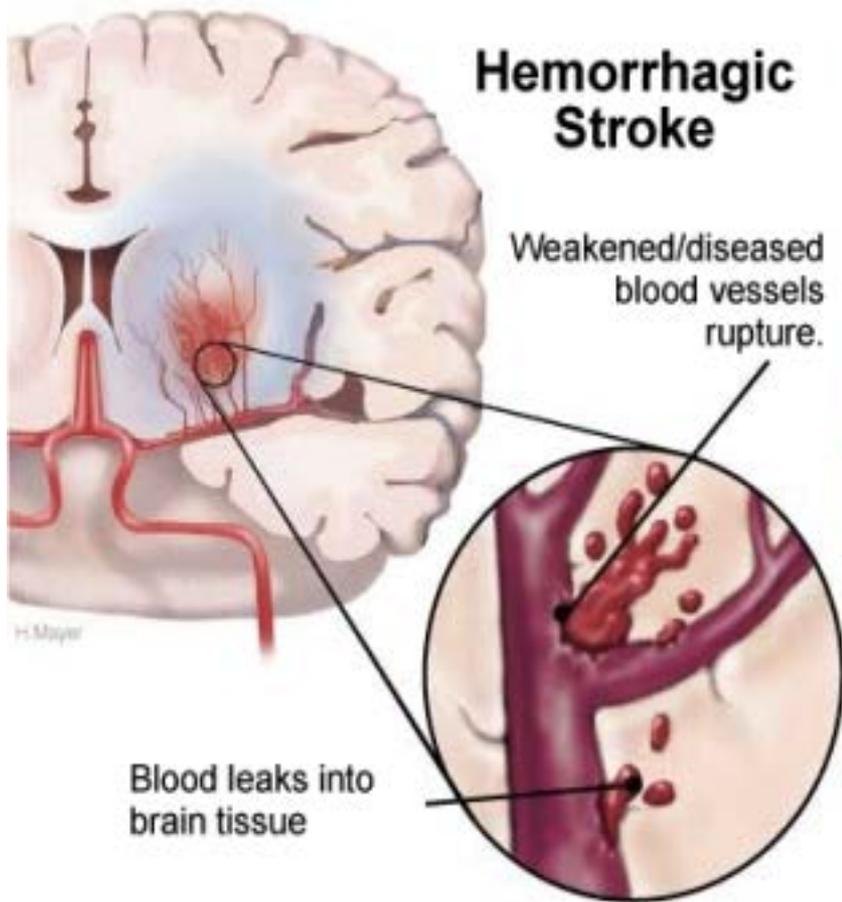
- Overview of Stroke Pathophysiology
- Incidence of stroke in women
- Risk Factors unique to women
- Signs and symptoms of stroke unique to women
- Treatment of stroke in women
- Stroke prevention in women
- Stroke outcomes in women

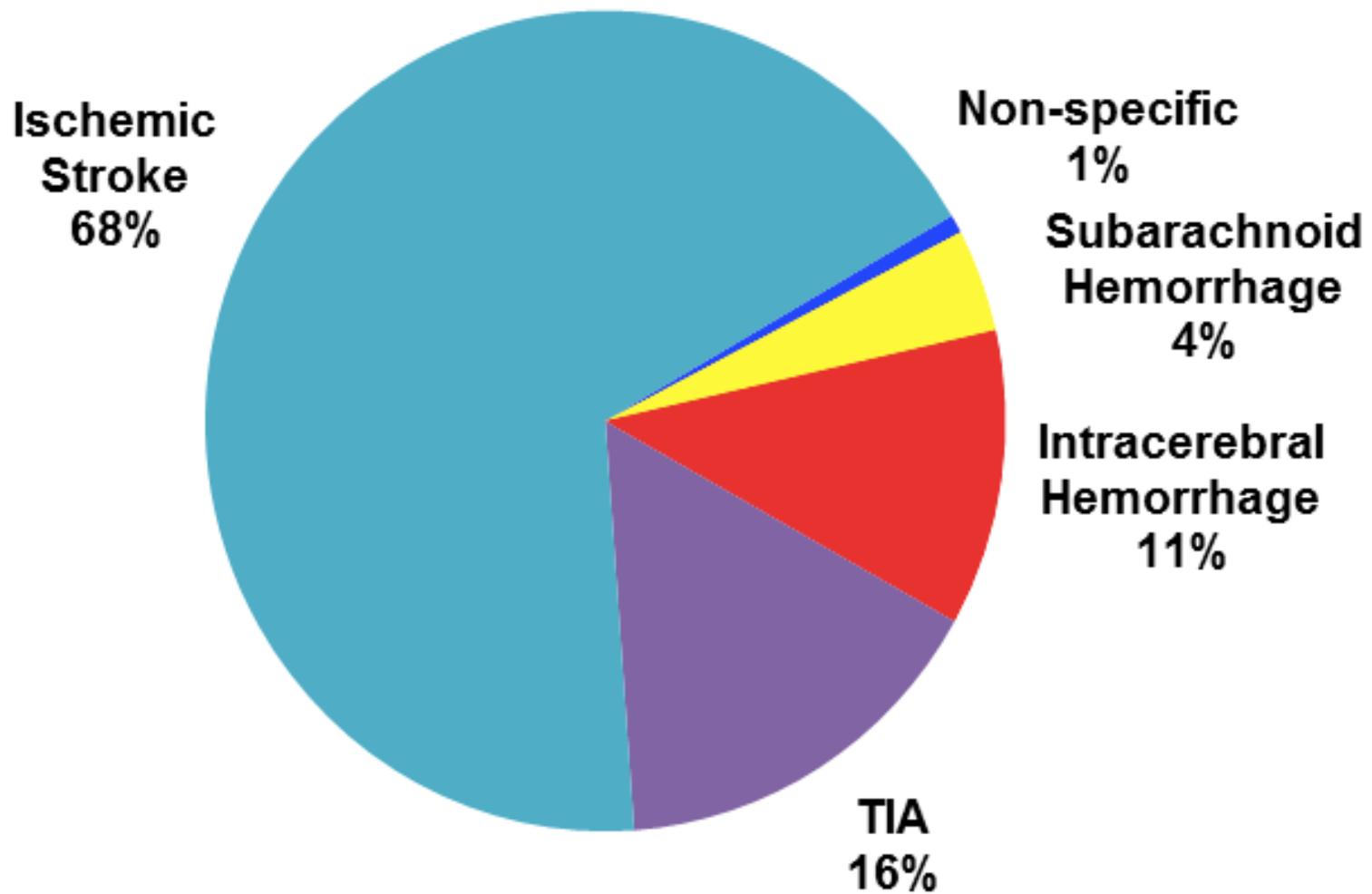


Stroke

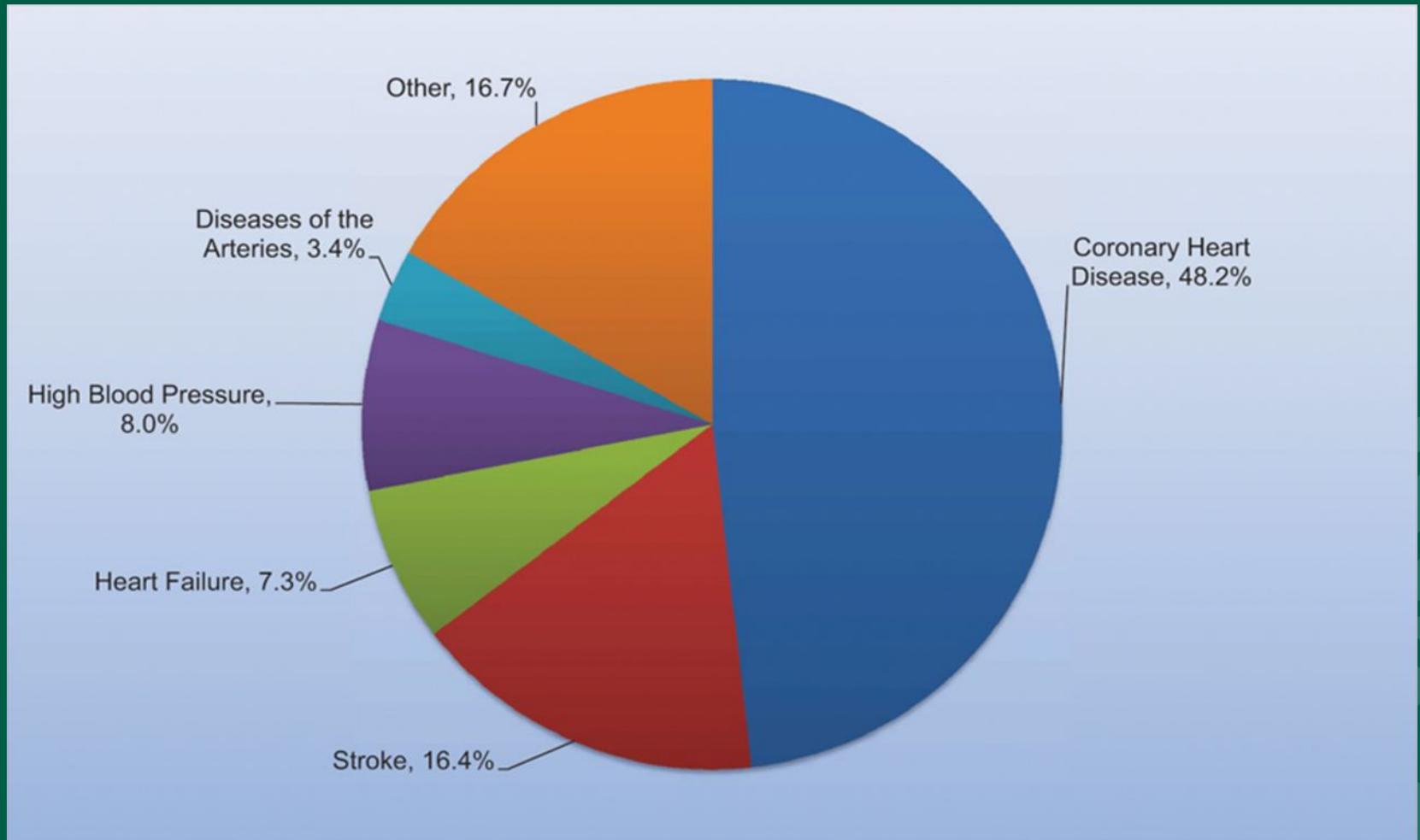
- Stroke is the loss of brain function due to a disturbance in the blood supply to the brain.
- This disturbance is due to either ischemia or hemorrhage.







Percentage breakdown of deaths attributable to cardiovascular disease (United States: 2010).



Alan S. Go et al. *Circulation*. 2014;129:e28-e292

Incidence of Stroke

- Relative stroke deaths declined by 35.1% over the past 10 years, total decline of 21.2%
- Every 40 seconds, someone in the United States has a stroke
- Approximately 795 000 experience a new or recurrent stroke
 - 610 000 (new) 185 000 (recurrent stroke events).
- Stroke accounts for 1/20 deaths in the United States.
 - Average one death from stroke every 4 minutes



Incidence of Stroke in Women

- 3.8 million stroke death yearly are women
- More than 53.5% of the estimated 795,000 new strokes in US occur in women
- 55,000 more strokes occur in women than men
- 5th leading cause death for men
- 4th leading cause of death for women 20-59 and 2nd leading cause of death women age > 60



Incidence of Stroke in Women Cont.

- Incidence of institutionalization is greater for women after stroke than men
- Ischemic stroke incidence higher after age 85
- SAH incidence related to aneurysmal rupture higher in women > 55
- ICH lower in women than men
- 60% of deaths from strokes are in women as opposed to men



Fact to Consider

- Stroke kills twice as many women as breast cancer every year
 - Estimated new female breast cancer cases and deaths US, 2015: 40, 290.
 - In 2011, stroke was the cause of death in 398,035 females.
 - Females represented 51.0% of deaths from CVD.

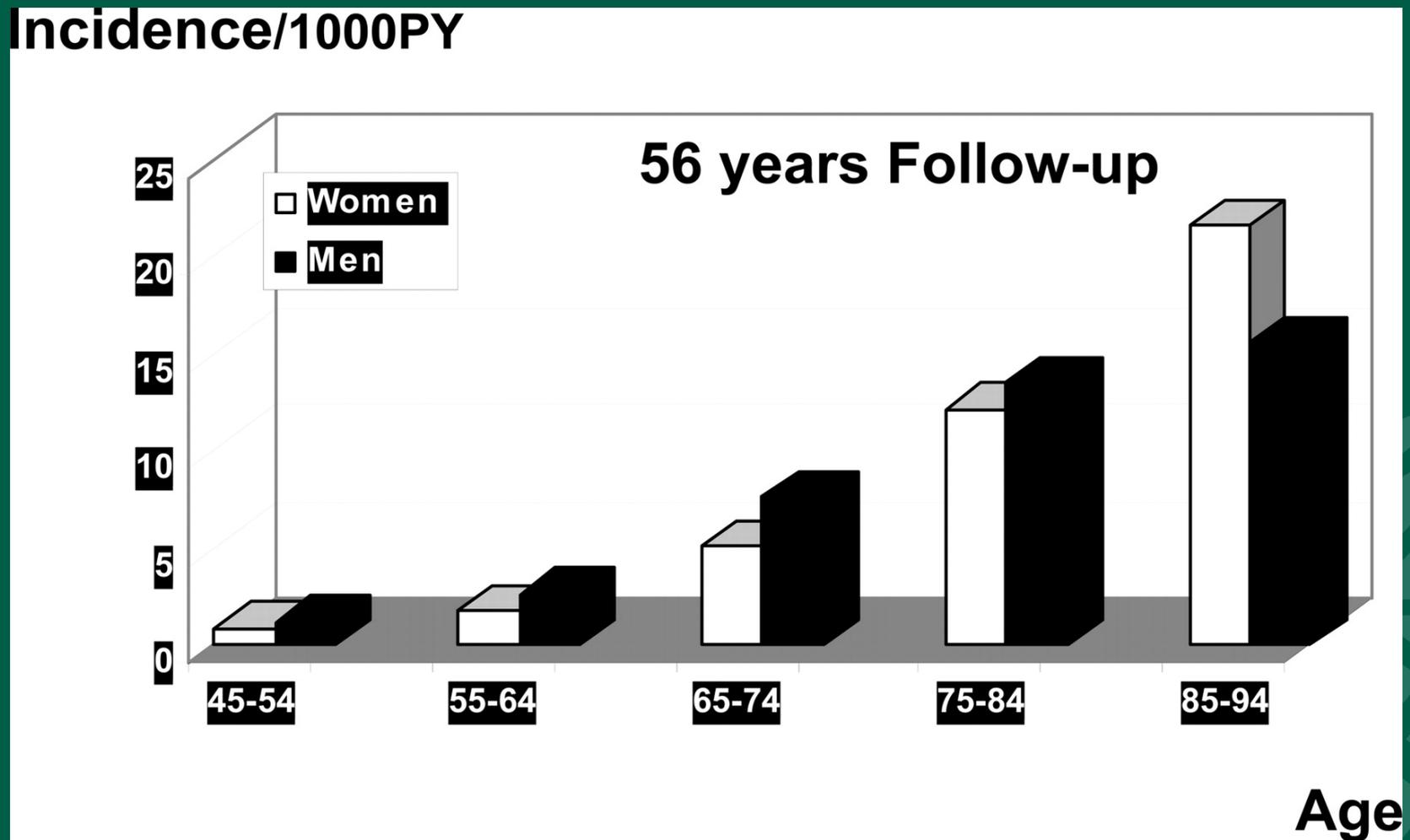


Women and Stroke

- Women have increased longevity compared to men
 - Relative risk of stroke in ages 55-75
 - Women 20% Men 17%
 - Women more likely to be widowed and live alone before stroke
 - Institutionalized post stroke



Figure 1. Incidence of stroke by age and sex over 56 years of follow-up.



Rodica E. Petrea et al. Stroke. 2009;40:1032-1037

Notable Trends in Women and Stroke

- Women have more stroke events than men
- Non-Traditional symptoms
- Less overall aggressive stroke care
- Increased life expectancy
- Increased incidence of Atrial Fibrillation and Hypertension



Gender Differences in Stroke

Arboix, A., Cartanyà, A., Lowak, M., García-Eroles, L., Parra, O., Oliveres, M., & Massons, J. (2014). Gender differences and woman-specific trends in acute stroke: Results from a hospital-based registry (1986–2009). *Clinical Neurology And Neurosurgery*, 12719-24. doi:10.1016/j.clineuro.2014.09.024

- Sample: 2318 Women and 2274 Men
 - Women older: Mean age 78 vs. 73.2
 - %> 85 women: 28.4% vs. 15.5%
 - MRI performed 33.8% men vs. 29.6% women
 - Lacunar infarcts > men: 21.5% vs. 12.2%
 - Cardioembolic infarcts > women: 26% vs. 15.6%
 - Rate of overall complications women > 31.5% vs. 26.1%
 - In hospital deaths > women 13.5% vs. 10.8%
 - > 12 days hospitalization 44.9% vs. 39%
 - Symptom free at discharge: men favorable 11.8% vs. 13.9%
 - Transfer to nursing home vs. rehab: Women 13.2% vs. 9.5%



Risk Factors Parallel in Men and Women

- Sedentary lifestyle
- Obesity
- Age
- Prior Cardiovascular Disease
- Smoking
- Metabolic Syndrome



Risk Factors More Prevalent in Women

- Migraine headaches with aura
- Atrial fibrillation
- Diabetes
- Hypertension
- Depression
- Psychological stress



Stroke
Symptoms
and **Risk Factors**
Unique to Women



Sex Explicit Risk Factors

- Pregnancy
 - Preeclampsia
 - Gestational diabetes
- Hormonal Use
 - Oral Contraceptive
 - Postmenopausal hormonal replacement therapy



Age	<55 (n:357)			55-64 (n:311)			65-74 (n:489)			>75 (n:365)		
	Female (%)	Male (%)	P	Female (%)	Male (%)	P	Female (%)	Male (%)	P	Female (%)	Male (%)	P
Atrial fibrillation	8.7	7.7	0.845	20.7	17.0	0.463	39.7	19.8	<0.0001	51.6	34.7	0.002
History of TIA	15.2	19.5	0.320	16.0	19.4	0.457	16.0	17.1	0.806	5.6	16.2	0.001
Hypertension	38.7	48.0	0.083	77.9	72.1	0.288	83.8	77.1	0.083	80.9	75.7	0.283
Prestroke disability (mRS 3-5)	4.0	3.9	1.000	4.9	2.5	0.446	12.6	8.4	0.226	17.7	8.3	0.026
mRS 3-5 at entry	66.0	64.7	0.823	65.2	63.1	0.722	80.6	73.1	0.051	88.9	75.7	0.001
Inability to lift arm	54.0	43.0	0.04	58.5	51.7	0.252	61.1	45.5	0.001	63.6	57.6	0.271
Inability to walk	60.7	55.6	0.385	72.6	65.3	0.178	81.0	66.1	0.0001	82.5	77.8	0.279
Aphasia	24.0	29.5	0.444	25.2	18.8	0.390	27.5	17.4	0.025	35.5	21.5	0.004
TACI	16.0	13.5	0.545	17.8	14.2	0.434	26.7	14.9	0.001	40.6	35.4	0.377
Large-artery atherosclerosis	4.0	17.4	0.0002	11.1	18.2	0.110	11.7	19.8	0.0197	9.2	11.1	0.593
Cardioembolism	24.0	18.8	0.240	23.7	26.1	0.693	42.5	28.5	0.0017	51.6	44.4	0.198
mRS 3-5 at discharge	40.7	41.6	0.909	43.4	38.9	0.526	60.7	39.7	0.0002	59.5	47.1	0.0191

TIA - Transient ischemic attack; mRS - Modified Rankin score; TACI - Total anterior circulation infarct

Atrial Fibrillation(Afib)

- Atrial Fibrillation higher in >85 women (1,203.7 per 100,000 persons) than in men (1,077.4 per 100,000 persons)
- Women with Afib have a moderately increased risk for embolic strokes
- Greater thromboembolic risk when not on anticoagulation
- Increased incidence with DM, HTN and CHF



Atrial Fibrillation and Women

Piccini, J. P., Simon, D. N., Steinberg, B. A. (2016). Differences in clinical and functional outcomes of atrial fibrillation in women and men: Two-year results from the ORBIT-AF Registry. *JAMA Cardiol*; (3):282-291

- Evaluate clinical and functional outcome of atrial fibrillation in women and men. Study concluded:
 - Women more symptomatic, less functional, had worse quality of life outcome despite less persistent Afib
 - Women more likely to undergo ablation
 - Women experience higher risk of stroke or systemic type embolism
 - Higher adjusted survival and lower risk cardiac death



Atrial Fibrillation and Women Stroke Risk

- Perez, M. v., Wang, P. J., Larson, J. C., et al. (2013) Heart, 99:1173-1178. doi:10.1136/heartjnl-2013-303798
 - Prospective observational study, evaluated the risk factors for Afib in postmenopausal women and measure the population burden of modifiable risk factors
 - Rates of Afib sig increased with age, higher for women with CHD rate of afib was relatively 2.8% with CHD and 4.9% with CHD
 - 42.4% had history of HTN
 - Diabetes
 - Heart failure strongest independent predictor
 - Developed Afib 1.02% per year

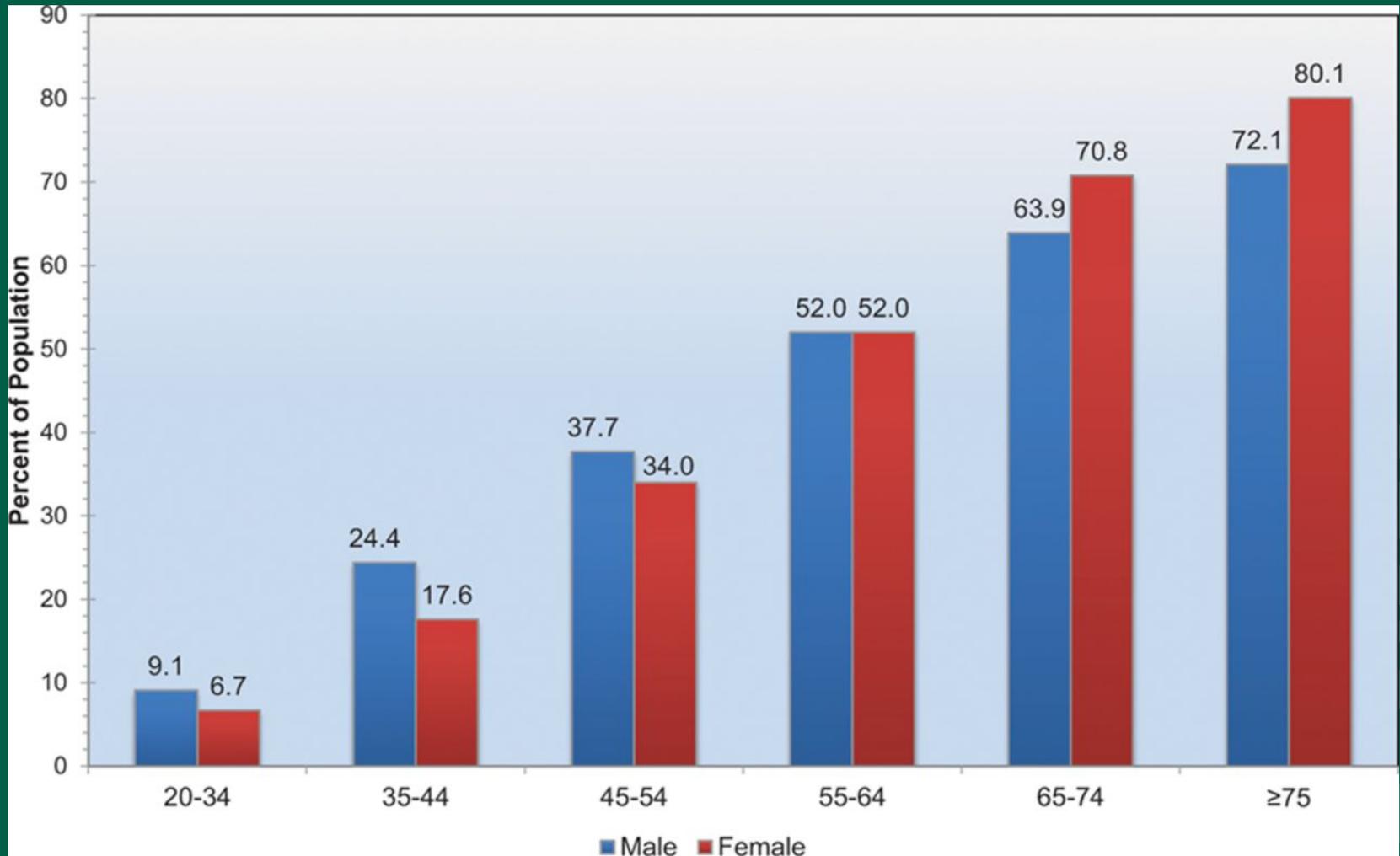


Stroke in Women and Diabetes

- Peters, S. E., Huxley, R. R., & Woodward, M. (2014). Diabetes as a risk factor for stroke in women compared with men: A systematic review and meta-analysis of 64 cohorts, including 775385 individuals and 12539 strokes. *Lancet*, 383 North American Edition(9933), 1973-1980. doi:10.1016/S0140-6736(14)60040-4
 - Estimate comparative sex difference that exists for the risk of diabetes-related to stroke.
 - Results
 - After adjustment, the relative risk of stroke associated with diabetes was 2.28 (95% CI 1.93–2.69) for women and 1.83 (1.60–2.08) for men, and the ratio of relative risks between women and men with diabetes was 1.27 (1.10–1.46).
 - Conclusion: The risk of stroke in women with diabetes is significantly higher than that of men with diabetes independent of other risk factors.



Prevalence of high blood pressure in adults ≥ 20 years of age by age and sex (National Health and Nutrition Examination Survey: 2007–2010).



Alan S. Go et al. *Circulation*. 2014;129:e28-e292

Migraine Incidence

- 18% of American women, 6% of men, and 10% of children experience migraines
- Common between the ages of 25 and 55
- Affects approx. 28 million women in the U.S.
- 1 in 4 women will experience migraine in their lives
- Three times as many women than men suffer migraine in their adult lives



Migrainous Infarctions

- *Migrainous Infarctions*
 - One or more migraine aura symptoms associated with an ischemic brain lesion in the appropriate territory demonstrated by neuroimaging.
 - Migraine with aura similar to previous attacks except one or more aura type symptom last > 60 minutes
 - Infraction present on neuro-imaging
 - Symptoms cannot be explained by any other means
 - The stroke must occur in the area of the brain that can explain the aura symptoms



Migraine and Stroke Risk in Women

- Kurth, T., Slomke, M. A., Kase, C. S., Cook, N. R., Lee, M. I., Gaziano, J. M., Diener, H. C., and Buring, J. E. (2005). Migraine, headache, and the risk of stroke in women: A prospective study. *Neurology*, 64: 1020-1026
- Evaluated migraine headaches and stroke risk in women. This study concluded:
 - Participants who had migraine with aura showed a 1.5 fold increase in the risk of total strokes after adjusting for confounders
 - 1.7 fold increase in the risk of ischemic strokes
 - Women who reported migraine headache in the last year had increased risk for ischemic strokes
 - Increase in stroke was more prominent in women < 55 years



Contraception

- Increases the risk of stroke from 1.4-to 2.0-folds in young women
- Low absolute risk
- Risk increases with
 - Smoking
 - HTN
 - Hyperlipidemia
 - DM
 - Women who take even a low-estrogen birth control pill may be twice as likely to have a stroke than those who don't and the risk may increase if other risk factors are present (AHA, 2014)

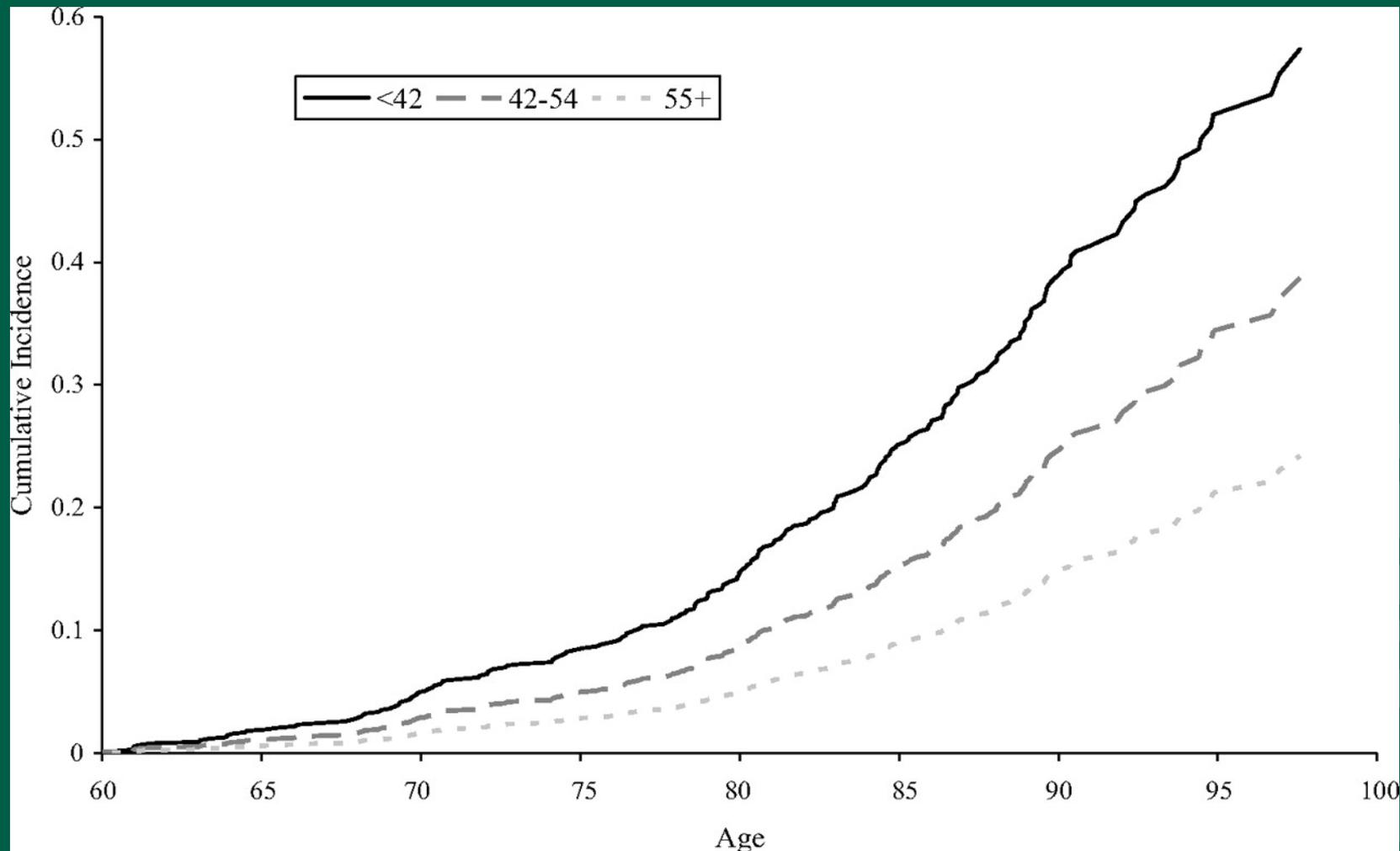


Menopause/Hormone Replacement Therapy

- Yang, D., Li, J., Yuan Z., (2013). Effects of hormone replacement therapy on cardiovascular outcomes: A meta analysis of randomized controlled trials. *PLoS ONE* 8(5): e62329. doi:10.1371/journal.pone.0062329
 - Combined hormone replacement therapy was associated with statistically significant in the risk of stroke when compared with placebo (RR, 1.25; 95% CI: 1.04-1.05; P= 0.01)
 - Estrogen therapy alone on stroke: Out of 12847 participants 423 had stroke events related to estrogen therapy. Showing that estrogen therapy increased stroke risk by 27% when compared with placebo (RR, 1.27; 95% CI: 1.06-1.53 P= 0.01)



Figure. Cumulative incidence of ischemic stroke by age and age at natural menopause among women in the Framingham Heart Study (n=1430).



Lynda D. Lisabeth et al. *Stroke*. 2009;40:1044-1049

Depression and Psychological Stress

Jackson, C. A, & Mishra, G. D. (2013)
Depression and risk of stroke in the mid-aged women: A prospective longitudinal study.
American Heart Association Inc.
doi:10.1161/STROKEAHA.113.001147

- Evaluated association with depression and stroke among middle aged women.
 - >2 fold greater odd of stroke (OR, 2.41; 95% CI, 1.78-3.27).
 - Strong association in middle aged women



Pregnancy

- Stroke risk increases significantly with pregnancy
 - Natural changes in the body increases stress on the heart
 - High blood pressure
 - Preeclampsia and eclampsia higher risk for coronary heart disease and stroke later in life
 - High blood pressure during pregnancy associated increased risk morbidity and mortality due to vascular disease
 - Increased risk during perinatal period



Stroke and Pregnancy

- Canoy, D., Cairns, B. J., Balkwill, A., Wright, L., Khalil, A., Beral, V., Green, J., & Reeves, G. (2016). Hypertension in pregnancy and risk of coronary heart disease and stroke: A prospective study in a large UK cohort. *International Journal of Cardiology*. 222:1012-1018
- Evaluated the relationship between history of HTN during pregnancy and development of CHD and ischemic and hemorrhagic stroke
 - Treatment for HTN warranted mid 50's 27% with hypertensive pregnancy vs. 10% without
 - Relative risk for CHD event with hypertensive pregnancy 1.25 (95% CI 1.27 to 1.31 non-hypertensive pregnancy)
 - Mortality r/t CHD 1.35 (95% CI 1.29 to 1.42)
 - Ischemic stroke 1.29 (95% CI 1.23 to 1.35)
 - Hemorrhagic stroke (1.14 [95% CI 1.07 to 1.21]).



Stroke and Pregnancy

- Crovetto, F., Somigliana, E., Peguero, A. & Fiqueras, F. (2013) Stroke during pregnancy and preeclampsia. *Women's Health*. 25(6).
doi:10.1097/GCO.0000000000000024.
 - Systematic review to summarize existing data regarding the association, diagnosis as well as management in preeclampsia/eclampsia
 - Pregnancy high risk for stroke, highest 2 weeks puerperium (postpartum) period. Pre-eclampsia and eclampsia most important risk factors
 - Hemorrhagic stroke most common
 - Headache and change in LOC evaluation promptly. Drugs to treat the hypertension and seizure prevention initiated
 - Prophylactic use of ASA before 16 week gestation in high risk group



Signs and Symptoms

- Mochari-Greenberger, H., Towfighi, A., & Mosca, L. (2014). National women's knowledge of stroke warning signs, overall and by race/ethnic group. *Stroke*, 45: 1180-1182
 - Cross sectional survey design to evaluate contemporary knowledge of stroke warning signs and intent to call 911 if warning signs occur, overall and by race and ethnic group, among a nationally represented sample
 - Sudden weakness/numbness of face limb or one side 51%... No diff by race or ethnicity
 - Loss of trouble talking or trouble understanding 44% > whites vs. Hispanic women
 - Severe headache 23%, sudden dimness or loss of vision in 1 eye 18%, unexplained dizziness 20%
 - 84% identified to call 911 with stroke symptoms



Stroke Symptoms

- Sudden numbness or weakness of face, arm, or leg (mainly on one side of the body)
- Sudden trouble seeing in one or both eyes
- Sudden trouble walking, dizziness, or loss of balance
- Sudden confusion or trouble talking or understanding speech
- Sudden bad headache with no known cause



Unique Stroke Symptoms in Women

- Sudden face and arm or leg pain
- Sudden hiccups
- Sudden nausea (feeling sick to your stomach)
- Sudden tiredness
- Sudden chest pain
- Sudden shortness of breath (feeling like you can't get enough air)
- Sudden pounding or racing heartbeat
- Loss of consciousness
- Agitation
- Hallucinations
- Sudden change in behavior
- Seizures



Stroke Symptoms Disparities

- Lisabeth, L. D., Brown, D, L., Hughes, R., Majersik, J. J., & Morgenstern, L. B. (2009). Acute stroke symptoms comparing Women and Men. *Stroke*, 40:2031-2036.
- Prospectively investigated gender differences in stroke symptoms
 - 51.8% (n=116) reported at least 1 nontraditional stroke/TIA symptom in comparison to 43.9% (n=104)
 - Nontraditional stroke/TIA symptom were 1.37 (95% CI, 0.95–1.98) times greater in women compared with men.
 - Most prevalent nontraditional symptom was mental status change
 - 23.2% of women and 15.2% of men (P=0.03).



Stroke Treatment Disparities

- De Ridder, I., Dirks, M., Niessen, L. & Dippel, D. (2013). Unequal access to treatment with intravenous alteplase for women with acute ischemic stroke. *Stroke* 2013;44:2610-2612
 - Analyzed data from the Promoting Acute Thrombolysis for Ischemic Stroke Study (PRACTISE) to evaluate the treatment difference for men and women with the use of alteplase in acute ischemic stroke.
 - 5515 Patients: 2778 women, 2737 men
 - Age variant: women 4 years older
 - Median NIHSS: 6 for women, 5 for men
 - Fewer women treated with intravenous alteplase (11 % vs. 14%; odd ratio, 0.8; 95% CI 0.7-0.9).
 - 27% of women arrived to the ED within 4 hours vs. 33% of men (CI, 0.7-0.9)
 - Door to onset of symptoms was 27 minutes longer for women



Stroke in Women

- Asdaghi, N., Romano, J. G., Kefeng, W., Ciliberti-Vargas, M. A., Koch, S., Gardener, H., & ... Dong, C. (2016). Sex Disparities in Ischemic Stroke Care: FL-PR CReSD Study (Florida-Puerto Rico Collaboration to Reduce Stroke Disparities). *Stroke* (00392499), 47(10), 2618-2626. doi:10.1161/STROKEAHA.116.013059
 - Evaluated sex specific differences in risk factor profile, presentation, thrombolytic rates and performance of the GWTG quality measures
 - Women more likely to have hypertension 67% vs. 63%
 - Women less likely to receive thrombolysis than men (odds ratio, 0.92; 95% CI 0.86-0.99; $P=0.02$)
 - Longer ER assessment time and less likely to have DTN time < 1hour (odds ratio, 0.83; 95% CI, 0.71-0.97; $P=0.02$) compared to men
 - Women older more likely to have experienced a prior stroke and have high prevalence of AFIB 19% vs. 16% $P<0.0001$



Treatment of Stroke in Women

- Rist, M. P., Buring, J. E., Kase, C. S., & Kurth, T. (2013). Effects of low-dose aspirin on functional outcome from cerebrovascular events in Women. *Stroke*. 2013;44:432-436
 - Utilized data from the Women's Health Study and examined the effects of randomized assignment of 100 mg of ASA every other day on functional stroke outcomes after cerebrovascular accident.
 - ASA group had sig lower risk TIA compared to non-ASA group (odds ratio= 0.77; 95% CI. 0.63-0.94
 - ASA group without or with a remote history of smoking showed a significant reduction in TIA (odds ratio = 0.67; 95% CI, 0.48-0.93 for mRS 0-1).
 - Slight increase risk hemorrhagic stroke with ASA slightly higher mRS
 - No significance found in reduction of functional outcomes

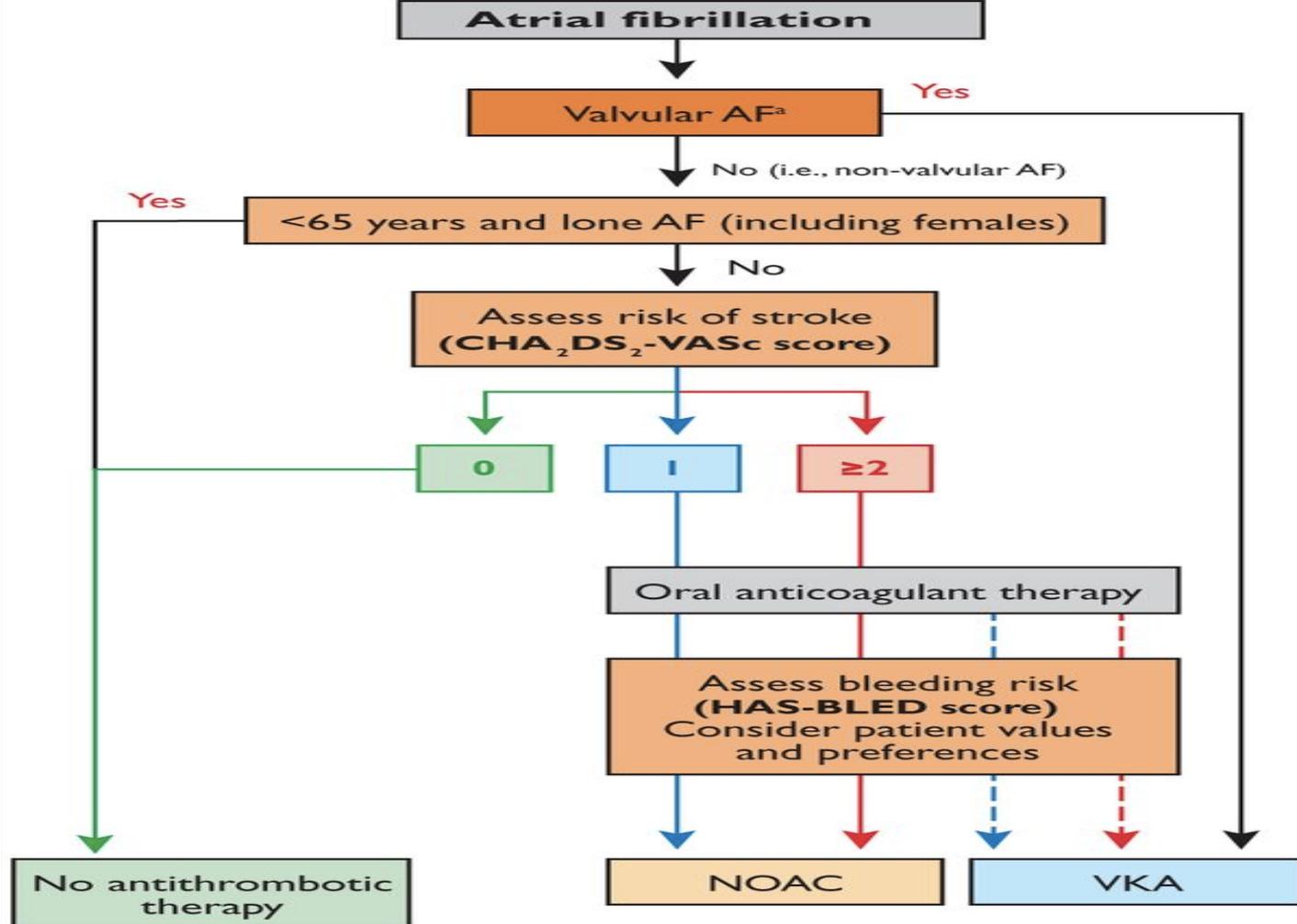


CHADS₂ → CHA₂DS₂VASc

CHADS2 Risk	Score
CHF	1
Hypertension	1
Age > 75	1
Diabetes	1
Stroke or TIA	2

CHA2DS2-VASc Risk	Score
CHF or LVEF ≤ 40%	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Stroke/TIA/ Thromboembolism	2
Vascular Disease	1
Age 65 - 74	1
Female	1

From ESC AF Guidelines
<http://escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-afib-FT.pdf>



Antiplatelet therapy with aspirin plus clopidogrel, or—less effectively—aspirin only, should be considered in patients who refuse any OAC, or cannot tolerate anticoagulants for reasons unrelated to bleeding. If there are contraindications to OAC or antiplatelet therapy, left atrial appendage occlusion, closure or excision may be considered.

Colour: CHA₂DS₂-VASc; green = 0, blue = 1, red ≥2.

Line: solid = best option; dashed = alternative option.

AF = atrial fibrillation; CHA₂DS₂-VASc = see text; HAS-BLED = see text;

NOAC = novel oral anticoagulant; OAC = oral anticoagulant;

VKA = vitamin K antagonist.

^aIncludes rheumatic valvular disease and prosthetic valves.

Table 2 10 Strategies for Preventing Stroke in Women

Recommendation	Class	Level of Evidence
Women with asymptomatic carotid stenosis should be screened for other treatable risk factors for stroke, and appropriate lifestyle changes and medical therapies should be instituted.	I	C
In women who are to undergo CEA, aspirin is recommended unless contraindicated, because aspirin was used in every major trial that demonstrated efficacy of CEA.	I	C
Prophylactic CEA performed with <3% morbidity/mortality can be useful in highly selected patients with an asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound).	Ila	A
For women with recent TIA or IS within the past 6 months and ipsilateral severe (70%-99%) carotid artery stenosis, CEA is recommended if the perioperative morbidity and mortality risk is estimated to be <6%.	I	A
For women with recent TIA or IS and ipsilateral moderate (50%-69%) carotid stenosis, CEA is recommended depending on patient-specific factors, such as age and comorbidities, if the perioperative morbidity and mortality risk is estimated to be <6%.	I	B
When CEA is indicated for women with TIA or stroke, surgery within 2 weeks is reasonable rather than delaying surgery, if there are no contraindications to early revascularization.	Ila	B
Aspirin therapy (75-325 mg/d) is reasonable in women with diabetes mellitus unless contraindicated.	Ila	B
If a high-risk (ie, 10-year predicted CVD risk $\geq 10\%$) woman has an indication for aspirin but is intolerant of aspirin therapy, clopidogrel should be substituted.	I	B
Aspirin therapy can be useful in women ≥ 65 years of age (81 mg/d or 100 mg every other day) if BP is controlled and the benefit for IS and MI prevention is likely to outweigh the risk of gastrointestinal bleeding and hemorrhagic stroke.	Ila	B
Aspirin therapy may be reasonable for women <65 years of age for IS prevention.	Ilb	B

Abbreviations: BP, blood pressure; CEA, carotid endarterectomy; CVD, cardiovascular disease; MI, myocardial infarction; TIA, transient ischemic attack; IS, ischemic stroke.

Stroke Prevention in Women

- Screen for HTN prior to starting oral contraceptives
- HTN in Preeclampsia should be treated with safe antihypertensive medications
- Migraine with aura should avoid smoking
- Regular exercise moderate physical activity
- Hormone replacement therapy not recommended for primary or secondary prevention of stroke



Stroke Prevention in Women Cont.

- History of preeclampsia should have early assessment of cardiovascular risk and lifestyle modification
- Recommendation for moderate HTN in pregnancy
 - Consider treating blood pressure 150-159 mm Hg systolic and 100-109 mm Hg diastolic
 - American congress of obstetrics and gynecology recommends treatment 160/110



Stroke Outcomes for Women

- Lai, S. M., Duncan, P. W., Dew, P., & Keighley, J. (2005). Sex differences in stroke recovery. *Preventing Chronic Disease, Public Health Research Practice and Policy*. 2(3).
 - Females less likely than men to gain independence with basic ADL 6 months post stroke
 - After three months 13% vs. 28% complete eight of nine IADL completely without assistance. Six months 18% vs. 34%
 - Less likely to score ≥ 90 on SF-36 PF scale 6 months post stroke



Summary

- Women have unique presentation of stroke symptoms
- Women have unique risk factors and treatment challenges
- It is pertinent to continually assess the unique characteristics of this disease in women in order to afford optimal care outcomes
- Plan sex specific interventions



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