Sex Differences in Stroke

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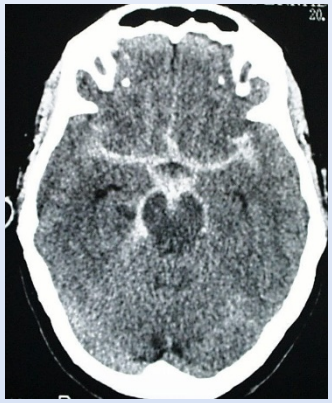
Disclosures

- I have no relevant disclosures

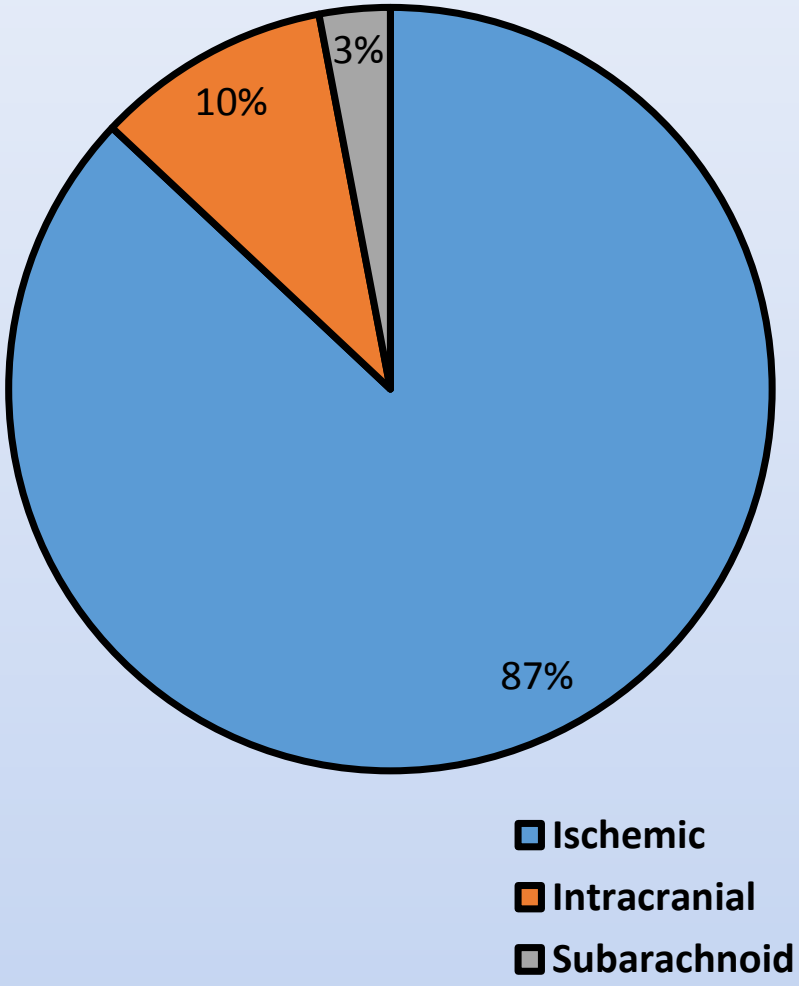
Types of Stroke

Intracranial Hemorrhage



Subarachnoid Hemorrhage

Ischemic



Source: AHA Disease Statistics
Circulation 2012;125 (e2-e220)

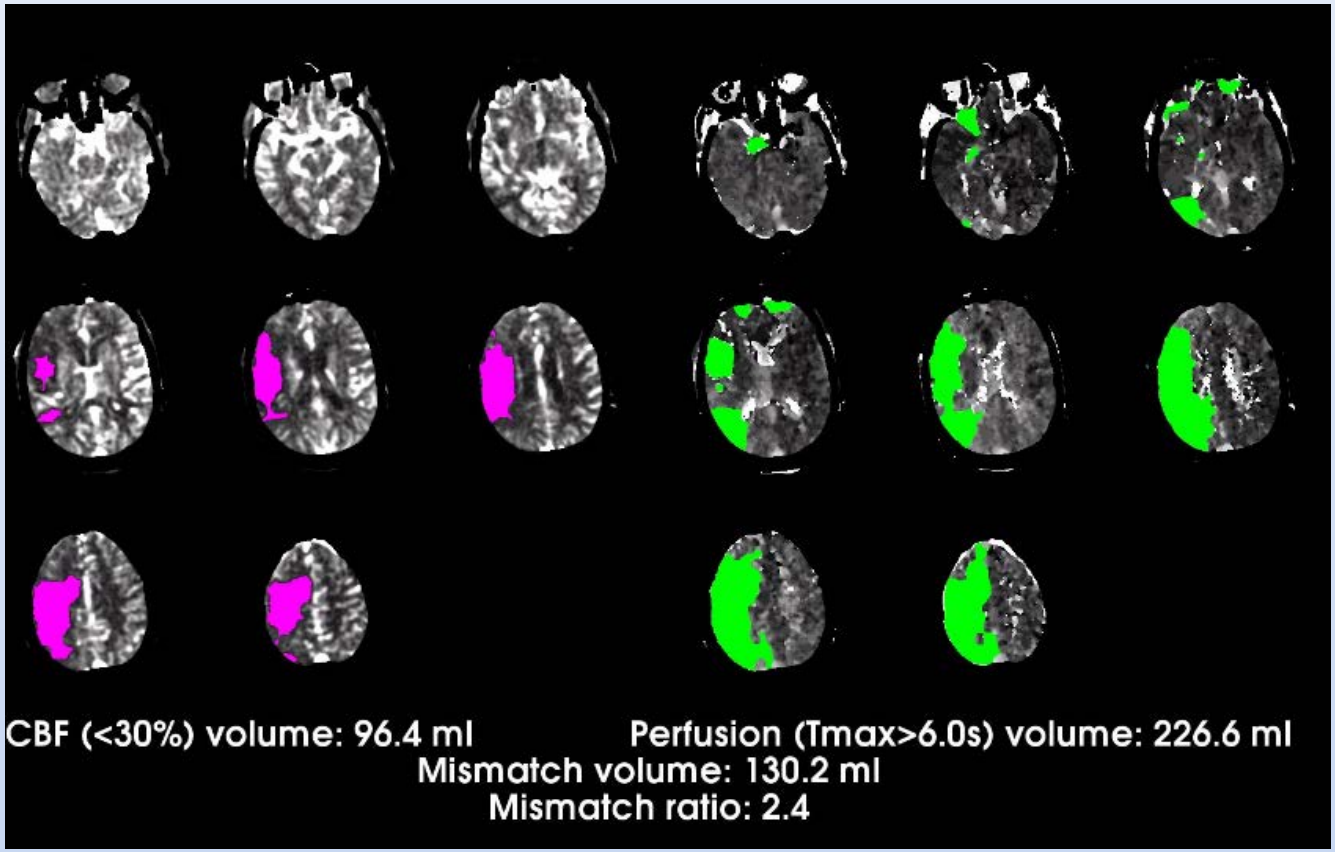
Case

- 85 F with recent loss of her longtime husband.
- She was found by her daughter in the afternoon, who visits weekly and spoke to her the day before.
- Focal?
- Exam shows left sided weakness, face and arm > leg.
- Gaze preference.
- Neglect.
- Where is it?

Case continued

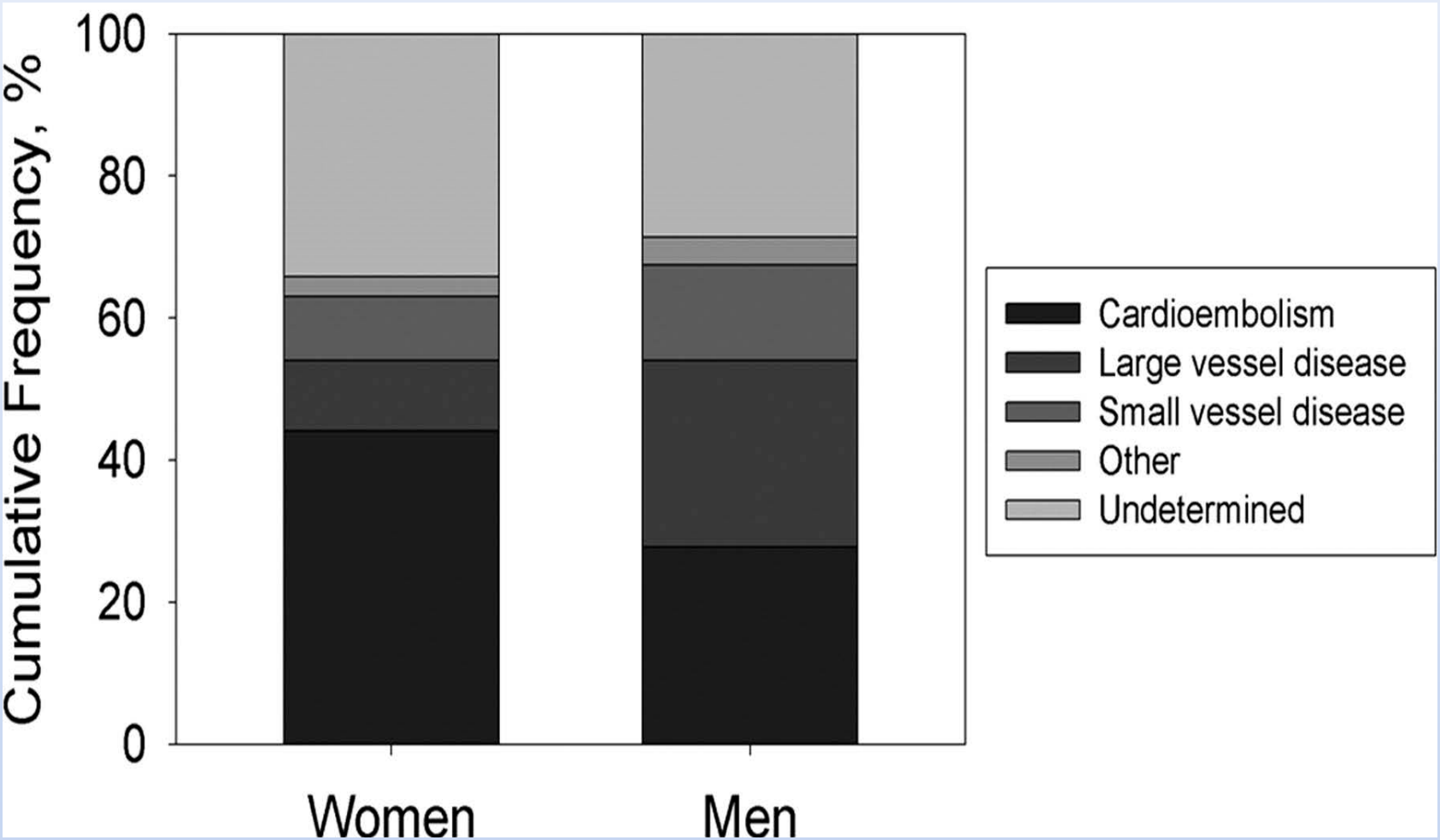
- CTA shows proximal right MCA occlusion at M1 but no significant stenosis in the contralateral carotid, minimal calcifications.
- Likely etiology?
- Time of onset was unknown.
- What would you do?

Acute Imaging
Anything to save?

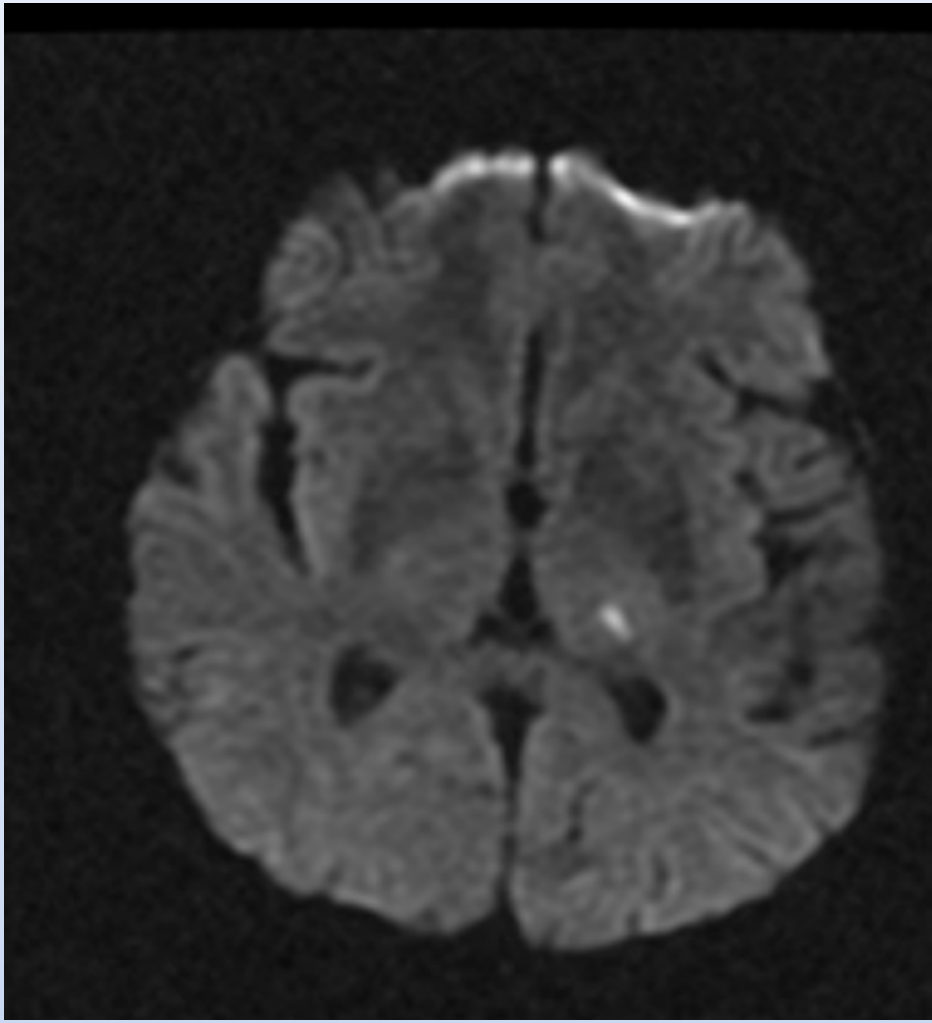


Etiology?

Cumulative frequency of stroke etiology in women and men with AIS



Forster, A. et al. Stroke 2009;40:2428-2432



Atrial Fibrillation

- Women experience more symptoms from AF
- Less likely to receive rhythm control or catheter ablation
- Poorer quality of life
- Higher risk for stroke and death than men with AF
- Biology vs. Sociology?
- Women are more likely to be living alone or widowed before (and after) a stroke
- Less likely to be anticoagulated compared to age-matched men? “frailty”?
- Under represented in clinical trials

Ko D. et al. Nat Rev Cardiol. 2017 Feb;14(2):113-124

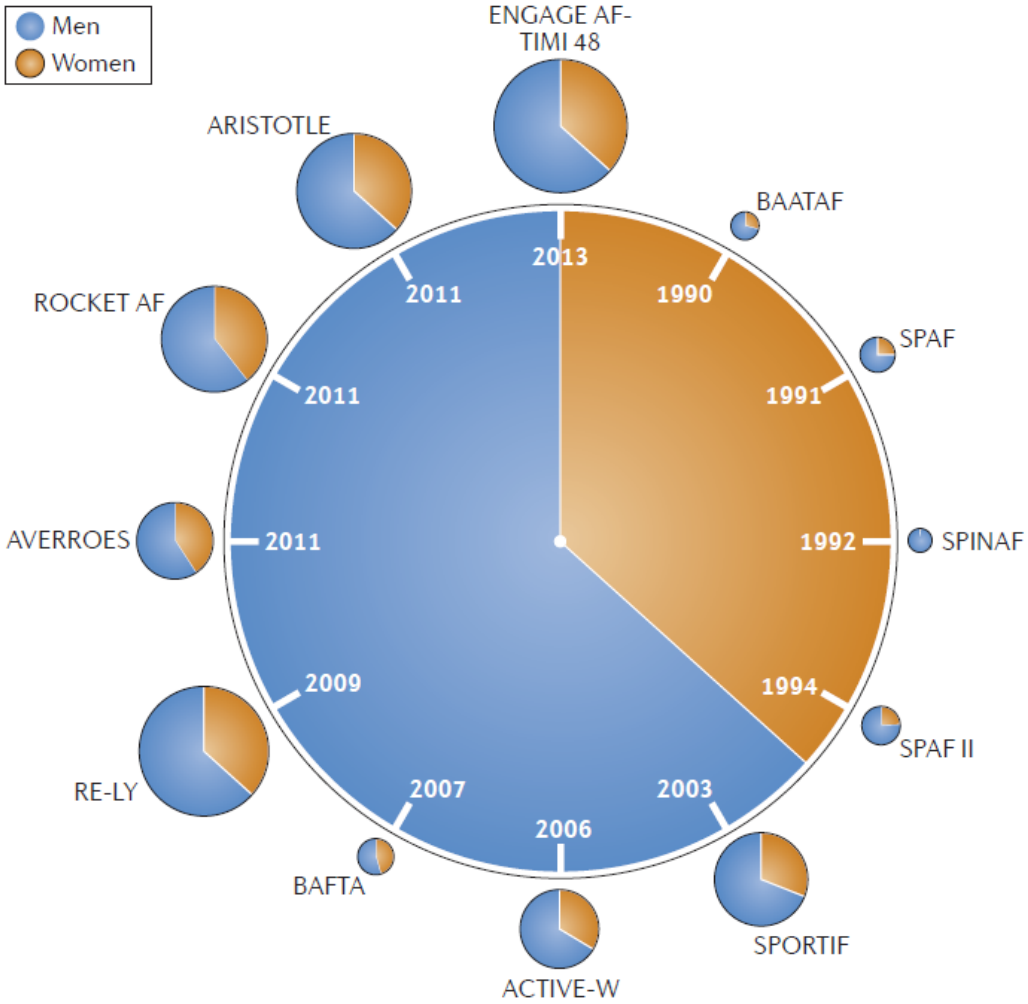
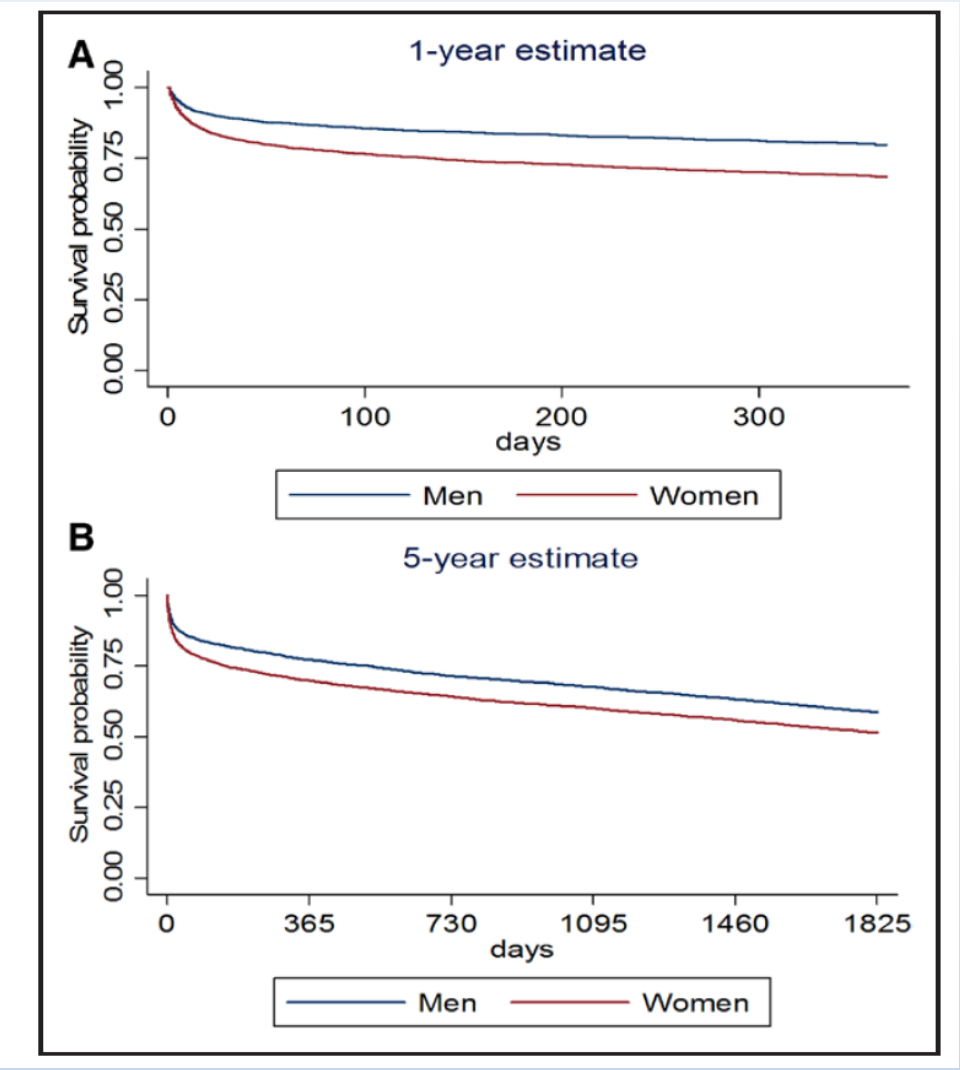


Figure 3 | **Participation of women in anticoagulation trials for stroke prevention in atrial fibrillation.** A pie chart showing proportion of women (orange) represented in anticoagulation trials compared with men (blue). The numbers indicate the year of publication of the study. The sizes of the individual pie charts correspond to the relative overall size of the trial.

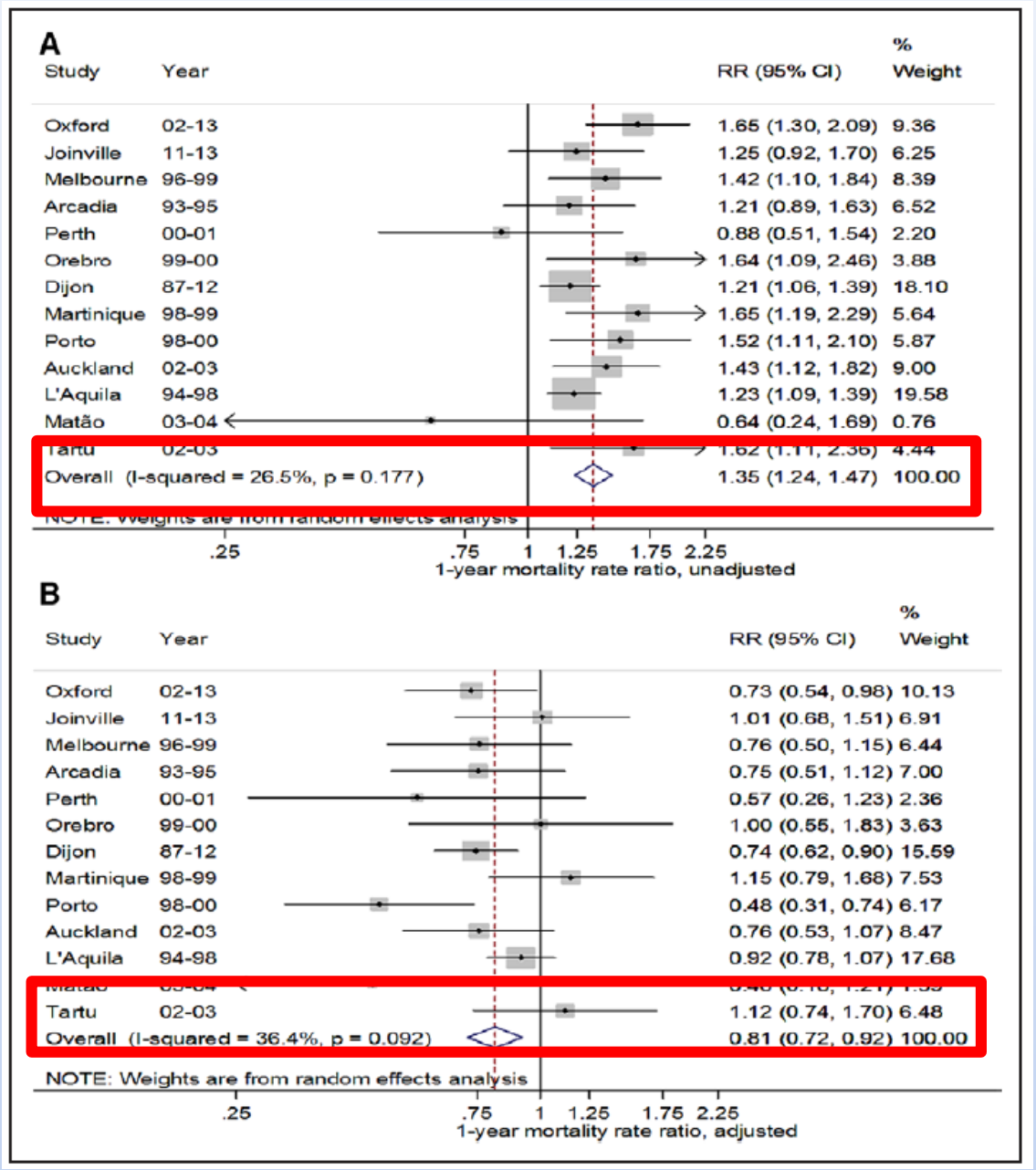
So how is this women going to do?

- More likely to be disabled by her stroke
- More likely to die from her stroke
- More likely to end up in a skilled nursing facility
- More likely to have cognitive disability after stroke
- More likely to develop post-stroke depression
- BUT also more likely to have functional deficits before her stroke
- AND more likely to live alone

Age and other factors matter in outcome



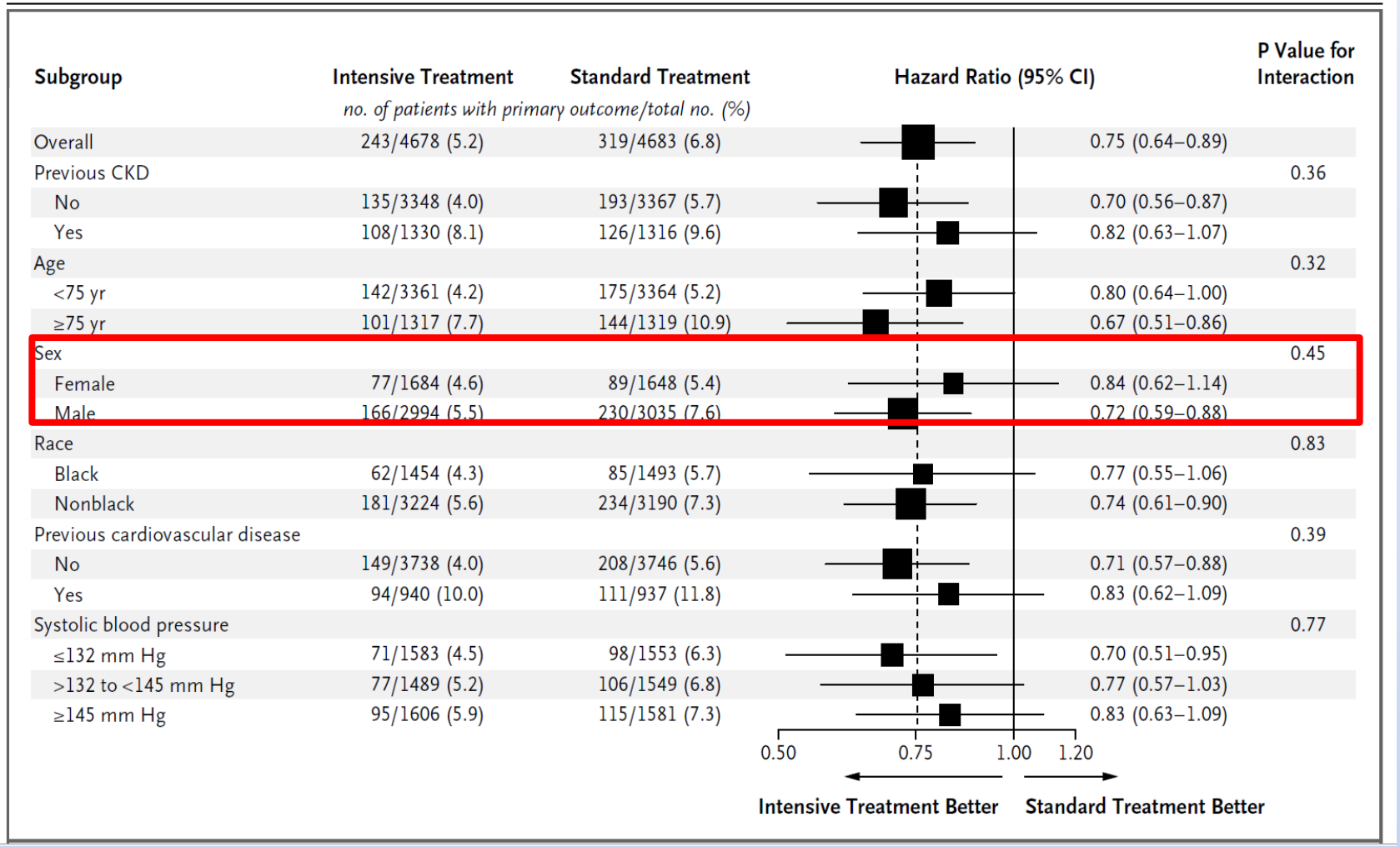
Phan HT. Epub 2017 Feb 22. Circ Cardiovasc Qual Outcomes. Sex Differences in Long-Term Mortality After Stroke in the INSTRUCT (INternational STRoke oUtComes sTudy): A Meta-Analysis of Individual Participant Data.


A
Study
Year
RR (95% CI)
% Weight
Oxford 02-13 1.65 (1.30, 2.09) 9.36
Joinville 11-13 1.25 (0.92, 1.70) 6.25
Melbourne 96-99 1.42 (1.10, 1.84) 8.39
Arcadia 93-95 1.21 (0.89, 1.63) 6.52
Perth 00-01 0.88 (0.51, 1.54) 2.20
Orebro 99-00 1.64 (1.09, 2.46) 3.88
Dijon 87-12 1.21 (1.06, 1.39) 18.10
Martinique 98-99 1.65 (1.19, 2.29) 5.64
Porto 98-00 1.52 (1.11, 2.10) 5.87
Auckland 02-03 1.43 (1.12, 1.82) 9.00
L'Aquila 94-98 1.23 (1.09, 1.39) 19.58
Matão 03-04 0.64 (0.24, 1.69) 0.76
Tartu 02-03 1.62 (1.11, 2.36) 4.44
Overall (I-squared = 26.5%, p = 0.177) 1.35 (1.24, 1.47) 100.00
NOTE: Weights are from random effects analysis
.25 .75 1 1.25 1.75 2.25
1-year mortality rate ratio, unadjusted
B
Study
Year
RR (95% CI)
% Weight
Oxford 02-13 0.73 (0.54, 0.98) 10.13
Joinville 11-13 1.01 (0.68, 1.51) 6.91
Melbourne 96-99 0.76 (0.50, 1.15) 6.44
Arcadia 93-95 0.75 (0.51, 1.12) 7.00
Perth 00-01 0.57 (0.26, 1.23) 2.36
Orebro 99-00 1.00 (0.55, 1.83) 3.63
Dijon 87-12 0.74 (0.62, 0.90) 15.59
Martinique 98-99 1.15 (0.79, 1.68) 7.53
Porto 98-00 0.48 (0.31, 0.74) 6.17
Auckland 02-03 0.76 (0.53, 1.07) 8.47
L'Aquila 94-98 0.92 (0.78, 1.07) 17.68
Tartu 02-03 1.12 (0.74, 1.70) 6.48
Overall (I-squared = 36.4%, p = 0.092) 0.81 (0.72, 0.92) 100.00
NOTE: Weights are from random effects analysis
.25 .75 1 1.25 1.75 2.25
1-year mortality rate ratio, adjusted

Policy: NIH to balance sex in cell and animal studies

http://orwh.od.nih.gov/research/index.asp

Hypertension and the SPRINT trial



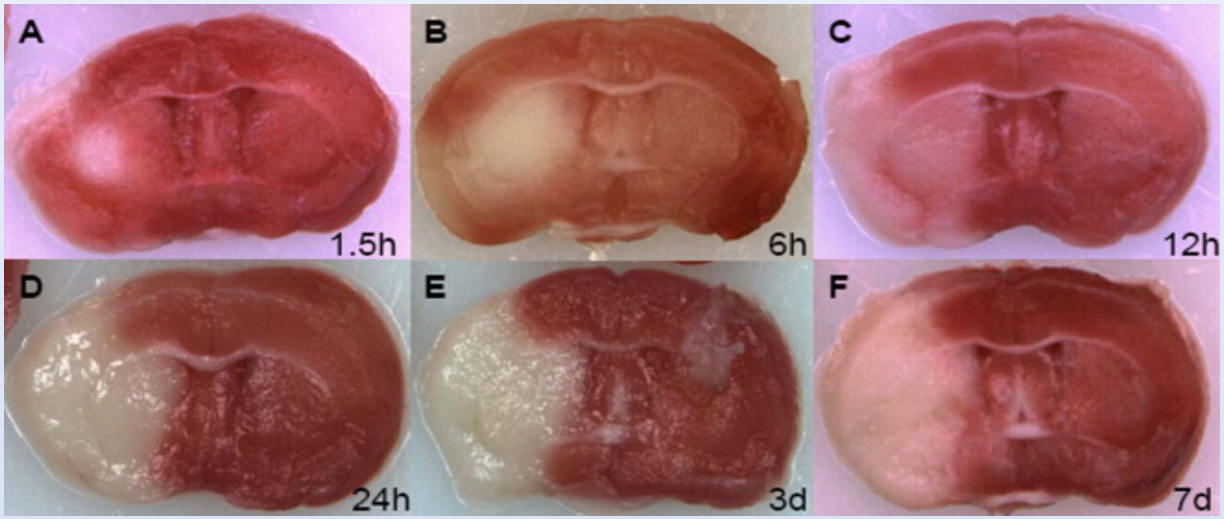
Subgroup	Intensive Treatment	Standard Treatment	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients with primary outcome/total no. (%)			
Overall	243/4678 (5.2)	319/4683 (6.8)	0.75 (0.64–0.89)	
Previous CKD				0.36
No	135/3348 (4.0)	193/3367 (5.7)	0.70 (0.56–0.87)	
Yes	108/1330 (8.1)	126/1316 (9.6)	0.82 (0.63–1.07)	
Age				0.32
<75 yr	142/3361 (4.2)	175/3364 (5.2)	0.80 (0.64–1.00)	
≥75 yr	101/1317 (7.7)	144/1319 (10.9)	0.67 (0.51–0.86)	
Sex				0.45
Female	77/1684 (4.6)	89/1648 (5.4)	0.84 (0.62–1.14)	
Male	166/2994 (5.5)	230/3035 (7.6)	0.72 (0.59–0.88)	
Race				0.83
Black	62/1454 (4.3)	85/1493 (5.7)	0.77 (0.55–1.06)	
Nonblack	181/3224 (5.6)	234/3190 (7.3)	0.74 (0.61–0.90)	
Previous cardiovascular disease				0.39
No	149/3738 (4.0)	208/3746 (5.6)	0.71 (0.57–0.88)	
Yes	94/940 (10.0)	111/937 (11.8)	0.83 (0.62–1.09)	
Systolic blood pressure				0.77
≤132 mm Hg	71/1583 (4.5)	98/1553 (6.3)	0.70 (0.51–0.95)	
>132 to <145 mm Hg	77/1489 (5.2)	106/1549 (6.8)	0.77 (0.57–1.03)	
≥145 mm Hg	95/1606 (5.9)	115/1581 (7.3)	0.83 (0.63–1.09)	

Psychosocial Factors

- Depression and psychosocial stress increase risk for incident stroke by 25% to 45% in women
- Higher serum inflammation? Compliance?
    - Social Isolation (loneliness) increases risk of mortality
    - Isolation increases risk of first stroke Isolation leads to poorer recovery (controlled for NIHSS)
    - Stroke patients with low social support have increased risk of recurrent stroke

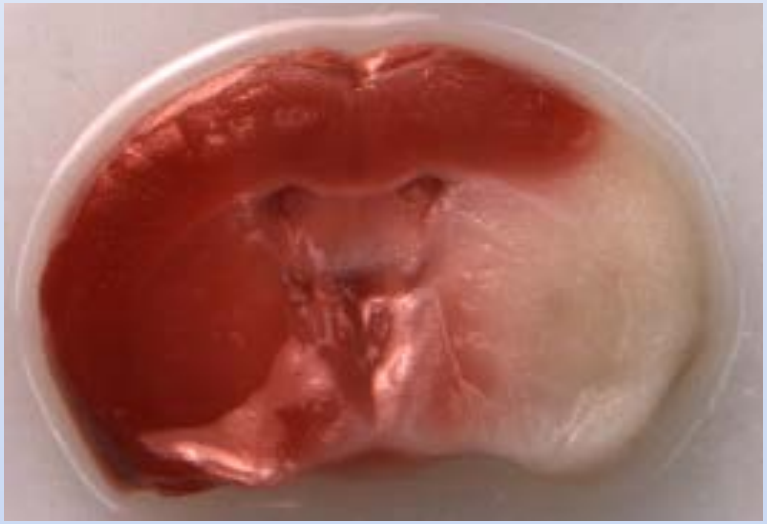
Epidemic of loneliness

- 52% of women live alone compared to 29% for men after the age of 80
- May outlive not only spouses/partners but also their friends and children
- Cardiovascular, nervous and immune targets


A
1.5h
B
6h
C
12h
D
24h
E
3d
F
7d

Biology: The detrimental effects of isolation can be modeled in animals!

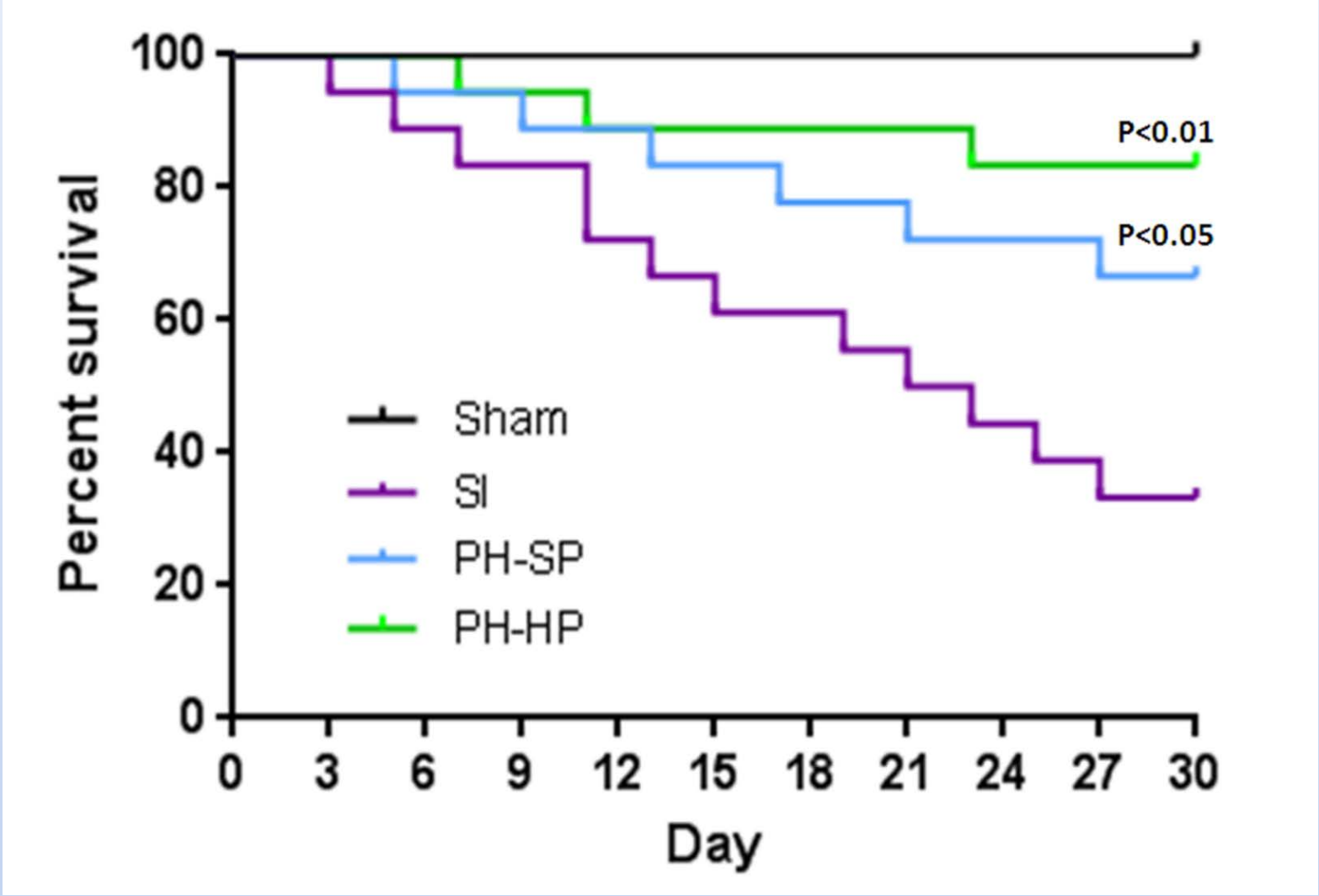
PH female



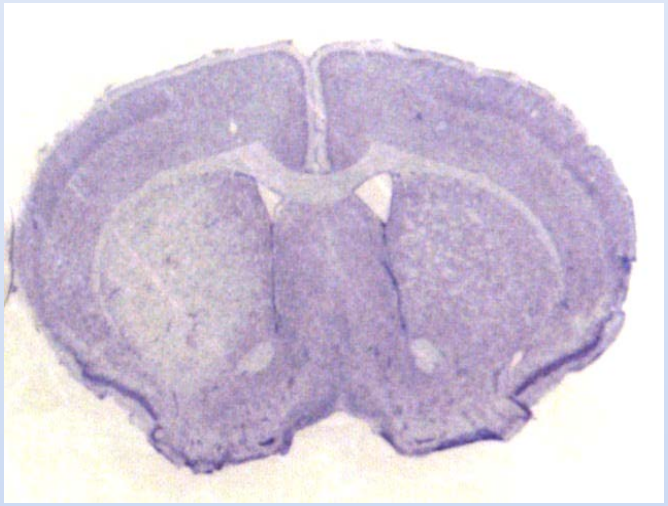
SI female

Infarct Size was equivalent at 30 and 90 days when isolation occurred three days after stroke (to control for infarct size)

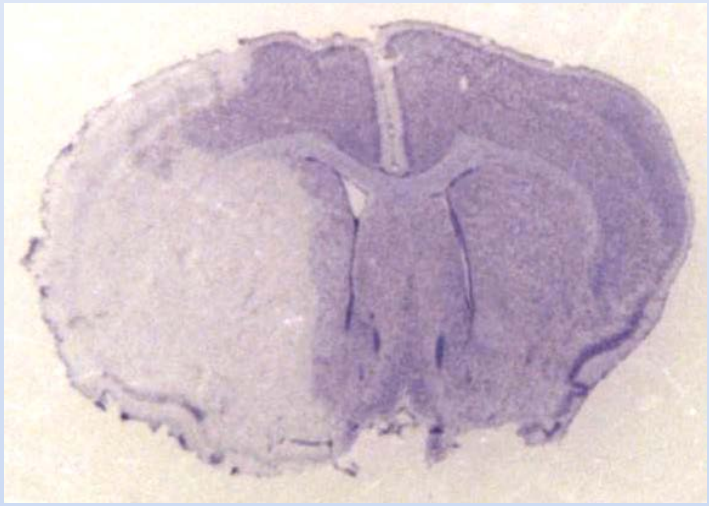
Mortality


Percent survival
100
80
60
40
20
0
0
3
6
9
12
15
18
21
24
27
30
Day
Sham
SI
PH-SP
PH-HP
P<0.01
P<0.05

Translational Failure: Estrogen

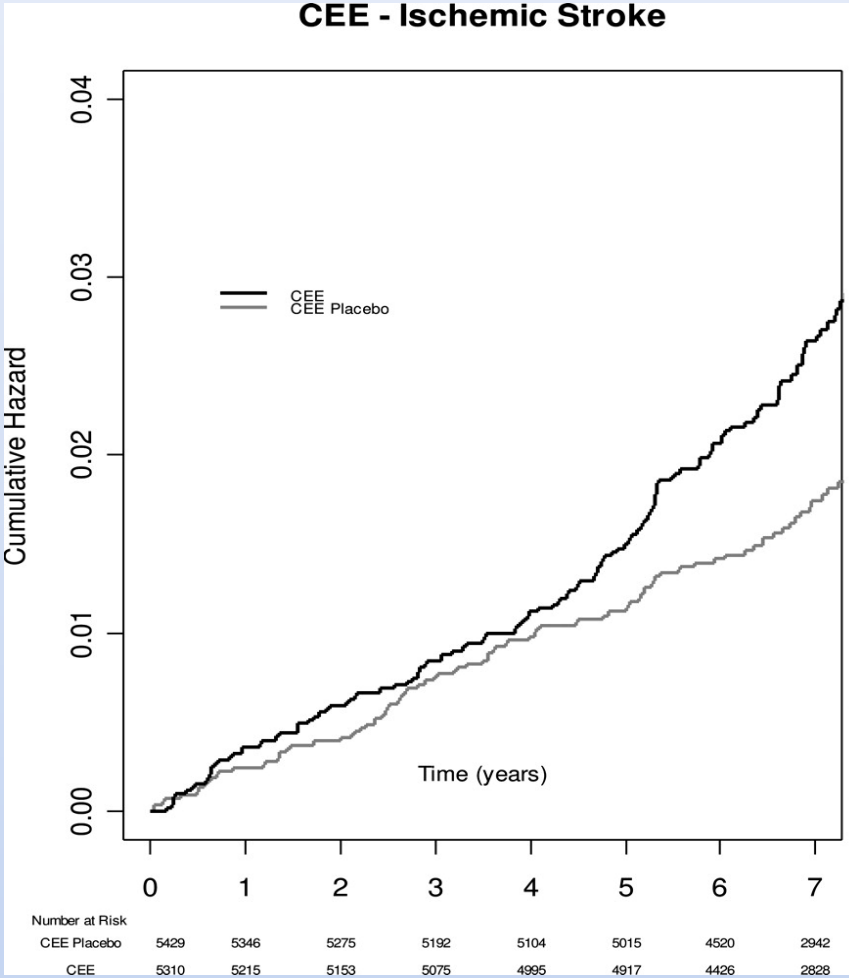


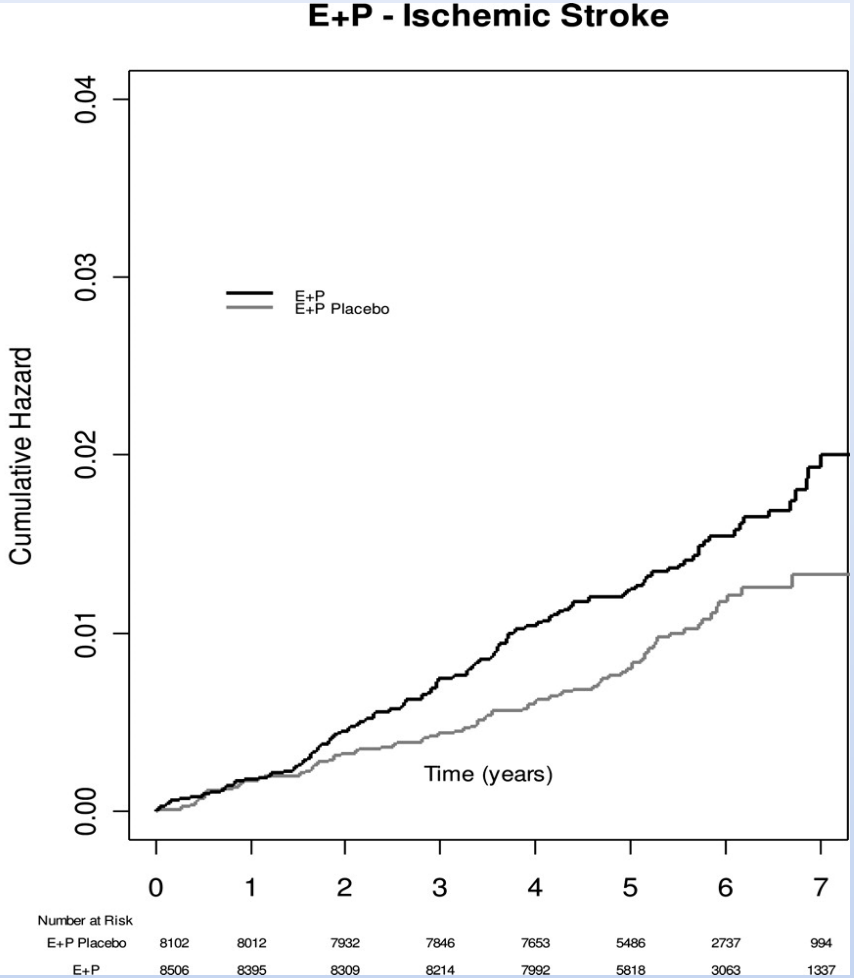
Female



OVX Female

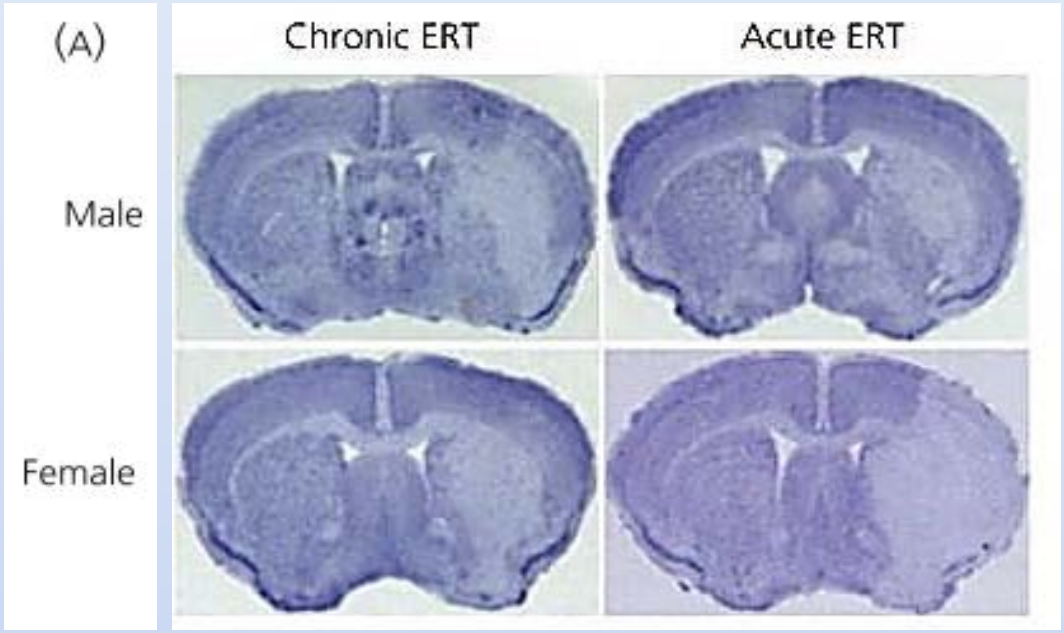
Ischemic stroke risk- WHI hormone trial



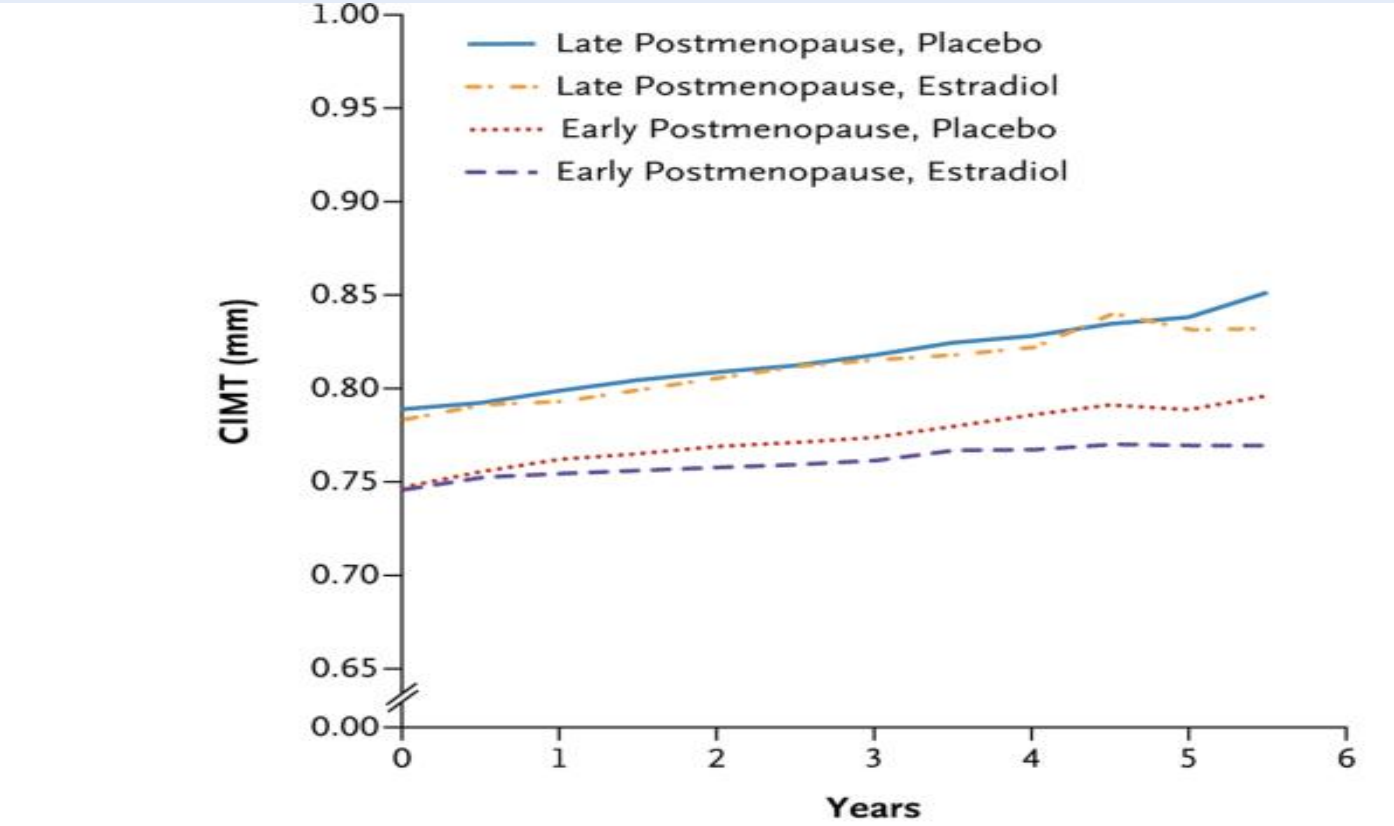


Hendrix, S. L. et al. Circulation 2006;113:2425-2434

Timing matters!



ELITE

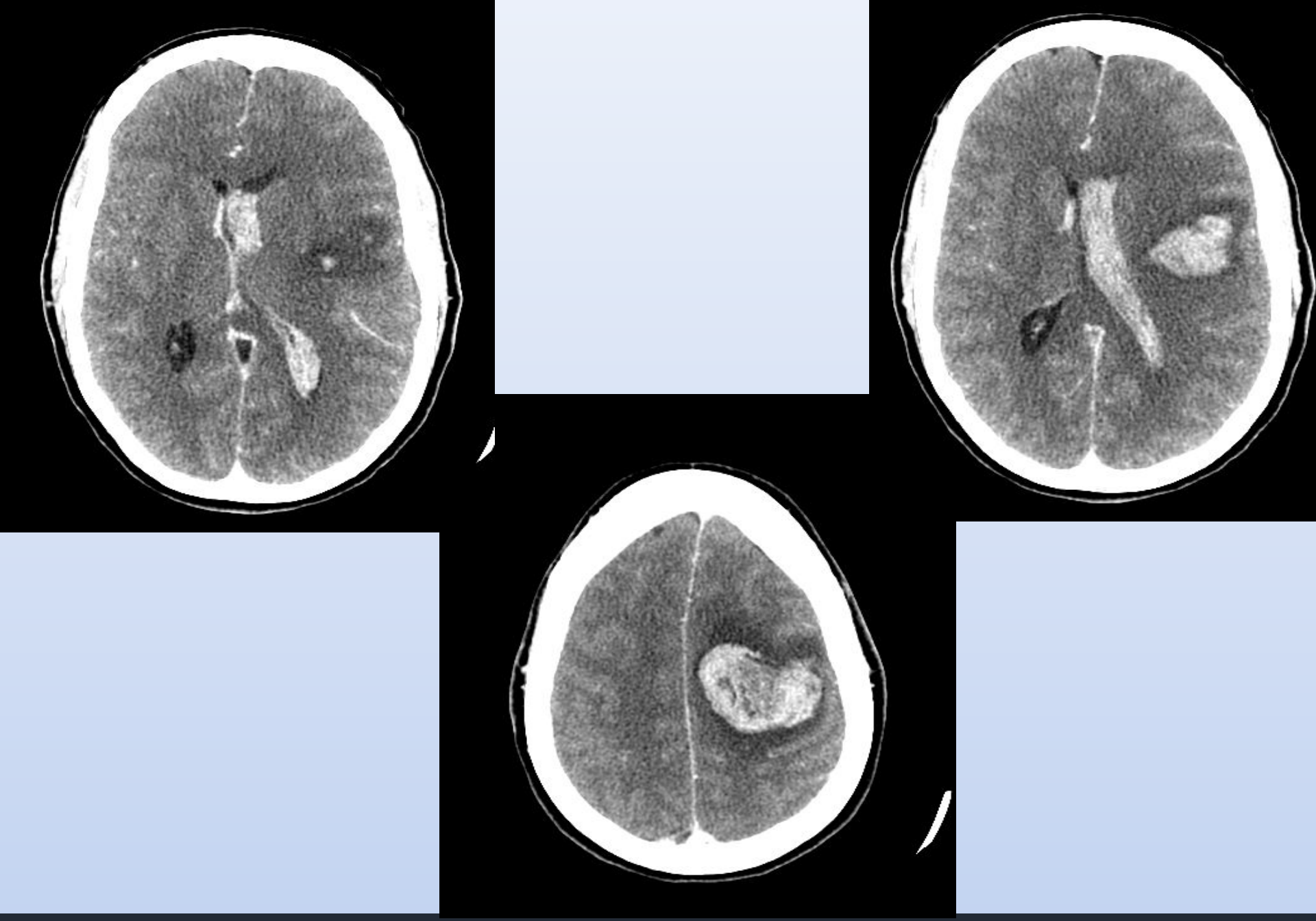


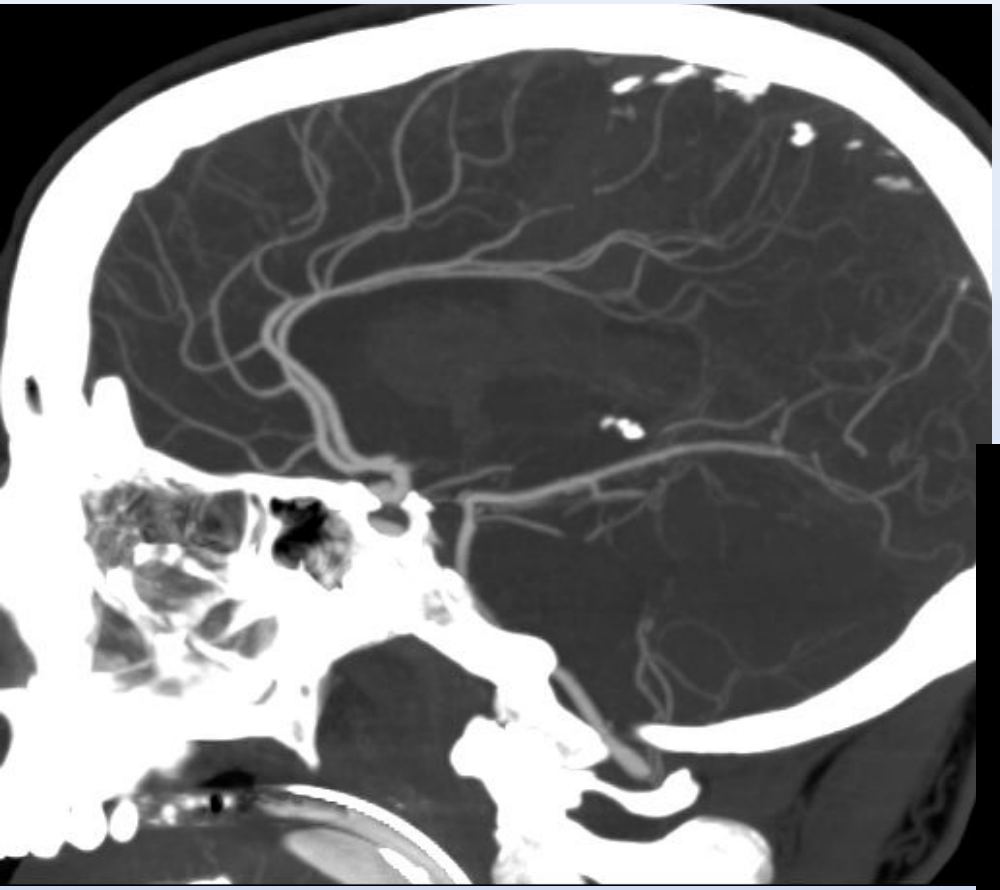
No. of Participants							
With CIMT data	643	533	522	515	424	295	56
Who completed or discontinued study	0	106	119	128	215	345	582
Without CIMT data	0	4	2	0	4	3	5

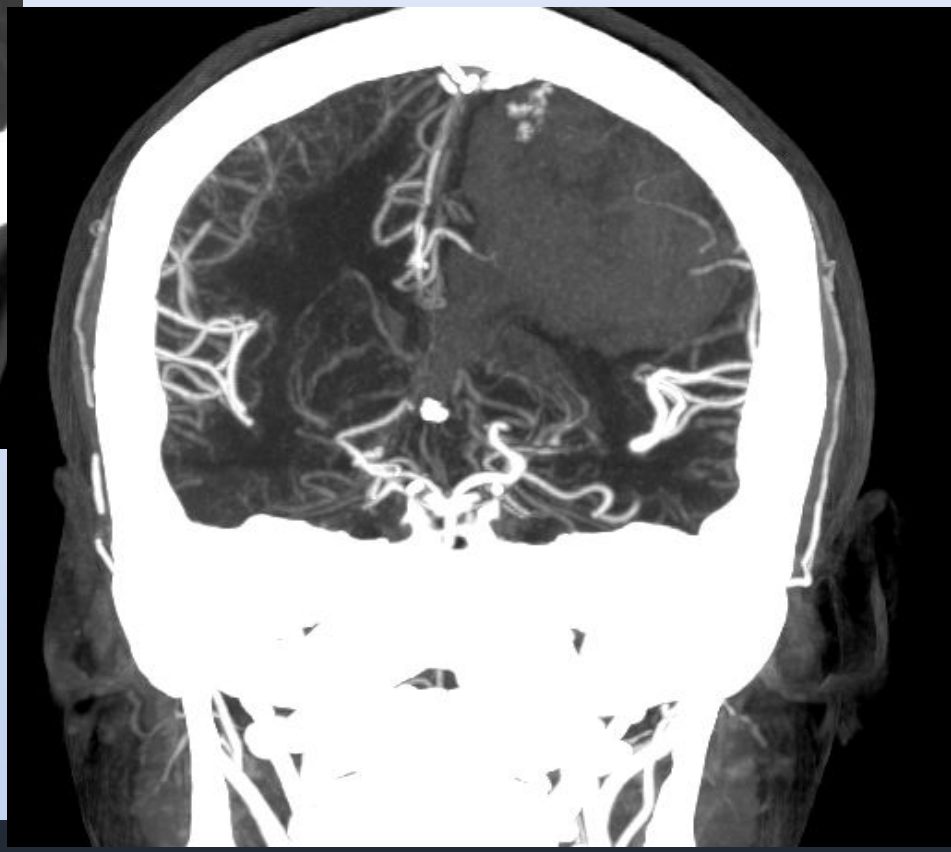
N Engl J Med. 2016 Mar 31;374(13):1221-31. doi: 10.1056/NEJMoa1505241.

Case

- **41 yo G5P4 presented with an acute onset of right hemiparesis and aphasia at 9am**
- **Last seen at 8:30 am, called husband “not feeling well”**
- **On arrival she was mute, lying on the floor**
- **In ED she had a NIHSS of 22. Alert, awake, global aphasia, left gaze preference, visual field cut, normal pupils, right facial, 0/5 on right ar moving spontaneously on left.**
- **5 months pregnant-What next?**
- **TPA?**



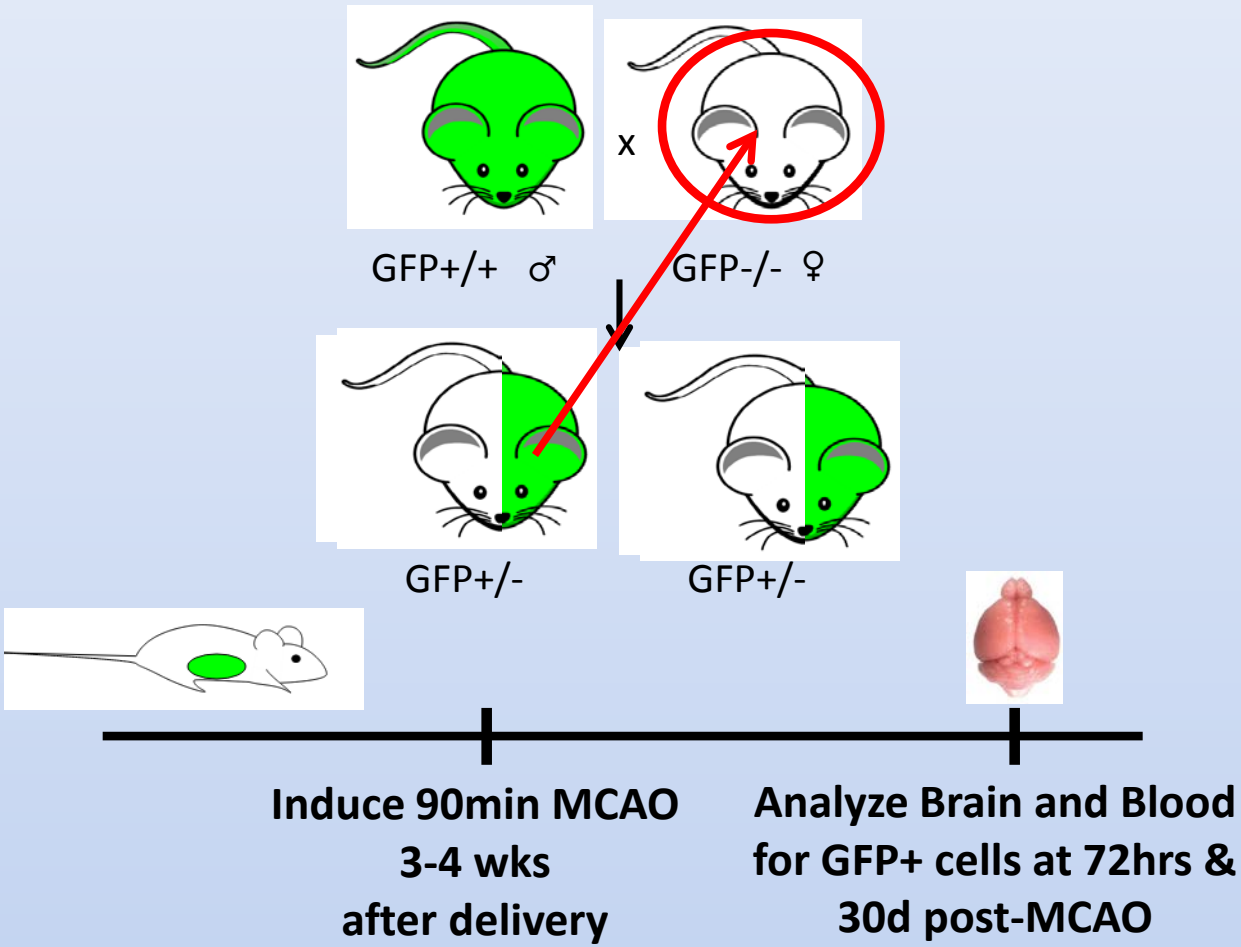




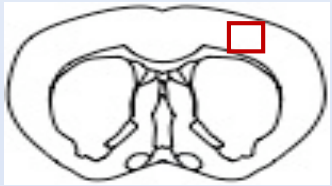
Microchimerism and Disease

- Humans…how these cells identified in humans
- “Good Microchimerism” Hypothesis: cure
- “Bad Microchimerism” Hypothesis: cause

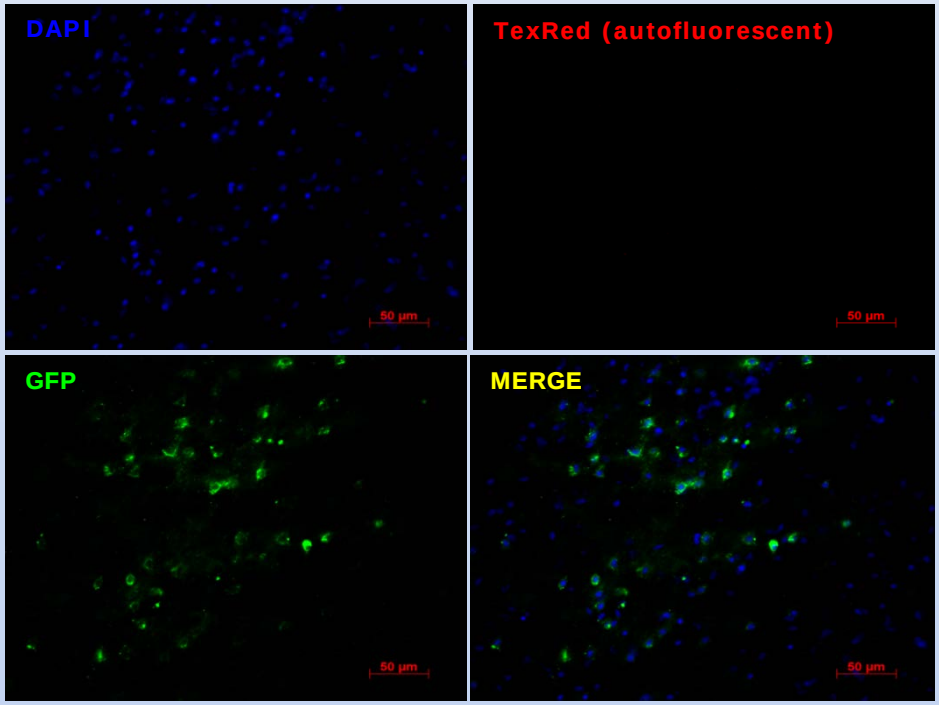
Mouse Model: **Fetal** Microchimera

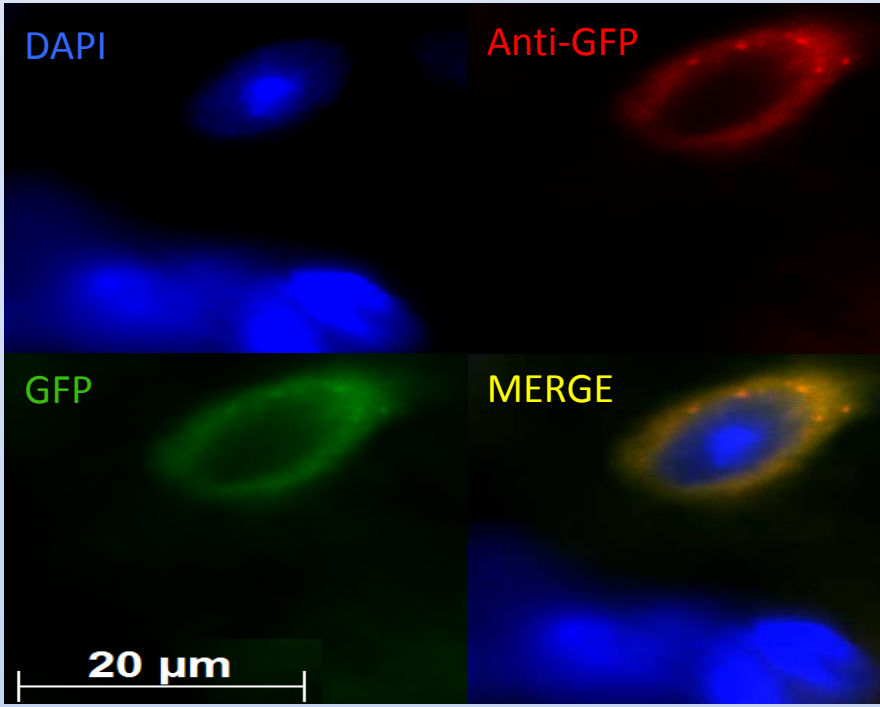


GFP+ Fetal Cells are Present in the Maternal Ischemic Brain



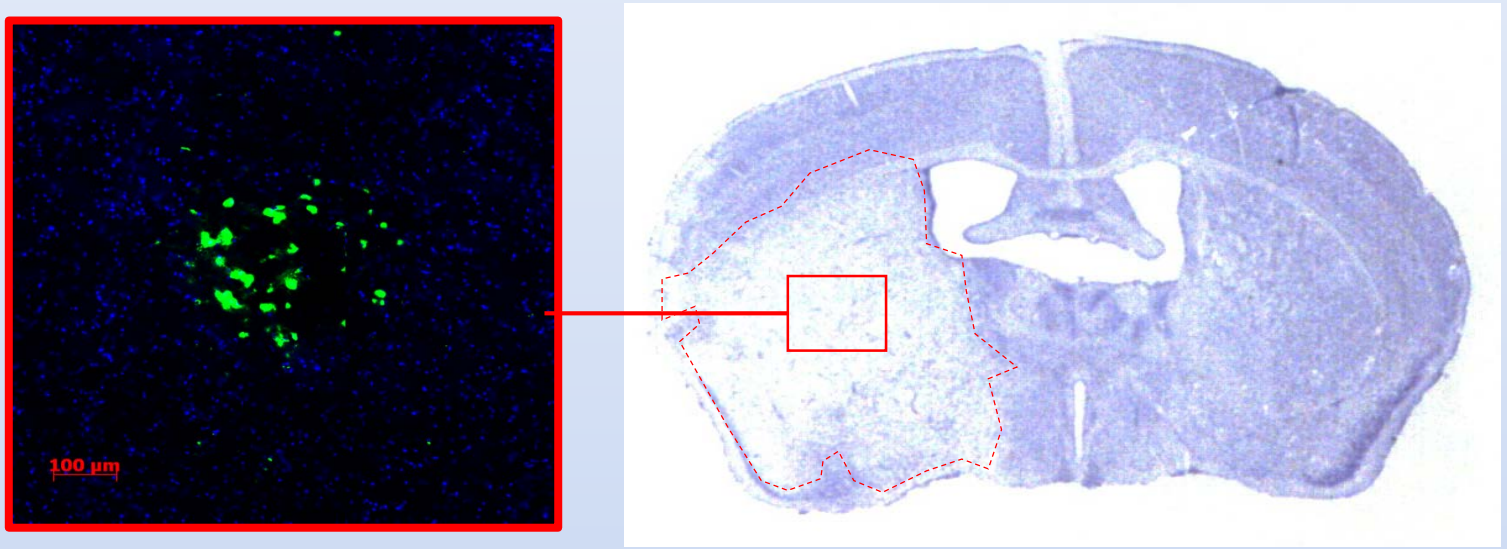
Non-Stroke Side Stroke Side





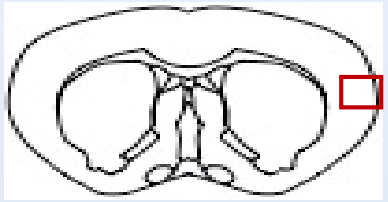
Homing of Fetal Cells to Ischemic Injury

Fetal Microchimera: 90min,72hr, 3-4 weeks post-partum



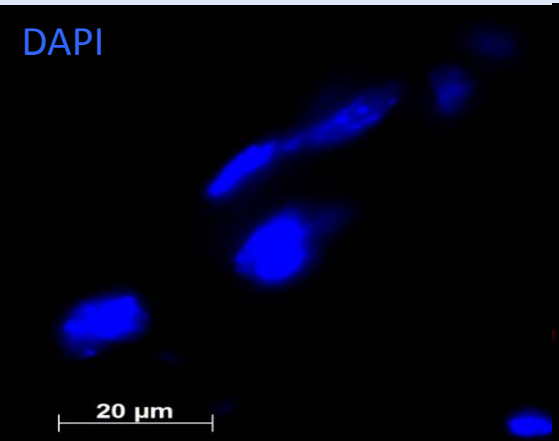
CV stain of adjacent section

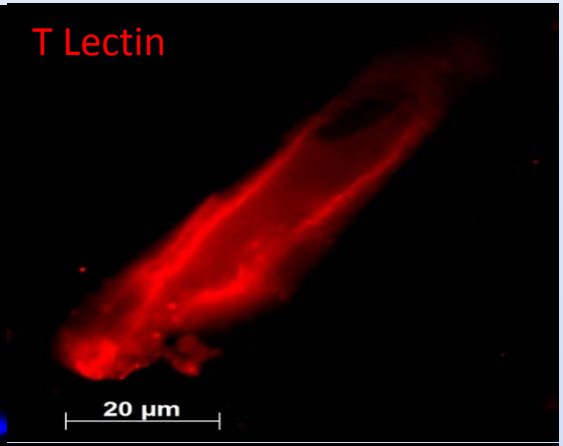
30 days after Stroke

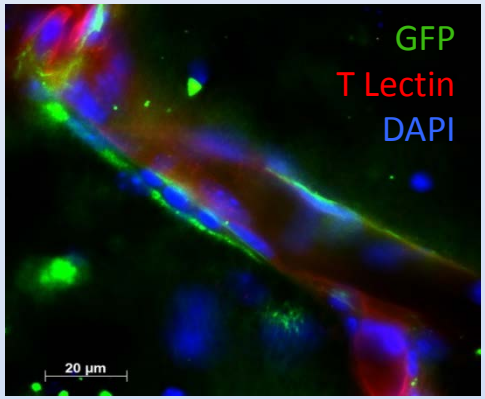


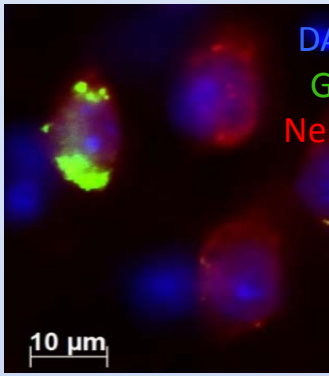
Non-Stroke Side

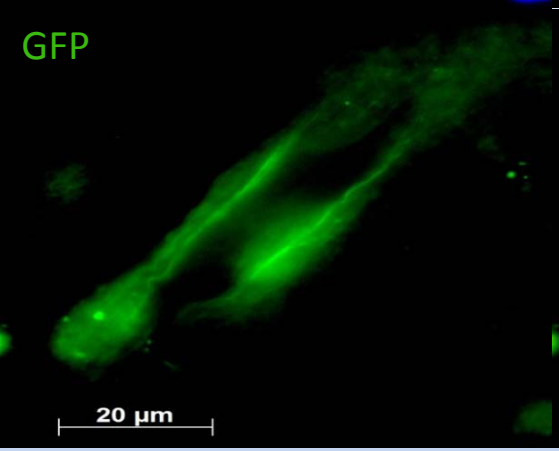
Stroke Side

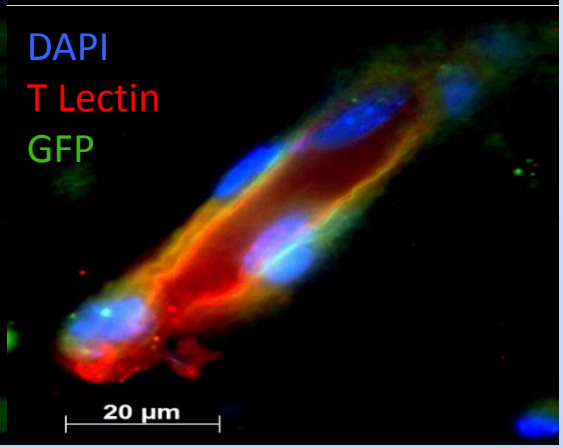


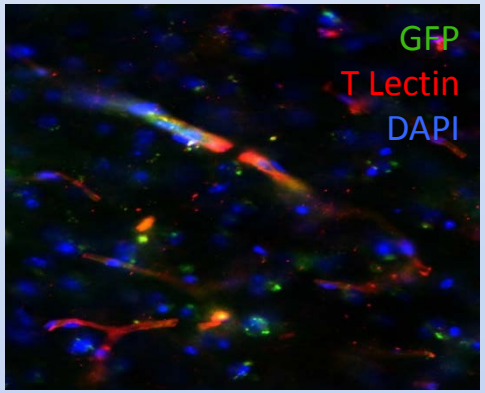










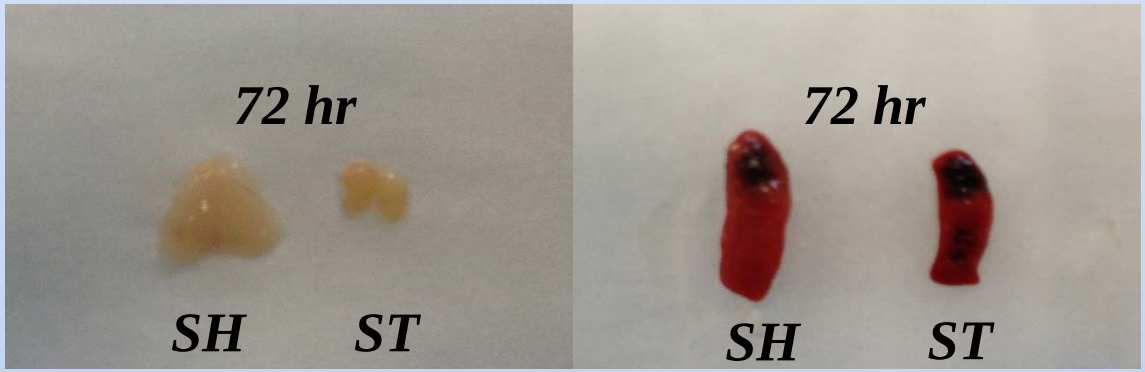


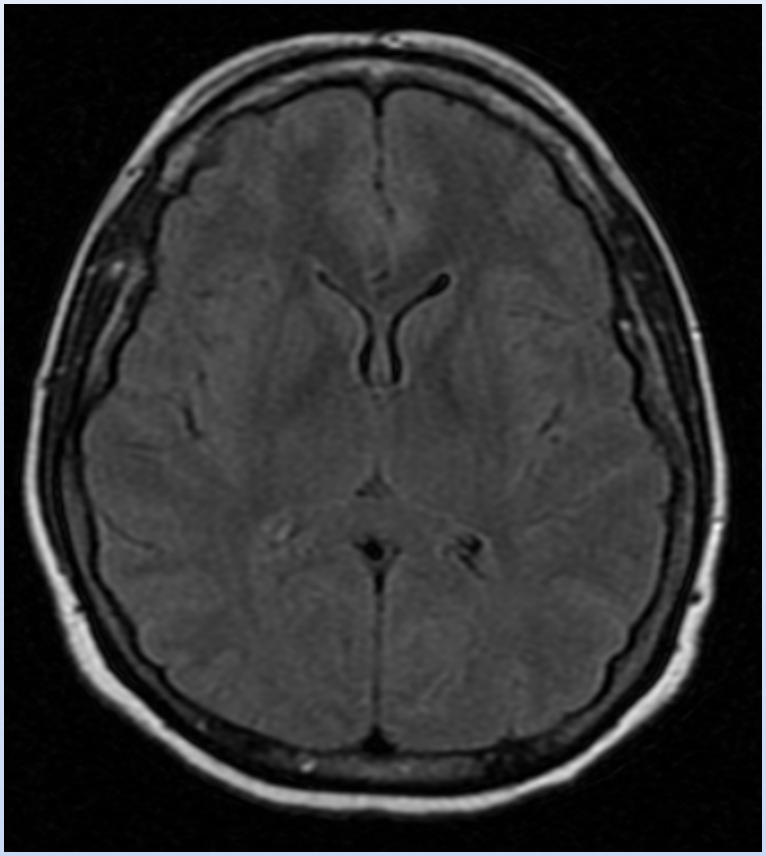
Background: Neuroimmunology

- Bi-directional communication between the immune system and the nervous system
- The CNS as an immune privileged site
- Inflammation plays a role in the etiology of a variety of neurological diseases

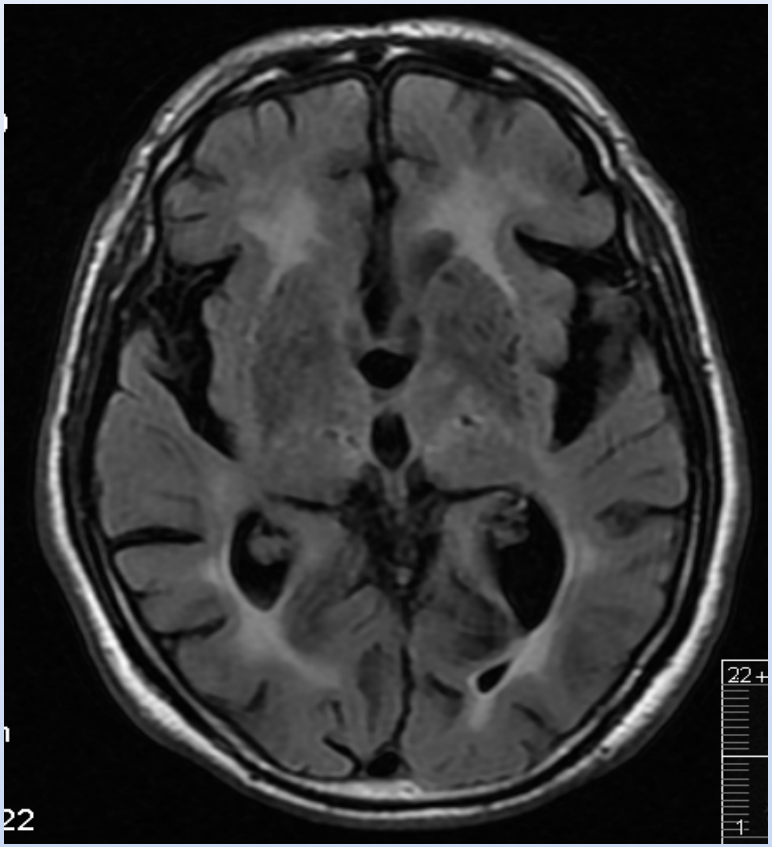
Systemic Effects of Stroke

- Peripheral Effects
- Role of Peripheral Leukocytes/Myeloid Cells
- Local Response…Microglia/Astrocytes?
- Aging… T cell deficits? Infections?

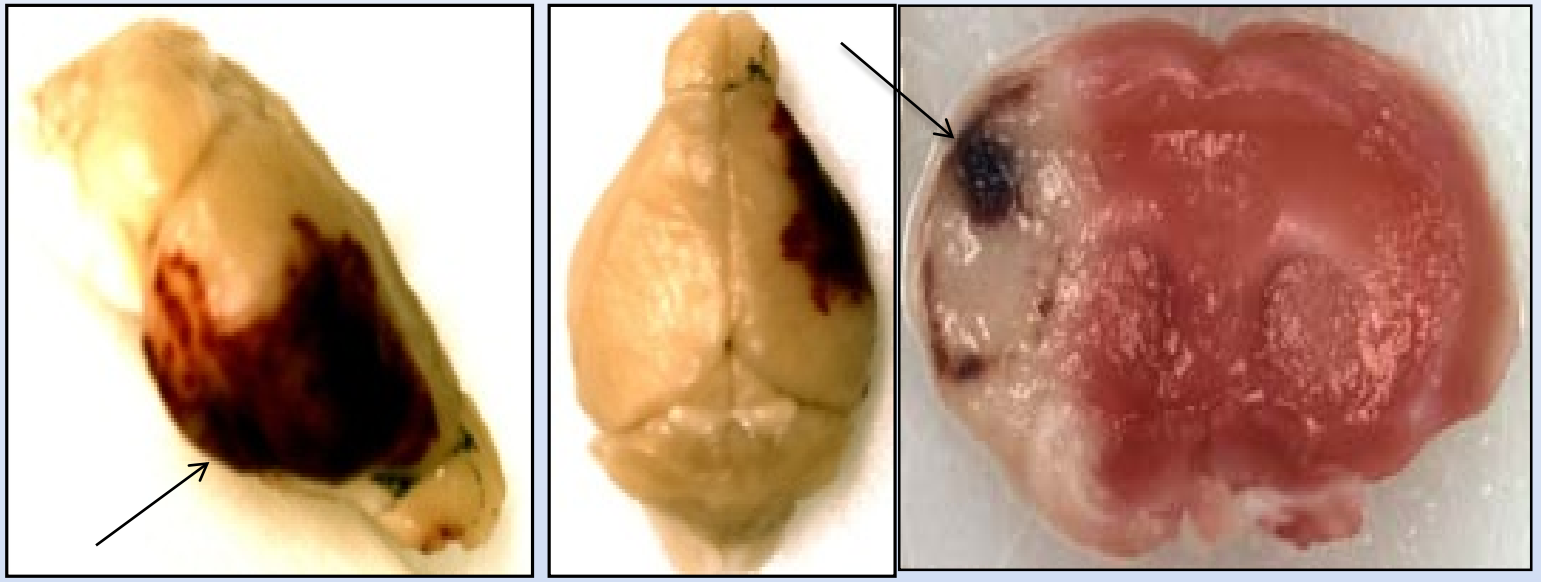




32 year old



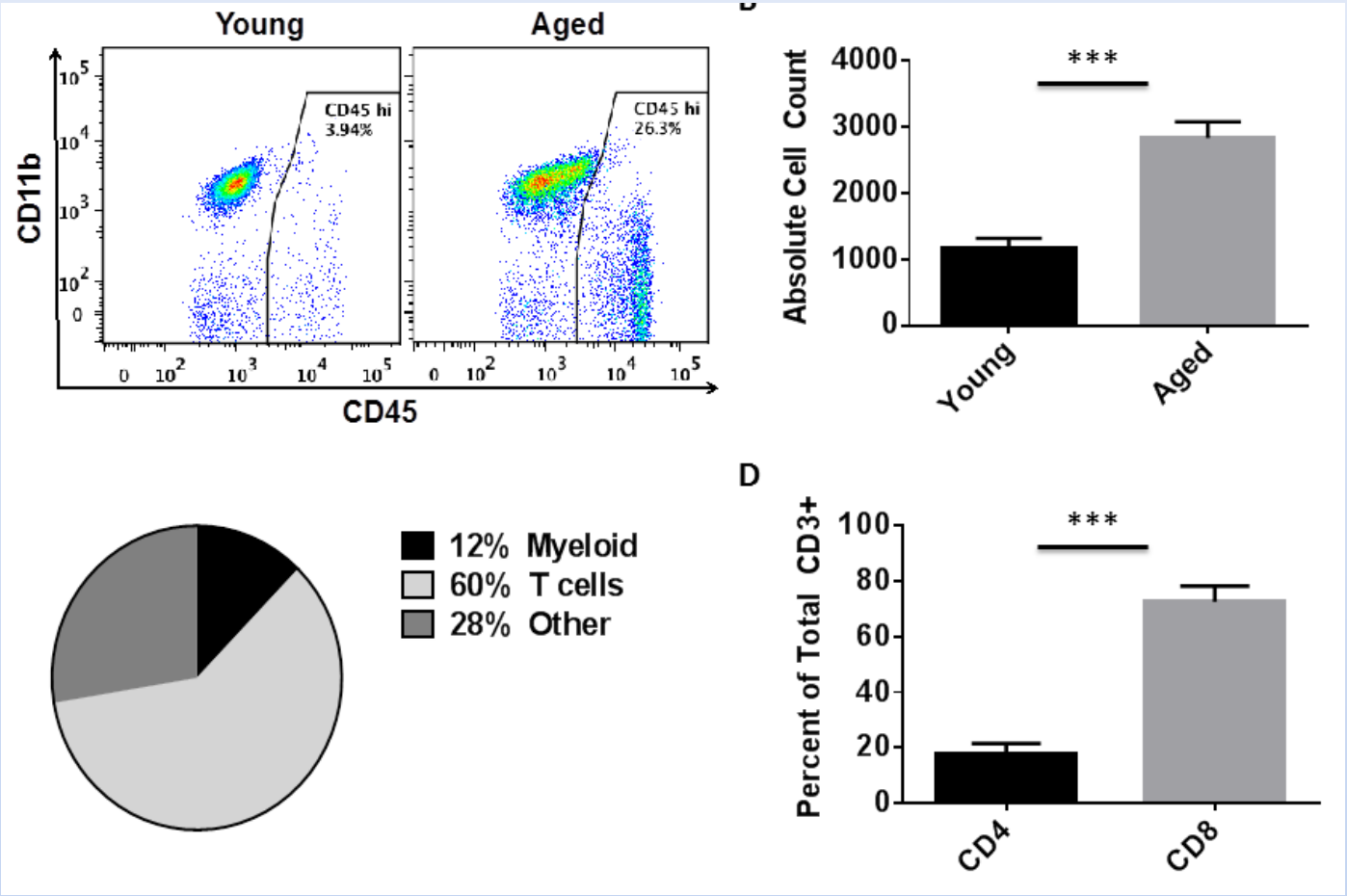
78 year old



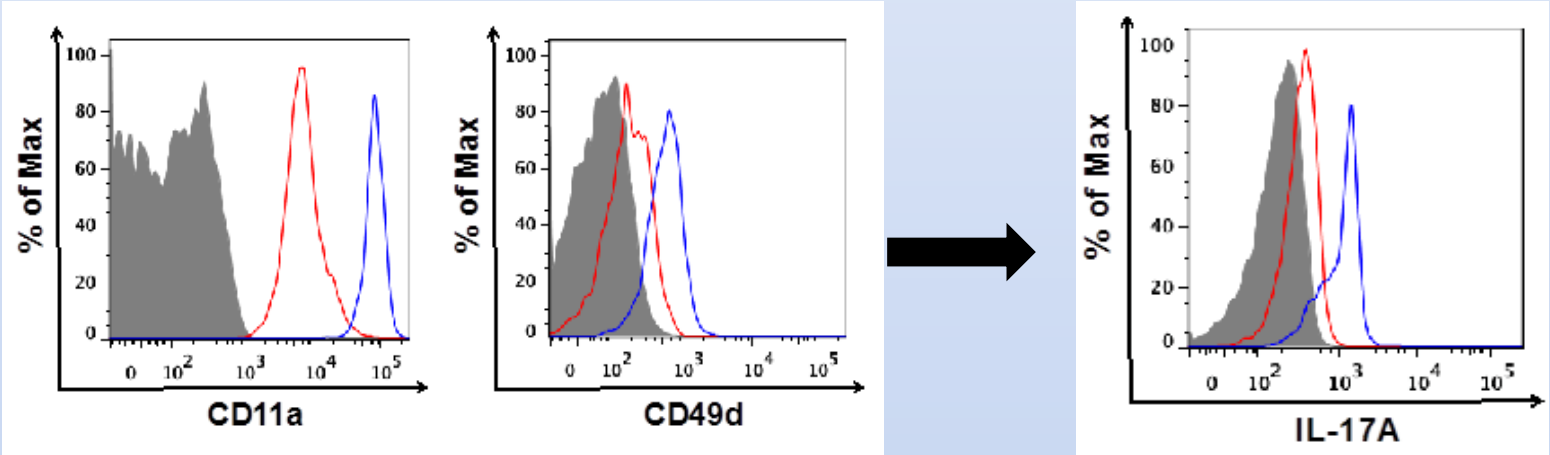
Hemorrhagic transformation (HT) after experimental stroke in aged mice: Blood marked by arrows-mimics clinical populations

Fat in aged versus young mice

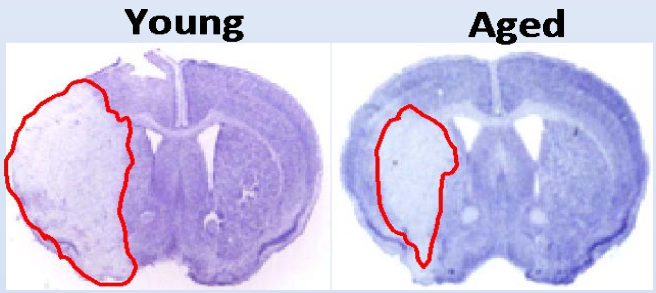
Significantly higher peripheral cells in the aged brain AT BASELINE

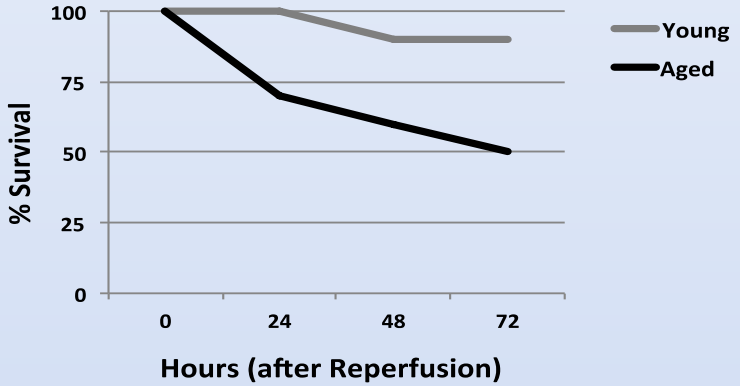


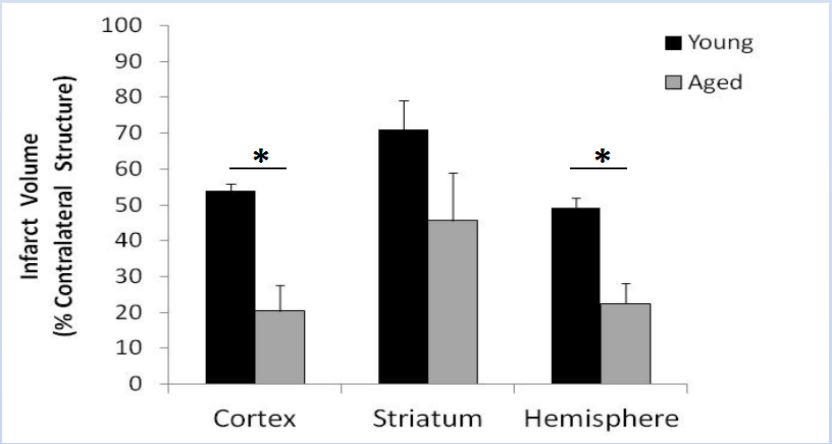
High expression of T cell adhesion markers on CD8 T cells in aged in blood and brain compared to young mice



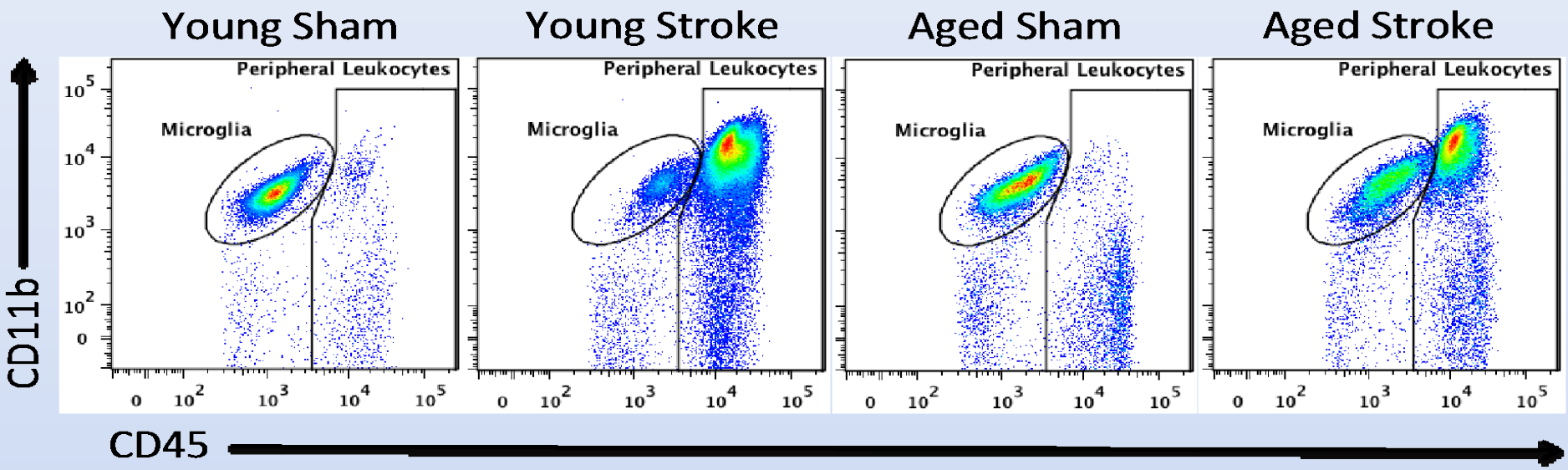
Aged mice have smaller infarcts but much poorer recovery and high mortality

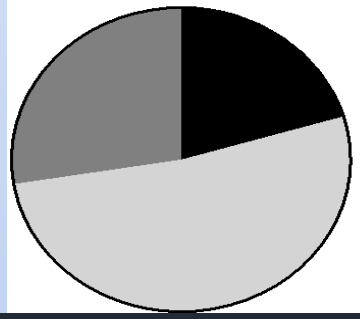






The Composition of Infiltrating Leukocytes Differs with Age

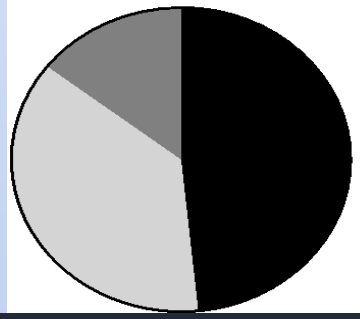




20% Ly6G$^+$ Neutrophils
52% Ly6C$^+$ Monocytes
28% Ly6G$^-$/Ly6C$^-$ Other

YOUNG

Monocytic

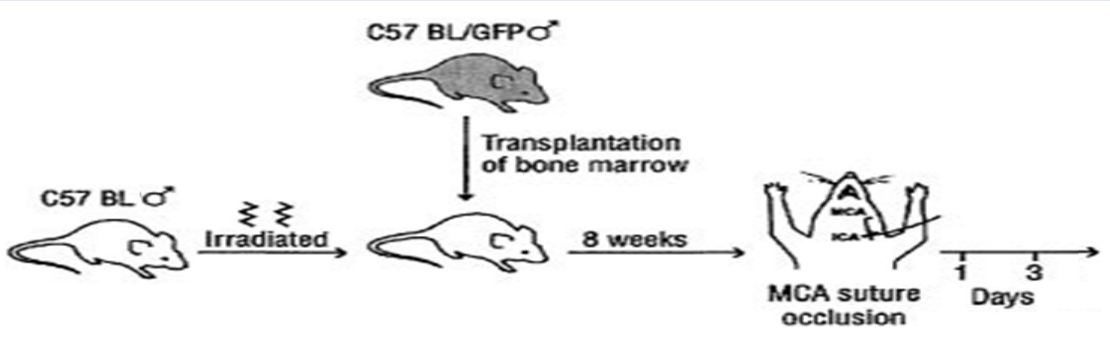


48% Ly6G$^+$ Neutrophils
37% Ly6C$^+$ Monocytes
15% Ly6G$^-$/Ly6C$^-$ Other

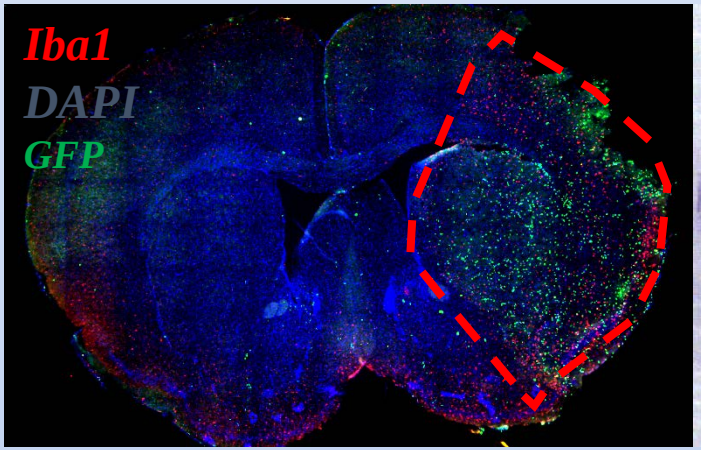
AGED

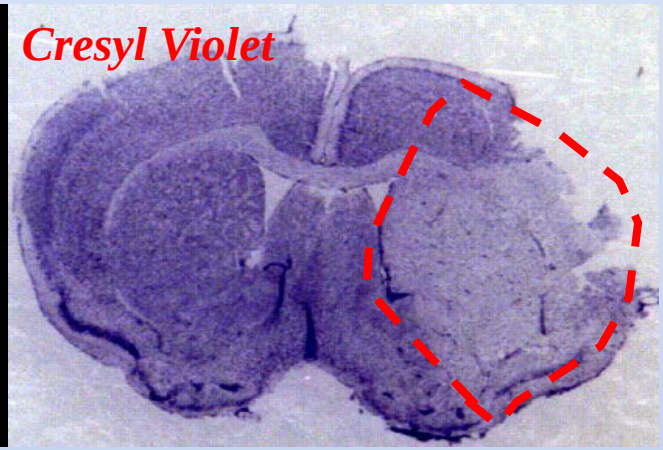
Neutrophilic

Generating Heterochronic Bone Marrow Chimeras (hBMC)

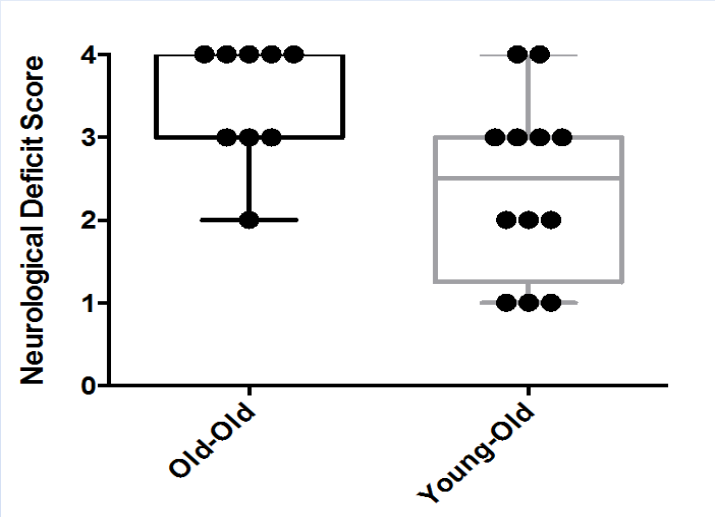


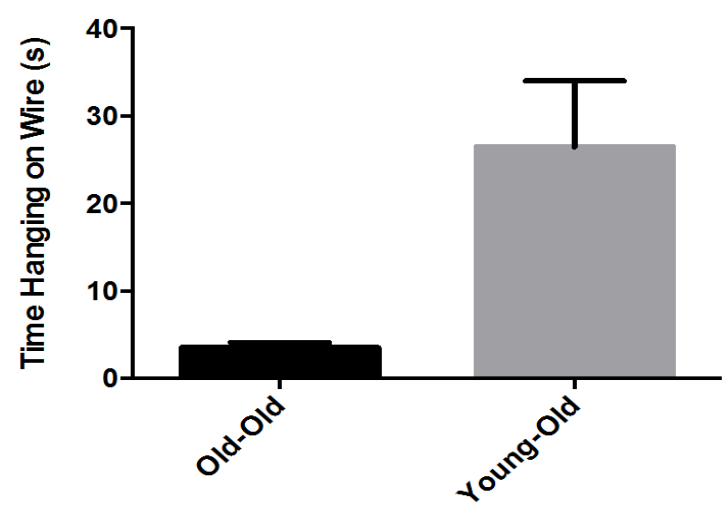
Young → Young
Old → Young
And
Young → Old
Old → Old

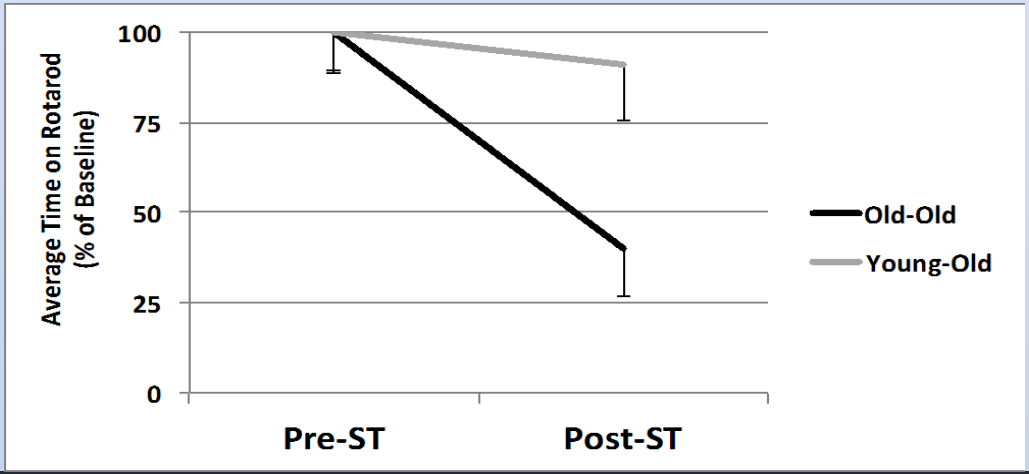




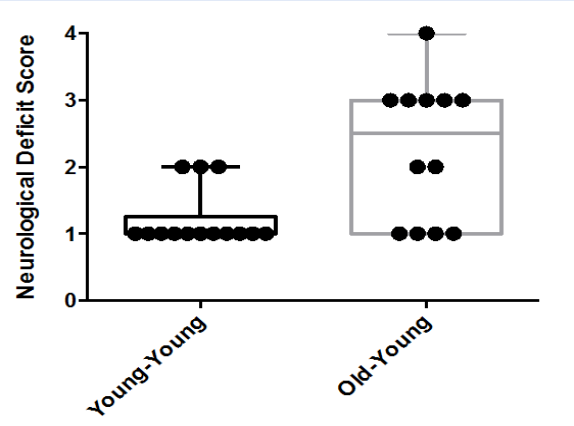
Young bone marrow contributes to enhanced recovery in aged mice

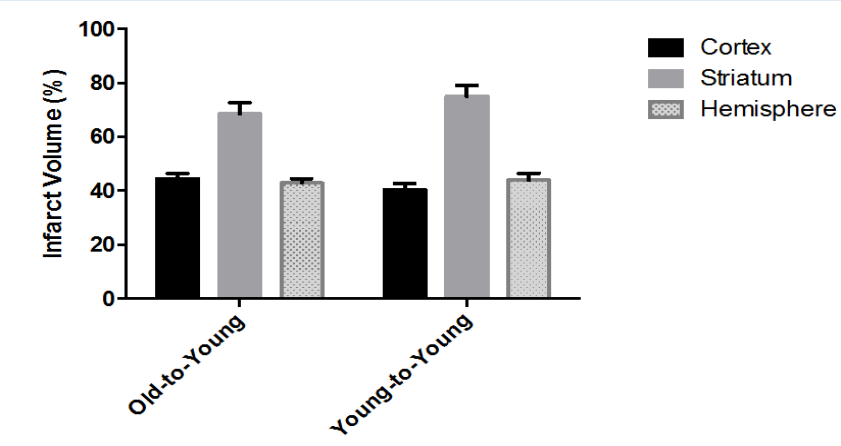


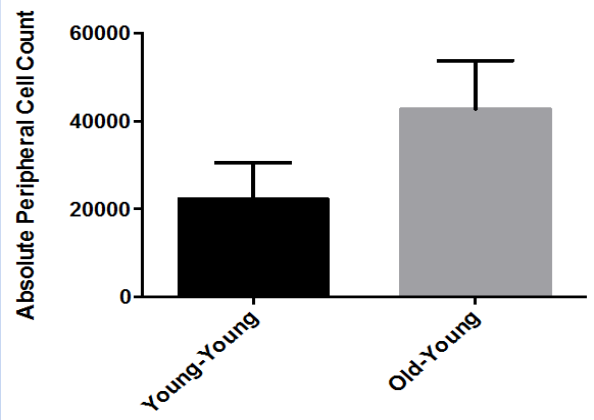


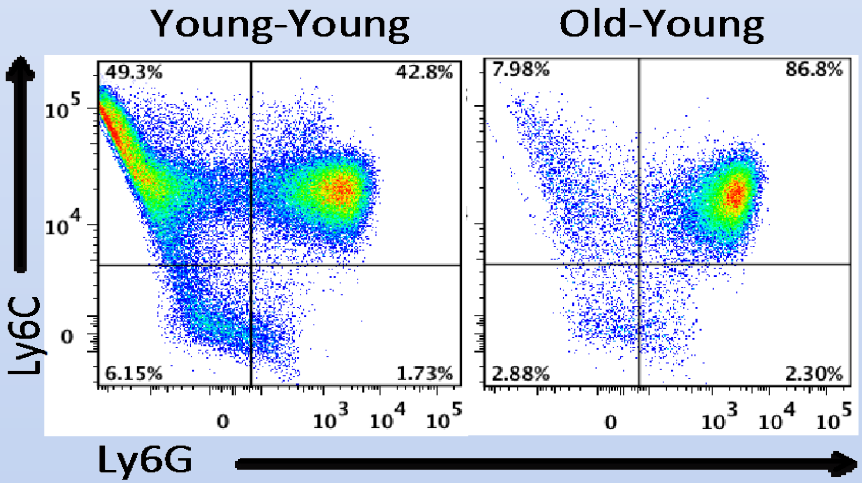


Aged bone marrow contributes to poorer recovery in young mice

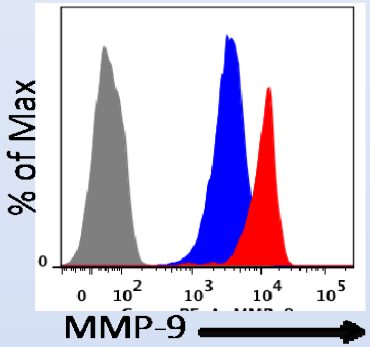


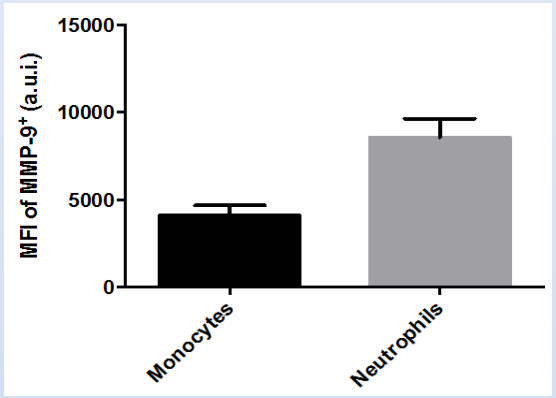


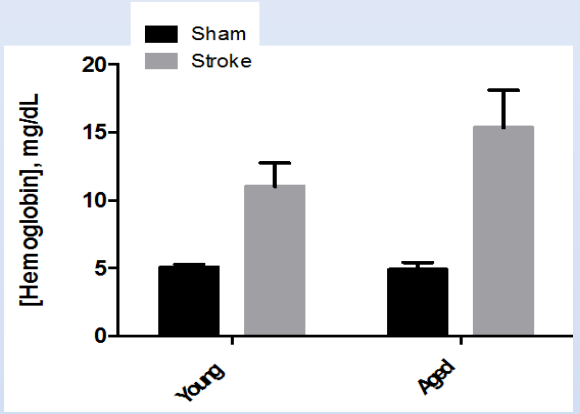


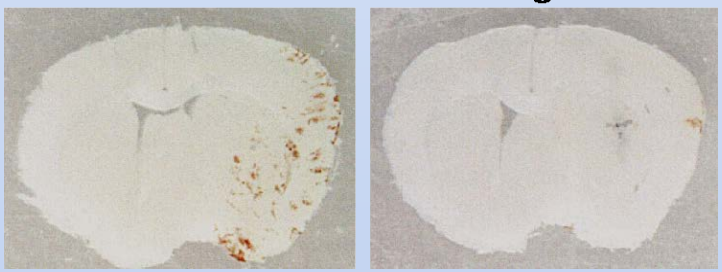


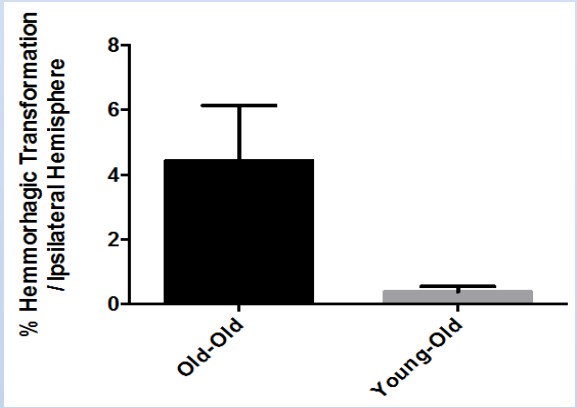
Aged bone marrow increased hemorrhagic transformation in young mice and young BMT reversed this in aged mice



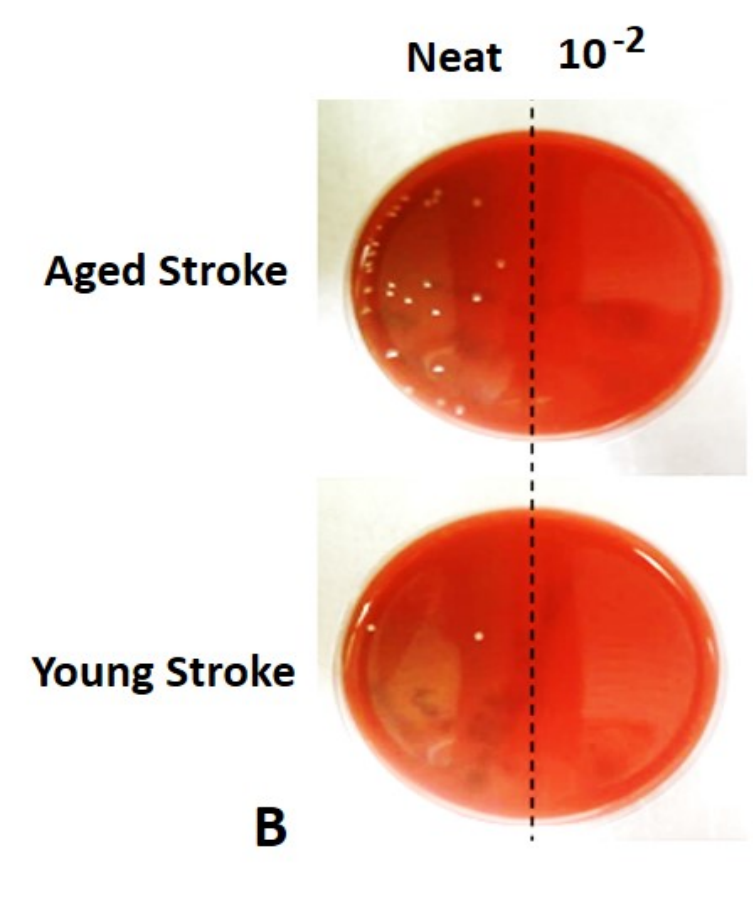


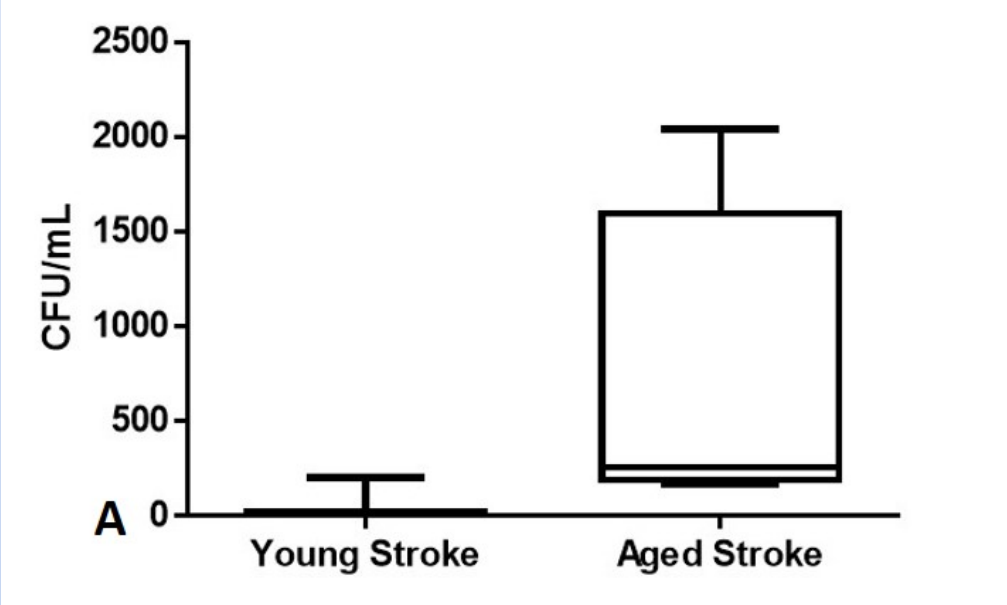






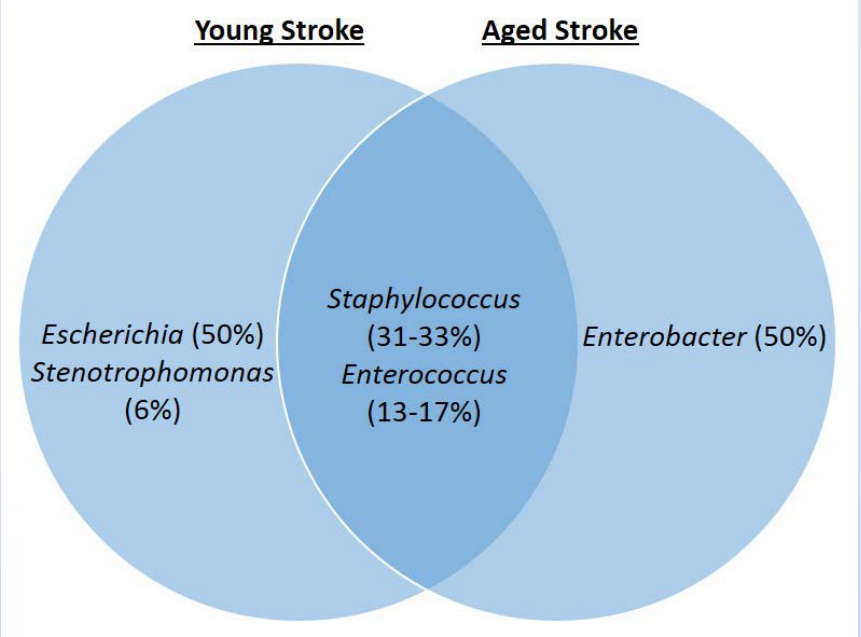
Age and the Systemic Response to Stroke



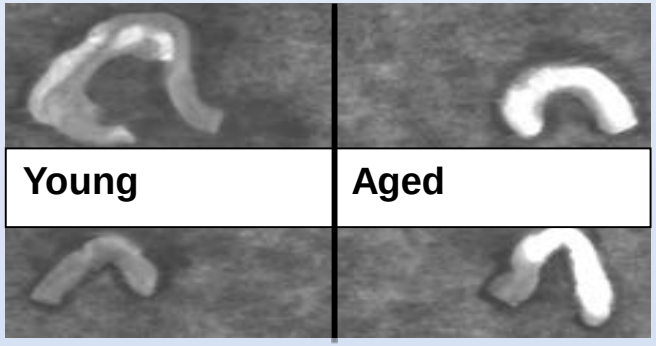


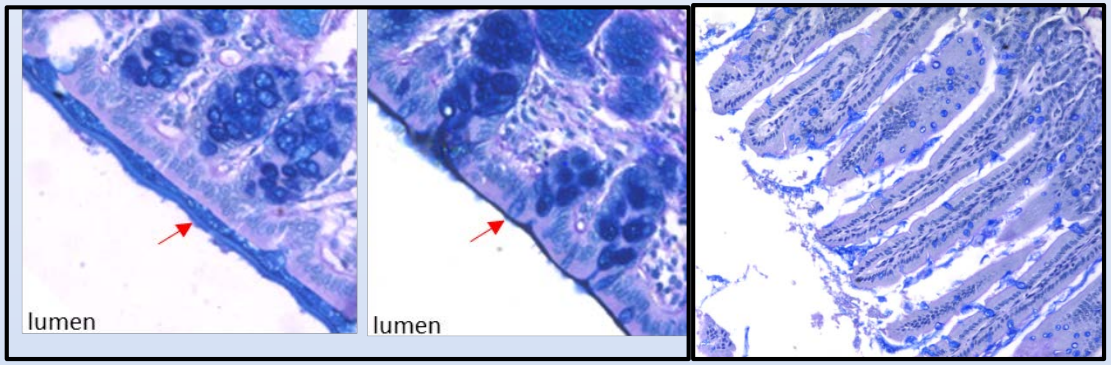
The amount AND the composition of systemic bacteria differ in young vs. aged mice

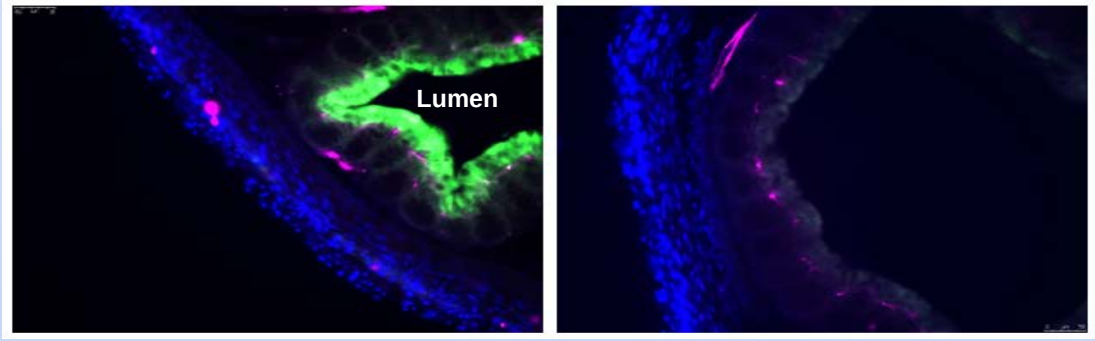
	Young Sham	(%)	Young Stroke	(%)	Aged Sham	(%)	Aged Stroke	(%)
MLN	1/7	14.3	5/7	71.4	3/8	37.5	6/7	85.7
Spleen	0/6	0	4/10	40	1/8	12.5	6/7	85.7
Liver	0/7	0	8/10	80	2/8	25	7/7	100
Lung	0/7	0	3/10	30	1/8	12.5	5/7	71.4



Aging and stroke impair GI barrier function and allow for bacterial translocation

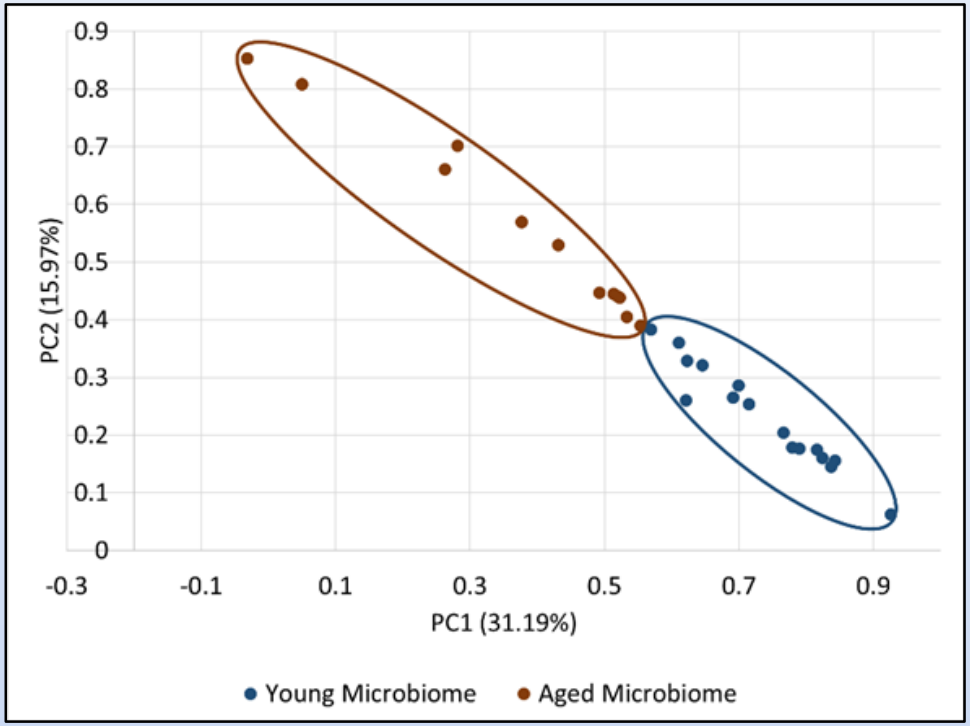






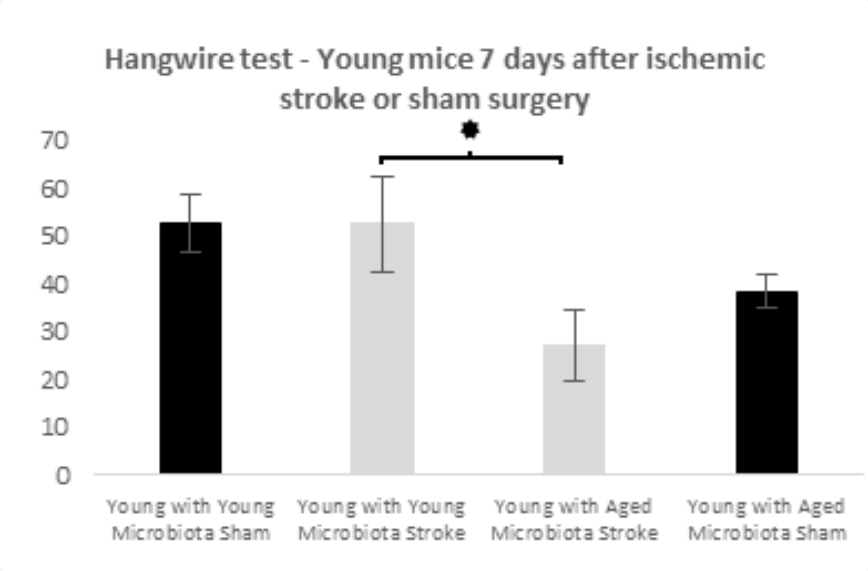
Stroke-induced loss of the gut hypoxic barrier, O2 sensing pimonidazole (green)

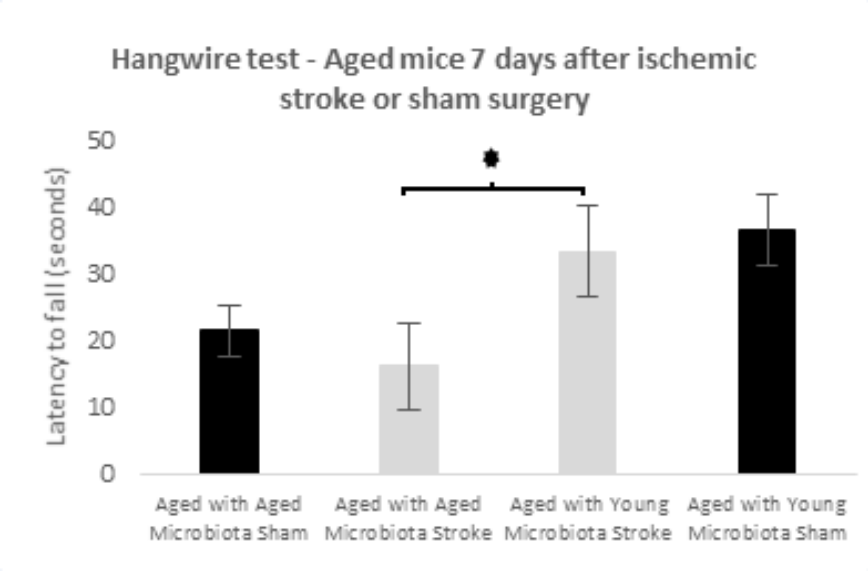
Age differences in the microbiome



A principle component analysis (PCA) showed significant separation between age groups (ANOSIM *p* value = 0.005) Principle component 1 (PC1) explained 31.19% of variation seen in samples while PC2 (15.97%) further separated the different microbial populations from different microbiome. PCA plots were generated using the raw abundances of microbial groups after 16s rRNA sequencing.

Biome transfers influence behavioral recovery





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