Gender Disparities in Ischemic Stroke

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Disclosures

• Speakers Bureau: Genentech
Gender Differences in Stroke: From Prevention to Outcomes

- Epidemiology
- Risk Factors
- Primary Prevention
- Minority women and stroke
- Outcomes
- Treatment Effect
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
Gender-Specific Stoke 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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Comparators</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Age group</td>
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<tr>
<td>35-44 years</td>
<td>Women*</td>
<td>1.2%</td>
<td>1.0%</td>
<td>1.2142</td>
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<tr>
<td>45-54 years</td>
<td>Men*</td>
<td>2.5%</td>
<td>1.0%</td>
<td>2.3903</td>
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<td>55-64 years</td>
<td></td>
<td>3.4%</td>
<td>3.0%</td>
<td>1.1256</td>
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</tbody>
</table>

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 factors\(^1\)
  - 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 risk\(^2\)

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 study\(^2\) 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)

\(^1\)Reeves MJ Stroke 2009 (GWTG)
\(^2\)Fang 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

Bushnell C Stroke 2014 (AHA/ASA Guidelines)
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 >/>= 6 weeks post partum

Bushnell et al. Stroke 2014 (AHA/ASA Guidelines)
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 OCPs\textsuperscript{1}

- Nuvaring, transdermal patch, IUDs have not been fully evaluated
  - Nuvaring has been associated with 2.49 fold increased risk\textsuperscript{2}

- Risk is increased further when combined with cigarette smoking, HTN, migraine headaches

\textsuperscript{1}Chakhtoura Z Stroke 2009, \textsuperscript{2}Lidegaard O NEJM 2012
Migraine with Aura

• 4x more common in women\(^1\)
• Stroke Prevention in Young Women Study – a case-control, population based study\(^2\)
  – 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)

\(^1\)Merikangas KR Headache 2013, \(^2\)MacClellan LR Stroke 2007\(^*\)
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

Ridker P et al, NEJM 2005 (WHS)
Gender Differences in Aspirin for Primary Prevention of IS and MI

Ridker et al, NEJM 2005 – meta analysis
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.”

Bushnell C Stroke 2014 (AHA/ASA Guidelines)
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 analysis\(^1\)
  – 1% longer door to doctor intervals
  – 15% longer door to image intervals
  – Remained evident even when restricting patients to those within a treatment window

(1) Gargano JW, Wehner S, Reeves MJ Stroke 2009
Differential Response to Treatment

- **IV tPA**
  - Women who receive IV tPA are more likely to benefit\(^1\)

- **IA tPA**
  - Women benefit more from endovascular thrombolysis\(^2\)

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

\(^2\) Hill 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

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<thead>
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<th>Study</th>
<th>Male</th>
<th>Female</th>
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- **5-year stroke risk reduction of ischemic stroke following CEA**
  - ACST*: 8.2% vs. 4.1% (p = 0.10)
  - More risks in women with stenting.
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

²Shah SH et al Neurology 2006; Arnold M Stroke, 2007
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

Women

Older
Atypical presentations
Longer time to diagnosis
More likely to present alone

Ethnic Minorities

High blood pressure – starts at younger age and more severe in blacks
Increased salt sensitivity
Sickle cell anemia and other genetic factors
Obesity and Diabetes occur at high rates

Increase Risk + Delays in presentation

www.cdc.gov/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

Howard VJ et al. JAMA Neurology 2018
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

Ferris A et al.
Race and Income are Strong Predictors of Acute Stroke Treatment

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

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Kimball, MM et al
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

Boehme et al 2014
Conclusions

- Epidemiology
- Risk Factors
- Primary Prevention
- Minority women and stroke
- Outcomes
- Treatment Effect

Stroke is the 5th leading cause of death for men, but the 3rd leading cause of death for women.

Aspirin has differential effects for primary stroke prevention.

Conclusions

Typical stroke risk factors affect women differently and women have unique risk factors.

Quality of life after stroke is worse for women than for men.

Alteplase has a greater effect on outcomes in women.
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!