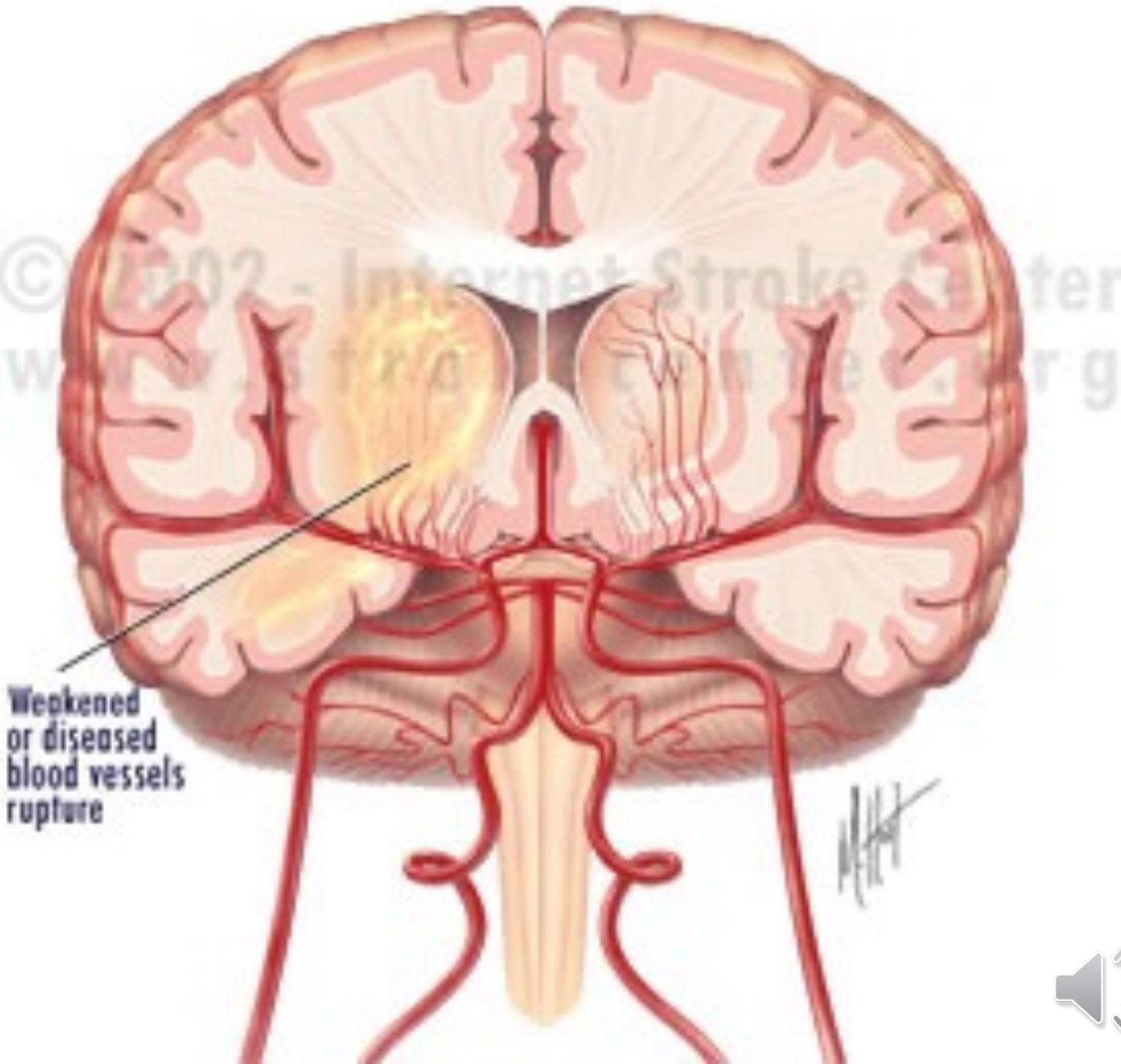
Basic Epidemiology

- Primary Spontaneous ICH
- Accounts for roughly 10-15% of all strokes
- 40-50% mortality rate
- Over 70% of survivors with significant morbidity/disability
- Half of the mortality occurs in the first two days after stroke

Branching

- In most vascular beds, large arteries branch into medium arteries which then branch into smaller arteries and then most importantly into
- Arterioles (smaller than arteries) mediate most of that blood pressure
- Thus, the pressure at the feeding vessel is distributed across a large vascular bed.


Weakened
or diseased
blood vessels
rupture

Hypertension and Cerebral Small Vessel Disease

- Theoretically, the pressure on lenticulostriates and small capillaries branching off of the MCA and Basilar artery without an intervening resistance bed is very high
- Population attributable risk is proportion of disease that would have been prevented if the risk factor did not exist

Univariate Attributable Risk for ICH, Lobar ICH, and Nonlobar ICH

	Risk (95% CI)		
	All ICH (n=188)	Lobar ICH (n=67)	Nonlobar ICH (n=121)
First-degree relative with ICH	0.05 (0.02–0.08)	0.05 (0.0–0.16)	0.04 (0.005–0.08)
Previous ischemic stroke	0.13 (0.09–0.18)	0.09 (0.02–0.16)	0.14 (0.08–0.20)
Frequent alcohol u			
Hypertension			
ApoE2 or E4			

Table 2.

Attributable Risk in Percentages: Univariate Analysis[1]

Risk Factor	Type of Stroke	Odds Ratio	Attributable Risk, %	95% CI
Hypertension	All ischemic	1.7	27	7–43
Diabetes	All ischemic	2.7	21	11–29
History of MI	All ischemic	2.1	9	2–16
Hypertension	Small vessel	5.0	68	31–85
Diabetes	Small vessel	4.4	30	10–45
Diabetes	Cardioembolic	3.1	25	4–40
History of MI	Cardioembolic	3.6	21	4–35

Importance of Location

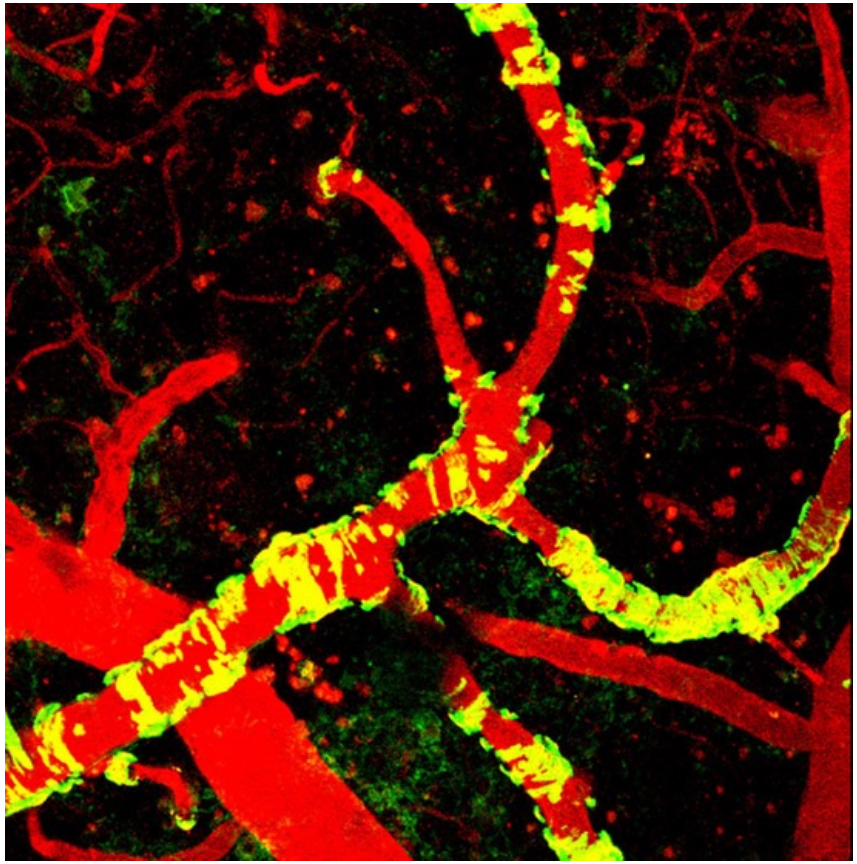
- At one time, hypertension was felt to be the cause of ICH in all locations and cerebral amyloid angiopathy to be a rare cause of ICH
- Population-based studies –
  - To determine the attributable risk of each risk factor
  - To control for regional differences in risk factor

Cerebral Amyloid Angiopathy

- Amyloid plaques made of beta-sheets of proteins, make blood vessels more rigid and fragile.
- CAA occurs in 70% of Alzheimer's disease patients
- In less than 10% of people less than 70 years of age but more than 50% of people age >90 years
- Occurs almost exclusively in the lobar regions of the brain and cerebellum

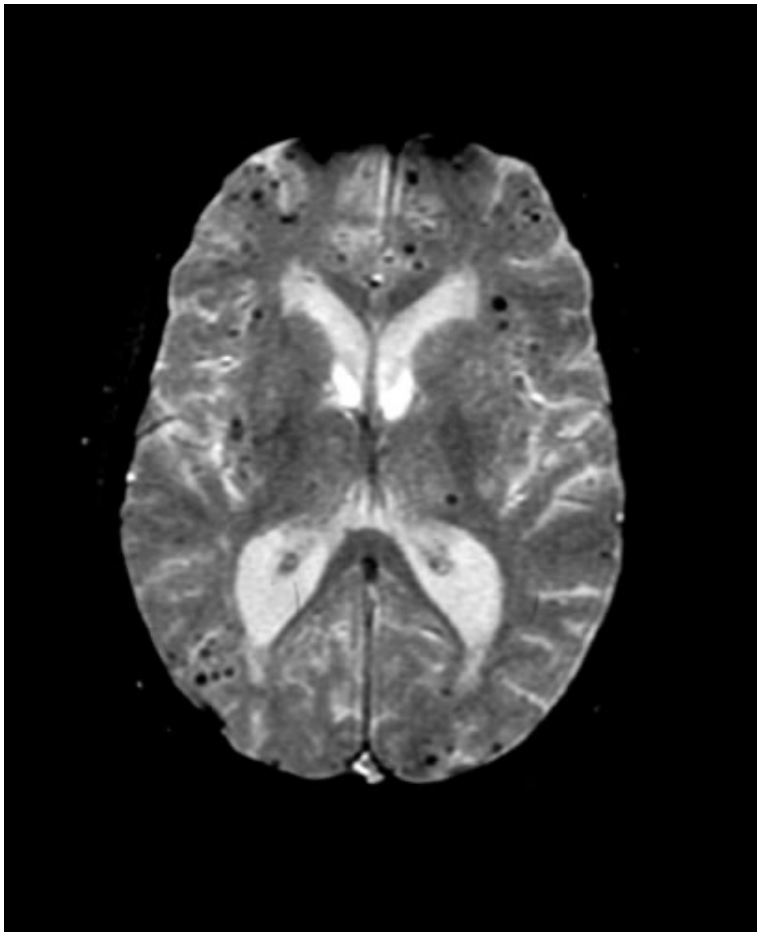
Cerebral Amyloid Angiopathy

- Disease of the elderly (~50% of ICH in >80)
- Deposition of amyloid protein in media/adventitia of small cortical arteries, arterioles and capillaries
- Cortex and cerebellum



Cerebral Amyloid Angiopathy

- Pathology
  - Destruction of normal cortical vasculature
- Microbleeds on MRI GRE sequences
  - More common in blacks with ICH?*
  - (Microbleeds also caused by HTN)
- Lobar ICH
- Association with Apo E2/E4



*(Kidwell) Neurology 2008;71:1176-1182.

On the importance of Intraventricular Hemorrhage

- Rupture of hemorrhage into the ventricles is an independent risk factor for worse outcomes and death
- Ventricular hemorrhage may lead to hydrocephalus, may require management with ventriculostomy or thrombolytic agent into the ventricles
- Over 945 patients with deep basal ganglia hemorrhages, rates of IVH varied by location ($p<0.0001$)
  - Caudate: 89%
  - Putamen: 23%
  - Thalamus 64%

	GERFHS – Discovery Set				ERICH – Replication Set			
Variables	Incontinence		Dysmobility		Incontinence		Dysmobility	
	OR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value
IVH Volume	1.50 (1.10, 2.06)	0.0117	1.58 (1.17, 2.15)	0.0031	1.42 (1.27, 1.60)	<.0001	1.40 (1.24, 1.57)	<.0001
Age (per year)	1.07 (1.04,1.10)	<.0001	1.06 (1.03, 1.09)	<.0001	1.04 (1.03, 1.05)	<.0001	1.04 (1.03, 1.05)	<.0001
ICH Volume	1.78 (1.25, 2.54)	.0015	1.85 (1.32, 2.60)	0.0004	1.77 (1.51, 2.06)	<.0001	2.22 (1.91, 2.58)	<.0001
Location								
-Lobar	0.33 (0.15,0.72)	.005	0.18 (0.09, 0.40)	<.0001	0.51 (0.36,0.72)	.0001	0.27 (0.19, 0.37)	<.0001
-Deep	REF	REF	REF	REF	REF	REF	REF	REF
-Brainstem	5.22 (1.05, 25.95)	.043	1.84 (0.35, 9.62)	.4712	3.39 (1.83, 6.29)	.0001	3.71 (2.06,6.69)	<.0001
-Cerebellar	1.73 (0.62, 4.83)	.30	1.48 (0.55, 3.99)	.4419	0.70 (0.41, 1.20)	.19	0.77 (0.48 1.24)	.28
-Primary IVH					1.72 (0.58, 5.03)	.33	1.54 (0.55, 4.32)	.42
GCS at presentation (per point)	0.89 (0.77 1.03)	.1198	0.88 (0.76, 1.03)	0.1020	0.90 (0.87, 0.94)	<.0001	0.88 (0.84, 0.93)	<.0001
mRS before ICH	1.65 (1.24, 2.18)	.0006	1.71 (1.29, 2.26)	.0002	1.62 (1.38, 1.91)	<.0001	1.45 (1.22, 1.71)	<.0001
Female	1.42 (0.79, 2.57)	0.2412	0.99 (0.56, 1.75)	0.9648	1.51 (1.15, 2.00)	0.0036	1.68 (1.29, 2.18)	0.0001

Importance of Untreated Hypertension

TABLE 3. Multivariable Risk Factors for Hemorrhagic Stroke

	AHS		All ICH	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Untreated hypertension	3.5 (2.3–5.2)	<0.0001	3.9 (2.3–6.5)	<0.0001
Treated hypertension	1.4 (1.0–1.9)	0.0271	1.4 (1.0–2.0)	0.0710
History of hypercholesterolemia	0.52 (0.39–0.69)	<0.0001	0.53 (0.37–0.75)	0.0004
Increasing BMI (5 U)	0.84 (0.75–0.93)	0.0012	NS	
Use of anticoagulants	3.1 (1.8–5.3)	<0.0001	3.6 (2.0–6.8)	<0.0001

Not all Hypertension?

- Untreated hypertension is a markedly greater risk of ICH than treated hypertension, especially for regions of the brain that are associated with hypertensive ICH.
- Although lack of treatment may explain the higher rate of ICH among Hispanics, AAs have similar rates of awareness, treatment and controlled HTN as whites
- Is there some other risk factor?

Hypercholesterolemia and Intracerebral Hemorrhage

- 1976 – Konishi et al; Autopsy study in the Akita Prefecture found little arteriosclerotic change in cerebral blood vessels of hypertensive ICH patients; no risk from hypercholesterolemia
- 1988 – Ueda et al; Prospective population-based study; Higher serum cholesterol level associated with 50% reduction in rate of ICH.

Hypercholesterolemia and Intracerebral Hemorrhage

- 1989 – Honolulu Heart Program
- 1993 – Akita Pathology Study
- 1994 – MRFIT Study
- 1995 – Copenhagen Stroke Study
- 1996 - Kaiser Permanente Medical Care Study
- 1996 - Melbourne Risk Factor Study
- 1997 – Kim et al
- 1999 – Segal et al

Hypercholesterolemia and Intracerebral Hemorrhage

- 2001 – Korea medical insurance co. study
- 2002 – GERFHS - Cincinnati
- 2003 – Ariesen et al – Meta-analysis
- 2003 – Ko et al -
- 2004 – GERFHS – Statin and ICH
- 2007 – NOMAS
- 2012 – Martini et al

Hypercholesterolemia

- High cholesterol, high LDL and low HDL have been consistently associated with a paradoxical decreased association with ICH
- Some studies suggest that this is true predominately for non-lobar ICH
- Statin use has been variably associated with no to minimal effect on ICH risk but seems to offer no benefit to reducing risk
- Could AAs have less hypercholesterolemia and thereby a higher risk of non-lobar ICH?

By Location

- Non-lobar ICH:
  - OR 0.58 (0.45-0.71; $p<0.001$);
  - AR: -29.9
- Lobar ICH:
  - OR 0.85 (0.61-1.19; $p=0.34$)
  - AR: N.D.
- Almost a third of non-lobar ICH is attributable to effects from Cholesterol but no protective effect appears for lobar ICH

Brain and Cholesterol

- The brain is the largest repository of cholesterol in the human body (moreso than even the liver)
- Largely in myelin sheaths but also essential to inflammation, neurovascular unit and vascular blood-brain barrier integrity
- 95% of all brain cholesterol is synthesized locally.
  - Minor uptake of serum cholesterol
  - Brain cholesterol is metabolized locally but synthesized using the same processes as liver

Apolipoprotein E

- Apo E is a major lipoprotein
  - Transport of chol from liver to tissues
  - Reverse transport from tissue to liver
  - E4 – associated with Alzheimer's and cardiovascular disease and lobar ICH
  - E2 – Protective of AD and CV disease but a risk for lobar ICH

Table 1. Demographics of Patients

	Lobar			Non-Lobar		
	Cases	**Controls**	**P-val**	**Cases**	**Controls**	**p-val**
N	204	508		354	936	
Age (years ± SD)	66.4 ± 16.2	63.1 ± 15.6	0.01	64.7 ± 15.1	61.3 ± 14.0	0.0001
Sex (% M)	91 (44.6%)	216 (42.5%)	0.6	188 (53.1%)	468 (50%)	0.3
Race (% B)	30 (14.7%)	73 (14.4%)	0.9	82 (23.2%)	227 (24.3%)	0.7
Education category			<0.0001			<0.0001
<12 years	48 (24%)	62 (12.2%)		94 (26.9%)	109 (11.7%)	
HS grad	74 (37%)	166 (32.7%)		133 38.21%)	330 (35.3%)	
>12 years	78 (39%)	279 (55.0%)		122 (35.0%)	497 (53.1%)	
Hypertension	111 (54.7%)	267 (53%)	0.6	262 (74.6%)	467 (50.0%)	<0.0001
Hypercholesterolemia	85 (41.7%)	223 (43.9%)	0.6	114 (32.2%)	400 (42.7%)	0.0006
Without statins	37 (18.1%)	96 (18.8%)	0.7	52 (14.6%)	201 (21.4%)	0.007
With statins	48 (23.5%)	127 (25%)	0.8	62 (17.5%)	199 (21.2%)	0.14
Frequent alc use (%)	14 (6.9%)	31 (6.1%)	0.7	24 (6.9%)	55 (5.9%)	0.5
First deg. Rel. with ICH (%)	10 (5.0%)	10 (2.0%)	0.03	19 (5.4%)	20 (2.1%)	0.002
Prior ischemic stroke (%)	16 (8.1%)	6 (1.2%)	<0.0001	39 (11.2%)	24 (2.6%)	<0.0001

Apo E2's effect modified by Hypercholesterolemia

	Lobar ICH cases		Lobar ICH controls		OR (95% CI)
	E2 containing	All others	E2 containing	All others	
No HC	33 (38.3%)	86 (72.2%)	53 (18.5%)	232 (81.4%)	1.7 (1.1-2.8)
HC	28 (33%)	57 (67%)	27 (12.1%)	196 (87.8%)	3.6 (1.9-6.5)

- Hypercholesterolemia roughly doubles the risk of lobar ICH with an Apo E2 containing genotype

Apo E4's effect not modified by Hypercholesterolemia

	Lobar ICH cases		Lobar ICH controls		OR (95% CI)
	E4 containing	All others	E4 containing	All others	
No HC	42 (35.3%)	77 (64.7%)	73 (25.6%)	212 (74.3%)	1.5 (0.8-2.3)
HC	33 (38.8%)	52 (61.2%)	73 (32.7%)	160 (71.7%)	1.4 (0.8-2.3)

- Stratifying by HC did not affect risk of Apo E4 containing genotypes for lobar ICH

Statins

- SPARCL study – Ischemic stroke cases in secondary prevention with high dose Lipitor
  - Found an increased risk of ICH with statin treatment
- McKinney et al – Meta-analysis of over 90,000 cases and 90,000 controls (sometimes treated with low dose statins) and found no increased risk of ICH.

Table: Association of high cholesterol and cholesterol treatment with Lobar and Non-Lobar ICH

	Lobar ICH		Non-Lobar ICH	
	OR [95% CI]	**p-value**	**OR [95% CI]**	**p-value**
High Cholesterol	0.91 [0.66, 1.27]	0.6	0.64 [0.49, 0.82]	0.0006
Treated with Statins*	0.93 [0.62, 1.35]	0.7	0.79 [0.57, 1.08]	0.14
Not treated with Statins**	0.95 [0.63, 1.45]	0.8	0.63 [0.45, 0.88]	0.007

* Comparison group is all normocholesterolemia plus hypercholesterolemia not treated with statins

** Comparison group is all normocholesterolemia plus hypercholesterolemia treated with statins

Statin use by Apo E Genotype

- Compared to Apo E3/E3
- No significant differences in non-lobar ICH
- In lobar ICH:
  - E4/E4 with statins: OR=4.5 (1.3-16.2; p=0.02)
  - E2/E4 with statins: OR=11.3 (2-64; p=0.005)
  - E2/E3 with statins: OR=2.8 (1.0-7.5; p=0.06)
- Without statins:
  - E4/E4: OR=1.6 (0.27-9.4; p=0.63)

To summarize

- Hypercholesterolemia is well established to have a protective association with ICH
- This protective effect appears to be greatest in non-lobar ICH
- But the protection appears to go away with statin use – suggests it is the actual cholesterol level and not a confounder

To summarize

- In lobar ICH, Apo E2's risk is increased in the setting of hypercholesterolemia
- Statin use increases the risk of lobar ICH for Apo E4 containing genotypes, particularly E2/E4 and E4/E4
- OR statin plus Apo E3 is most protective

Microbleeds

- Microbleeds: punctate, homogeneous, rounded, hypointense parenchymal lesions < 5-10 mm visualized on T2* MRI sequences
  - Asymptomatic microhemorrhages
  - Marker of bleeding-prone microangiopathy
- Microbleed frequency
  - ~5-6% healthy elderly population
  - ~60% (range 17-80%) ICH population
  - ~21-26% ischemic stroke population
- Microbleed risk factors
  - Cerebral amyoloid angiopathy (lobar MBs)
  - Hypertension (predominantly deep and infratentorial MBs)

Background: Microbleeds

- Microbleeds presence and burden associated with
  - Recurrent symptomatic ICH
  - Cognitive impairment
  - Severity of small vessel disease and leukoaraiosis
- Recent studies suggestive of racial / ethnic differences in microbleed frequency, burden, and associated risk factors
- Goal of current analysis
  - Explore by race/ethnicity the frequency and characteristics of microbleeds in patients enrolled in ERICH
  - Explore impact of microbleeds on long-term functional outcome

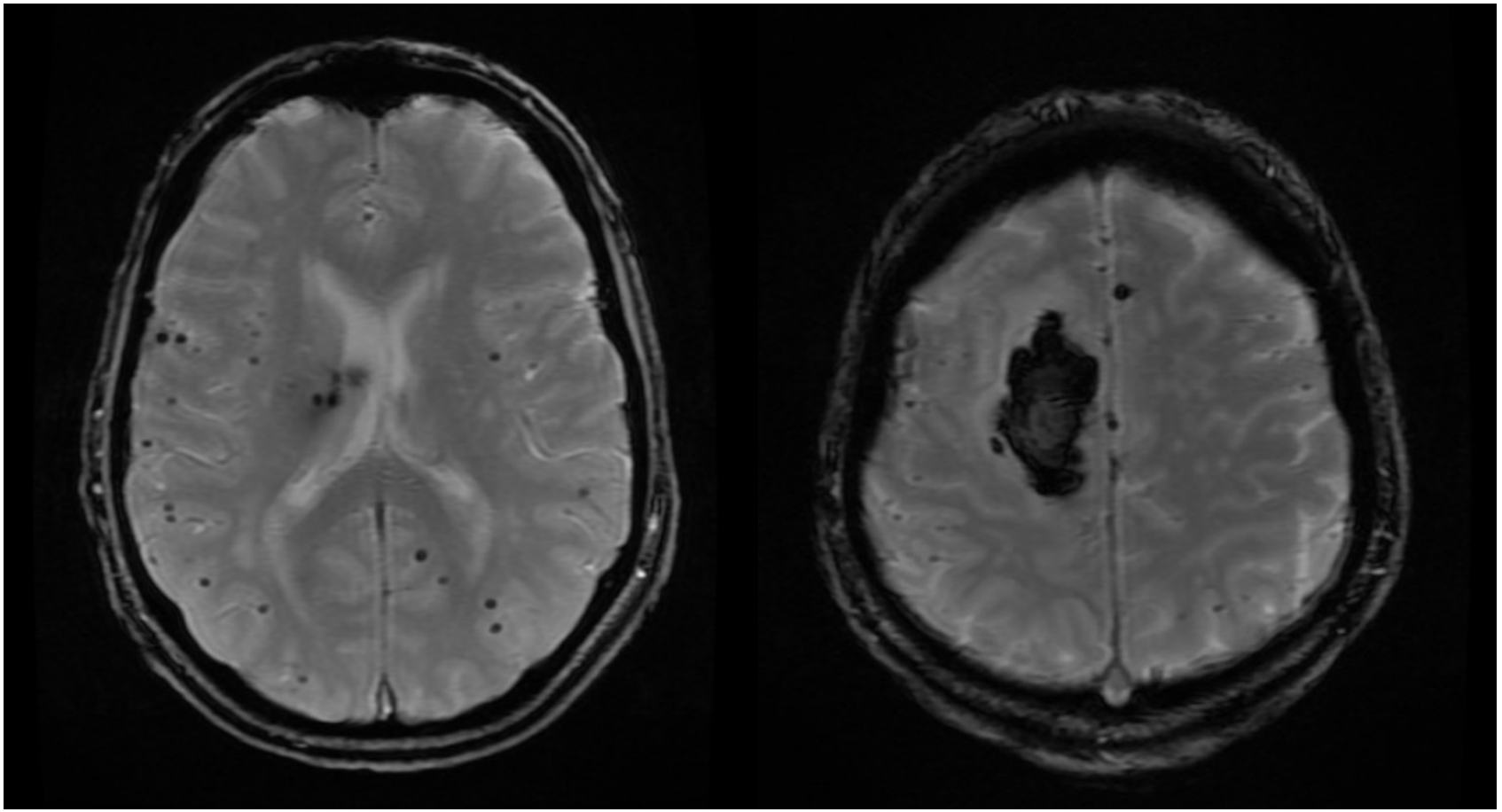
Results – Patient Characteristics

	N=642
Mean Age (SD)	60 yo (13.5)
Male Gender	56.9%
Race	
White	29.0%
Black	38.6%
Hispanic	32.4%
Hypertension	80.5%
Prior Stroke	15.7%
Mean WBC Count (SD), $10^3/\mu L$	9.4 (4.5)

Results – Imaging Characteristics

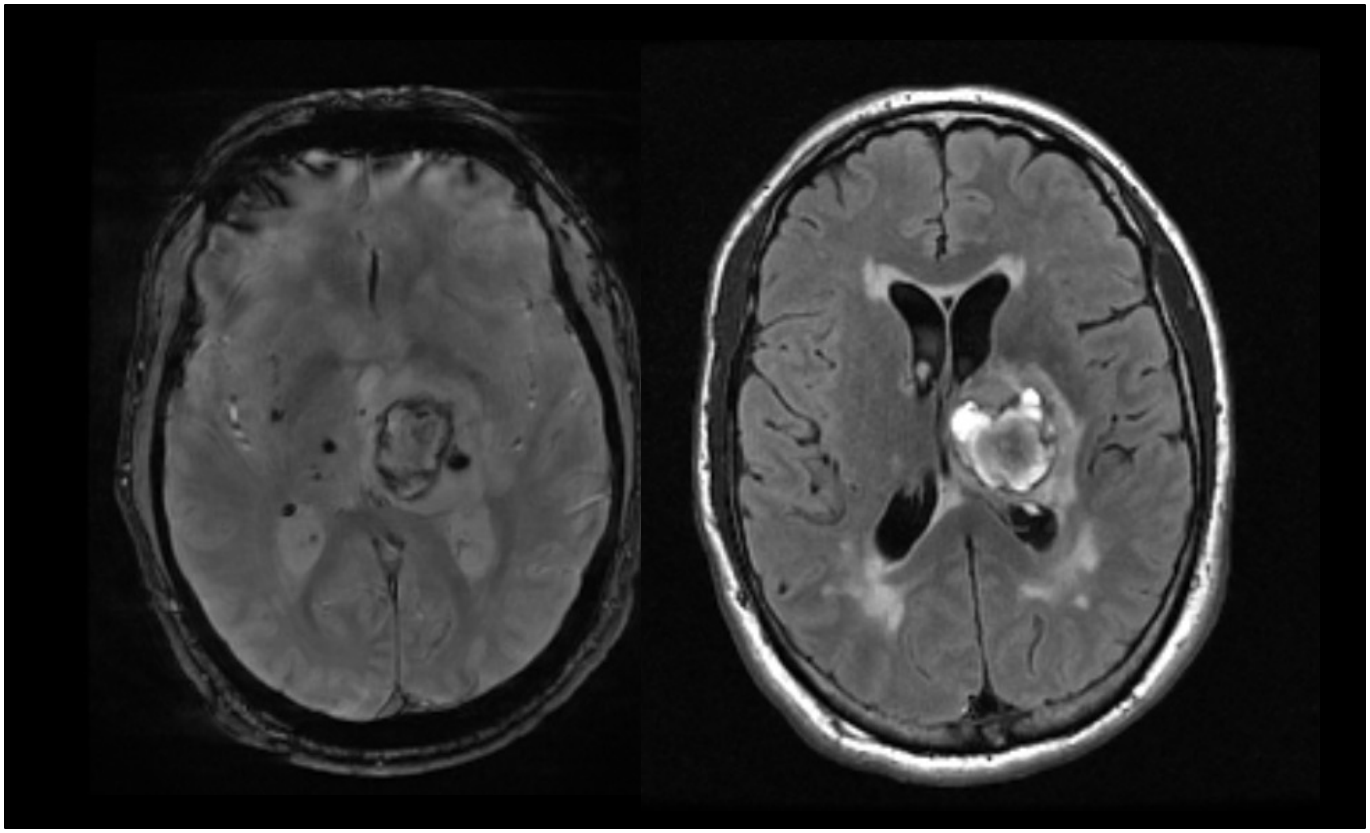
	N=642
Mean ICH Volume, cc	15.6 (18.2)
Presence of MBs	48.9%
MB count	
Mean	13 (27)
Median (IQR)	4 (2-11)
Median WMD Score (IQR)	6 (4-8)

Case Example 1



54 yo male with HTN, DM, lobar ICH;
predominantly lobar MBs

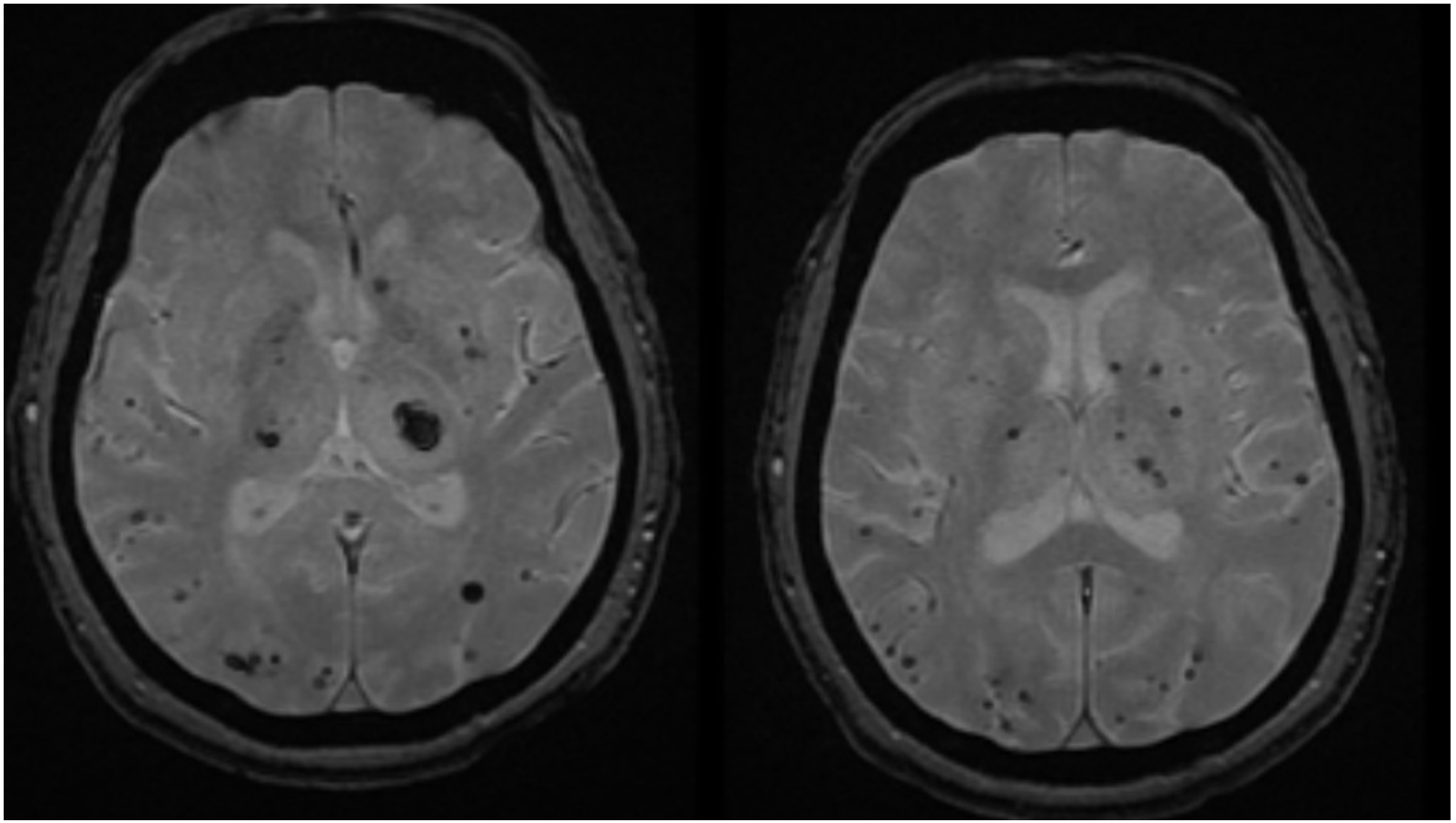
Case Example 2



GRE FLAIR

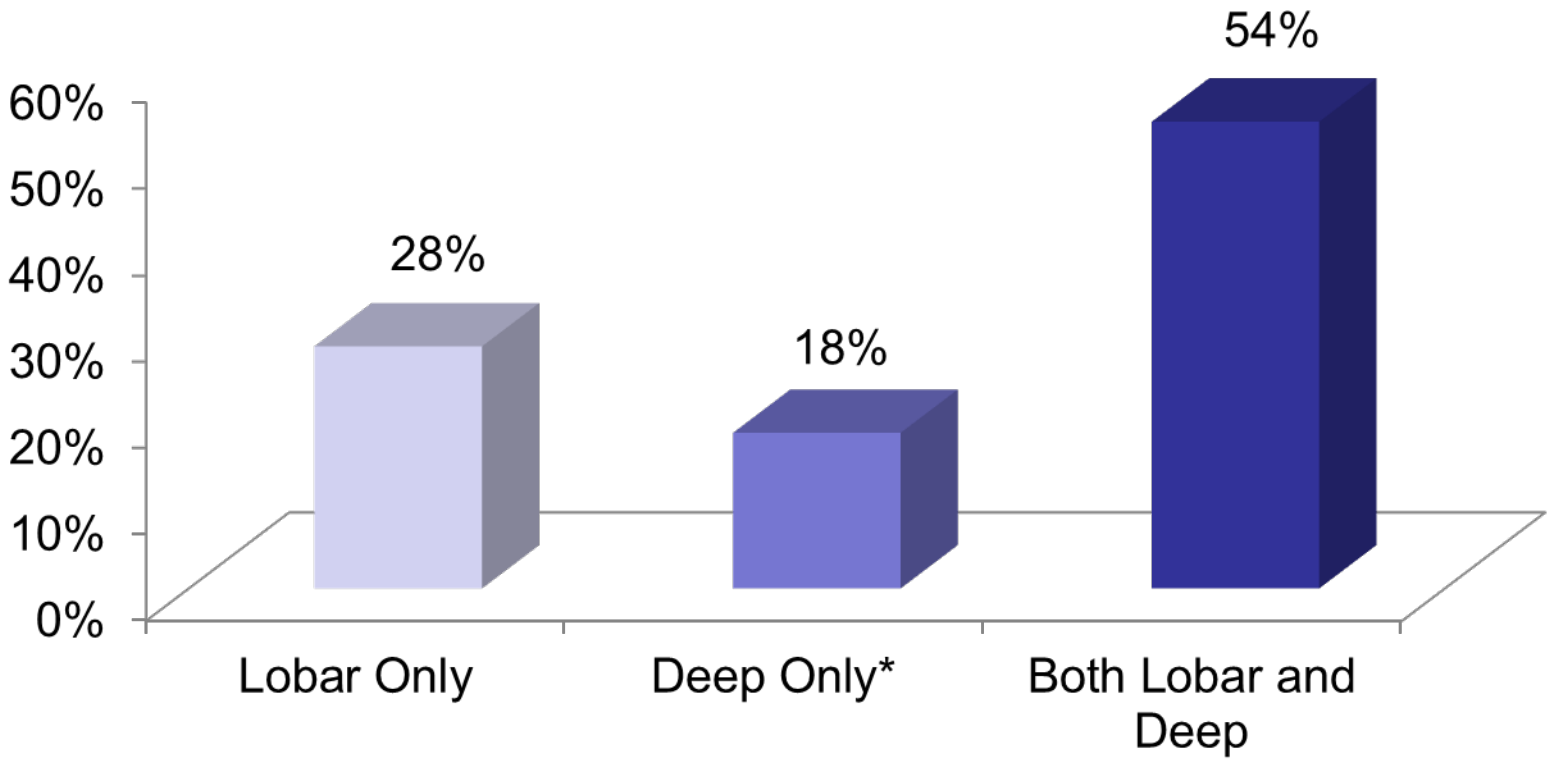
39 yo male with deep ICH and predominantly deep MBs; moderate leukoaraiosis

Case Example 3



64 yrs male with HTN and left deep ICH, both lobar and deep MBs

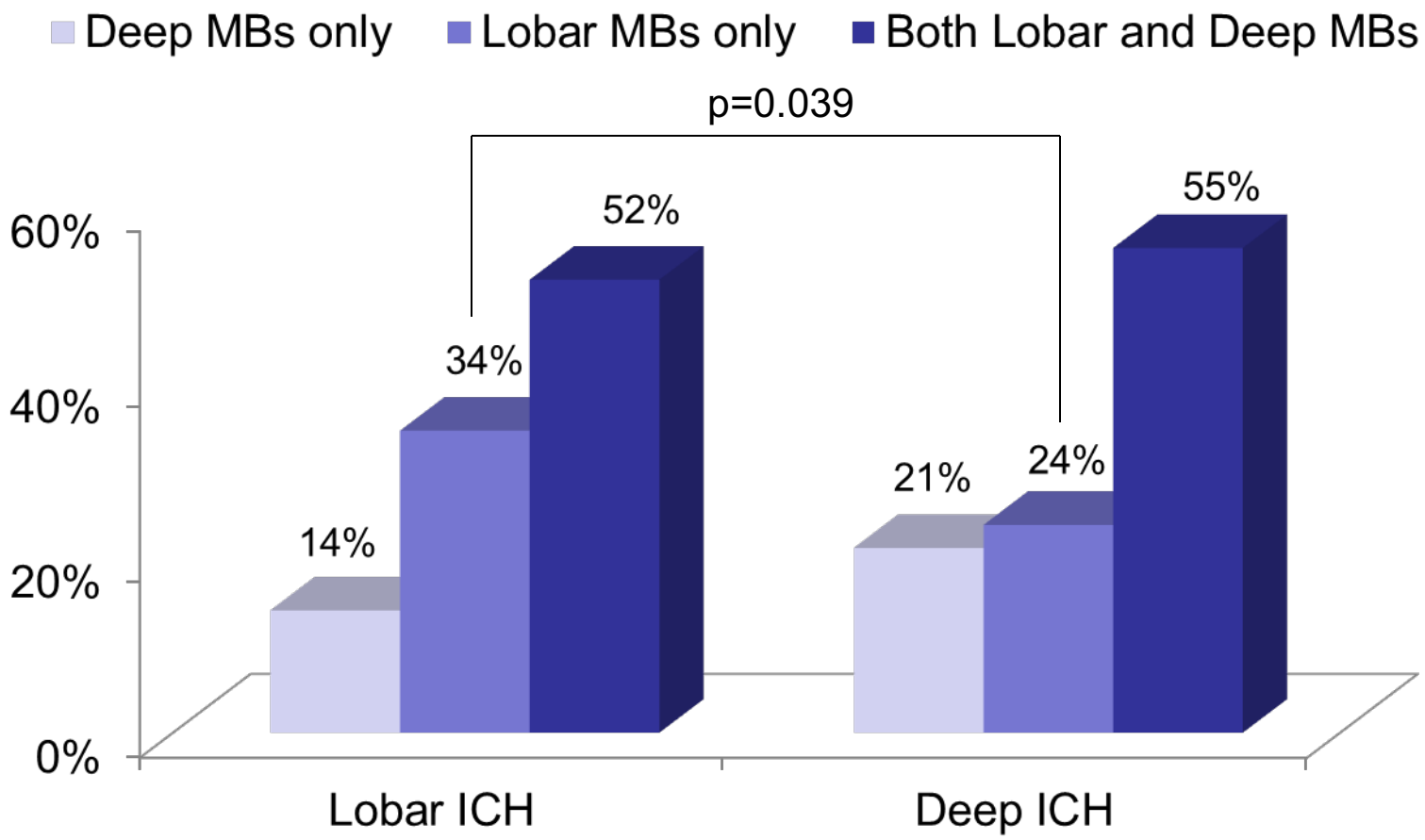
Microbleed Locations



*Deep includes infratentorial

n=314

Microbleed Location by ICH Location



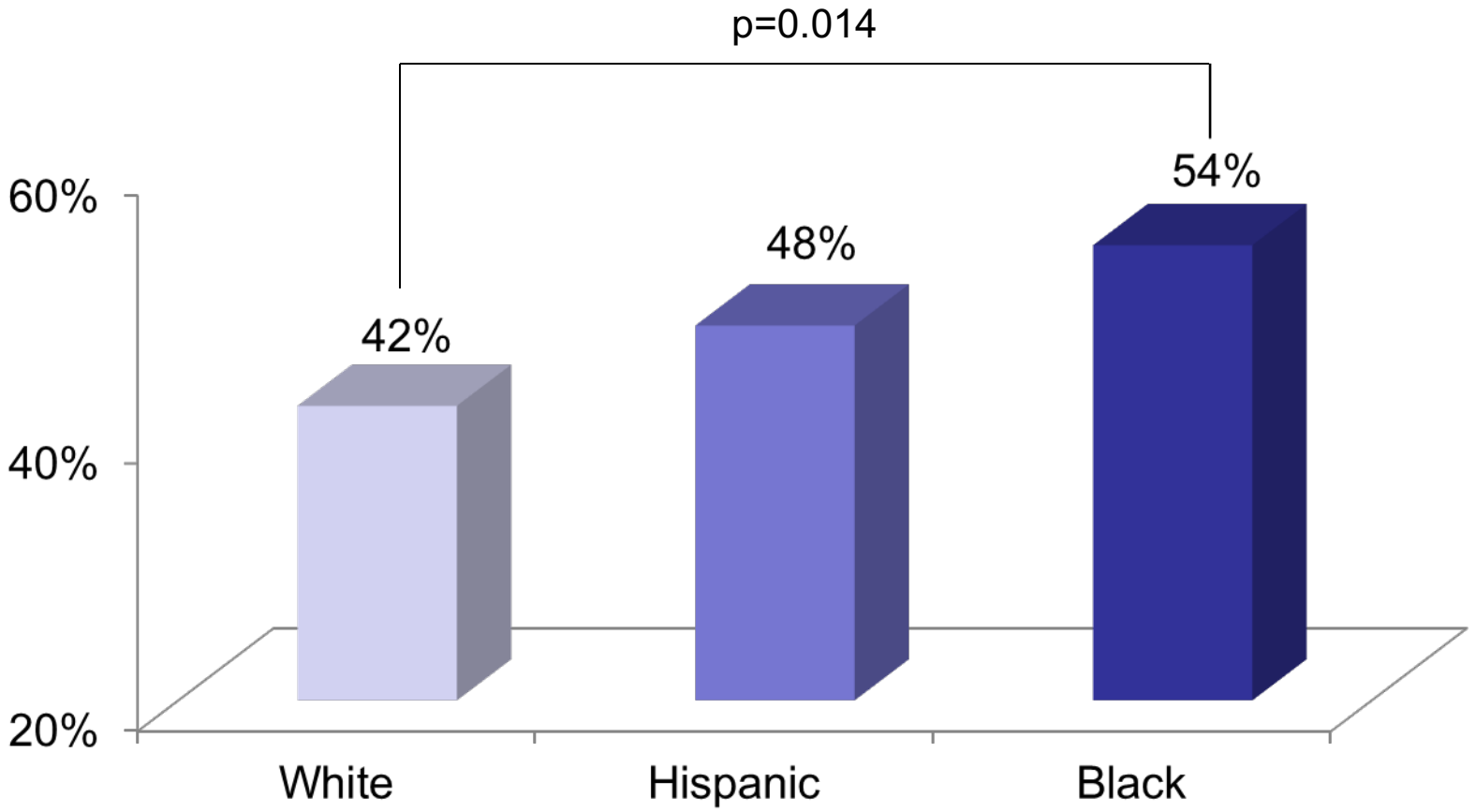
Overall p=0.0001

n=312

Univariate Analysis: Microbleed Presence

	MB + n=314	MB - n=328	p value
Age (SD)	60.5 (12.8)	59.9 (14.2)	0.531
Hypertension	86%	76%	**0.001**
Prior Stroke	21%	11%	**<0.001**
Baseline WBC Count (SD)	9.7 (5.3)	9.0 (3.6)	**0.038**
Pre-stroke Antiplatelet	39%	40%	0.78
Pre-Stroke Anticoagulation	8%	7%	0.759
Median WMD Score (IQR)	8 (6-10)	4 (4-6)	**<0.001**
Mean ICH Volume (SD)	13.6 (16.3)	17.4 (19.7)	**0.01**

Microbleed Frequency by Race/Ethnicity



Overall p=0.046

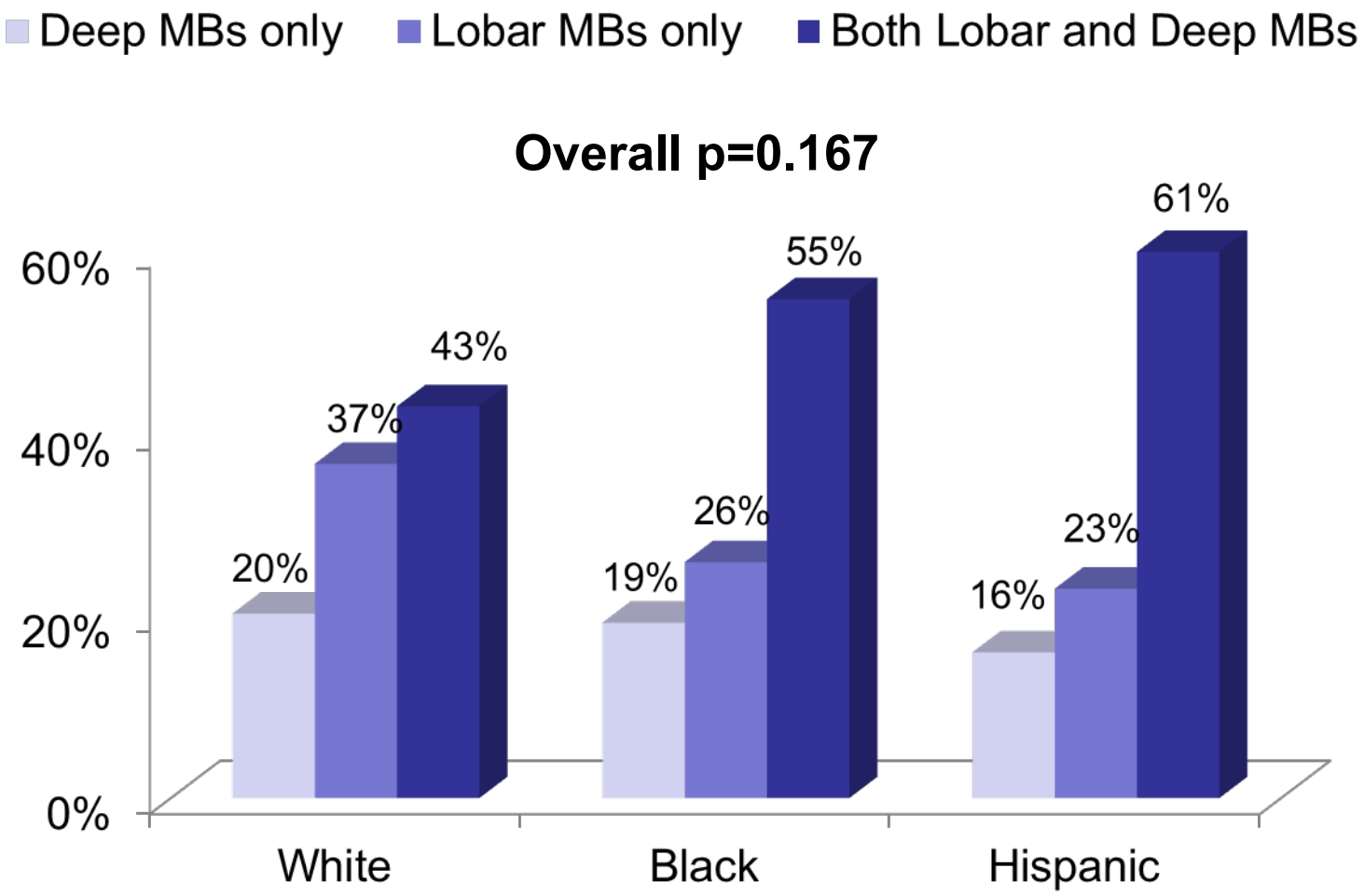
n=642

Univariate Analysis: Racial Comparison of MB+ Cases

	White n=186	Black n=248	Hispanic n=208	p value
Age (SD)	67.5 (13.0)	58.3 (11.0)	58.1 (13.0)	**<0.0001***
Hypertension	79.7%	95.5%	79%	**<0.001†**
Prior Stroke	13.9%	28.1%	17%	**0.0244‡**
Baseline WBC Count (SD)	10.1 (4.0)	9.4 (6.8)	9.9 (3.5)	0.593
Pre-stroke Antiplatelet	44.3%	37.8%	36%	0.498
Pre-Stroke Anticoagulation	11.4%	6.7%	6%	0.343
Median WMD Score (IQR)	8 (4-8)	8 (6-10)	6 (5-9)	**0.028±**
Mean ICH Volume (SD)	16.7 (20.7)	13.6 (16.3)	11.3 (11.3)	0.09

*p<0.0001 for W vs. B, and W vs. H
†p<0.001 for W vs. B, and for B vs. H
‡p= 0.017 for W vs. B, and p=0.046 for B vs. H
±p=0.04 for B vs. W, 0.06 for H vs. W, and 0.042 for B vs. H

Microbleed Location by Race



n=314

Multivariable Logistic Regression: Presence of Microbleeds

	OR	p value
Hypertension	1.62	0.037
WMD Score	1.36	<0.0001
WBC Count (10^3/μL)	1.06	0.012
Race/ethnicity		0.111
Black vs. White	1.53	0.056
Hispanic vs. White	1.49	0.078

Multivariable Logistic Regression: Poor Outcome (6 Month mRS 4-6)

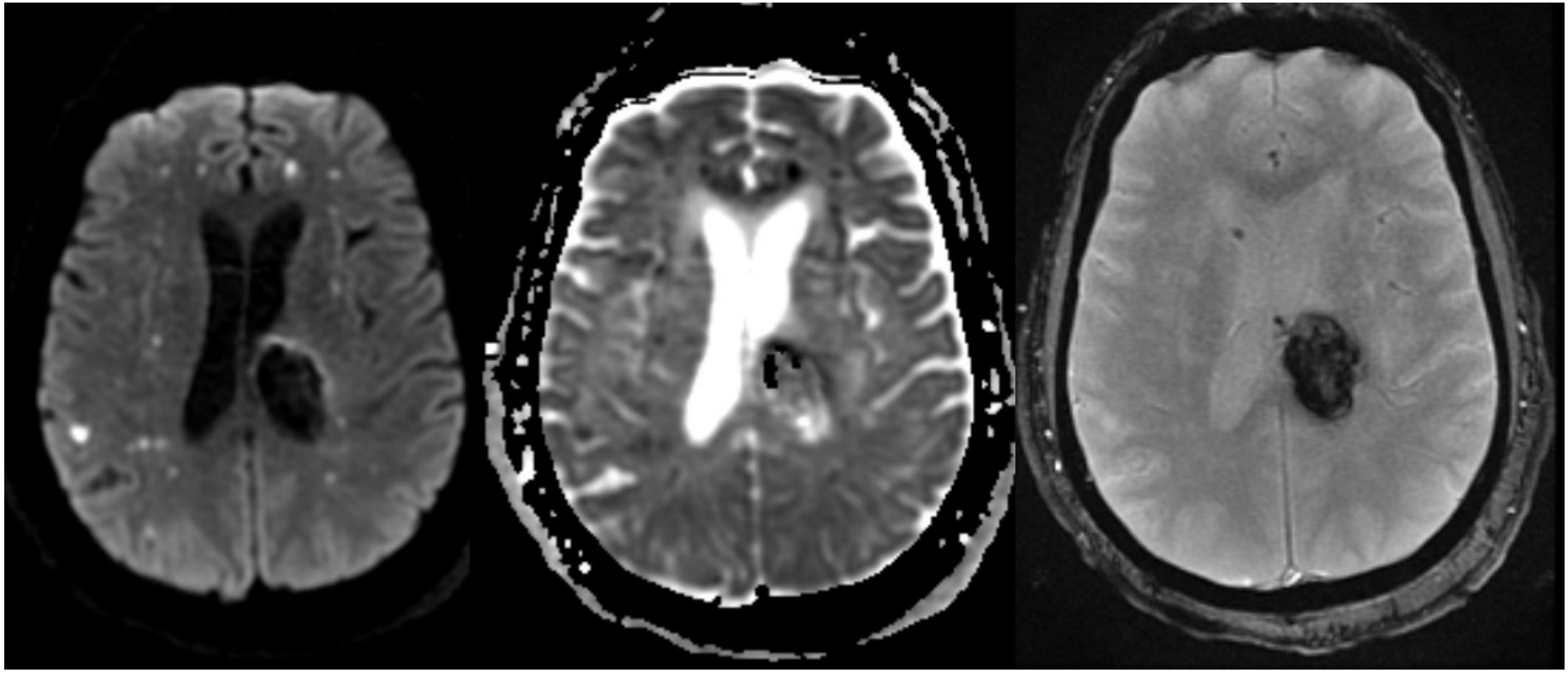
	OR	p value
Presence of Microbleed(s)*	2.21	0.001
ICH Volume	1.04	<0.001
GCS Score	0.82	<0.001
Intraventricular Hemorrhage (IVH)	1.98	0.003
Age (5 year OR)	1.21	<0.001

*WMD score and presence of microbleeds highly colinear

Conclusions

- This study demonstrates substantial differences in microbleed rates across race/ethnicities
- This is the first study to report an intermediate microbleed rate among Hispanics relative to white and black ICH cases
- In addition to hypertension and leukoaraiosis, our model suggests that inflammation may be an important factor contributing to microbleeds
- As a biomarker of progressive vasculopathy and poor outcome, microbleeds may provide a valuable surrogate measure in future studies of therapies targeting optimal approaches to risk factor control

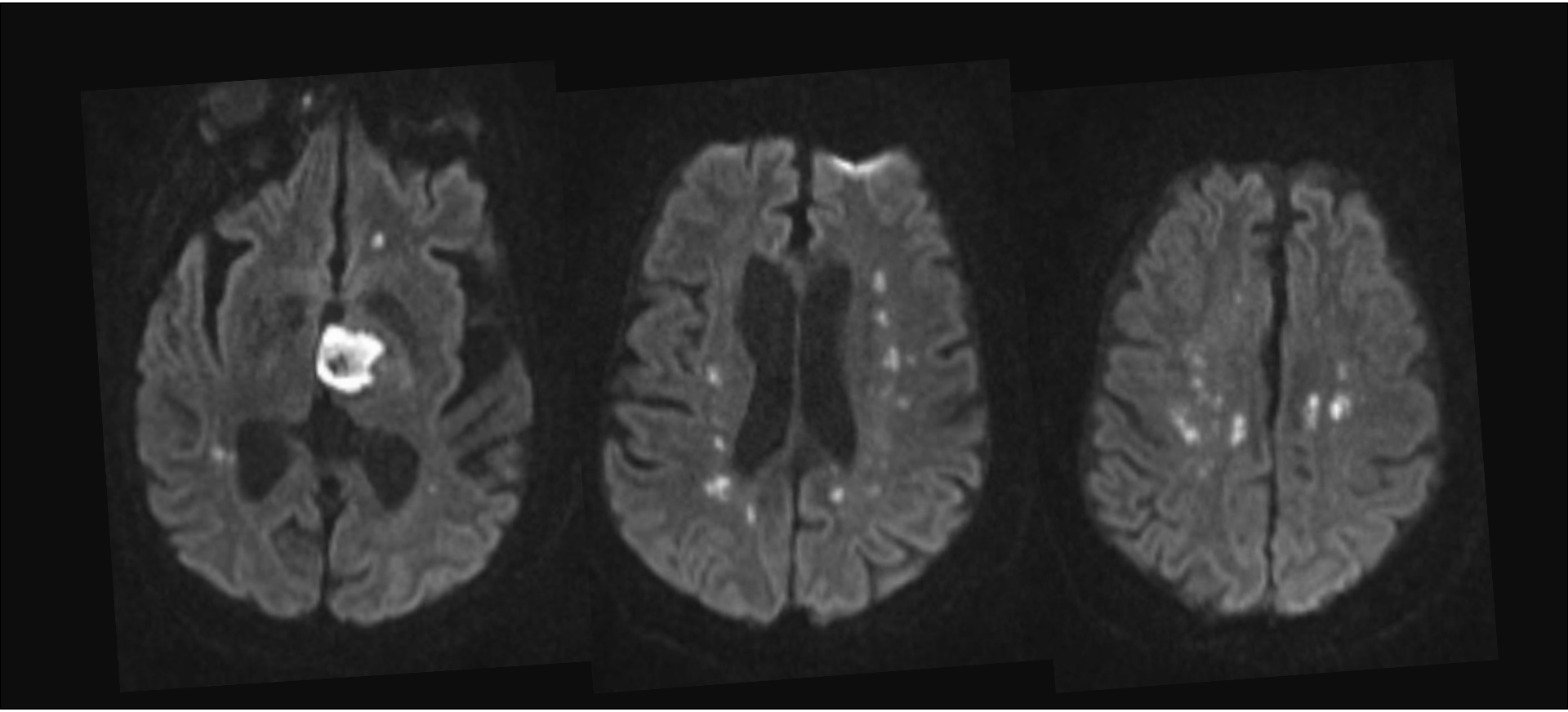
Case Example 1



DWI **ADC** **GRE: GRADIENT ECHO**

Left periventricular ICH in 45 yo black male with hx of HTN;
ΔMAP was 106 mmHg

Case Example 2

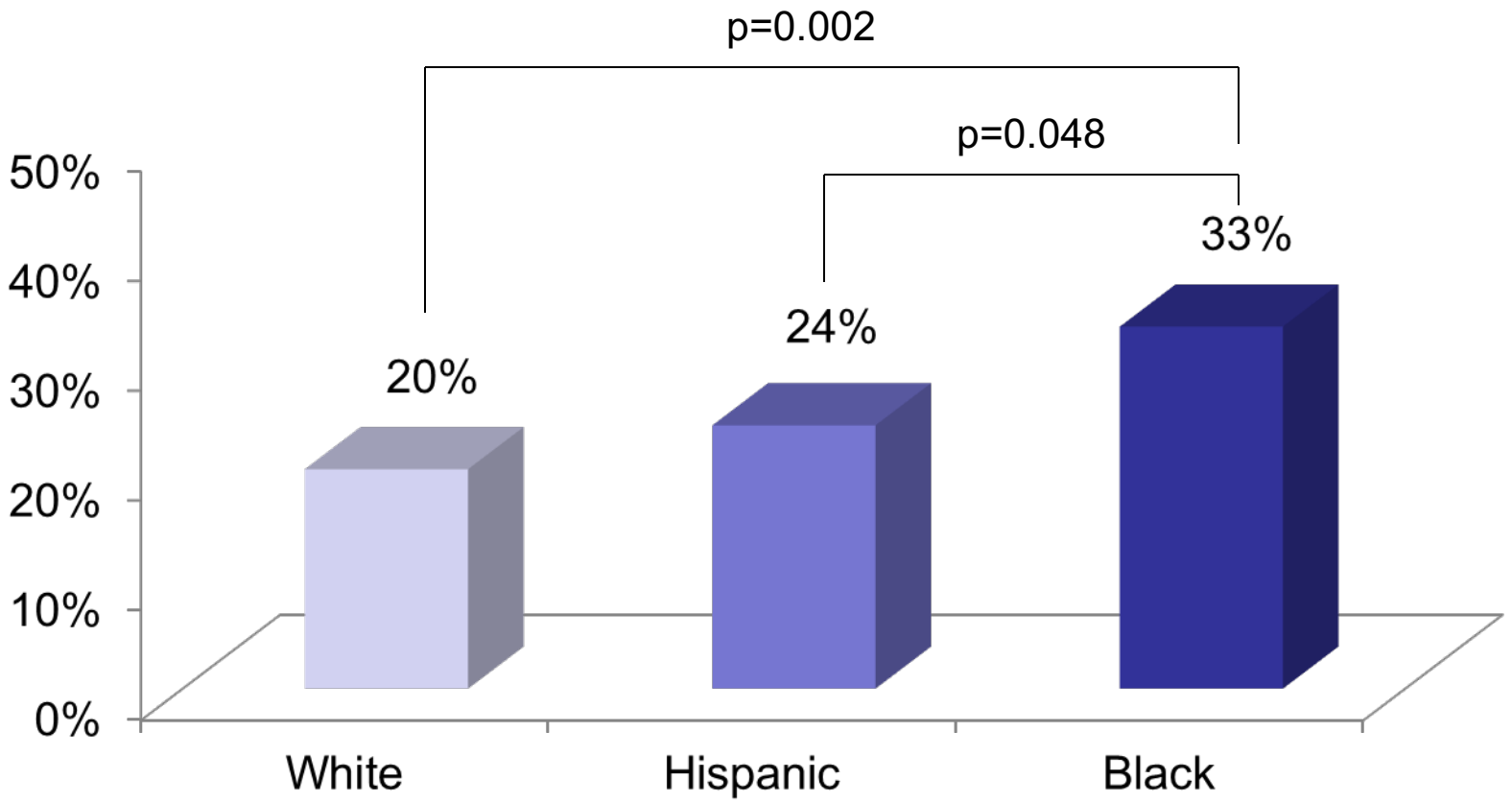


Left thalamic ICH in 50 yo Hispanic male with hx of HTN;
ΔMAP was 125 mmHg

Univariate Analysis

	DWI + n=156	DWI – n=445	p value
Mean Age (SD)	57.3 (13.3)	61.9 (13.6)	**< 0.001**
Race/Ethnicity			**0.005**
White	19.6%	80.4%	
Black	33.3%	66.7%	
Hispanic	24.3%	75.7%	
Male Gender	62.8%	52.8%	**0.03**
Hypertension	81.9%	78.3%	0.347
Prior Stroke	21.8%	14.2%	**0.026**
Mean Delta MAP, mmHg (SD)	52.2 (28.2)	40.3 (23.3)	**<0.001**

DWI Frequency by Race/Ethnicity



Overall p=0.005*

n=601

Multivariable Model for DWI Lesions

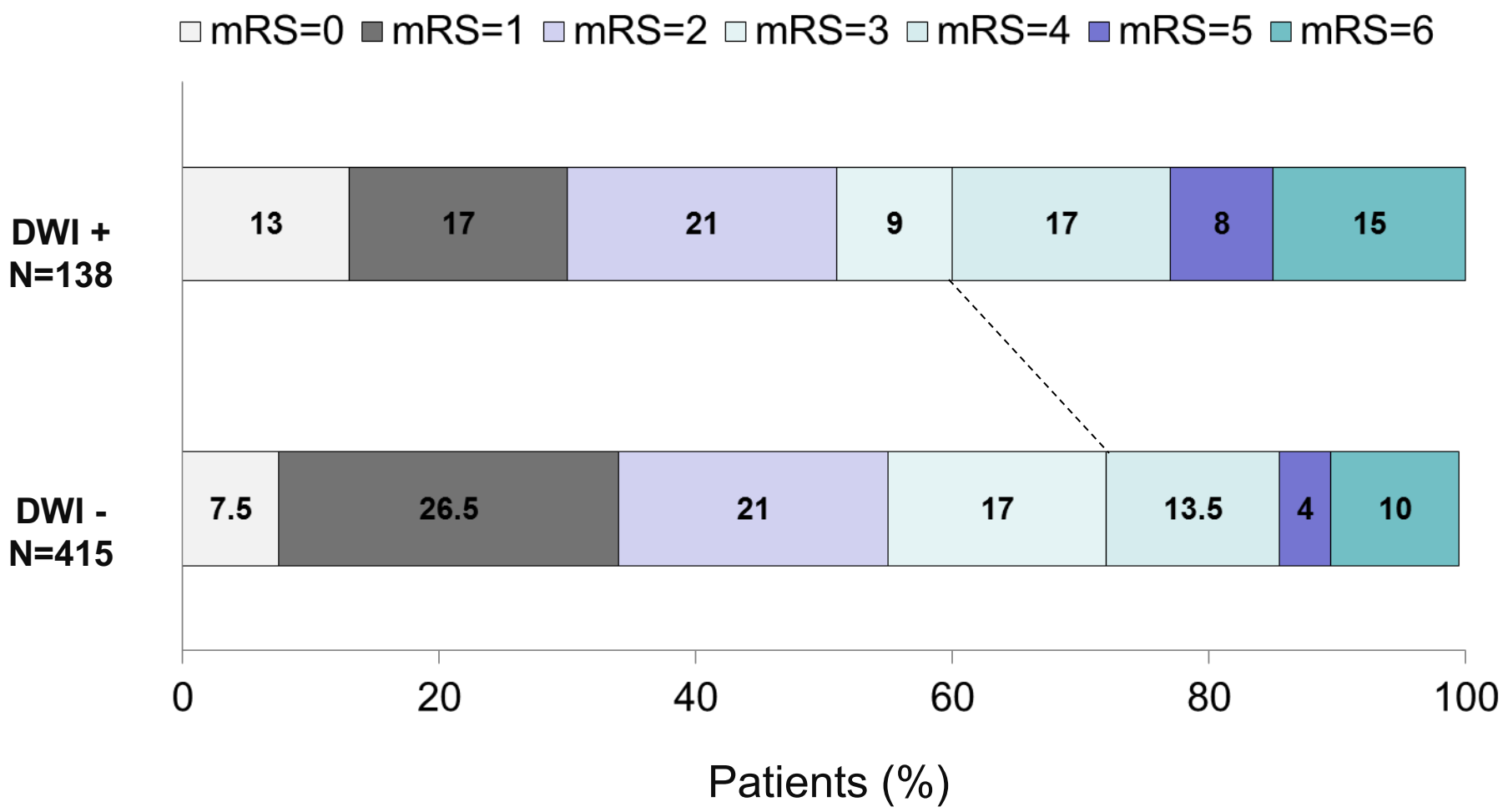
	OR	p value
Age (10 year)	0.68	<0.001
Delta MAP (10 mmHg)	1.16	<0.001
WMD Score	1.16	<0.001
Presence of MBs	2.12	0.001

Multivariable Model for Poor Outcome

Poor Outcome = 6 month mRS 4-6

	OR	p value
Age (10 year)	1.44	<0.0001
GCS (1 unit)	0.86	<0.0001
ICH Volume (cc)	1.35	<0.0001
Presence of IVH	2.10	0.002
DWI Lesion Presence	1.84	0.021

6 Month mRS


mRS=0
mRS=1
mRS=2
mRS=3
mRS=4
mRS=5
mRS=6
DWI +
N=138
13
17
21
9
17
8
15
DWI -
N=415
7.5
26.5
21
17
13.5
4
10
0
20
40
60
80
100
Patients (%)

Conclusions

- The ERICH study confirms that
  - Large fluctuations in blood pressure during the acute hospitalization period are associated with DWI lesions
  - DWI lesions are associated with poor outcomes
- We hypothesize that
  - Substantial reductions in BP precipitate acute small vessel ischemia in those ICH patients with a more severe underlying diseased vasculature
  - Or, alternatively, DWI lesions may be a biomarker of autoregulatory failure
- If DWI lesions are precipitated by BP