Intracerebral microbleeds: what are they? And should be care?

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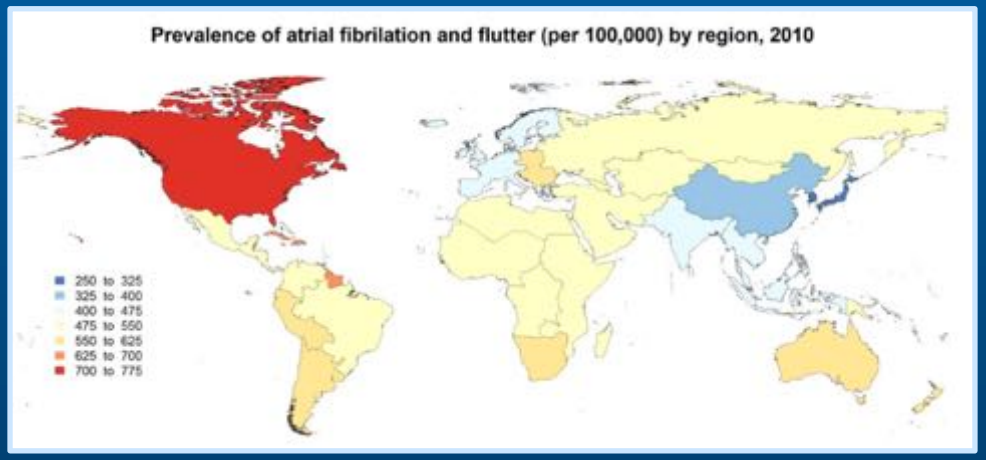
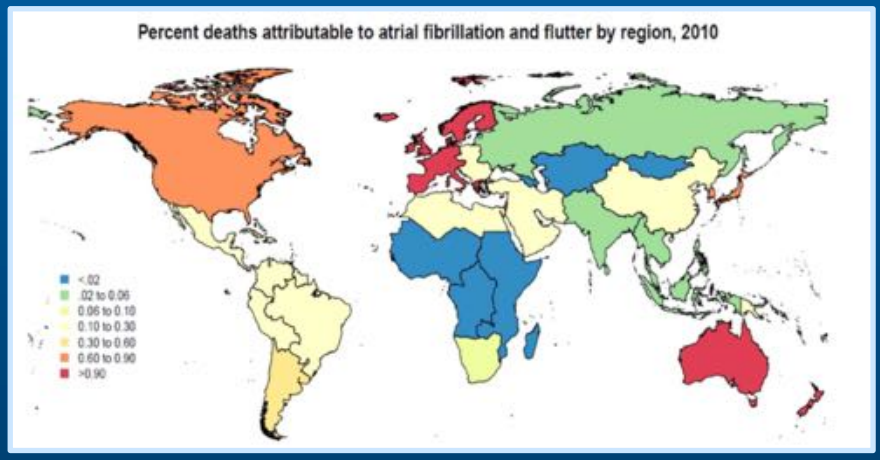
- Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, and its prevalence increases with age, sedentary lifestyles, and obesity.
- AF is also a significant cause of morbidity and mortality worldwide.

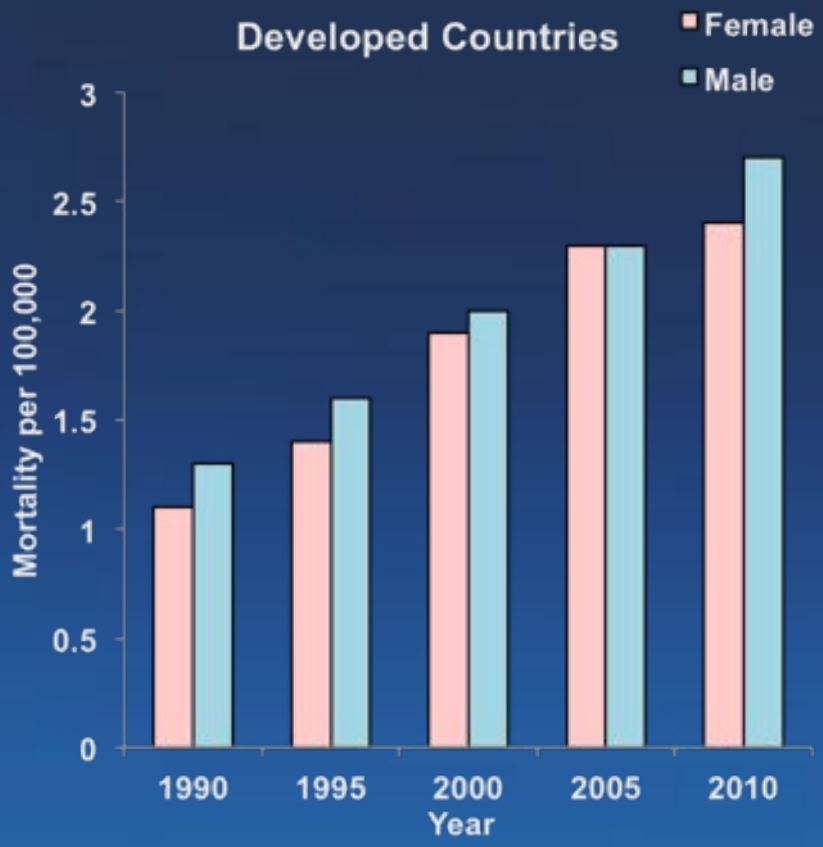


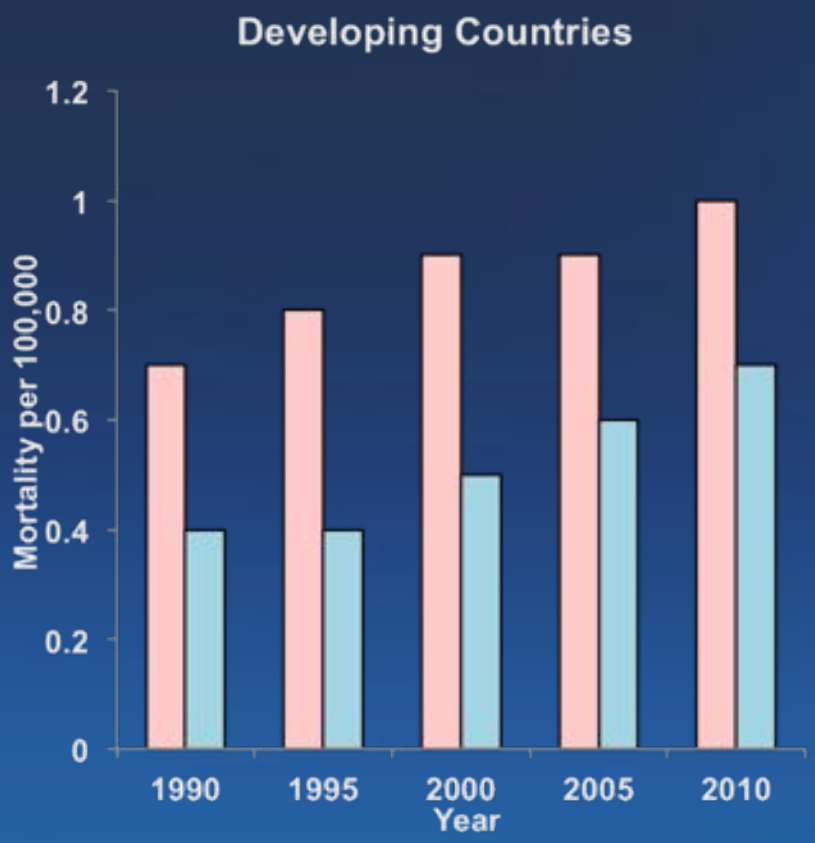


Chugh SS, Circulation 2014; 129:837-847

Higher Mortality in Women

Driven by AF-Associated Mortality in Developing Nations





Chugh SS, et al. Circulation 2014;129:Online

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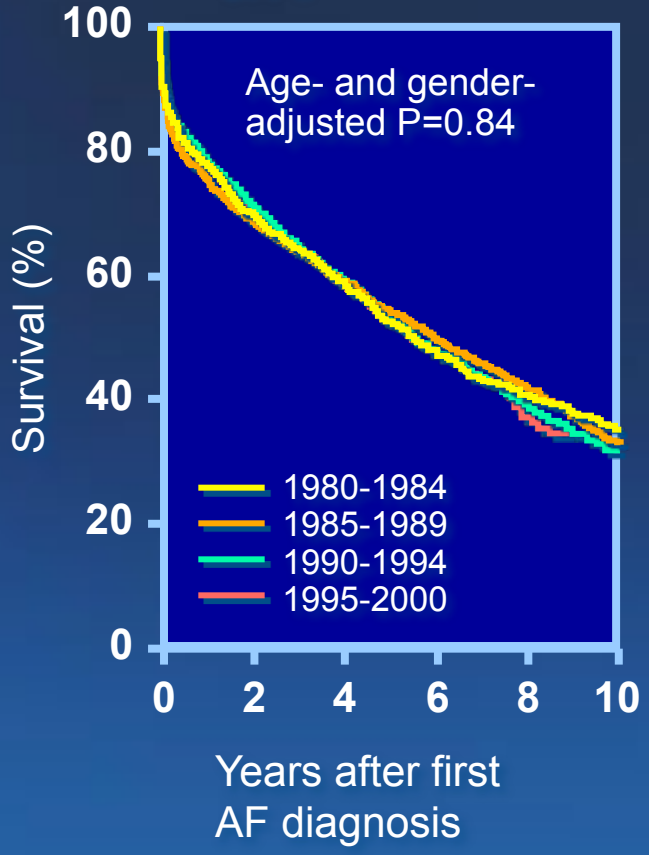
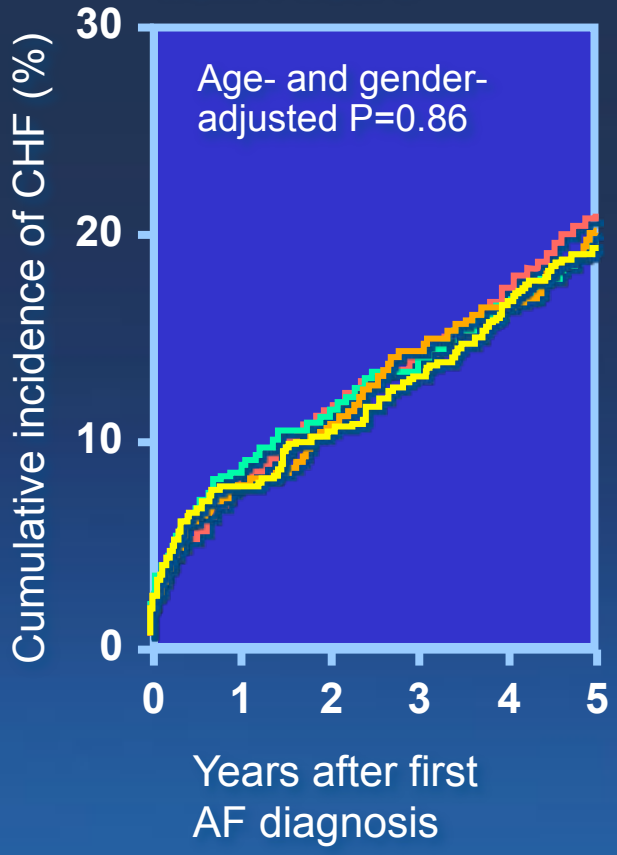
Trends of AF Outcomes

Mortality Trends of AF



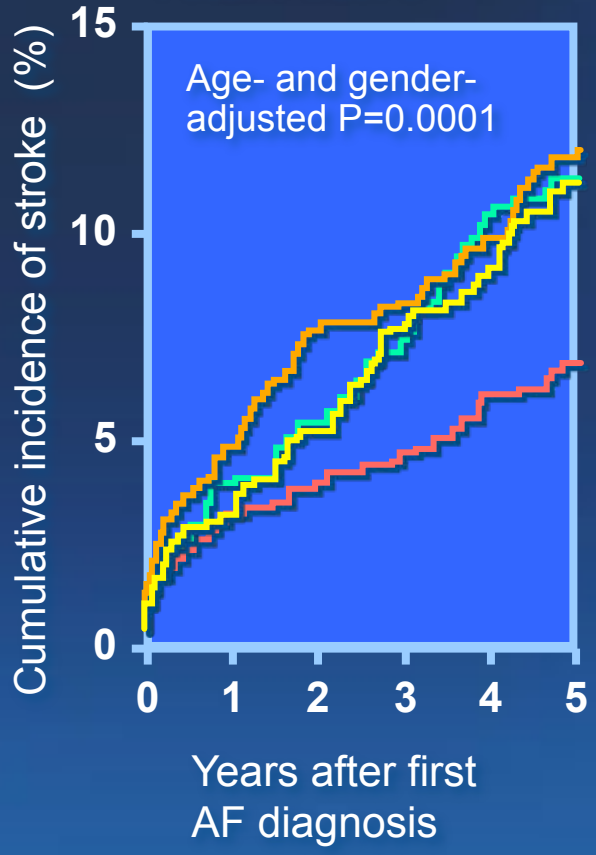
Miyasaka et al: JACC 49:986, 2007

Heart Failure Incidence Trends from First AF



Miyasaka et al: EHJ 27:936, 2006

Time Trends of Ischemic Stroke After First AF



Miyasaka et al: Stroke 36:2362, 2005

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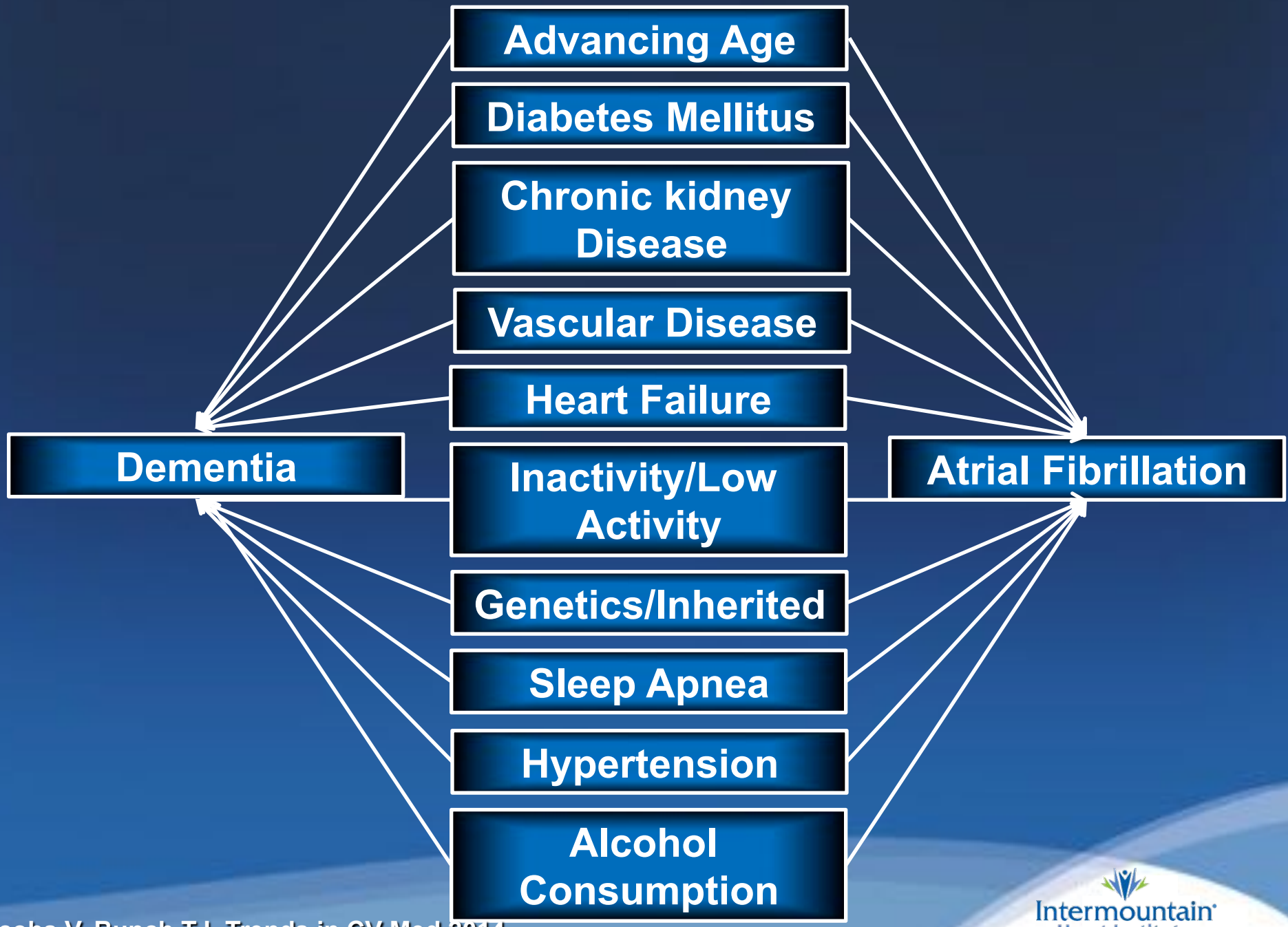
Dementia

- Dementia is a disorder that is characterized by impairment of memory and at least one additional cognitive domain.
- Significant cause of morbidity and mortality worldwide

Shared Risks Factors for Atrial Fibrillation and Dementia



acobs V, Bunch TJ. Trends in CV Med 2014

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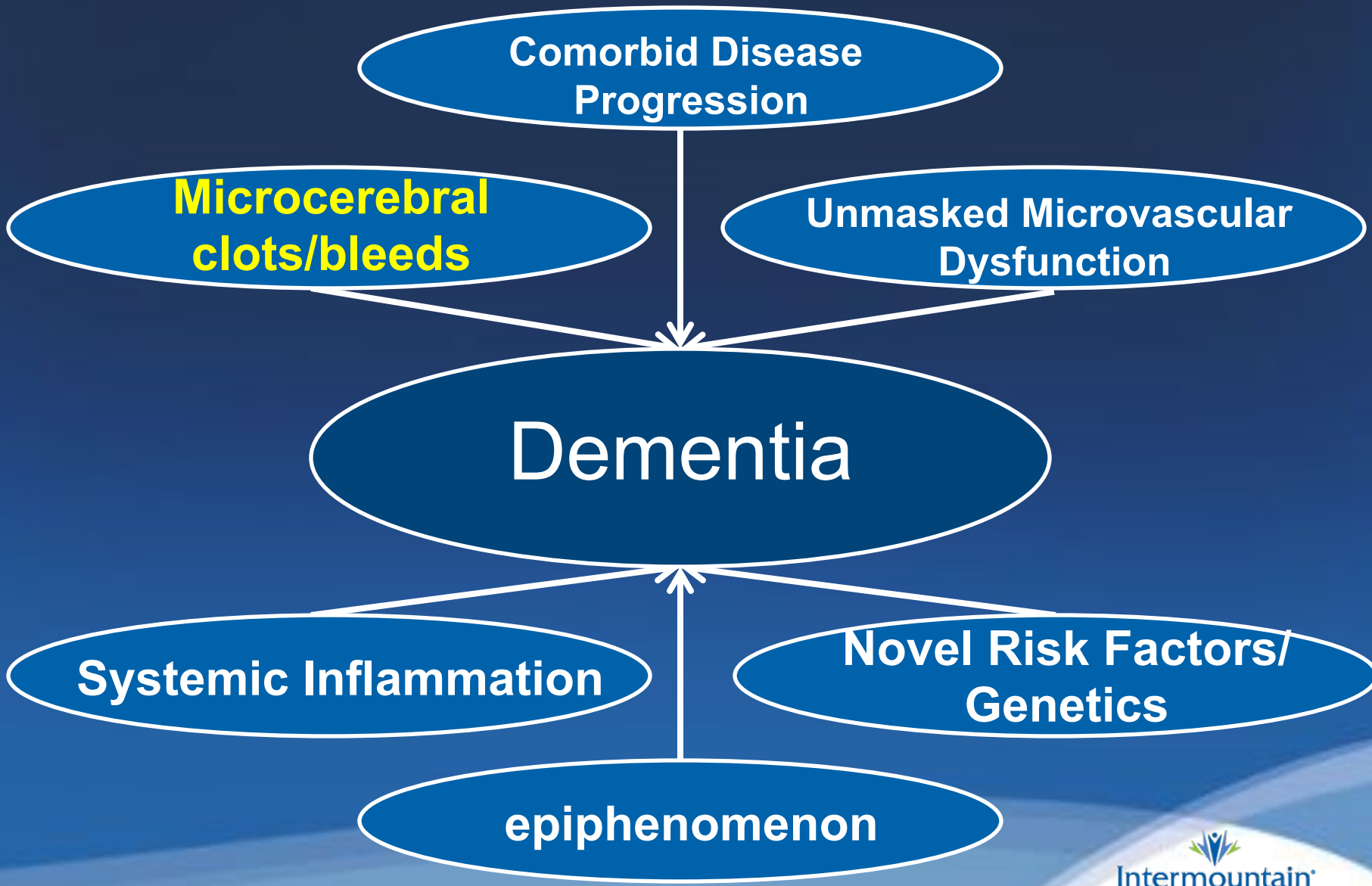
Potential Mechanisms Underlying the Association of Dementia and Atrial Fibrillation



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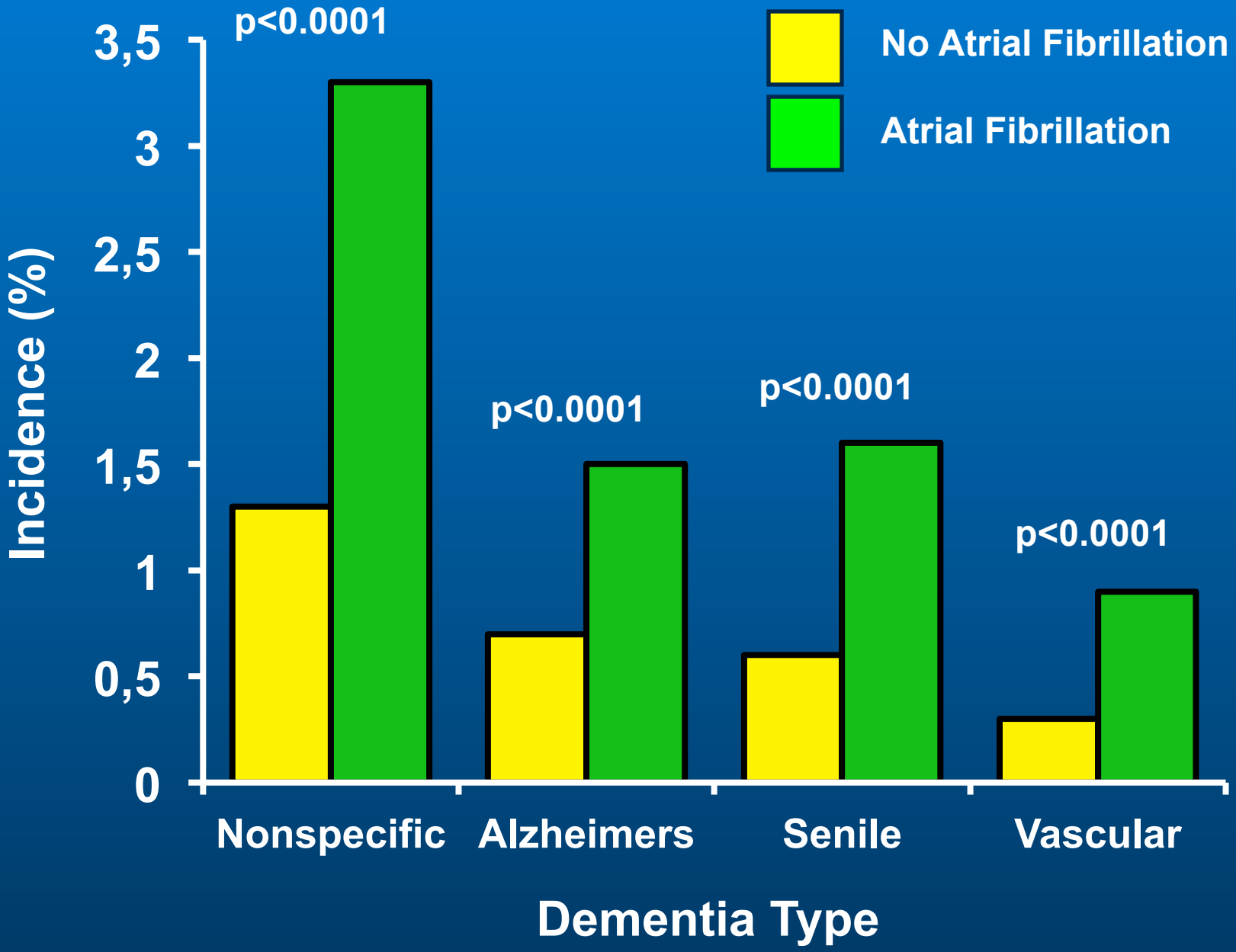
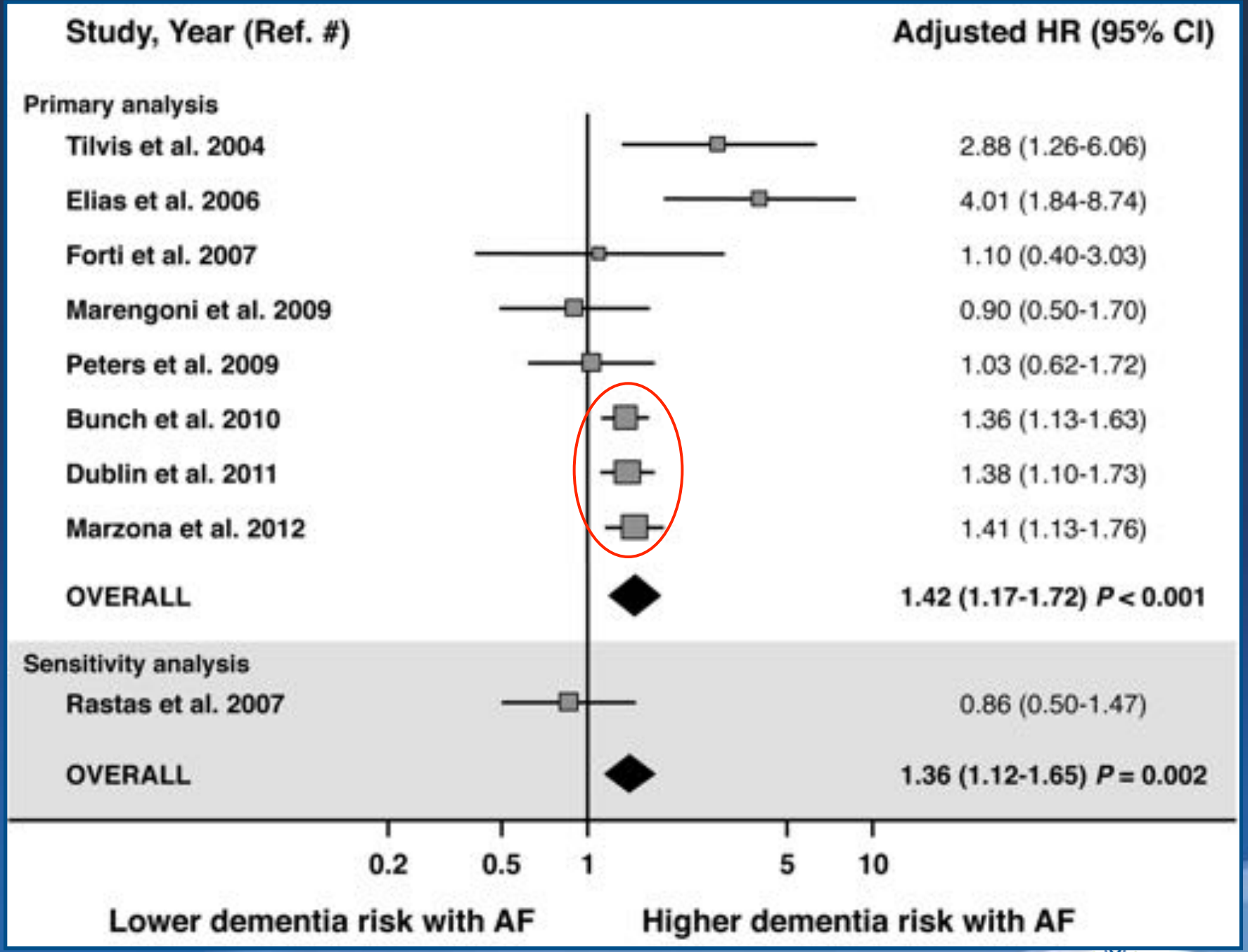


Bunch TJ, HeartRhythm J, 2010

Odds Ratios for Association of AF based on Age and Dementia Type

Dementia	Overall	≤70	70-79	80-89	≥90
Vascular	1.73 p=0.001	2.22 p=0.004	1.68 p=0.02	1.31 p=0.45	------
Senile	1.39 p=0.005	3.34 p<0.0001	1.60 p<0.0001	0.93 p=0.004	0.54 p=0.41
Alzheimers	1.06 p=0.59	2.30 p=0.001	1.07 p=0.68	0.81 p=0.29	0.81 p=0.37
Nonspecific	1.44 p<0.0001	2.87 p<0.0001	1.49 p=0.001	0.96 p=0.77	0.60 p=0.44



Santangeli, Heart Rhythm J, 2012

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Research

Original Investigation

Association Between Atrial Fibrillation and Dementia in the General Population

Renée F. A. G. de Bruijn, MD; Jan Heeringa, MD, PhD; Frank J. Wolters, MD; Oscar H. Franco, MD, PhD; Bruno H. C. Stricker, MD, PhD; Albert Hofman, MD, PhD; Peter J. Koudstaal, MD, PhD; M. Arfan Ikram, MD, PhD

Table 1. Baseline Characteristics

Characteristic	Atrial Fibrillation, No. (%)[a] Not Prevalent (n = 6196)	Prevalent (n = 318)	*P* Value for Difference[b]
Age, mean (SD), y	68.3 (8.5)	75.7 (8.1)	<.001
Female, sex	3678 (59.4)	161 (50.6)	<.001
BMI, mean (SD)	26.3 (3.7)	26.0 (3.6)	.48
Blood pressure, mm Hg, mean (SD)			
Systolic	139 (22)	142 (25)	.40
Diastolic	74 (11)	73 (13)	.52
Blood pressure-lowering medication	1367 (22.1)	109 (34.9)	<.001
Diabetes mellitus	609 (9.9)	64 (20.1)	<.001
Cholesterol, mean (SD), mg/dL			
Total	258.7 (46.3)	239.4 (46.3)	<.001
HDL	54.1 (15.4)	46.3 (11.6)	<.001
Lipid-lowering medication	151 (2.4)	9 (2.8)	.09
Smoking			
Former	2548 (42.2)	136 (44.3)	.74
Current	1429 (23.3)	56 (18.2)	.35
Apolipoprotein E ε4 carrier	1646 (27.8)	82 (26.5)	.95
Educational level			
Primary	2235 (36.6)	126 (40.8)	1 [Reference]
Lower vocational	1006 (16.5)	51 (16.5)	.08
Lower secondary	673 (11.0)	29 (9.4)	.68
Intermediate vocational	1463 (24.0)	80 (25.9)	.09
General secondary	198 (3.2)	6 (1.9)	.54
Higher vocational	470 (7.7)	16 (5.2)	.63
University	64 (1.0)	1 (0.3)	.32
Ever use of oral anticoagulant medication	1386 (22.4)	87 (27.4)	<.001
Coronary heart disease	468 (7.9)	53 (18.0)	<.001
Heart failure	152 (2.5)	58 (18.8)	<.001

Table 2. Atrial Fibrillation and the Risk of Dementia

Characteristic	Dementia Cases, No. (%)	HR (95% CI) Model I[a]	Model II[b]	Alzheimer Disease Cases, No. (%)	HR (95% CI) Model I[a]	Model II[b]
Including Stroke						
Atrial fibrillation						
Prevalent (n = 6514)	994 (15.3)	1.34 (1.03-1.74)	1.33 (1.02-1.73)	787 (12.1)	1.30 (0.96-1.75)	1.29 (0.95-1.75)
Incident (n = 6194)	932 (15.0)	1.13 (0.90-1.41)	1.23 (0.98-1.56)	741 (12.0)	1.09 (0.85-1.40)	1.18 (0.91-1.54)
Censored for Stroke						
Atrial fibrillation						
Prevalent (n = 6314)	844 (13.4)	1.35 (1.01-1.81)	1.33 (0.99-1.78)	705 (11.2)	1.31 (0.94-1.81)	1.28 (0.93-1.78)
Incident (n = 6019)	793 (13.2)	1.14 (0.89-1.49)	1.24 (0.96-1.61)	665 (11.0)	1.08 (0.82-1.42)	1.15 (0.87-1.54)

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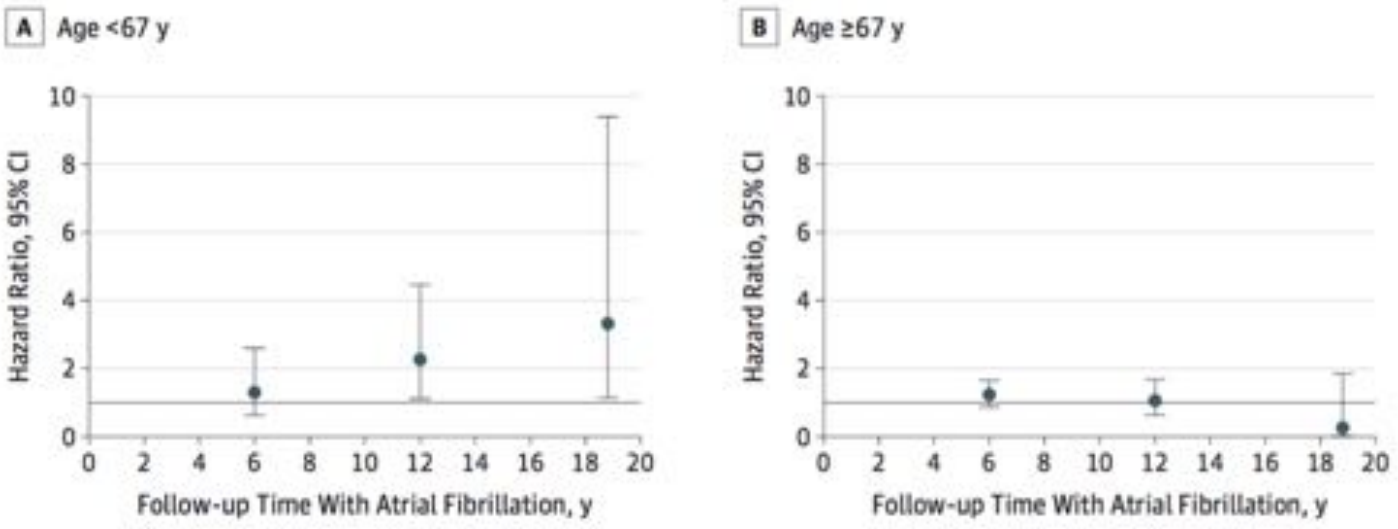
Highest Relative Risk in the Young

Table 3. Atrial Fibrillation and the Risk of Dementia, Stratified for Age at Median[a]

Characteristic	Dementia, HR (95% CI)			
	No./Total No. (%)[b]	Age, <67 y	No./Total No. (%)[b]	Age, ≥67 y
Atrial fibrillation				
Prevalent	213/3096 (6.9)	1.91 (0.85-4.26)	781/3418 (22.8)	1.28 (0.97-1.70)
Incident	206/3049 (6.8)	1.81 (1.11-2.94)	726/3145 (23.1)	1.12 (0.85-1.46)

Figure. Hazard Ratios for Dementia per Category of Follow-up of Time With Atrial Fibrillation



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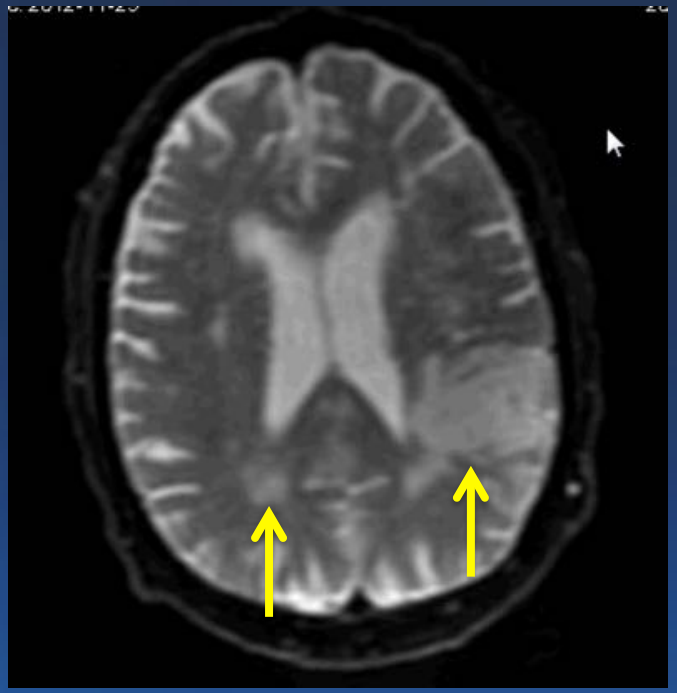
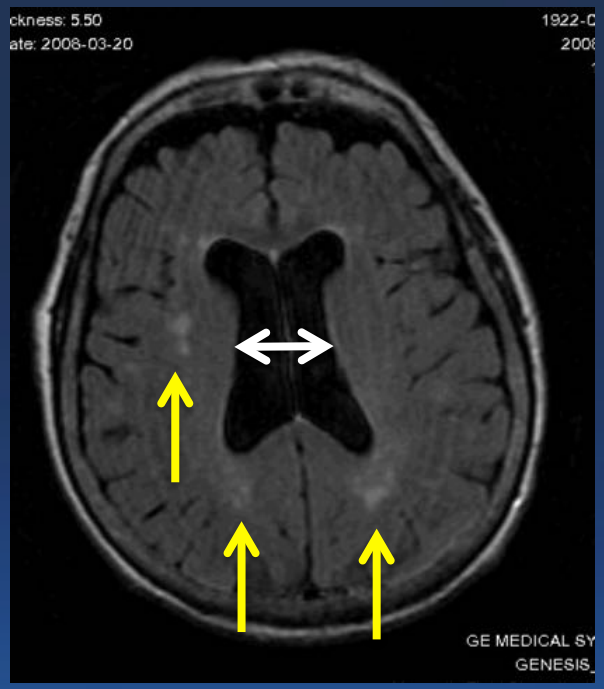
Spectrum of Cerebral Injuries from Atrial Fibrillation and Atrial Fibrillation Management





Macro Emboli

Micro Emboli ± Micro Bleed

Macro Bleed

acobs V, Bunch TJ. Trends in CV Med 2014

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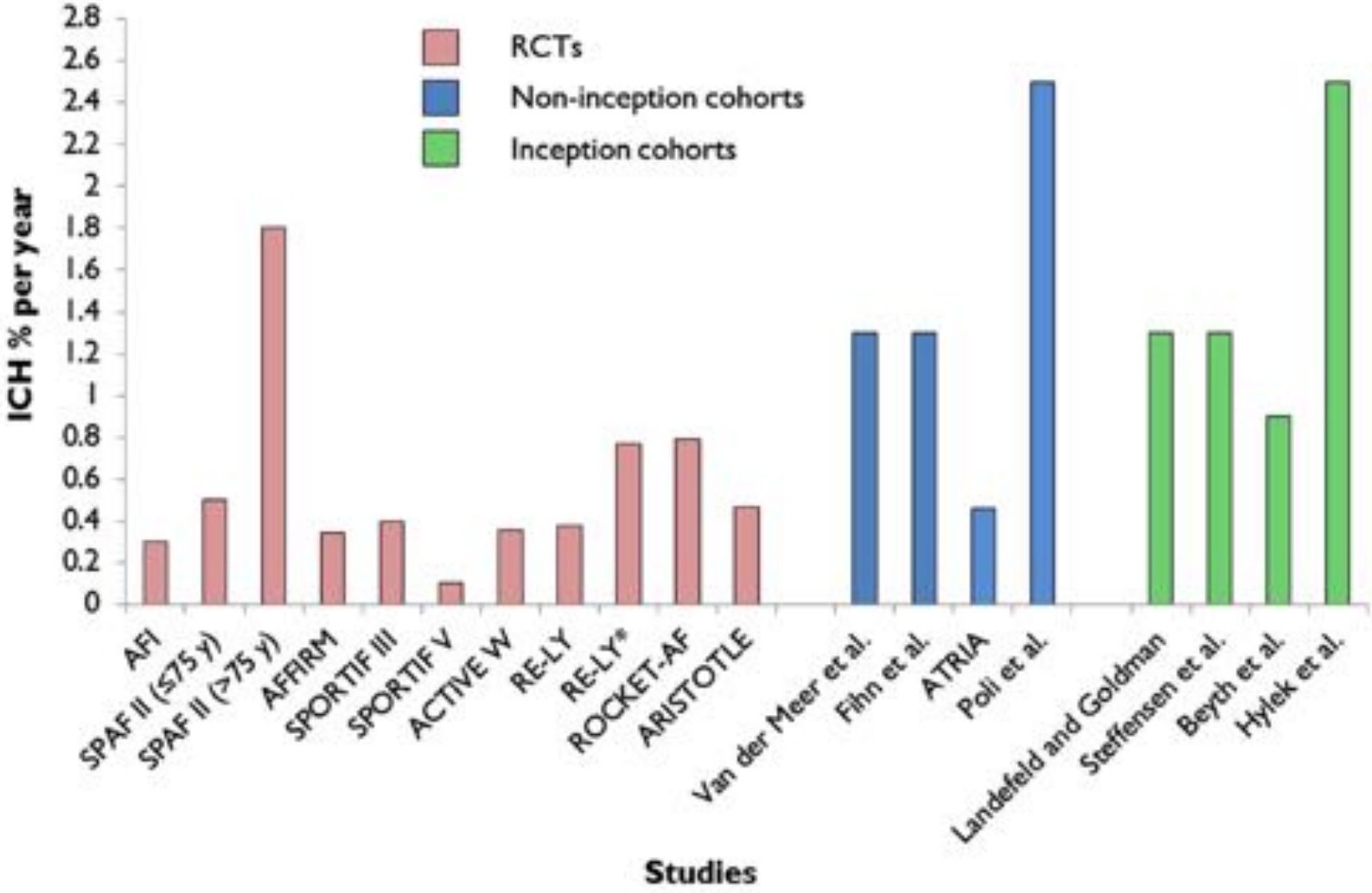
Annualized Rates of Intracranial Bleeds on Warfarin/Coumadin Anticoagulation



Charidimou, Front Neurol, 2012

Annualized Rates of Intracranial Bleeds on Warfarin/Coumadin Anticoagulation

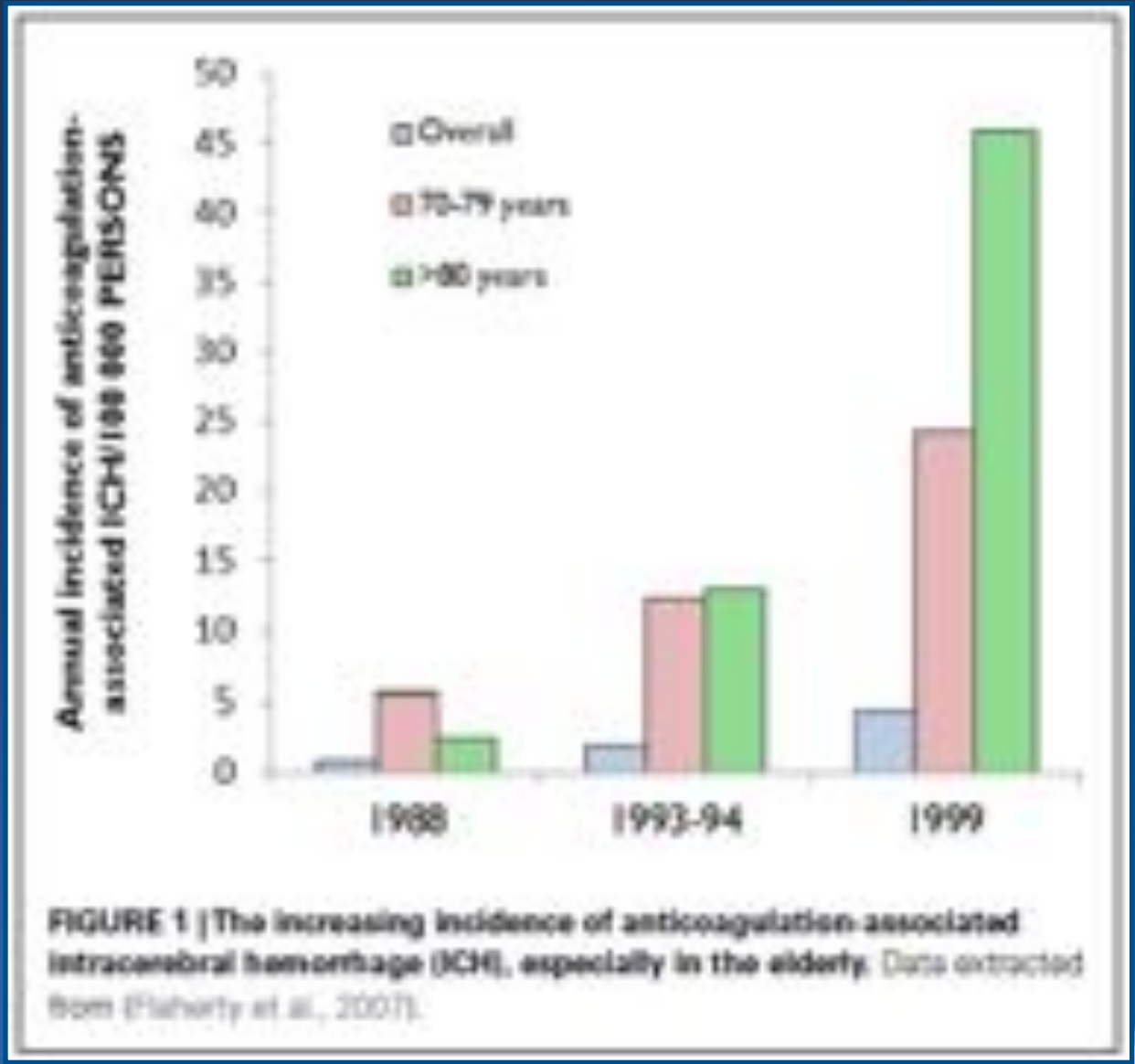
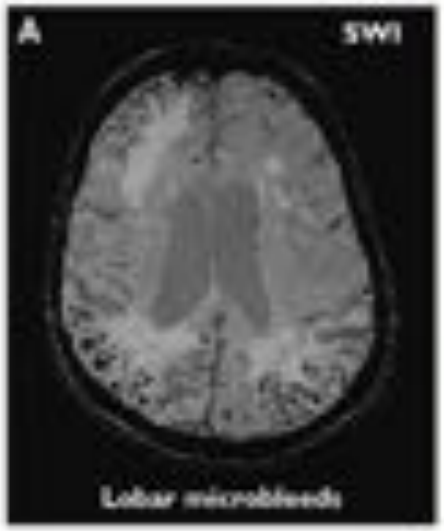
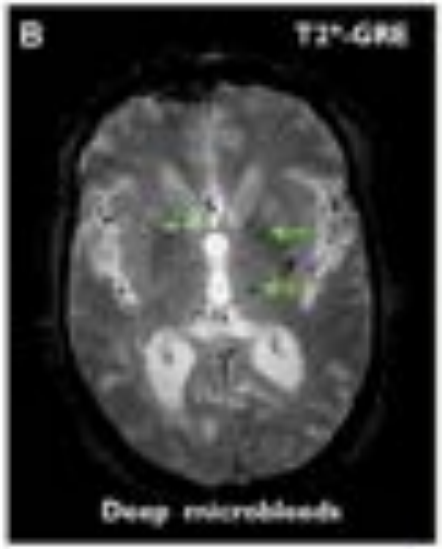


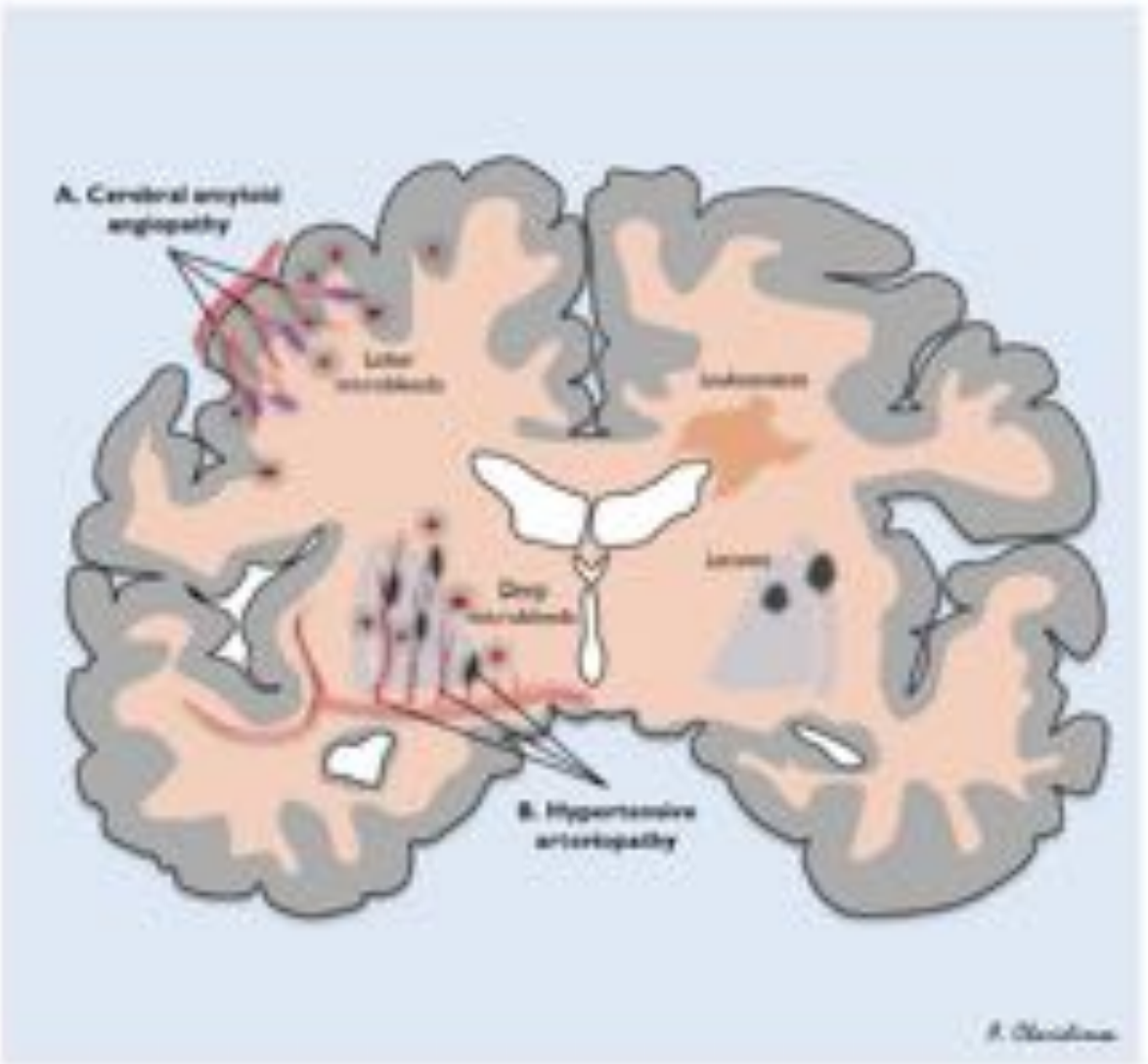
FIGURE 1 | The increasing incidence of anticoagulation-associated intracerebral hemorrhage (ICH), especially in the elderly. Data extracted from Flaherty et al., 2007).

Charidimou, Front Neurol, 2012

Annualized Rates of Intracranial Bleeds on Warfarin/Coumadin Anticoagulation

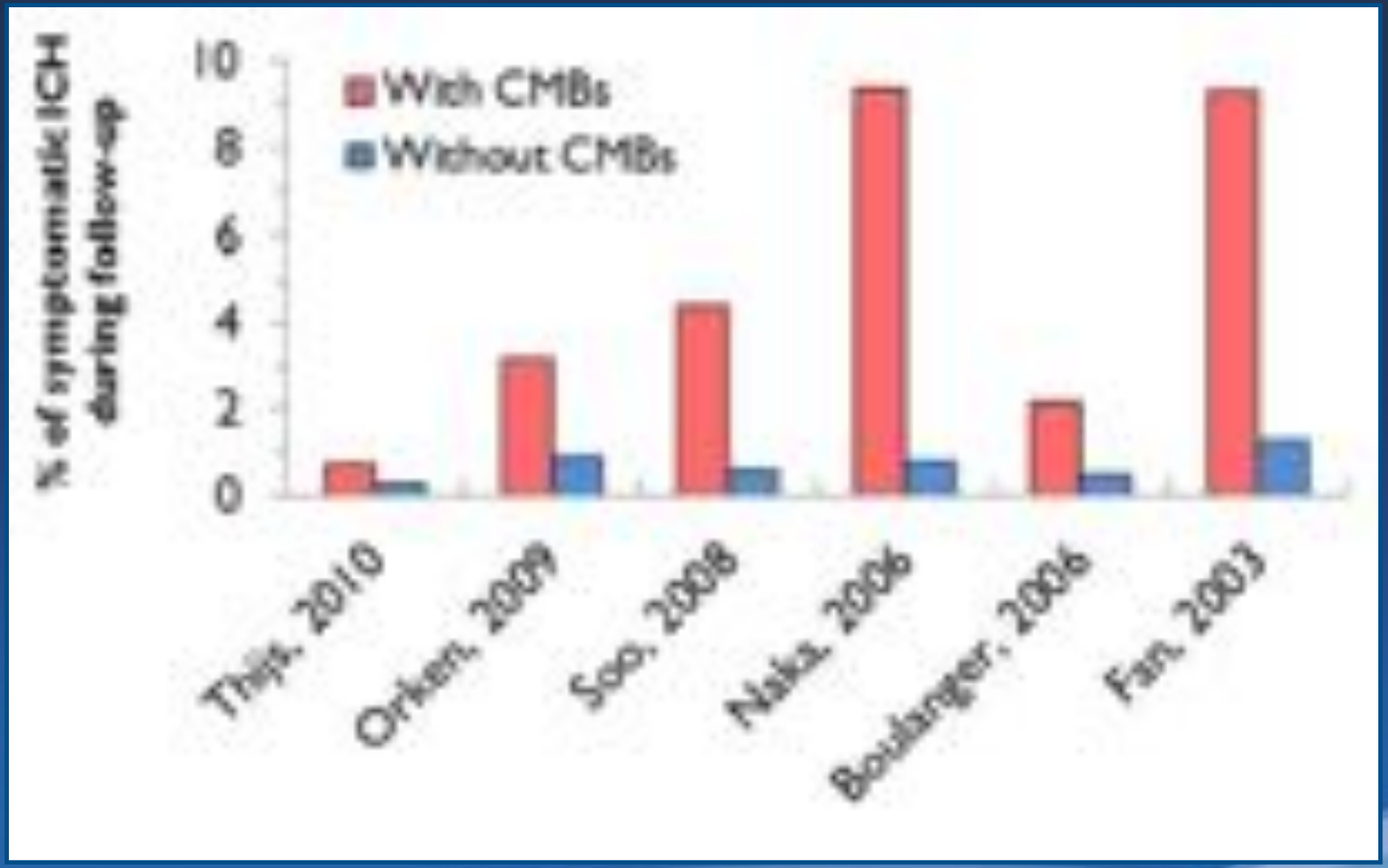






Charidimou, Front Neurol, 2012

Annualized Rates of Intracranial MicroBleeds on Warfarin/Coumadin Anticoagulation

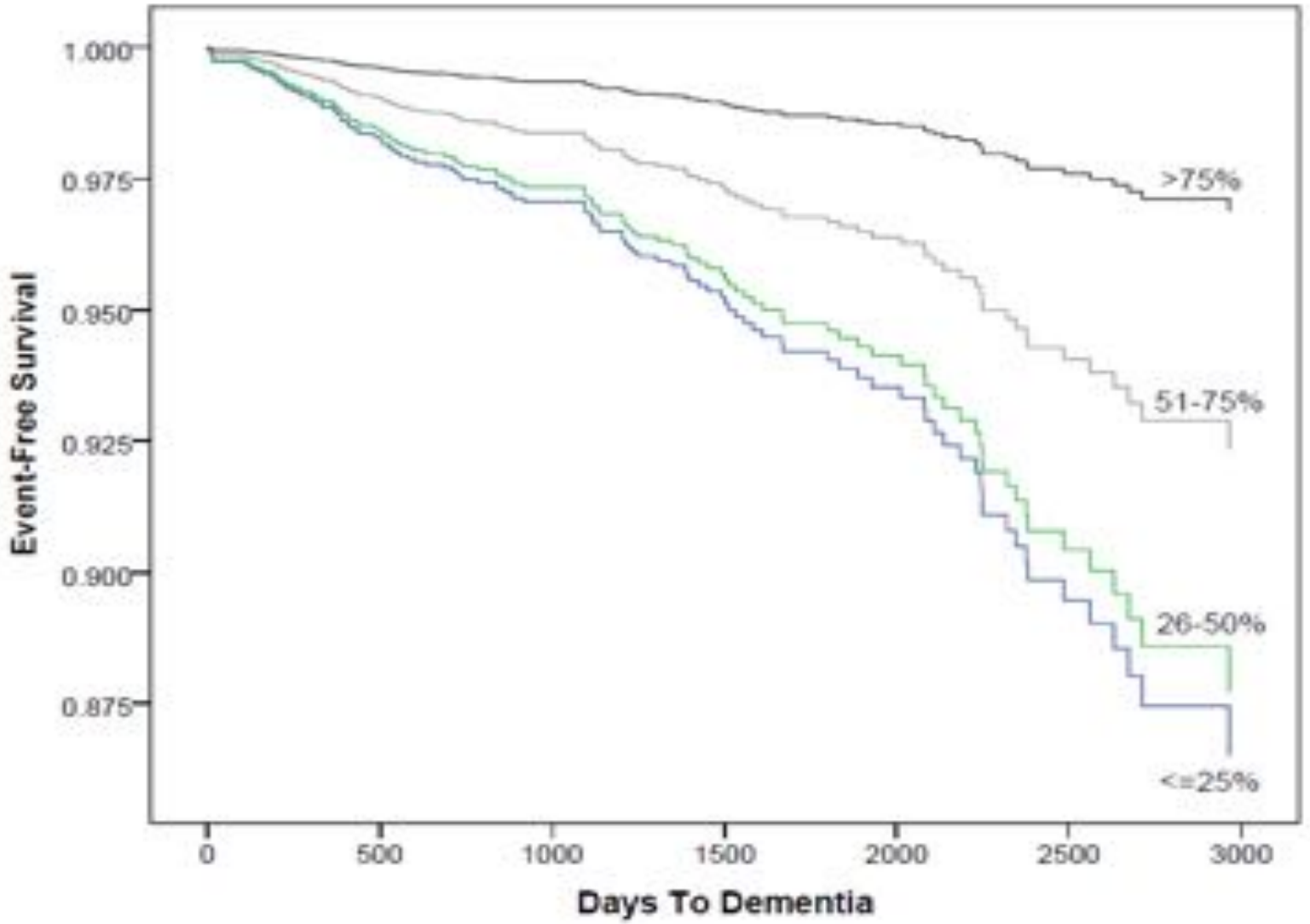


Charidimou, Front Neurol, 2012

If Macro/Micro Cerebral Ischemic Events Play a Role then Anticoagulation Matters

Dementia Risk in AF Patients on Warfarin by TTR

2,693 Pts, No prior dementia, Followed By CPAS



Average number of draws per patient was 44.2±39.4

Jacobs V, Bunch TJ. HeartRhythm J 2014

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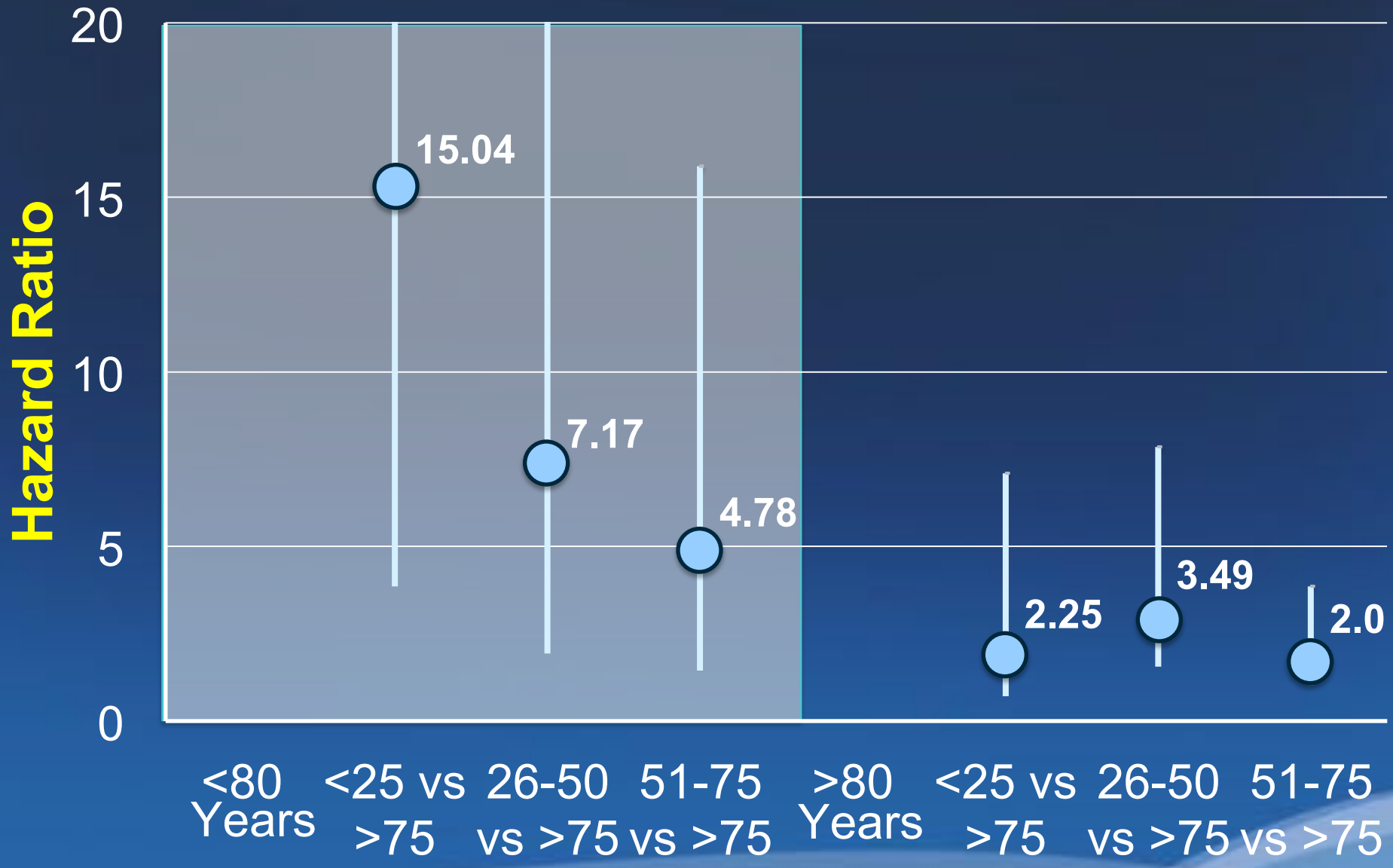
Dementia In AF Patients



acobs V, Bunch TJ. HeartRhythm J 2014

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Baseline Characteristics Total CPAS AF Clinic(n=3664)

Age: 74.5±10.7 (median: 76, range: 22-104)

Sex (male): 1918 (52.3%)

Hypertension: 3008 (82.1%)

Hyperlipidemia: 2578 (70.4%)

Diabetes: 1160 (31.7%)

Smoking: 813 (22.2%)

Heart failure: 1663 (45.4%)

Prior MI: 355 (9.7%)

Renal failure: 443 (12.1%)

Prior bleeding: 512 (14.0%)

Coronary artery disease: 1796 (49.0%)

Prior malignancy: 847 (23.1%)

CHADS2:

0: 238 (6.5%)
1: 654 (17.8%)
2: 1023 (27.9%)
3: 924 (25.2%)
4: 519 (14.2%)
≥5: 306 (8.4%)

AF Subtype

Paroxysmal: 55.4%
Permanent: 24.0%
Persistent: 42.3%

Aspirin Use and Abuse

Asprin use for "primary prevention"

- **Initial cardiovascular event**
- **Prevent cancer**

In this survey of more than 2,500 respondents (average age 60)

1. **Aged 45-75, 52% reported current aspirin use**
2. **Another 21% had used in in the past for this purpose**

Aspirin use had increased by 57% (from 2005 to 2010).

American Journal of Preventive Medicine, 2015

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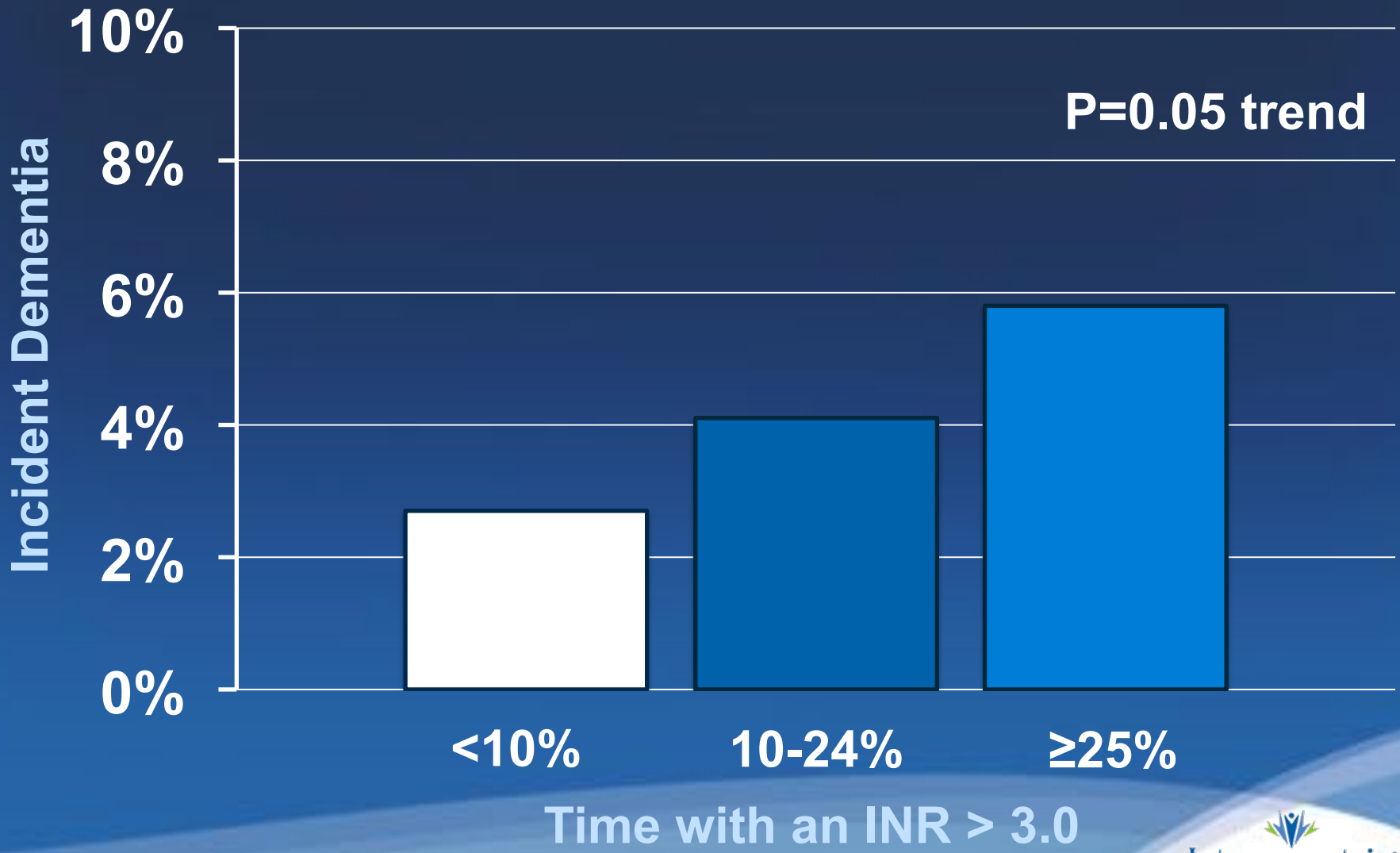
Long-Term Dementia Incidence By Time Spent with a Supratherapeutic INR



Jacobs V, Bunch TJ. JCE 2015

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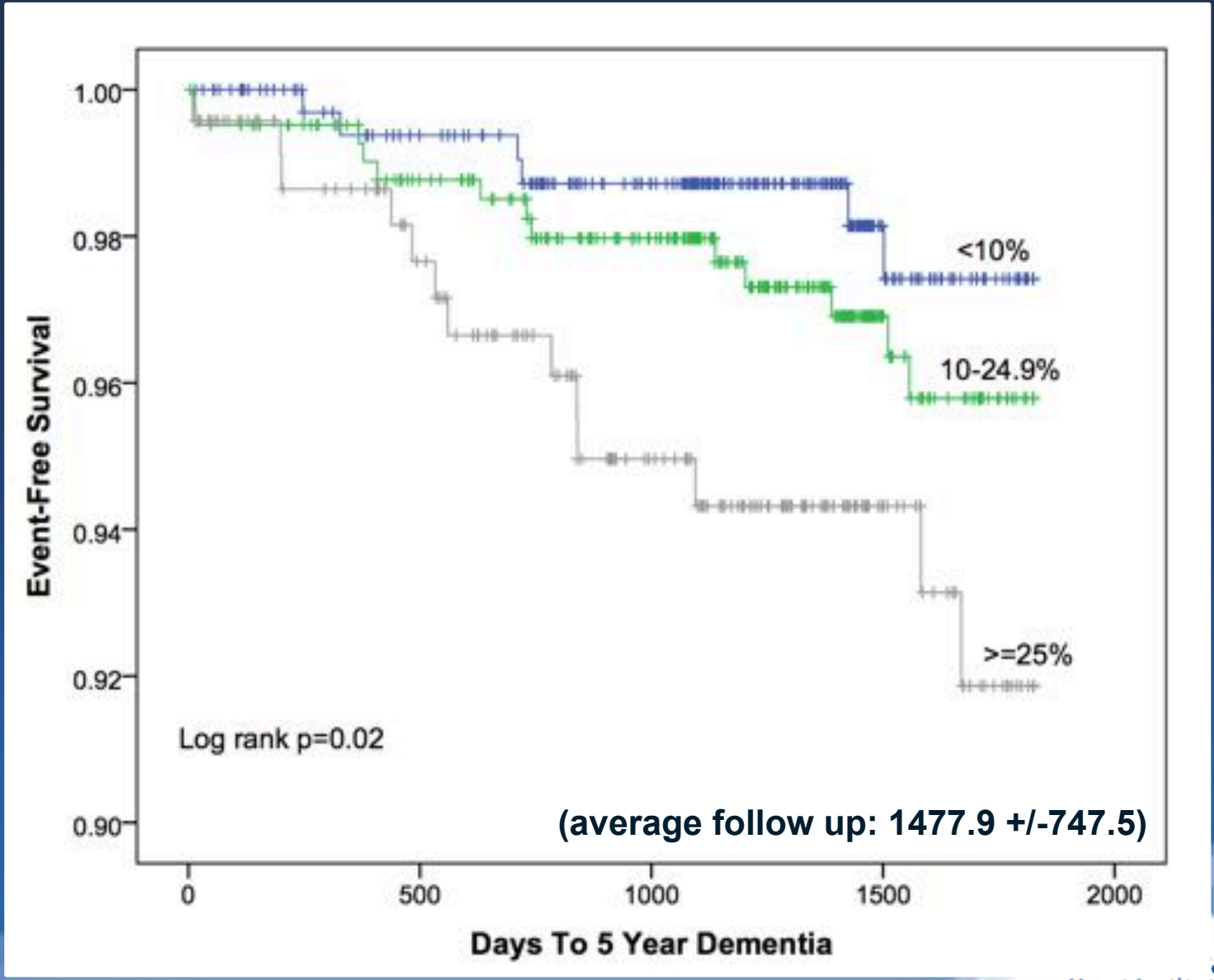
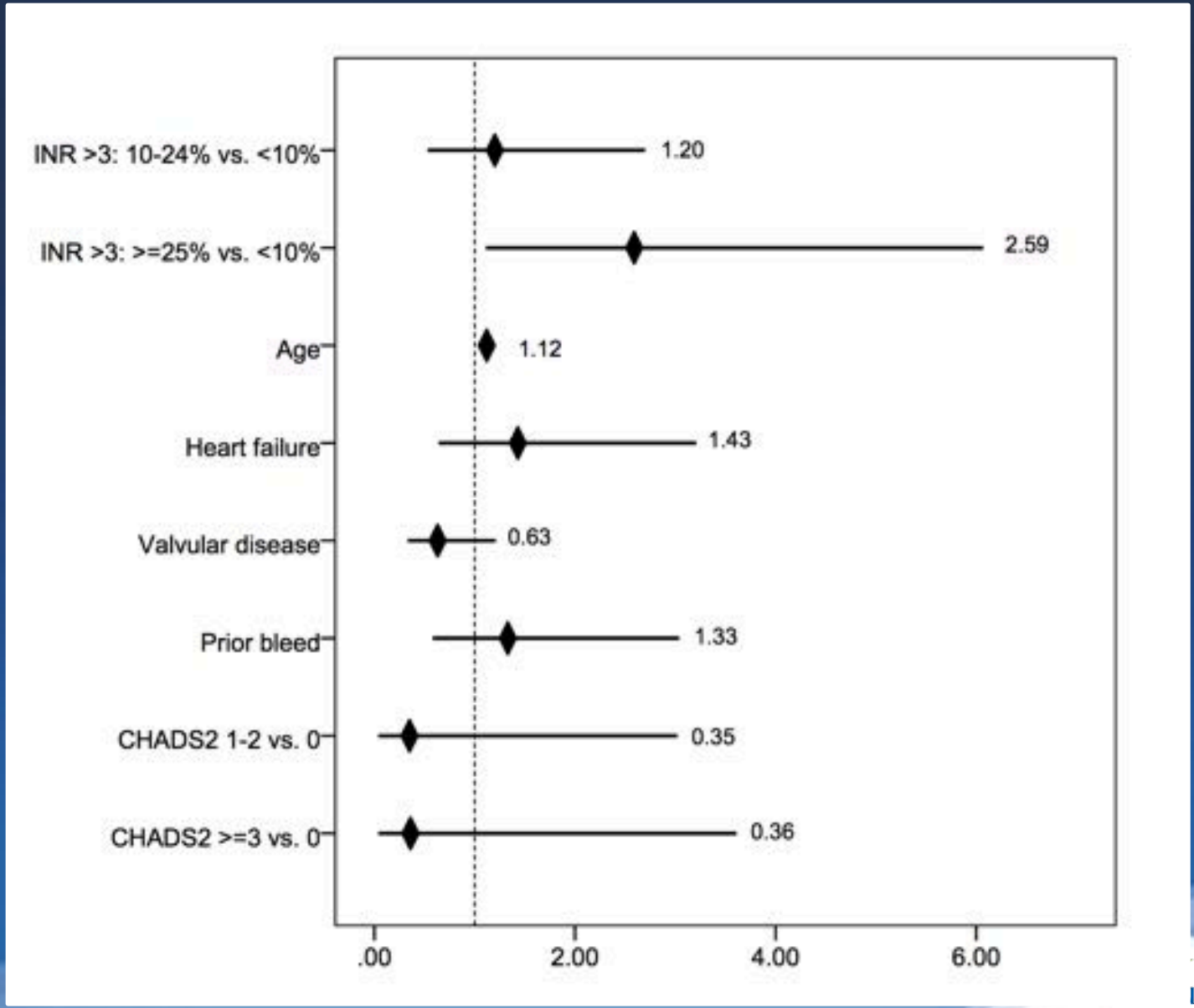
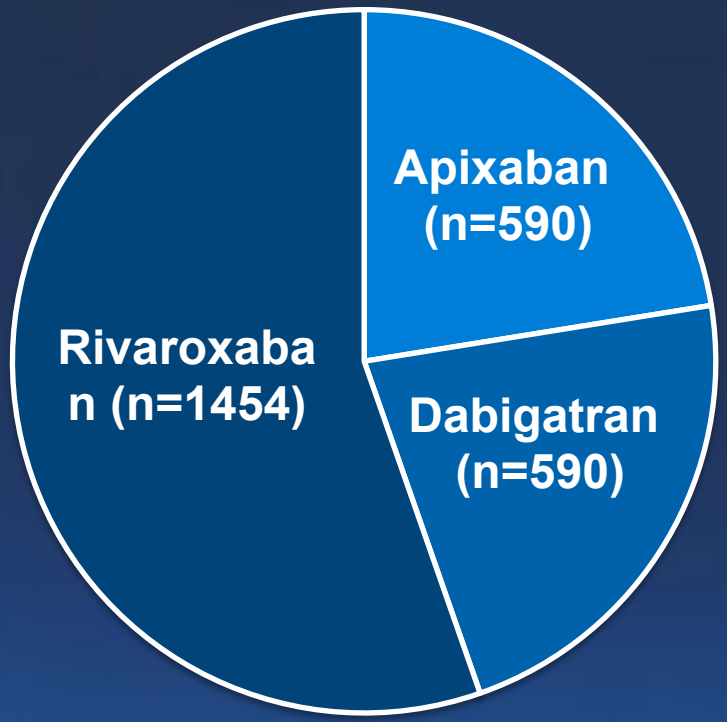
Long-term Risk of Dementia by Percent Time with an INR >3.0



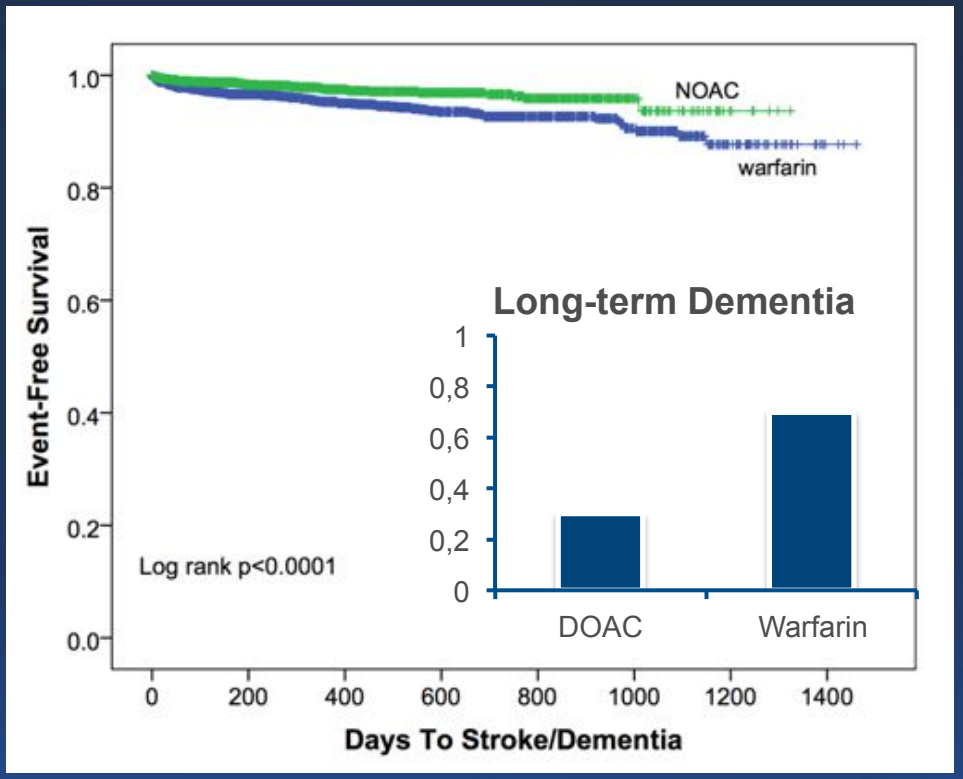
Multivariate Adjusted HRs for Development of Dementia in AF Patients

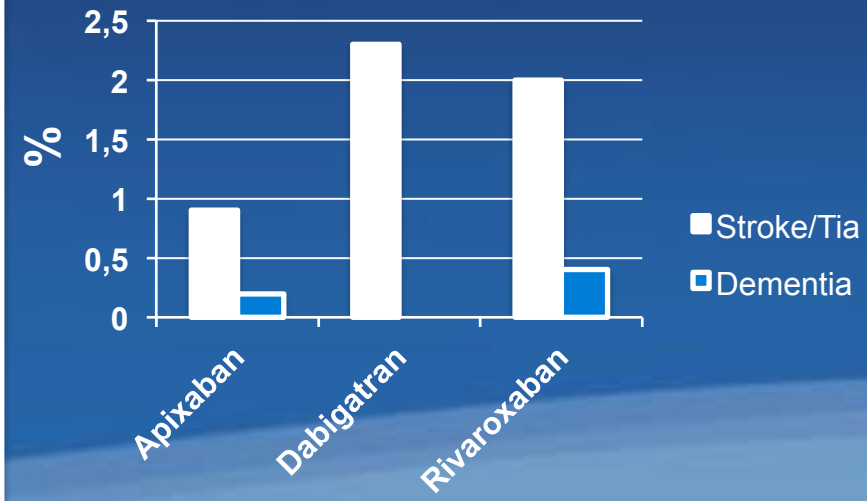


Direct Oral Anticoagulant Distribution



Propensity-Matched with a Warfarin Population (n=2,627)





Long-Term Total Events

Follow-up for Dabigatran >1 yr Longer than other DOACs

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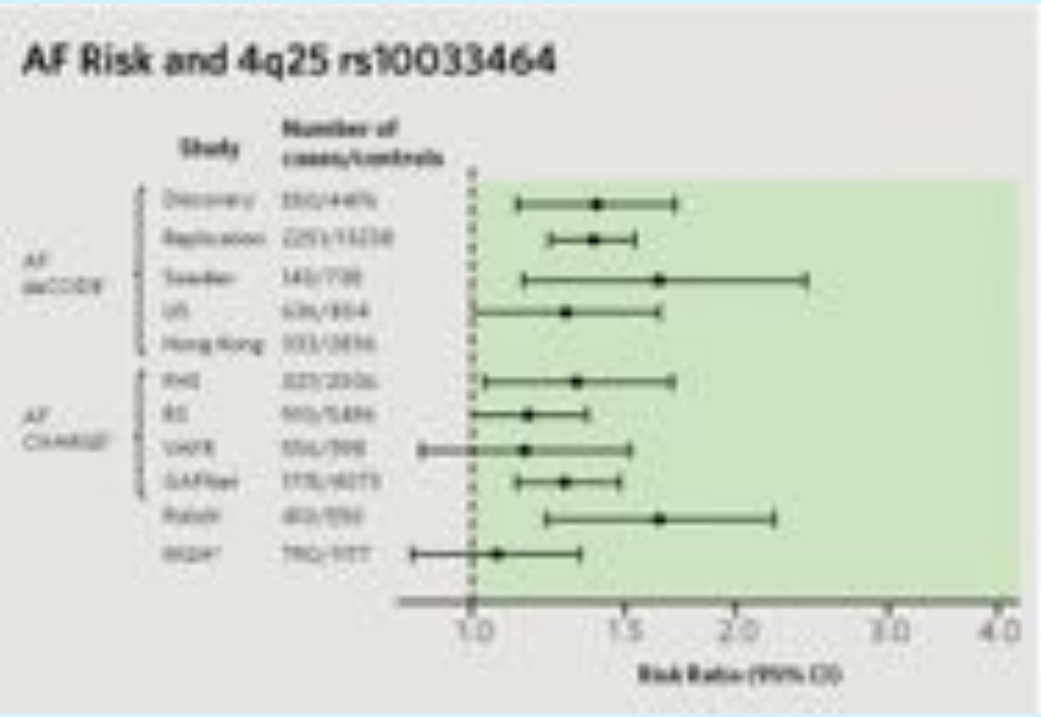

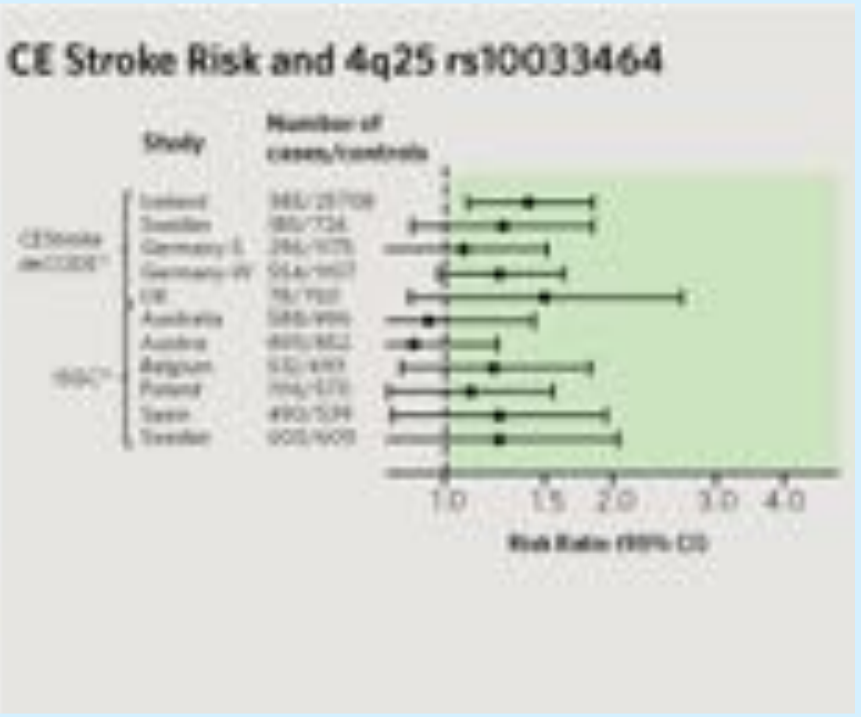

Candidate Genes for Early onset AF with increased risk of thromboembolism:

PITX2

rs2634073

rs2200733

ZFHX3

rs7193343

APOE e4 – where AF is a “second” hit to a dementia predispositon

http://www.bhlinc.com/clinicians/test-descriptions/4q25

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Associations for Genotypes for AF/Dementia – IMC (n=132 AF patients)

Conditional logistic regression results for genotypes and diseases of AF or dementia

	AF subjects		
	OR of Dementia*	95% CI	p-values
PITX2			
rs2634073	1.44	(0.86, 2.41)	0.166
rs2200733	2.15	(1.22, 3.77)	0.008
ZFHX3			
rs7193343	1.10	(0.65, 1.85)	0.727
APOE			
e4	1.79	(1.07, 3.00)	0.026

Rollo J, Bunch TJ (in press, PACE)

Conditional logistic regression results for interaction

		AF subjects OR of Dementia	95% CI
PITX2			
rs2634073	APOE no e4 allele	1.89	(0.87, 4.12)
	APOE e4 allele	0.97	(0.35, 2.72)
	Gene-Gene Interaction p-value =0.324		
rs2200733	APOE no e4 allele	2.86	(1.23, 6.67)
	APOE e4 allele	2.17	(0.64, 7.35)
	Gene-Gene Interaction p-value =0.805		
ZFHX3			
rs7193343	APOE no e4 allele	0.98	(0.45, 2.13)
	APOE e4 allele	0.87	(0.26, 2.86)
	Gene-Gene Interaction p-value =0.867		

Rollo J, Bunch TJ (in press, PACE)

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Treatment of Atrial Fibrillation and Outcomes (catheter ablation)

- 37,908 Intermountain Healthcare patients
  - 4,212 consecutive AF ablation patients
  - 16,848 age/gender matched controls with AF
  - 16,848 age/gender matched controls w/o AF
- 3 years follow-up
- Mean age: 65.0±13 years

Bunch TJ, et al. JCE 2011

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Baseline Demographics

Characteristic	No AF (n=16,848)	AF, no ablation (n=16,848)	AF, ablation (n=4,212)	p-value
Age (years)	64.1±13.0	66.0±13.3	64.8±12.7	<0.0001
Sex (male)	60.8%	60.8%	60.8%	1.00
Diabetes	19.0%	21.1%	16.3%	<0.0001
Hypertension	41.2%	45.3%	47.8%	<0.0001
Hyperlipidemia	58.4%	37.3%	44.0%	<0.0001
CHF	14.5%	23.6%	29.5%	<0.0001
Renal Failure	5.6%	7.8%	7.5%	<0.0001
TIA History	4.0%	4.2%	4.6%	0.16
CVA History	4.4%	6.3%	4.5%	<0.0001
MI History	10.0%	6.4%	6.4%	<0.0001
Valve History	11.6%	15.3%	27.7%	<0.0001

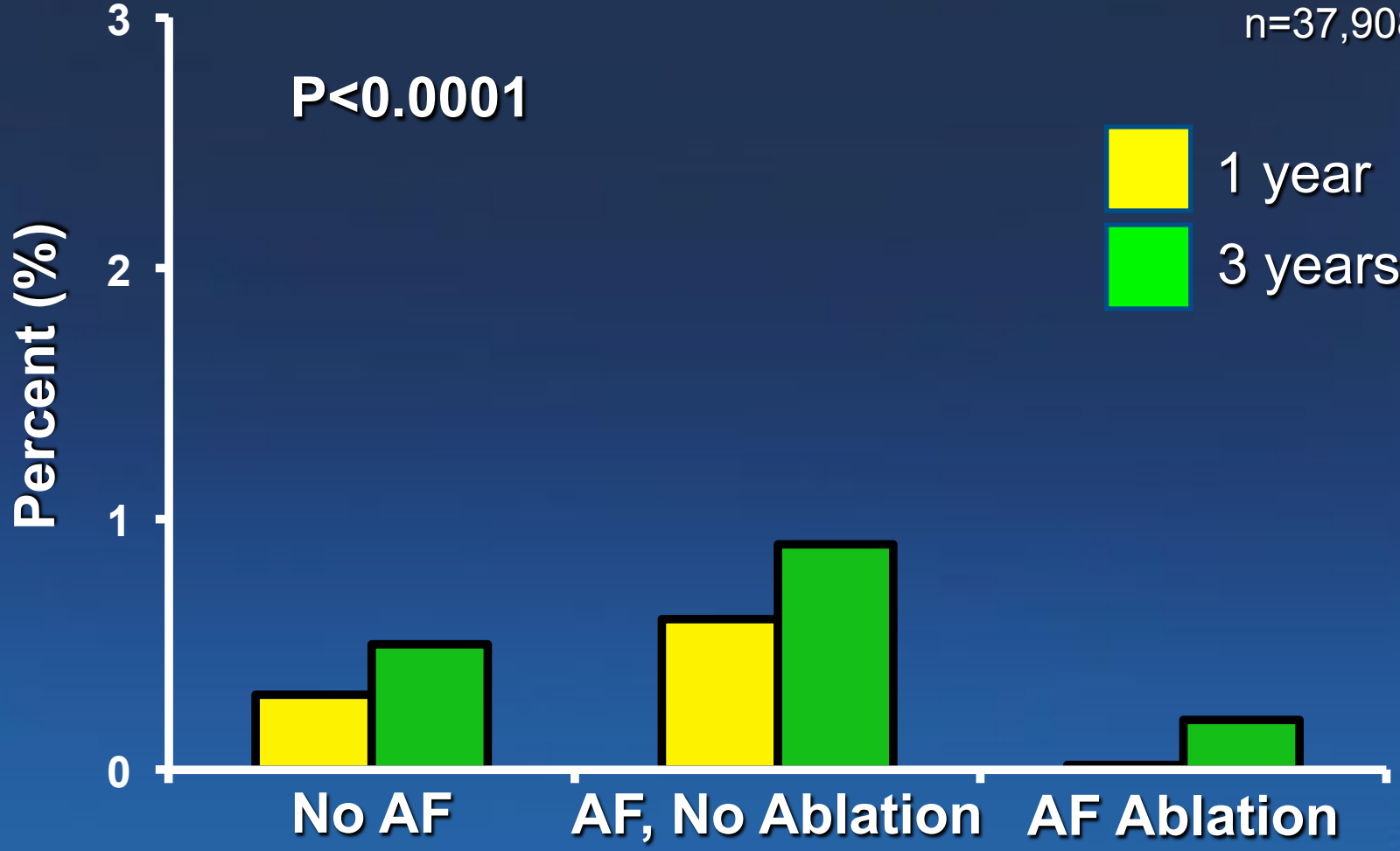
Bunch TJ, et al. JCE 2011

Ablation Results (n=4,212)

- 3 Year Success Rate (no antiarrhythmics, no AF recurrences): 64.4%
- Repeat procedure: 1,162 (27.6%)
- Complications:
  - -Pericardiocentesis: 25 (0.6%)
  - -AV fistula: 7 (0.2%)
  - -TIA 16 (0.4%)
  - -Esophageal perforations: 2 (0.05%)
  - -Pulmonary vein stenosis: 4 (0.1%)
  - -Death: 2 (0.05%)

Bunch TJ, et al. JCE 2011

Incidence of Alzheimer's Disease



Bunch TJ, et al. JCE 2011

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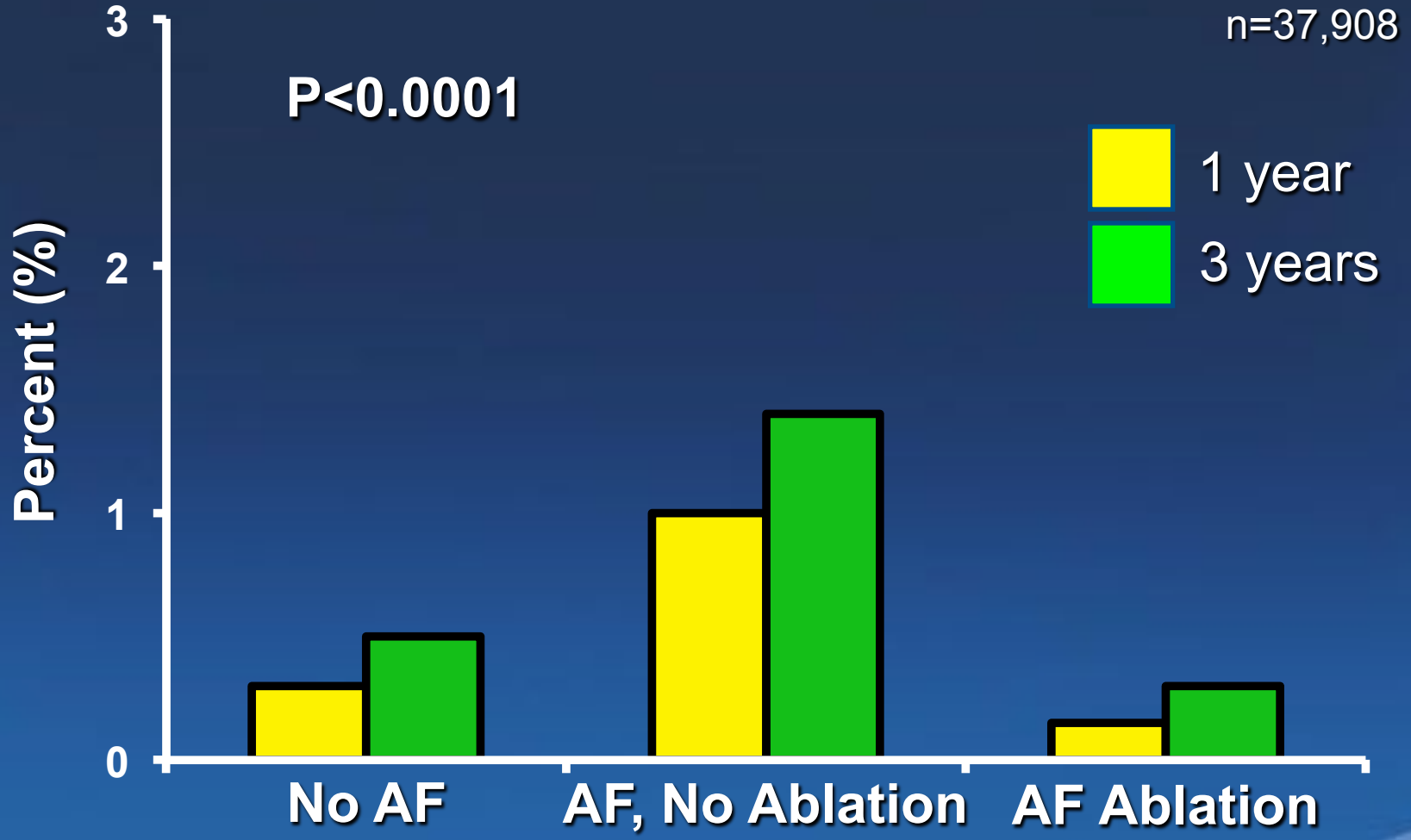
Incidence of Other Dementias

Vascular and Senile



Bunch TJ, et al. JCE 2011

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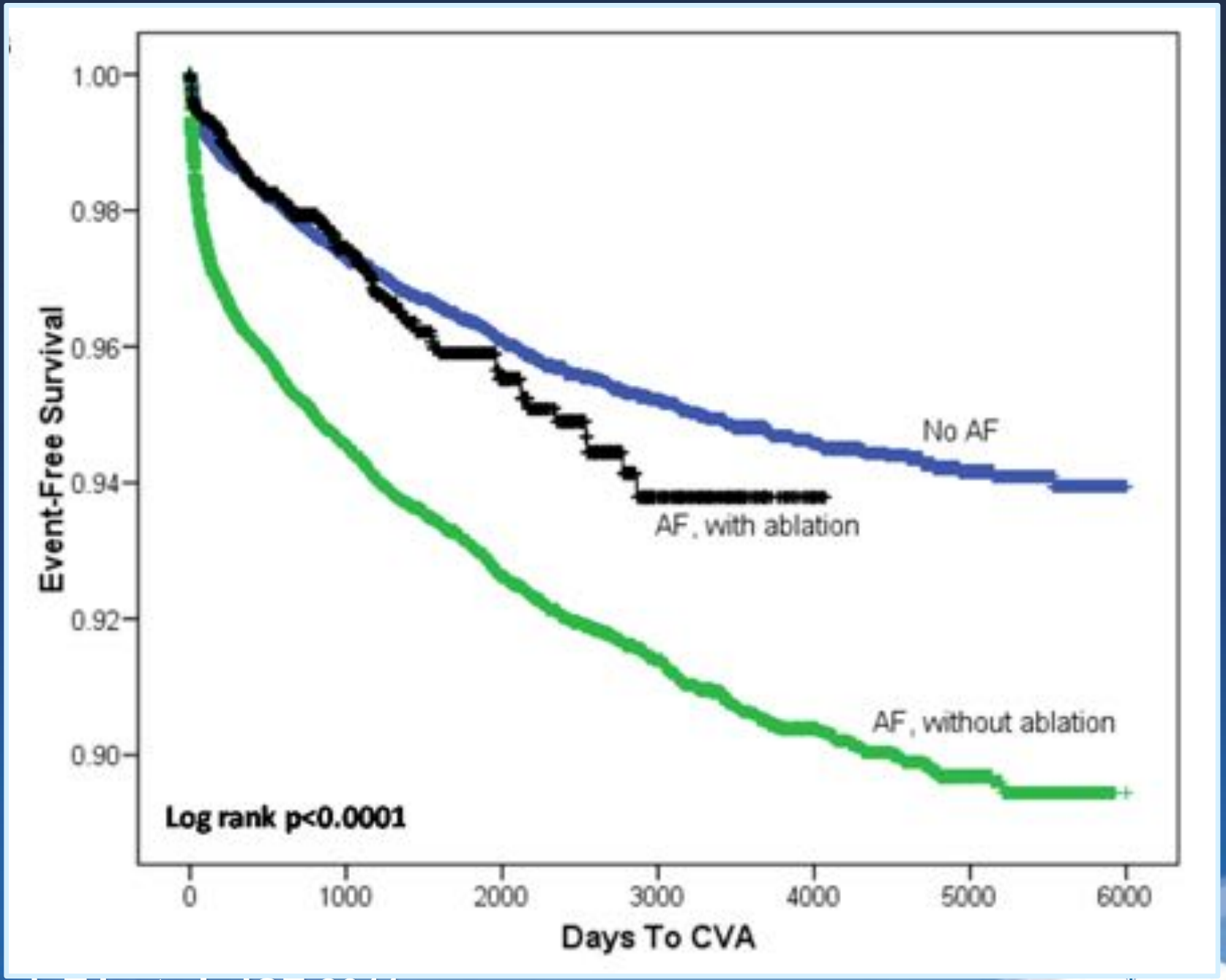
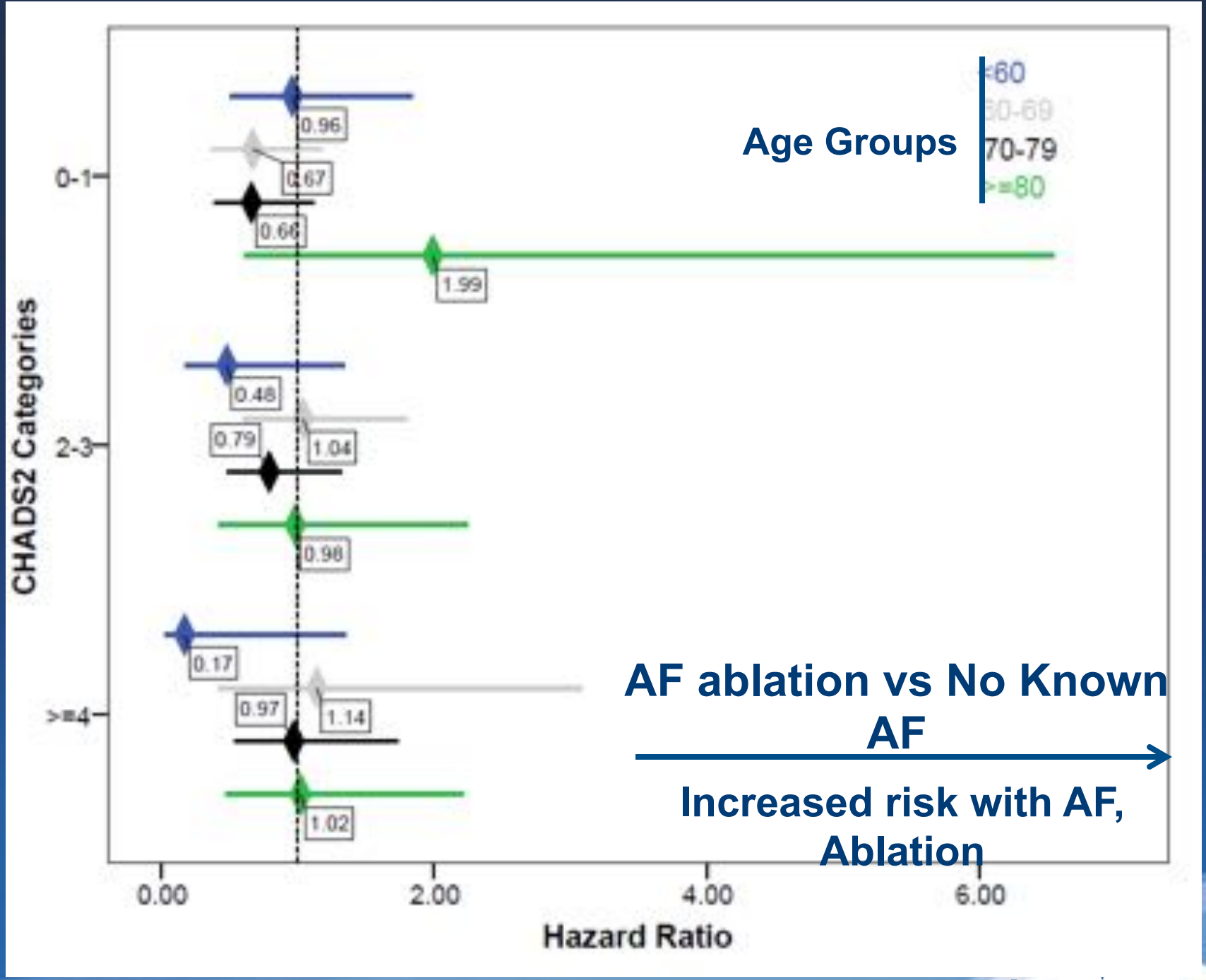


Bunch TJ, et al. JCE 2011



Bunch TJ, et al. Heart Rhythm 2015

Should Patients with a CHADS Score of 2 or 3 Continue to Take Warfarin Long-Term After a Successful Atrial Fibrillation Ablation?

John D.. Day, MD, Brian G. Crandall, MD, Jeffrey S. Osborn, MD, J. Peter. Weiss, MD, Donald L. Lappe, MD, Tami Bair, MS, Heidi T. May, PhD, Jeffrey L. Anderson, MD, Brent Muhlestein, MD, Jennifer Nelson, RN, T. Jared Bunch, MD.

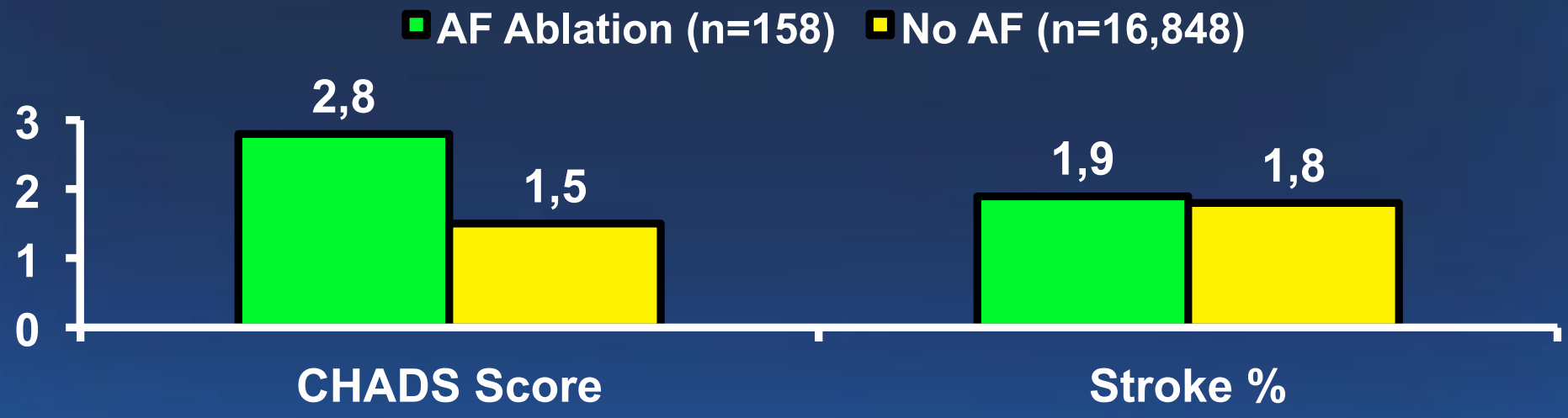
Intermountain Medical Center, Salt Lake City, UT

Intermountain Heart Institute

Patients

	Ablation (n=158)	Control, no AF (n=16,848)
Heart Failure	63.9%	14.5%
Hypertension	96.8%	41.2%
Age	68.0±9.0	64.1±13.0
Diabetes	46.2%	19.0%
CVA/TIA	6.3%	4.0%
CHADS	2.8	1.5

Results at 2 Years (597±440 days)



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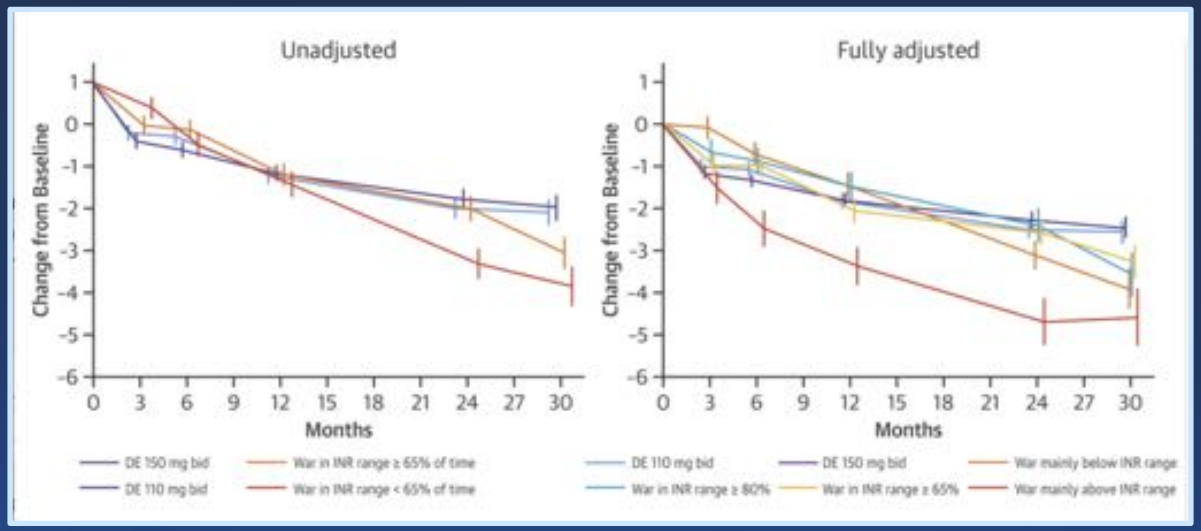
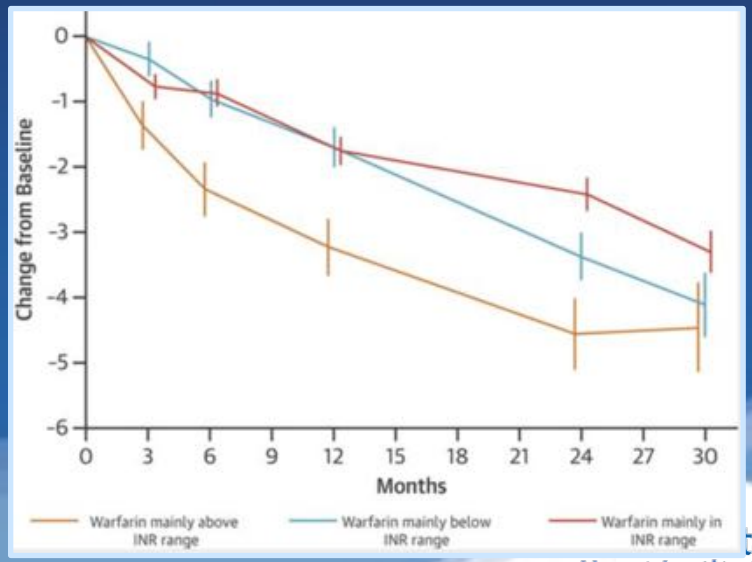
Beyond the Brain

Changes in Renal Function in Patients With Atrial Fibrillation: An Analysis From the RE-LY Trial.





J Am Coll Cardiol. 2015;65(23):2481-2493.

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Conclusions

- Atrial fibrillation in multiple cohorts of study has been shown to be associated with Alzheimers, Senile, and Vascular Dementia
  - The combined disease state is associated with a significantly higher risk of mortality
- Anticoagulation strategy can influence risk of dementia development in AF patients without dementia
- Both over- and under-anticoagulation increase risk supportive of cerebral ischemic injury as a mechanism both from clot and bleed
- Novel anticoagulants may lower risk of both macro- and micro cerebral events
- Genetic markers of arrhythmia and stroke risk are associated with increased risk of dementia and made help identify patients at highest risk

Thank You

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Silent Cerebral Emboli

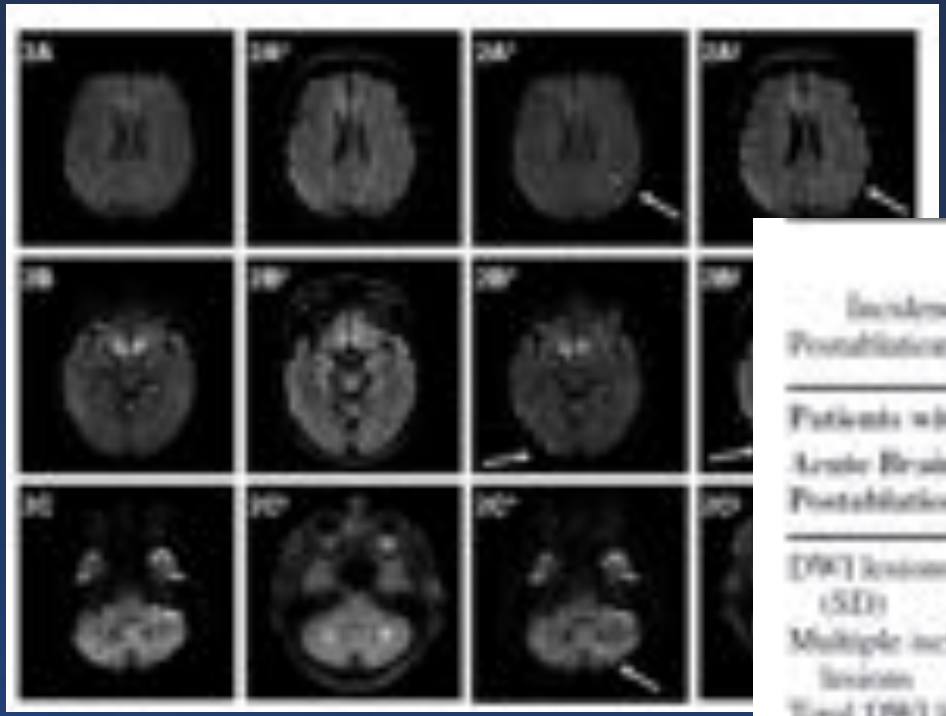


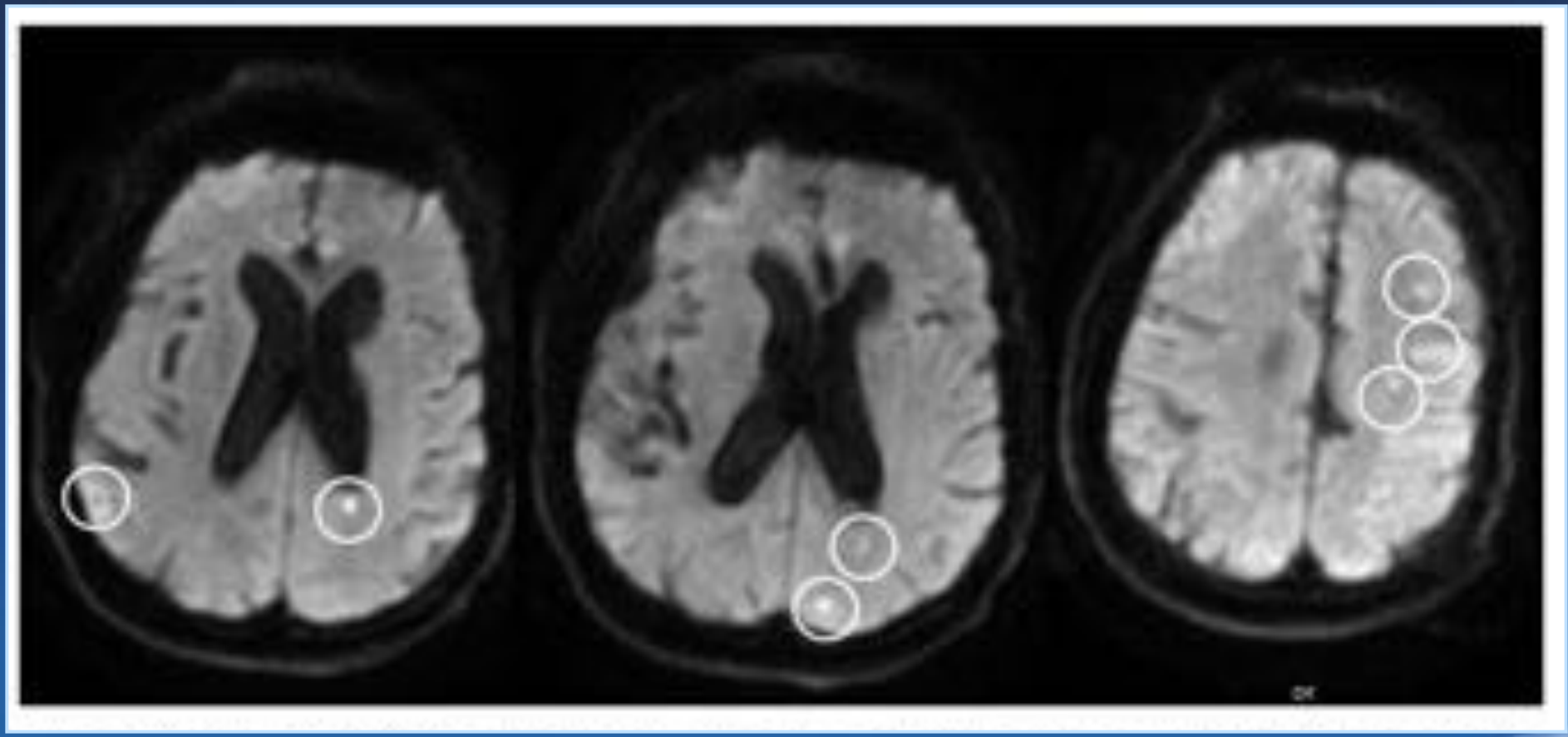
TABLE 2

Incidence and Localization of MRI-Detected Acute Brain Lesions Postablation in Affected Study Patients (n = 15) According to Study Arms

Patients with Acute Brain Lesions Postablation	Σ (n = 15/37)	IBD Mode A® (n = 4/11)	Arctic Front® (n = 11/22)	P*
DWI lesions; n, mean (SD)	2.2 (1.5)	3.2 (2.1)	1.8 (1.2)	0.214
Multiple ischemic lesions	8 (53.3)	3 (75.0)	5 (45.5)	0.568
Total DWI lesion volume per patient: mm³, median (IQR)	70.0 (11.6–118.4)	94.3 (28.8–147.2)	25.7 (5.0–70.0)	0.361
Affected hemisphere; n (%)				0.289
Right	5 (33.3)	–	5 (45.5)	
Left	4 (26.7)	2 (50.0)	2 (18.2)	
Both	6 (40.0)	2 (50.0)	4 (36.4)	
Affected vessel territory				
Arteria cerebri media	9 (60.0)	3 (75.0)	6 (54.4)	0.604
Arteria cerebri anterior	3 (20.0)	–	3 (27.3)	0.316
Arteria cerebri posterior	7 (46.7)	3 (75.0)	4 (36.4)	0.282
Vertebral/basilar artery	3 (20.0)	2 (50.0)	1 (9.1)	0.154

HAEUSLER, JCE 2012

78 year old 2 weeks after catheter ablation for atrial fibrillation



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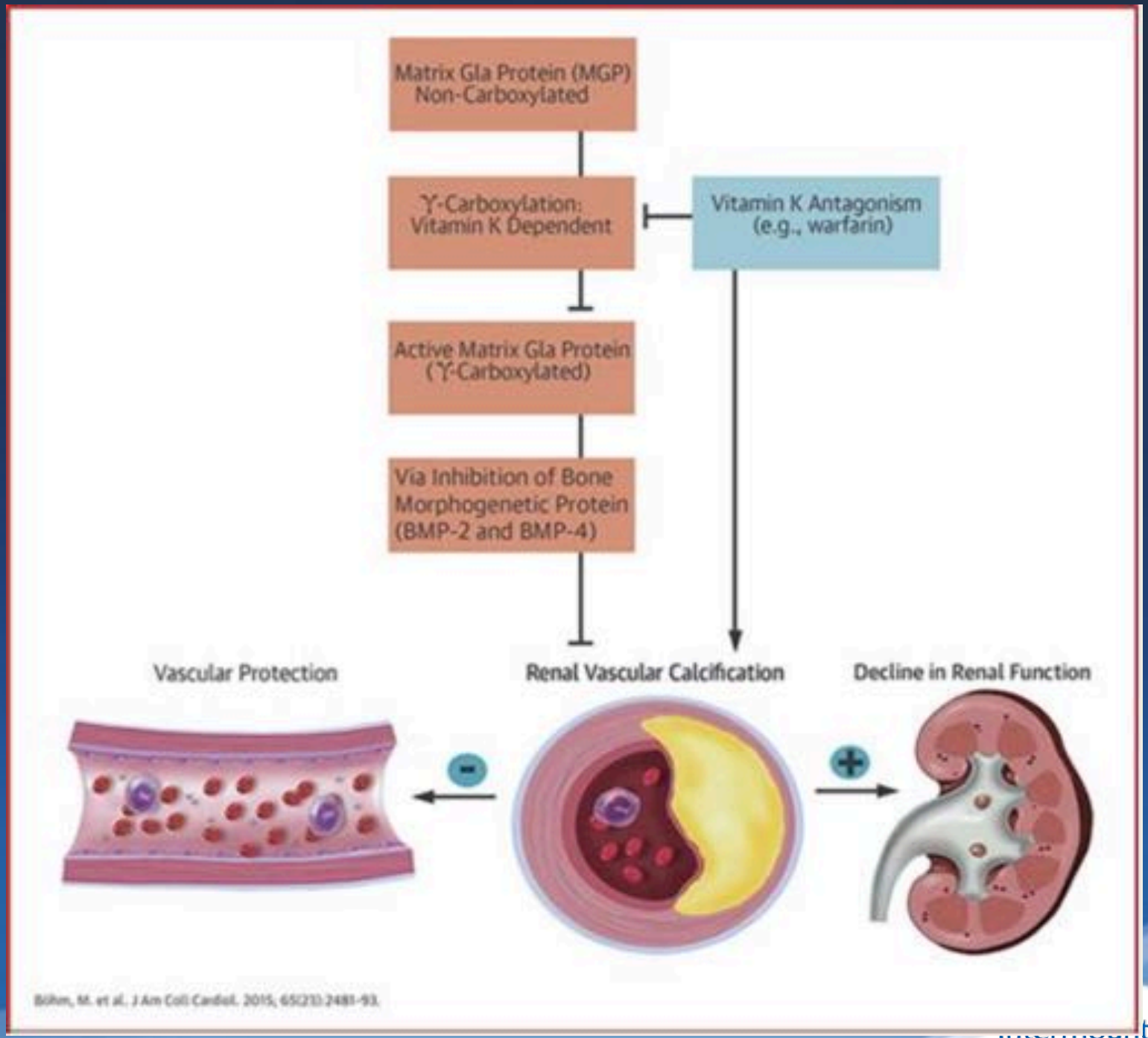
Matrix Gla Protein (MGP)
Non-Carboxylated
γ-Carboxylation:
Vitamin K Dependent
Vitamin K Antagonism
(e.g., warfarin)
Active Matrix Gla Protein
(γ-Carboxylated)
Via Inhibition of Bone
Morphogenetic Protein
(BMP-2 and BMP-4)
Vascular Protection
Renal Vascular Calcification
Decline in Renal Function
Böhm, M. et al. J Am Coll Cardiol. 2015; 65(21):2481-93.