

Gender Disparities in Ischemic Stroke

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Disclosures

- Speakers Bureau: Genentech

Gender Differences in Stroke: From Prevention to Outcomes

Epidemiology

Minority women and
stroke

Risk Factors



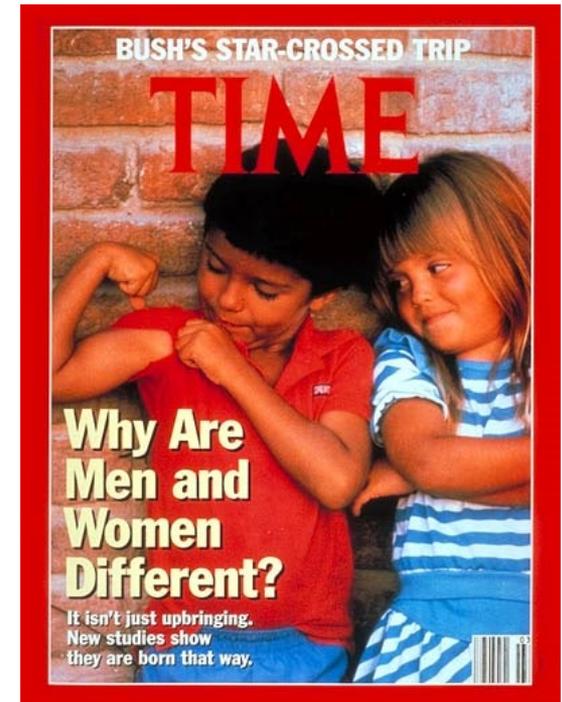
Outcomes

Treatment Effect

Primary Prevention

Pertinent Clinical Questions

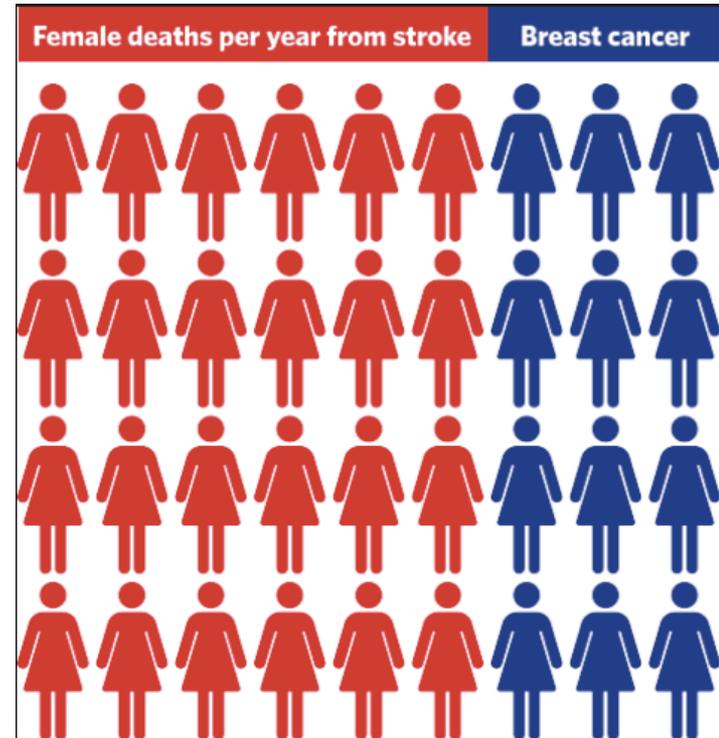
- Why do we persistently see differences between men and women?
 - Genetic
 - Hormonal
 - Environmental
- Are these differences clinically relevant?
 - Should we approach men and women the same?
 - Should we counsel women and men differently?



EPIDEMIOLOGY

Epidemiology

- 795,000 strokes in the US every year
- Lifetime risk of stroke is 1 in 6 men; **1 in 5 women**
- 55,000 more women have a stroke than men each year
- 5th leading cause of death for men; **3rd for women**



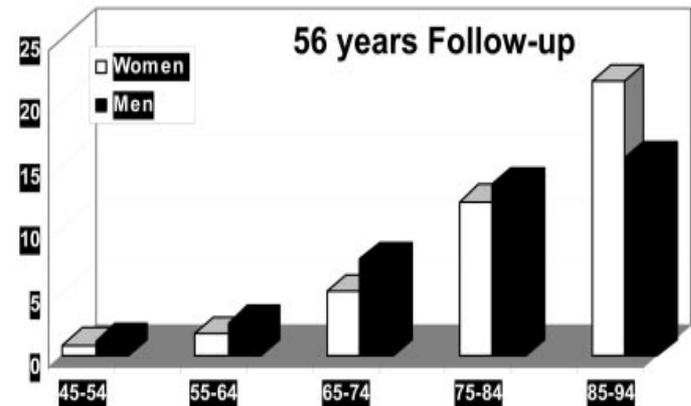
The Framingham Study: The Natural History of Stroke

- N = 10,076/ 5394 females
- 45 years, stroke-free and were followed to first stroke incident
- Population is of white or European descent only

Results

- 1136 strokes (638 women)
- Women were older
- Higher lifetime incidence driven by the oldest age group
- No significant difference in stroke subtype, severity or case fatality
- **Women were more likely to be disabled at 3 and 6 months, more likely to be single and 3.5 times more likely to be institutionalized**

Incidence/1000PY



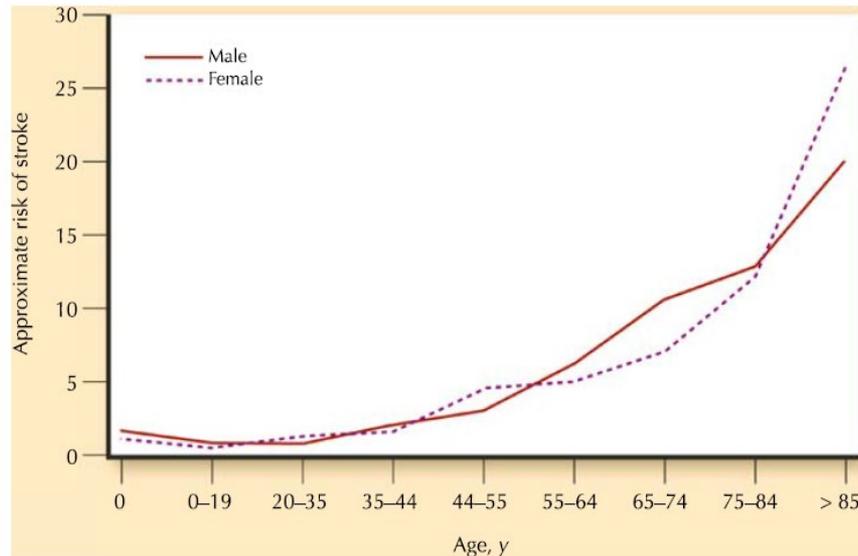
Age

Gender-Specific Stroke Risk by Age

Table 1 Comparison of stroke prevalence in men vs women and across age groups 35 to 64 years in NHANES 1999 to 2004

Variable	Comparators		Odds ratio	95% CI	p Value
	Women*	Men*			
Age group					
35-44 years	1.2%	1.0%	1.2142	0.4715-3.1268	0.6876
45-54 years	2.5%	1.0%	2.3903	1.3205-4.3267	0.0040
55-64 years	3.4%	3.0%	1.1256	0.6218-2.0376	0.6961

Tofighi A. et al Neurology 2007



Persky RW Curr Cardiol Rep 2010

GENDER-SPECIFIC RISK FACTORS

Stroke Risk Factors

Non-modifiable

- Age
- Sex
- Race
- Genetics
- Migraine (with aura)
- Hormonal status

Modifiable

- Hypertension
- Hypercholesterolemia
- Diabetes Mellitus
- Tobacco use
- Atrial fibrillation
- Metabolic syndrome
- Exogenous hormones
- Pregnancy

More About Gender-Specific Risk

- Women have lower rate of stroke without comorbidities, but a greater rate with four or more risk factors¹
 - HTN, atrial fibrillation and DMII occur more in men, but women with these comorbidities demonstrate higher stroke risk
 - Metabolic syndrome doubles ischemic stroke risk in women, but has no effect on men's risk²

Atrial Fibrillation and Stroke

- Increases risk of stroke 4 – 5 fold
- Risk is dependent on other risk factors
 - Example: Age
 - Risk of stroke is 1.5% in those aged 50 – 59%
 - 25% in those > 80 years old (WOMEN!)
- Women with a fib are less likely to receive anticoagulation (aOR 0.93; 95% CI, 0.88 – 0.98)¹
- The ATRIA study² in Sweden showed
 - Age by sex interaction in women with a fib
 - A greater reduction in stroke in women compared to men with warfarin use (60% vs 40% RR)

¹Reeves MJ Stroke 2009 (GWTG)

²Fang MC Circulation 2005 (ATRIA study)

Pregnancy and Preeclampsia

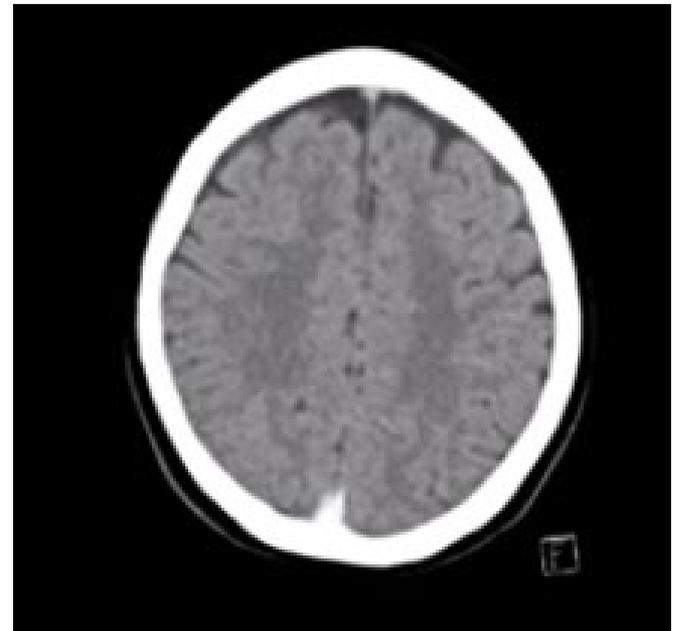
- Risk is small (34/100K deliveries) but higher than non-pregnant young women
 - Acquired hypercoagulable disorder
 - Increased risk of vasculopathy
- Complications of pregnancy are associated with higher risk for CVD and stroke in the future (18.2% vs 1.7% within 10 yrs)
 - Preeclampsia
 - Gestational DM

Preeclampsia and Pregnancy: Recommendations

- Women with chronic HTN or history of pregnancy-related HTN should take low-dose aspirin from 12th week of gestation until delivery (Class I Level A)
- Control HTN: methyldopa, labetalol, nifedipine (Class I Level A)
 - Atenolol, ACEI, ARBS are contraindicated
- Consider screening women with preeclampsia 6 months to 1 year post-partum
- Evaluate and treat other stroke risk factors (Class IIa, Level C)
- Document preeclampsia as a stroke risk factor

Female-Specific Risks: Central Venous Thrombosis

- More prevalent in women
 - Incidence in women is 1.86/100K compared to 0.75/100K in men
 - **As high as 2.78/100K from 31 – 50 y/o**
- Increased risk attributable to:
 - Inheritable pro-thrombotic conditions
 - Acquired conditions (cancer, infection)
 - Female specific (OCPs, pregnancy)
- Recurrence risk is low, but specific data is sparse



CVT Recommendations

- **Work up: look for inherited and acquired coagulopathies**
 - CBC, PT, aPTT
 - Genetic mutations: Factor V, II mutations, anti-thrombin III mutation
 - Coagulation specific: Protein C and S, lupus anticoagulant
 - Underlying inflammatory/autoimmune disorder (ESR, CRP, ANA, ANCA)
 - Medication history
- **Treatment: anticoagulation (Class IIb; Level C)**
 - Provoked – 3-6 months
 - Unprovoked – 6 -12 months
 - Recurrent or severe thrombophilia – indefinite
 - During Pregnancy
 - LMWH in full anticoagulant doses throughout pregnancy
 - Continue for \geq 6 weeks post partum

Female-Specific Risks: Oral Contraceptives

- OCPs – 10.7 million women in the US
 - Low risk (3.4/100K) in women aged 15 – 19
 - HIGH RISK (64.4/100K) in women aged 45 – 49
 - No increased risk with progesterone only OCPs¹
- Nuvaring, transdermal patch, IUDs have not been fully evaluated
 - Nuvaring has been associated with 2.49 fold increased risk²
- Risk is increased further when combined with cigarette smoking, HTN, migraine headaches

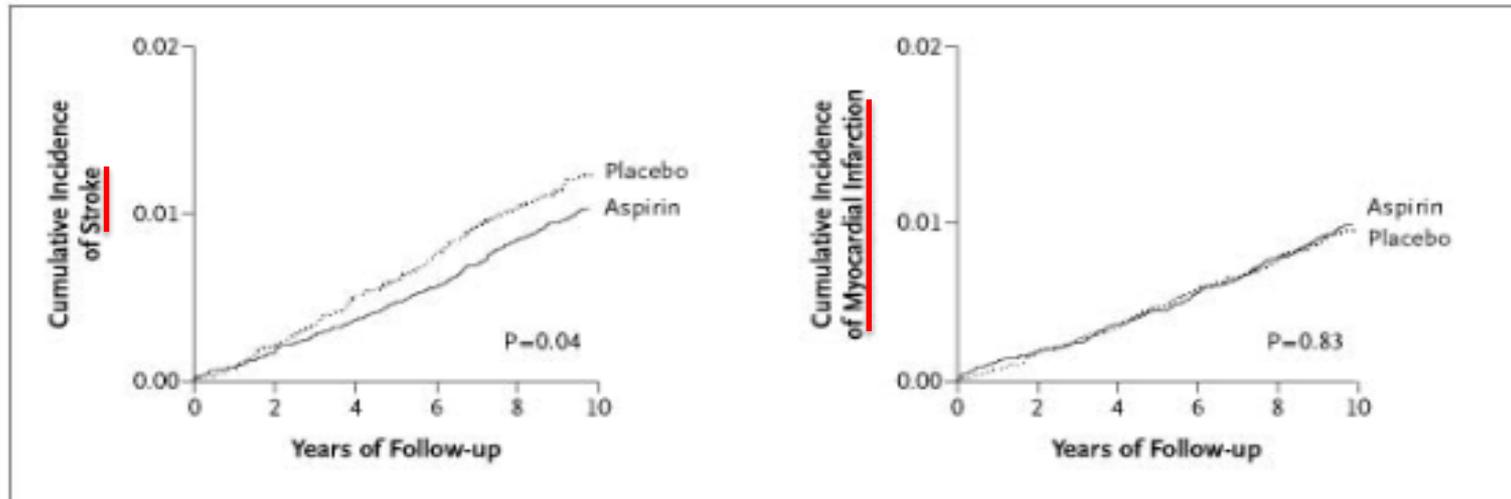
Migraine with Aura

- 4x more common in women¹
- Stroke Prevention in Young Women Study – a case-control, population based study²
 - Women with migraine with visual aura had a 1.5 fold increased odds of stroke
 - Add cigarettes and OCPs → 8 fold higher odds of stroke compared to those who did not smoke or use OCPs
- Clinical approach:
 - It is unclear if reducing number of headaches → stroke risk reduction
 - Counsel young women on smoking cessation
 - Screen for other risk factors (Class IIb, Level C)
 - Routine screening for pro-thrombotic mutations before initiation of hormonal contraception is not useful (Class III; Level A)

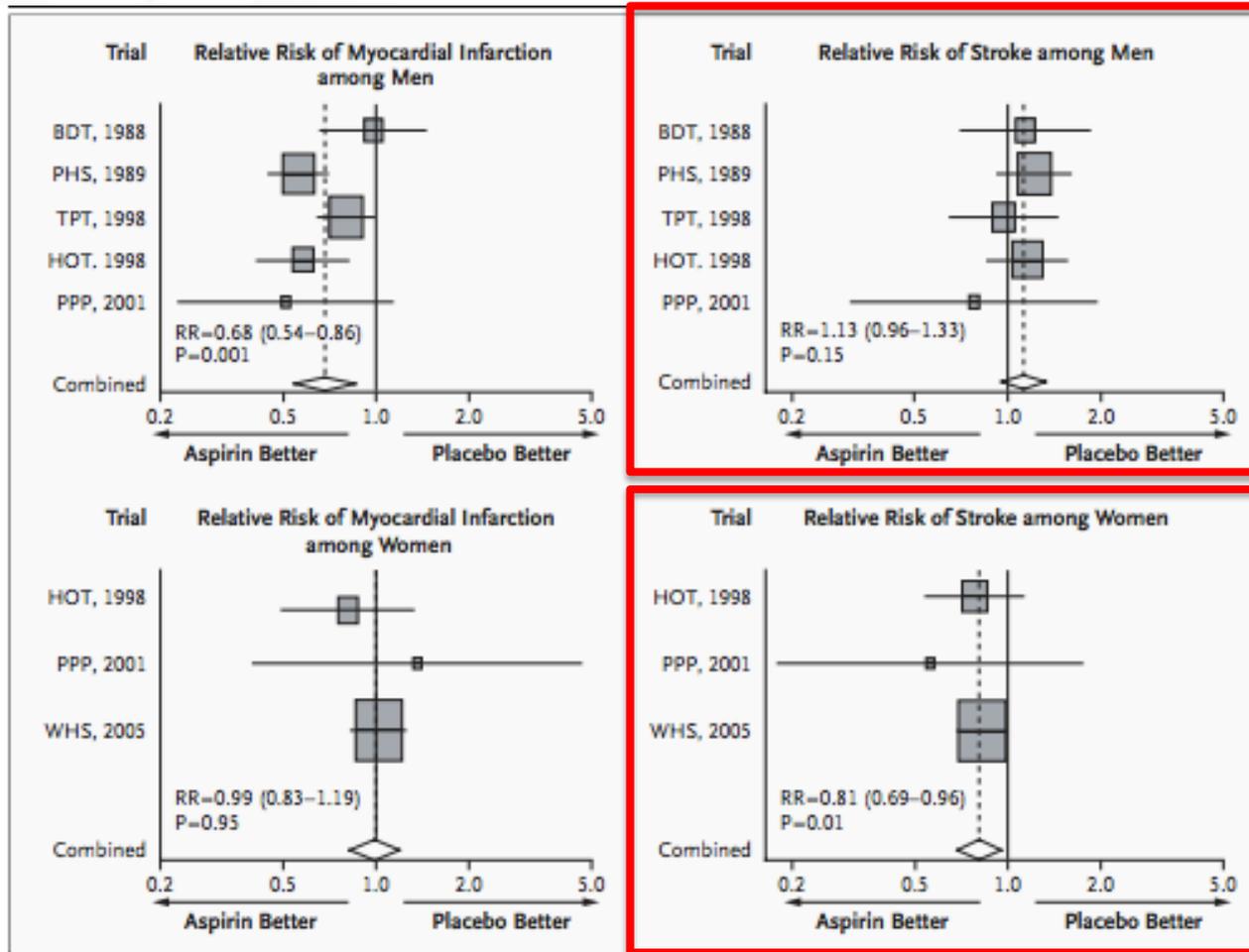
PRIMARY PREVENTION

Primary Stroke Prevention: Aspirin

- Women's Health Study (N = 39,987 healthy women 45+ years of age)
 - A randomized trial of low-dose aspirin in primary prevention of cardiovascular disease in women Followed for 10 years for a first major CV event (MI, stroke, death)
 - 24% in risk reduction of ischemic stroke (RR 0.76; 95% CI 0.63 – 0.93)
 - Non-significant increase in risk of hemorrhagic stroke; increase in GI bleeding
 - Most significant benefit was in women > 65 years of age at study entry



Gender Differences in Aspirin for Primary Prevention of IS and MI



Summary and Recommendations for Primary Prevention of Stroke

- Updated guidelines for the prevention of stroke in women remain similar to prior recommendations
 - “Aspirin is recommended for primary prevention for women after consideration of the 10-year risk of CVD and whether this and age outweigh the risk of hemorrhage.”

Risk factors, Presentation and Treatment

GENDER DIFFERENCES IN STROKE TREATMENT

Women Have Greater Variability in Symptoms at Presentation

- Similar to the cardiology literature, women are more likely to present with non-traditional symptoms
 - Mental status change is most common
 - Pain, lightheadedness, headache

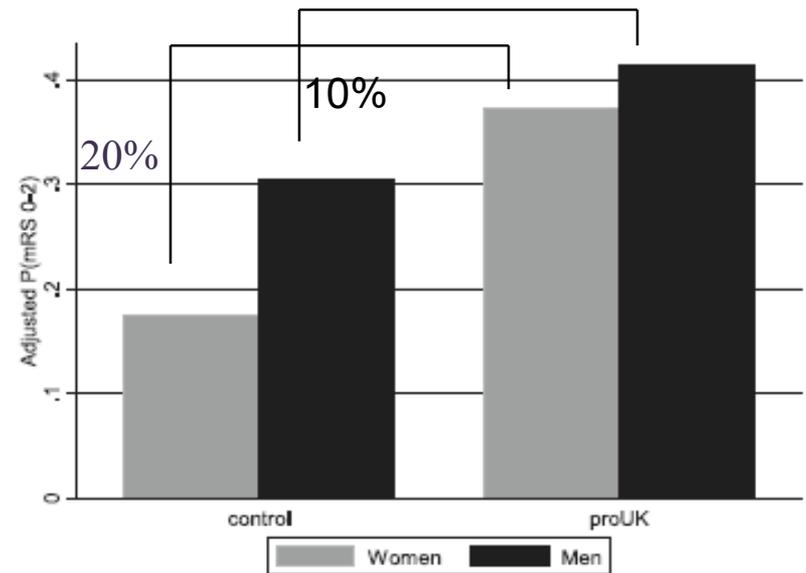
Women Are Less Likely to Receive Alteplase

- Odds ratio of receiving IV alteplase
 - 0.56 for women compared to men (n = 1584; statewide registry)
 - 0.4 when looking at only those eligible patients arriving in < 3h
- In an adjusted analysis¹
 - 1% longer door to doctor intervals
 - 15% longer door to image intervals
 - Remained evident even when restricting patients to those within a treatment window

Differential Response to Treatment

- IV tPA
 - Women who receive IV tPA are more likely to benefit¹
- IA tPA
 - Women benefit more from endovascular thrombolysis²

Probability of independence after proUK in men and women



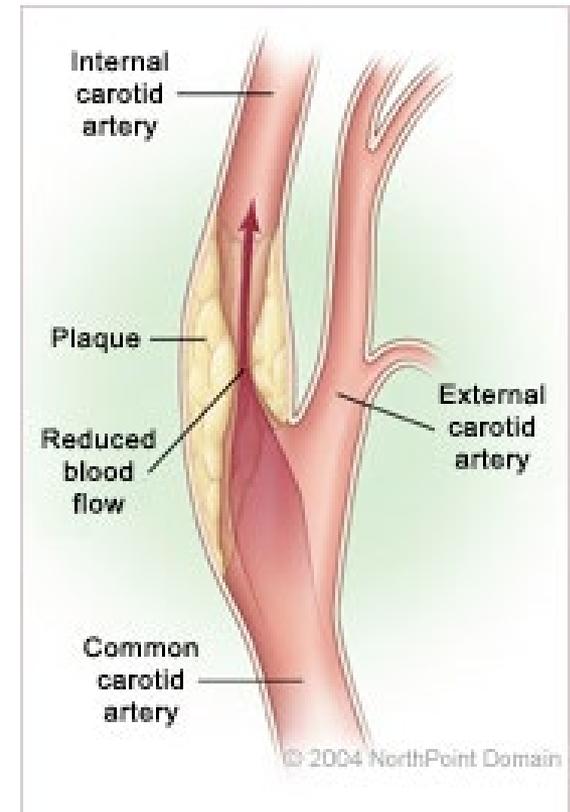
The ordinate axis represents the probability of independent outcome adjusted for age and baseline NIHSS score. In both instances, prourokinase treatment resulted in better outcome (41% versus 31% in men and 37% versus 17% in women).

¹Kent DM et al. Stroke 2005 (meta-analysis)

²Hill MD et al. Stroke 2006

Large Vessel (Carotid) Stenosis

- Treatment options for carotid artery stenosis
 - Medical management
 - Carotid endarterectomy
 - Carotid stenting
- Multiple large randomized trials importantly showed the benefit of surgical intervention on carotid artery disease for severe symptomatic carotid artery stenosis
- Theoretical differences between men and women because of differences in anatomy, atherosclerosis rates and plaque composition exist

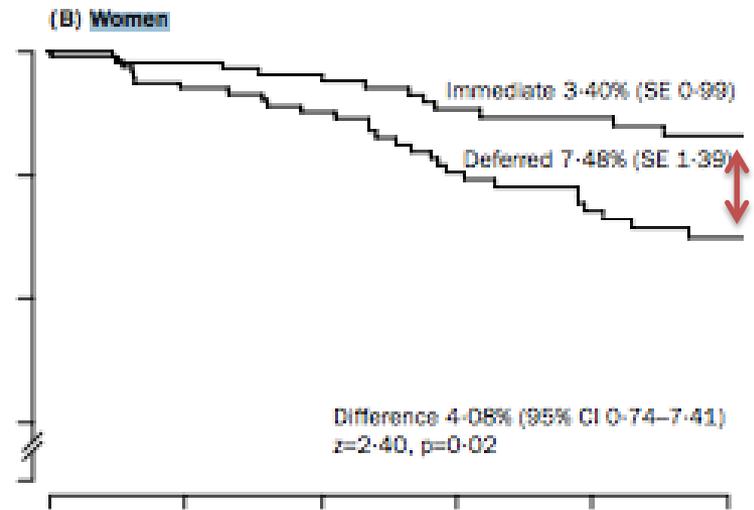
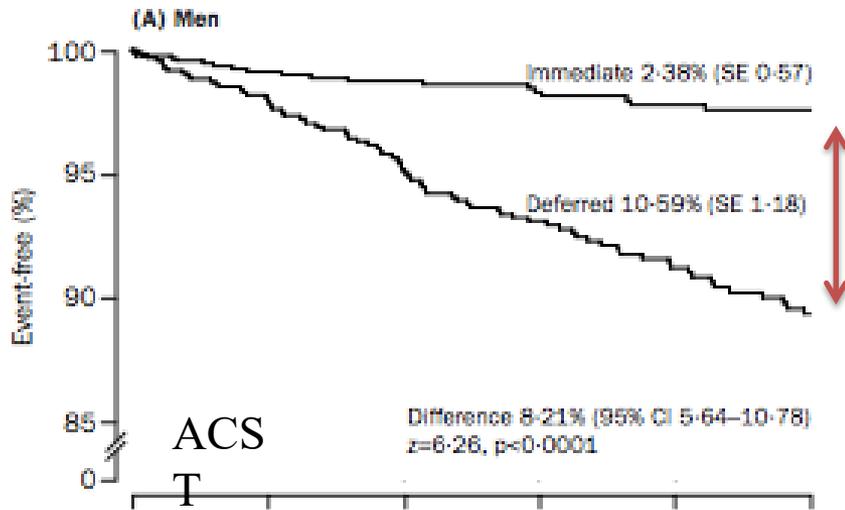


CEA and Stenting Trials

- [European] Asymptomatic Carotid Surgery Trial (ACST)¹
 - Is CEA an effective and safe treatment for prevention of stroke among patients with > 60% stenosis?
 - **Pre-specified sex subgroup analysis showed women had a lower absolute risk reduction at 5 years**
- European Carotid Surgery Trial (ECST)²
 - Assessed risks and benefits of CEA in patients with recently diagnosed **symptomatic** carotid stenosis
 - Overall outcome of major stroke or death benefited those with > 70- 80 % stenosis, for 2-3 years after randomization (Absolute benefit 11.6%)
- Asymptomatic Carotid Artery Stenosis (ACAS)³
 - Determined whether the addition of CEA to aggressive medical management can reduce stroke risk in asymptomatic patients (> 60% stenosis)
 - **Higher risk of operative stroke or death in women vs men (3.6 v 1.7%)**
- North American Symptomatic Carotid Endarterectomy Trial (NASCET)⁴
 - Assessed benefit of CEA in patients with symptomatic moderate stenosis (< 70%) with 8 years follow up
 - Patient's with moderate stenosis benefited (NNT = 15); **benefit greatest in men**
- Carotid Revascularization Endarterectomy vs Stenting Trial (CREST)⁵
 - Primary endpoint did not differ between carotid artery stenting and carotid endarterectomy in patients with symptomatic and asymptomatic stenosis.
 - **Pre-specified sex-specific analysis found higher risk in women especially for stenting**

Gender Differences in Carotid Artery Disease Management

	ACST* (2004)		ECST (1998)		ACAS (1995)		NASCET		CREST*	
	M	F	M	F	M	F	M	F	M	F



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Carotid Artery Disease Management Summary

- CEA to prevent stroke is less beneficial for women compared with men
- Women with symptomatic carotid disease have higher peri-procedural risk and lower risk of recurrent stroke on medical treatment.
- Asymptomatic carotid disease will be further investigated in CREST-2 trial
- Practitioners should be sure to treat women with optimal medical management, regardless of whether revascularization is pursued.
- Reasons for sex differences with carotid artery disease are not known, but plaque composition and comorbid conditions are possible explanations and need further review.

Sex-Specific Outcomes in Endovascular Treatment of Stroke

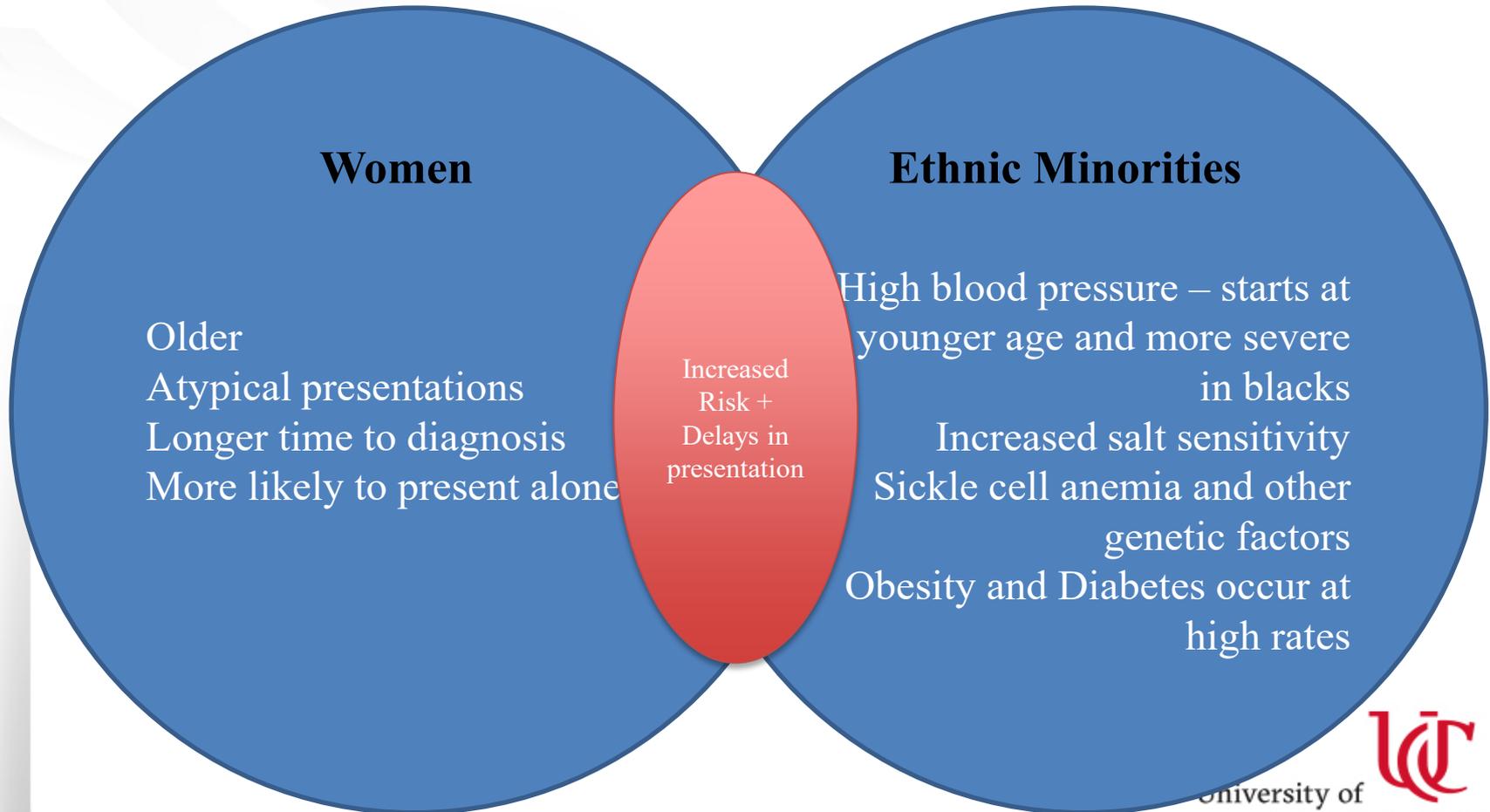
- Recanalization is the most important factor predicting good outcomes in patients with AIS and large-vessel occlusions
- While initial endovascular trials (IMSIII, MR RESCUE, SYNTHESIS-EXPANSION) showed no benefit in disability at 90 days, a second round of trials showed significant efficacy of thrombectomy (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT-PRIME)
- Retrospective analysis of MR CLEAN found that women had higher periprocedural complications and worse outcomes
- In the Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials (HERMES) pooled-analysis there was no sex-by-treatment effect seen.³

Acute Stroke Intervention Summary

- Women are 30% less likely to be treated with tPA
 - Primarily driven by symptom onset to time of presentation
 - Product of being older and living alone
- Minorities are less likely to be treated with tPA
 - Primarily driven by time from symptom onset to presentation
 - Product of access to health care and stroke education
- Endovascular treatment
 - Subgroup analysis of MR CLEAN trial women experienced more adverse effects
 - This effect was not verified in HERMES collaboration – individual patient data from several endovascular trials
 - Further data, such as access to endovascular treatment has not yet been examined

MINORITY WOMEN AND STROKE

Minority Women and Stroke



Gender and Race Differences in Stroke Risk

- Studies are often underpowered to study sex and race/ethnicity specific disparities
- Clinical trials have unequal enrollment from minorities and women, making results difficult to generalize
- Minority populations are more likely to have **hypertension, diabetes and heart disease**
- Stroke risk factors have more of an affect on **women** compared men – only in non-Hispanic white population.
- These risk factors have the same effect on black men and women

Women and Minorities are Less Educated About Stroke

- AHA and ASA conducted a national telephone survey to assess stroke risk awareness among women
 - 1024 respondents 25 years or older
 - 68% white, 12% black, 12% Hispanic
- More Hispanic women reported being not at all informed about stroke compared with whites (32 vs 19%) and blacks (32 vs 20%)
- More white women were aware of a clot busting medication compared with blacks (92 vs 84%) and Hispanics (92 vs 79%)
- Identification of stroke warning signs was low across the board
- **Stroke education in informal setting such as beauty shops, barbershops, community centers and churches have been successful**

Race and Income are Strong Predictors of Acute Stroke Treatment

Odds of intravenous thrombolysis use by race when compared to white patients

Race	OR	95% CI	P value
African American	0.58	0.52-0.66	<.001
Native American	0.59	0.39-0.91	.017
Hispanic	0.76	0.64-0.91	.002
Asian	0.96	0.74-1.23	.725
Other	0.91	0.75-1.11	.343

Odds of intravenous thrombolysis use by median income when compared to the poorest incomes

Median income quartile	OR	95% CI	P value
High	1.55	1.37-1.76	<.0001
Middle to high	1.48	1.33-1.64	<.0001
Low to middle	1.26	1.14-1.39	<.0001

Median income was a predictor of treatment in an income-dependent fashion

Black Women Are Significantly Less Likely to be Treated with tPA

- In a pre-specified four-group analysis of patients at two academic institutions (white women, black women, white men and black men):
 - High tPA utilization
- Black women were significantly less likely to be treated with tPA with primary reason being arrival to hospital > 3 hours from symptom onset
 - Especially notable in mild stroke (NIHSS < 7)
- Even when arriving within 3 hours of symptom onset, black women were less likely than other groups to receive tPA

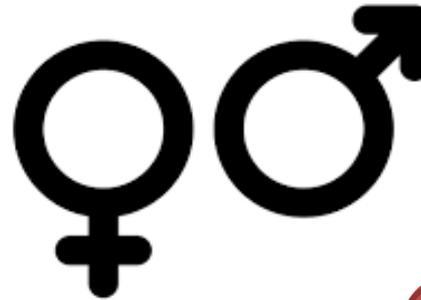
Conclusions

Epidemiology

Minority women and
stroke

Risk Factors

Outcomes



Treatment Effect

Primary Prevention

Conclusions

- While the need for education and risk factor control is universal, some demographic subgroups may benefit from earlier and more aggressive strategies
- More research is needed in areas of delays in door to needle times, differential outcomes and ways for better stroke prevention in women

Thank you!