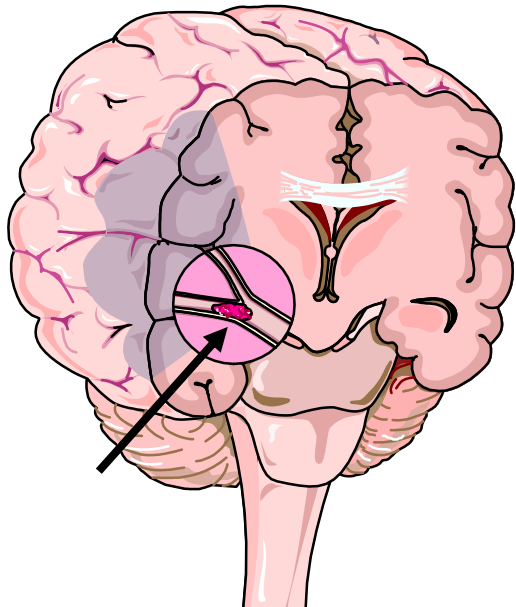


Starting or Resuming Anticoagulation or Antiplatelet Therapy after ICH: A Neurology Perspective

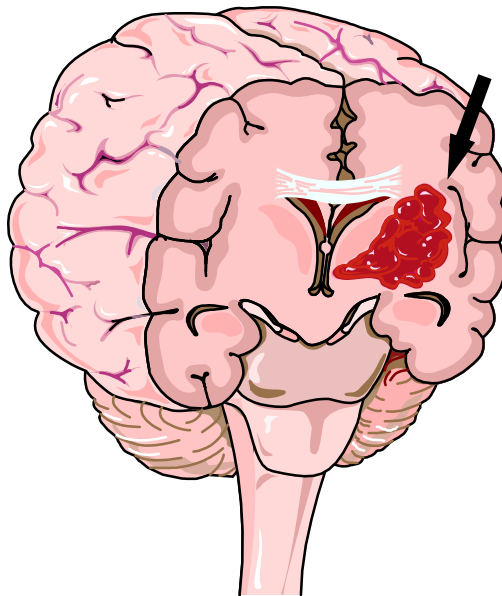
Cathy Sila MD

George M Humphrey II Professor and Vice Chair of Neurology
Director, Comprehensive Stroke Center and UH Systems Stroke Program
Neurological Institute, UH Cleveland Medical Center

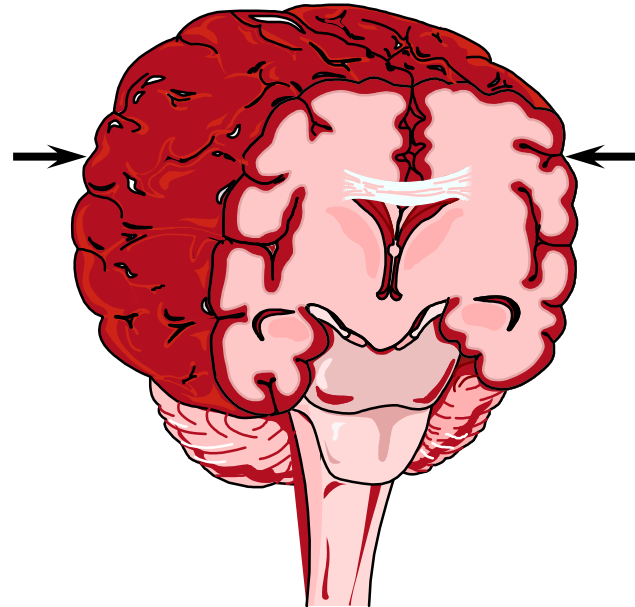
Ischemic Stroke



Intracerebral Hemorrhage



Subarachnoid Hemorrhage



Embolism- A Fib, Heart Failure
 Thrombo/embolism- Atherosclerosis
 Dissection
 Coagulopathy, infection, inflammatory

Hypertension
Coagulopathy
 Amyloid angiopathy
 AV Malformation

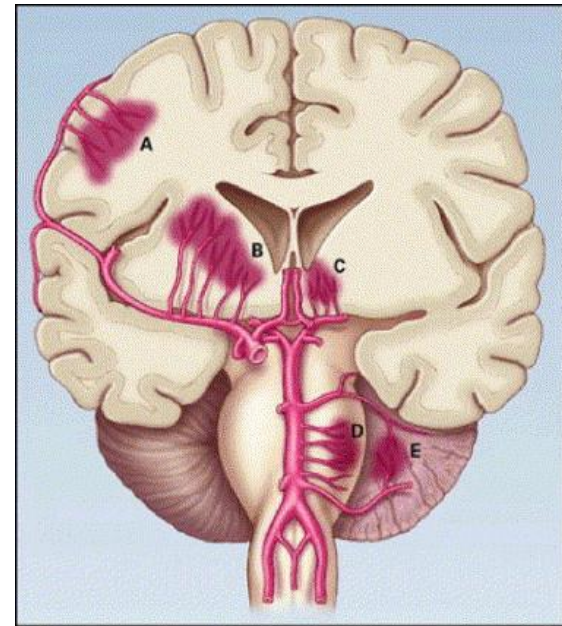
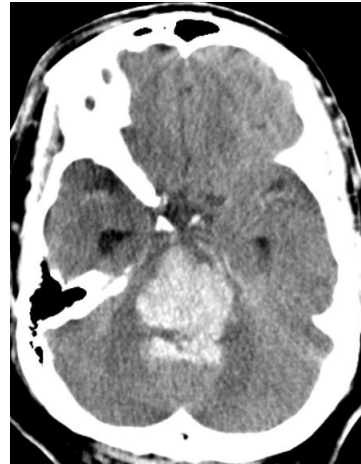
Traumatic/ contusion
Coagulopathy
 Aneurysm
 AV Malformation

Objectives

- Review the stroke subtypes- imaging features and causes
- Recommendations for antithrombotic therapy in acute ischemic stroke.
- Early risk of anticoagulant therapy with recent Intracerebral Hemorrhage
- Long-term risk of anticoagulant therapy with prior intracranial bleeding

Hypertensive-type Intracerebral Hemorrhage

Basal ganglia (60%) Thalamus (20%) Pons, cerebellar (10%)



Review, NEJM 2001

Cerebral Amyloid Angiopathy

Amyloid-beta deposition in leptomeningeal and cortical arteries, arterioles > veins and capillaries

Sporadic but associated with ApoE ϵ 4 and ϵ 2 alleles

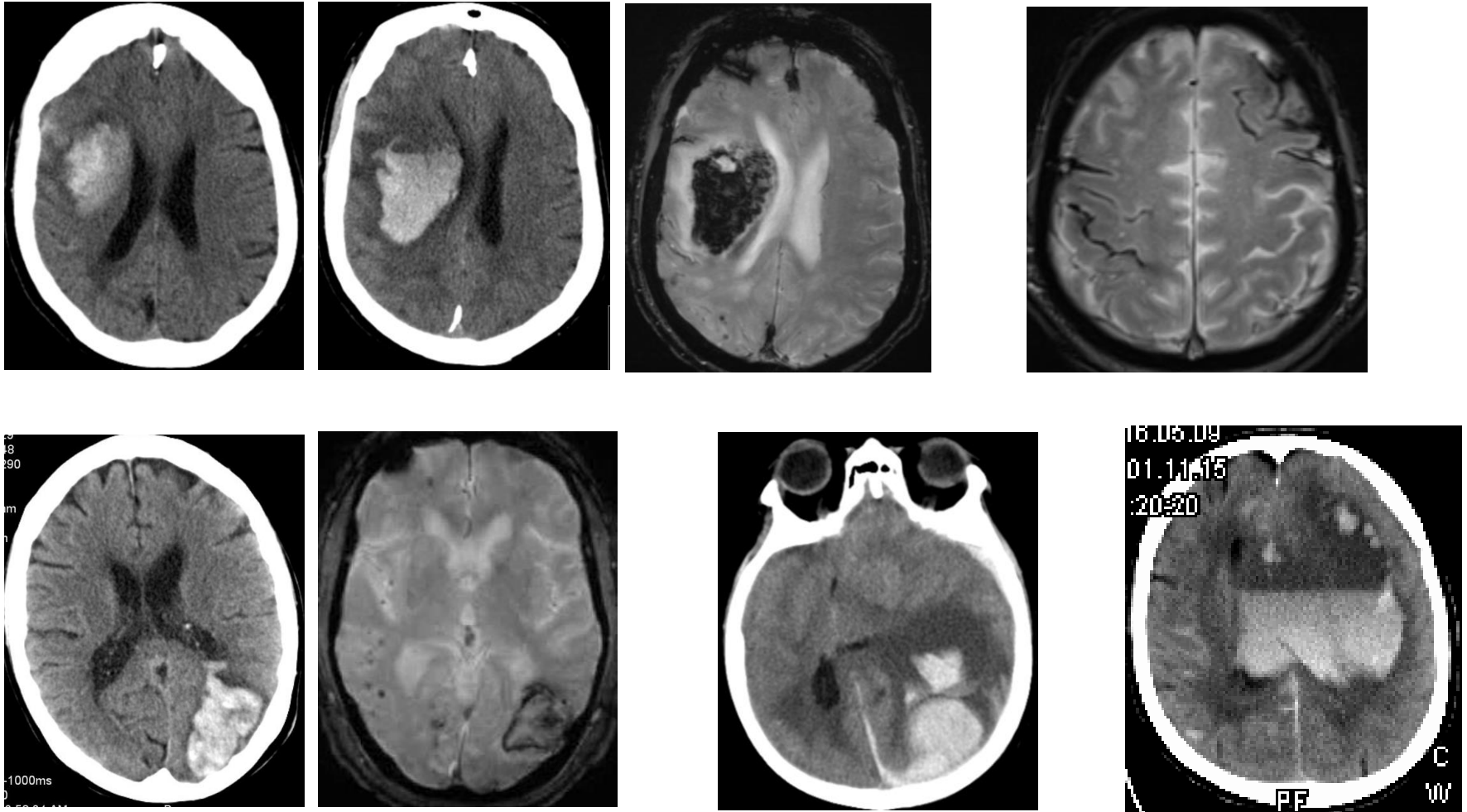
50% in those > 80 yrs old, 80% of patients with Alzheimer's disease

20-30% of brain hemorrhages in the elderly, especially if BP normal

- **Definite CAA** – autopsy evidence of hemorrhages with severe angiopathy
- **Probable CAA with supporting evidence** – clinical hemorrhage with pathological tissue (evacuated hematoma or cortical biopsy)
- **Probable CAA**- Age > 55 yr with appropriate clinical history, multifocal lobar, cortical and subcortical hemorrhages without an alternative cause or single lobar hemorrhage with superficial siderosis
- **Possible CAA**- Age > 55 yr with appropriate clinical history and single hemorrhage or superficial siderosis without an alternative cause

Modified Boston Criteria 2010, 1995

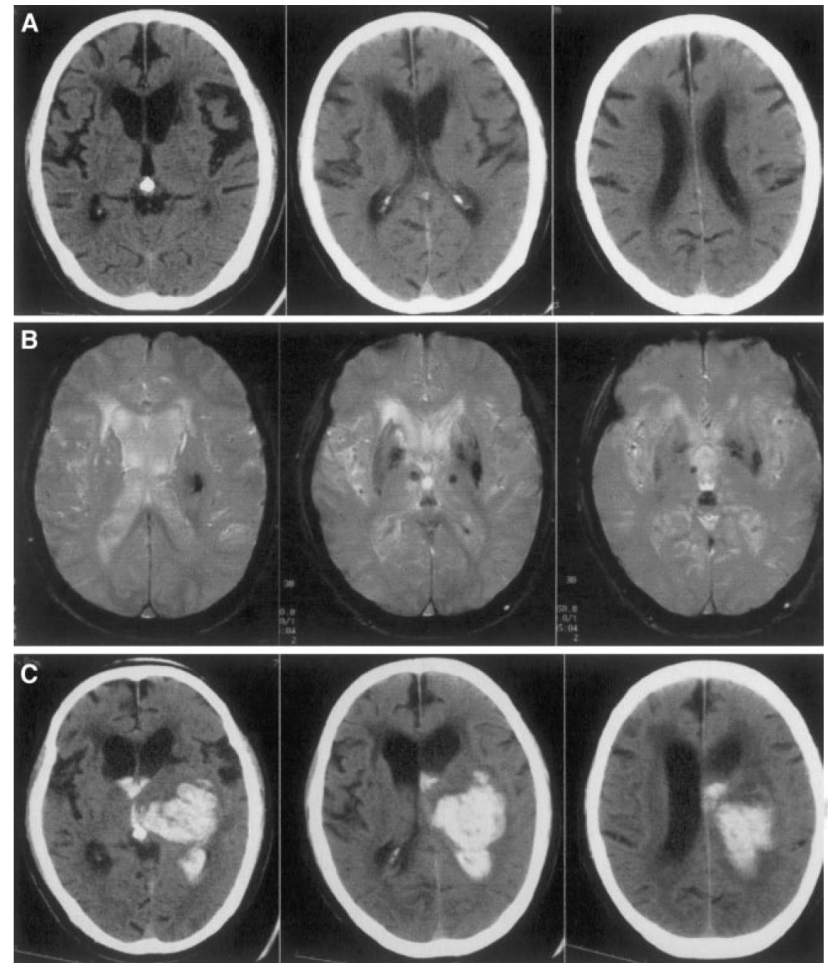
Cerebral Amyloid Angiopathy



Incidental MRI Microbleeds and Risk of Stroke

Meta-analysis of 5068 pts in 15 studies

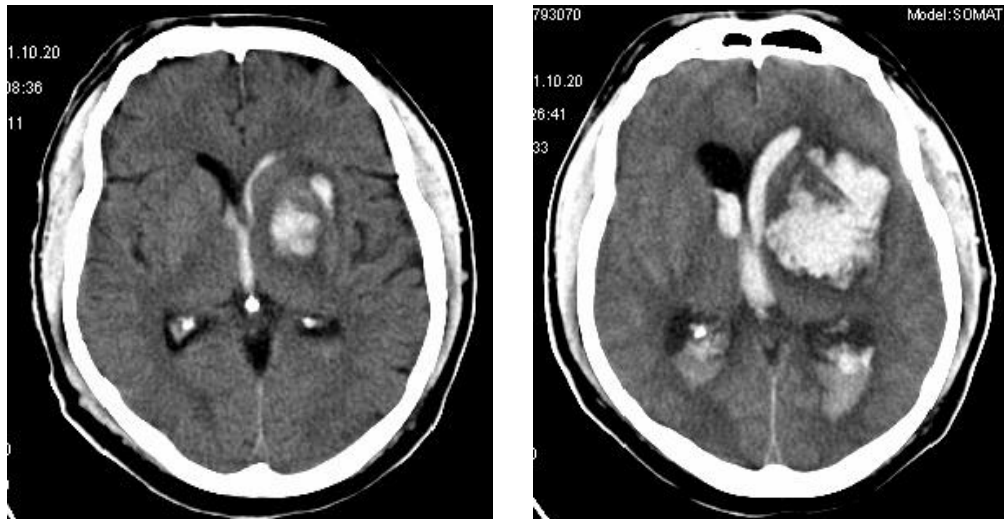
- Incidental MB 10-35%
- Associated with microangiopathic “small vessel” white matter disease
- Increased risk of stroke over ~2 yrs, Hemorrhagic > Ischemic
- Risk patterns:
 - ≥ 5 microbleeds
 - MB in lobar location
 - MB in cortical and subcortical locations



Stroke 2003; 34:1, Amer Heart J 2016; 178:145, Neurology 2016; 87:1501

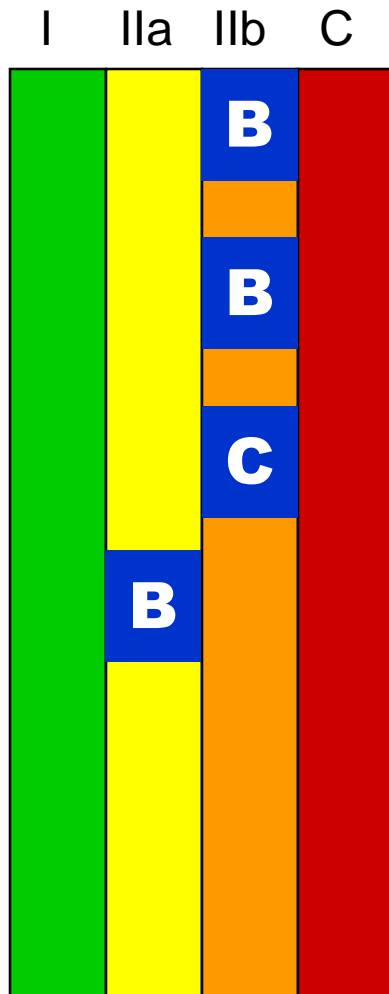
Early Expansion of Intracerebral Hemorrhage

- Prospective study of 103 patients with ICH noted significant hematoma expansion in
 - 26% within 1 hour, 38% within 24 hours
 - 70% within 24 hours with warfarin-associated ICH, associated with intensity of INR



Brott et al, Stroke 1997; 28:1

2015 AHA/ASA Intracerebral Hemorrhage Guidelines



- Anticoagulation after non-lobar ICH and antiplatelet therapy after any ICH might be considered when there are strong indications for their use.
 - Optimal timing is uncertain, delaying AC for 4 weeks in patients without PHV may reduce the risk of ICH.
- The usefulness of new oral anticoagulants to decrease bleeding risk is uncertain.
- When stratifying risk for recurrent ICH, consider
 - Lobar location of the ICH
 - Older age
 - Presence and number of MRI microbleeds
 - Ongoing need for anticoagulation
 - Presence of apolipoprotein E ϵ 2 or ϵ 4 alleles

Symptomatic Hemorrhagic Transformation of Acute Ischemic Stroke

- Risk factors: tPA therapy, warfarin use prior to stroke, infarct volume, age, hyperglycemia, renal impairment, embolism with delayed reperfusion
- Anticoagulant use was associated with more significant hemorrhage

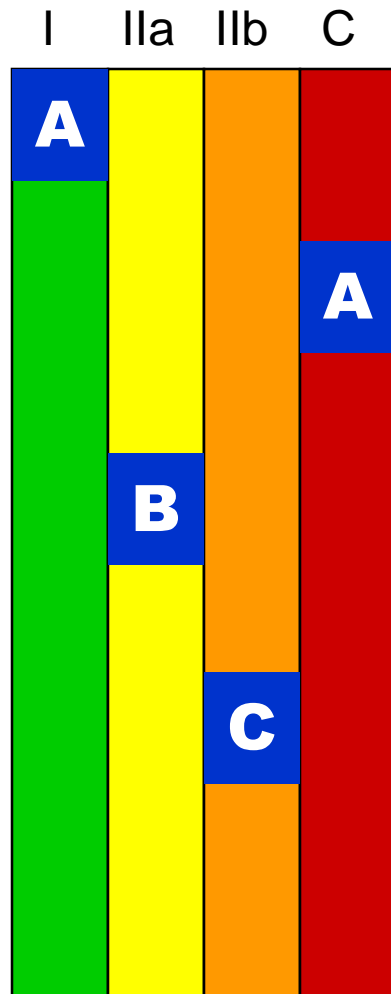


Initiation of Anticoagulation after Ischemic Stroke: Risk of Hemorrhagic Transformation

- 389 patients with ischemic stroke due to AF at 12 hospitals in Korea
- 67% patients were anticoagulated within the 1st week post-stroke
 - Exclusions: significant hemorrhagic transformation on initial imaging, post-thrombolysis, large infarcts > 50% MCA territory or posterior circulation infarcts
- 4.6% risk of symptomatic hemorrhagic transformation with early therapy
 - Large infarct (OR 6.38, 95% CI 1.16–35.14)
 - Previous hemorrhagic stroke (OR 10.67, 1.77–64.25)
 - Low platelet count (OR per 10^4 increase 0.87, 0.79–0.97)

Lee et al, Eur Neurol 2010; 64:193

2018 AHA/ASA Acute Ischemic Stroke Guidelines

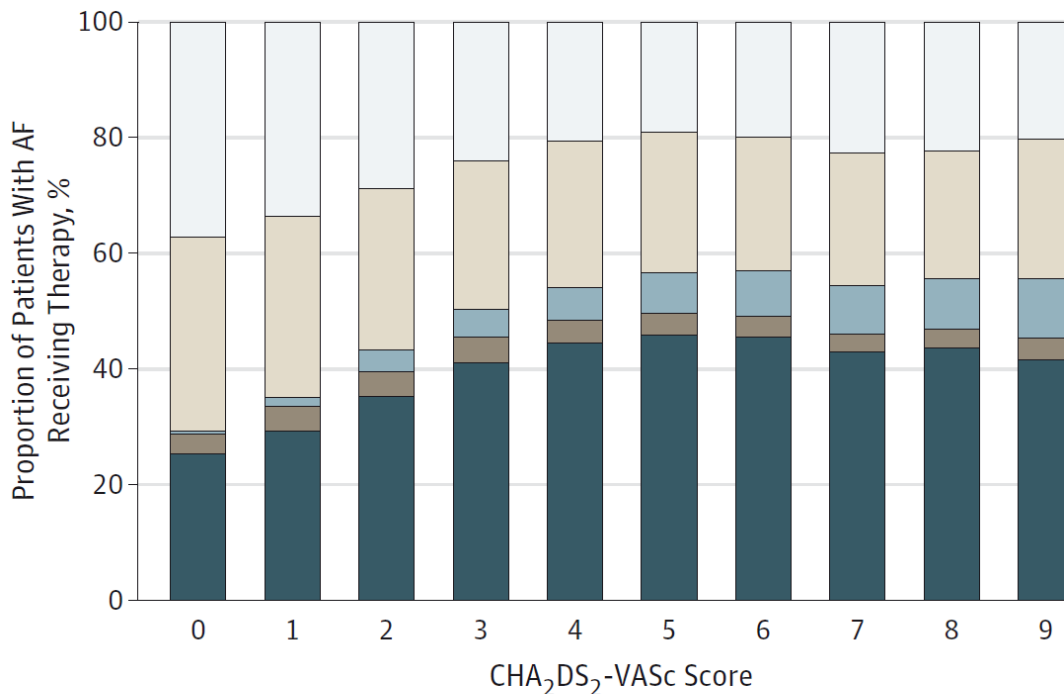


- Aspirin is recommended in patients with acute ischemic stroke within 24-48 hours of stroke onset.
- Urgent anticoagulation, with the purpose of preventing early recurrent stroke, is not recommended for patients with acute ischemic stroke.
- For most patients with acute ischemic stroke in the setting of atrial fibrillation, it is reasonable to initiate oral anticoagulants within 4-14 days of stroke onset.
- For patients with ischemic stroke, atrial fibrillation and coronary artery disease, the usefulness of adding antiplatelet therapy to oral anticoagulants is uncertain. Unstable angina and coronary artery stenting represent special circumstances where such management may be warranted.

Anticoagulation Therapy for AF across Stroke Risk

No antithrombotic therapy
 Aspirin only
 Aspirin plus a thienopyridine
 Non-vitamin K antagonist oral anticoagulant
 Warfarin sodium

B Prevalence of treatment strategies across the spectrum of CHA₂DS₂-VASc score



429,417 outpatients with AF from 2008-2012 cared for by cardiovascular specialists

45% treated with an oral anticoagulant, rates did not increase with stroke risk

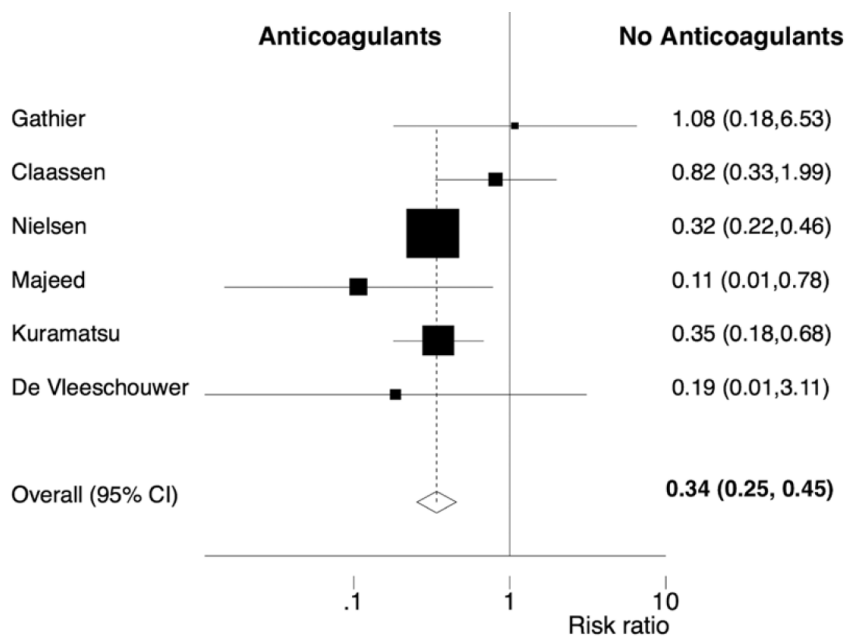
No. 12348 36976 61557 87008 97878 70212 37314 17814 6385 1161

Pinnacle Registry, JAMA Cardiol 2016; 1:55

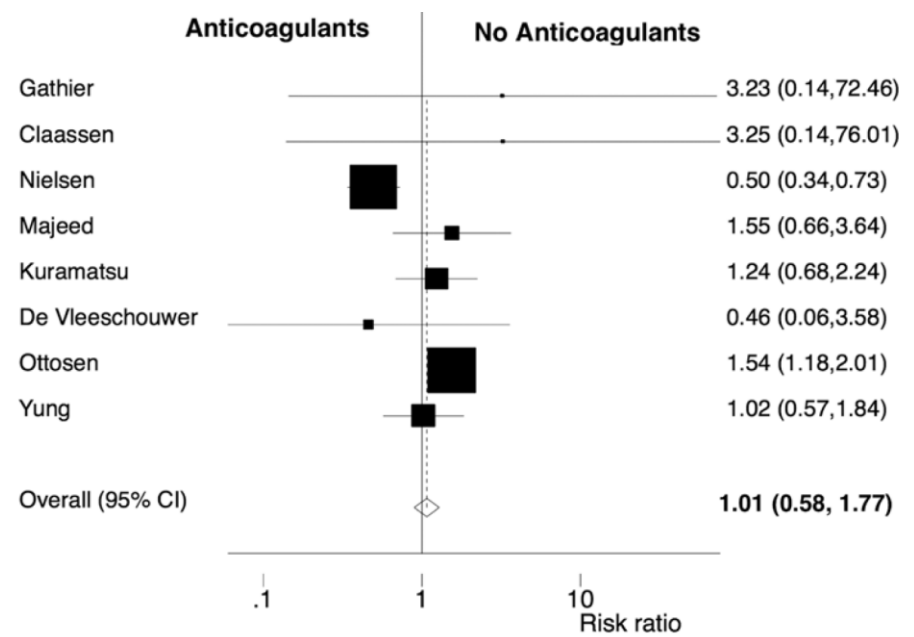
Restarting Anticoagulants after Intracranial Hemorrhage

Meta-analysis of 5306 pts, 8 studies, 36-38% treated onset median 10-39 days

Thromboembolic events
6.7% vs 17.6% (RR 0.34)



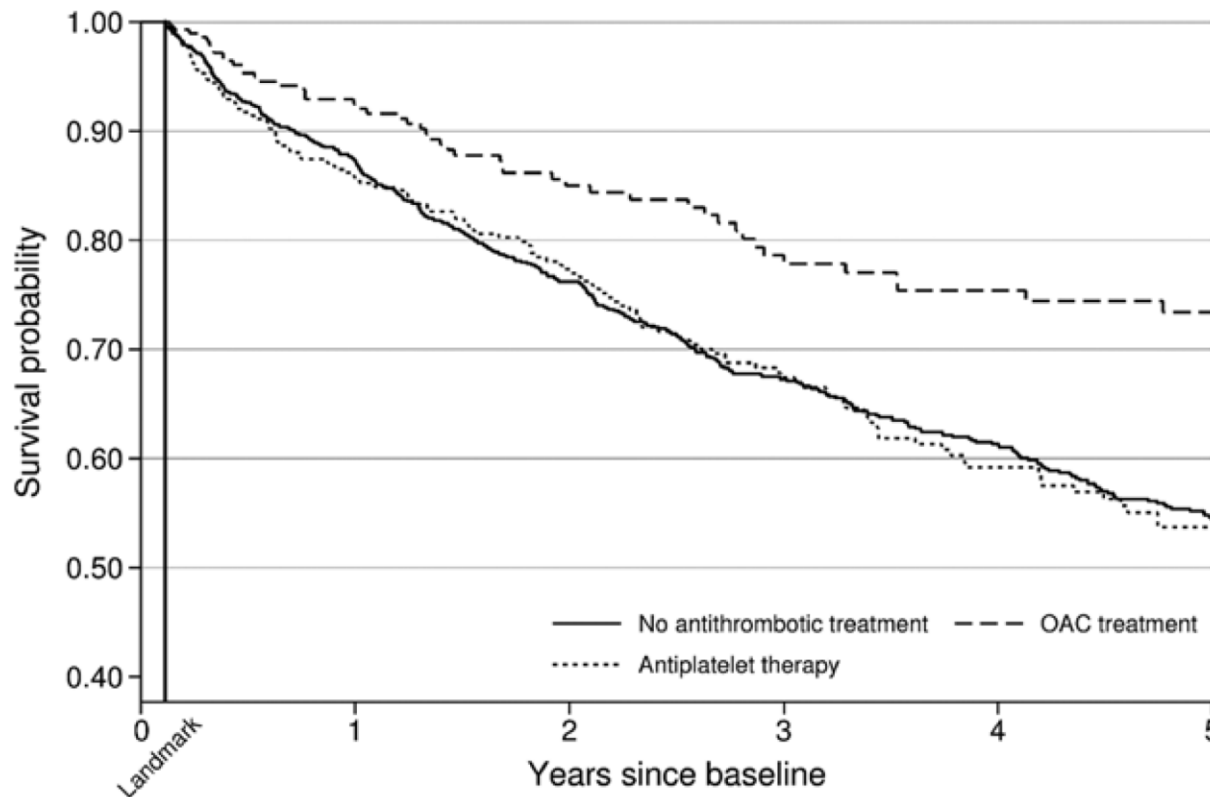
Recurrent intracranial hemorrhage
8.7% vs 7.8% (no difference)



Murthy et al, Stroke 2017; 48

Restarting Anticoagulants after Intracranial Hemorrhage

Nationwide registry of 6138 Danish residents with NVAF hospitalized with intracranial hemorrhage between 1997-2013 and treatment status at 6 wks



AC vs antiplatelet vs none

Stroke/ SE at 1yr

5.3% vs 10.3% vs 10.4%
(HR 0.59 for AC)

Recurrent ICH at 1yr

8% vs 5.3% vs 8.6%

Mortality at 1yr

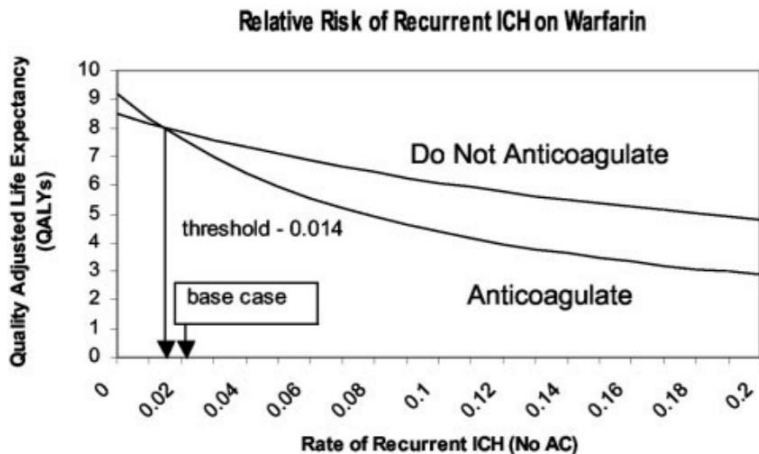
9.7% vs 19.5% vs 19.1%
(HR 0.55 for AC)

Nielsen et al, Circulation 2015; 132:517

Restarting Anticoagulants after Intracranial Hemorrhage

- Meta-analyses and registry data support restarting oral anticoagulation in patients with AF after brain hemorrhage
- Limitations:
 - Not randomized, not blinded to treatment
 - Nearly all with warfarin, few data using the newer oral anticoagulants
 - Heterogeneity of intracranial hemorrhage with variable recurrence of subtypes- lobar ICH (~15%), deep ICH (1-2%), SAH (rare after aneurysm treatment), vs subdural hematoma (~12%)
- How did providers select patients for restarting treatment?

Markov Decision Modeling- for warfarin use

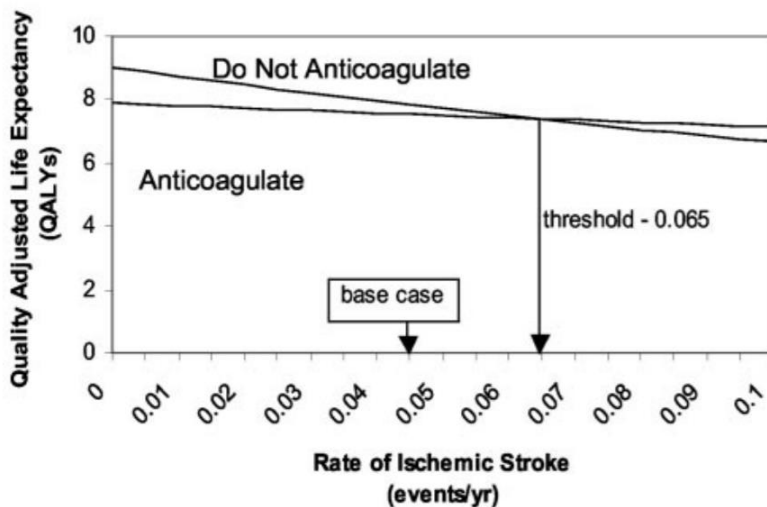


- **Deep (“hypertensive”) ICH**

Avoidance of warfarin results in + 0.3 QALYs

Warfarin could be preferred strategy if

- Risk of recurrent ICH is < 1.4%
- Risk of ischemic stroke is > 6.5%



- **Lobar (“amyloid angiopathy”) ICH**

Avoidance of warfarin results in + 1.9 QALYs

Warfarin is never the preferred strategy.

Eckman et al, Stroke 2003; 34:1710

Comparison of Efficacy and Safety of New Oral Anticoagulants vs Warfarin in AF

Meta-analysis of phase 3 trials of dabigatran, rivoroxaban, apixiban, edoxaban
42,411 receiving a new oral anticoagulant and 29,272 receiving warfarin

Primary Outcomes		
Stroke or Systemic Embolism	19% reduction	RR 0.81, 95% CI 0.73-0.91; p<.0001
Major Bleeding	NS	RR 0.86, 95% CI 0.73-1.00; p=.06
Secondary Outcomes		
Hemorrhagic Stroke	51% reduction	RR 0.49, 95% CI 0.38-0.64; p<.0001
Ischemic Stroke	NS	RR 0.92, 95% CI 0.83-1.02; p<.0003
All-cause Mortality	10% reduction	RR 0.90, 95% CI 0.85-0.95; p<.0003
Intracranial Bleeding	52% reduction	RR 0.48, 95% CI 0.39-0.59; p<.0001
Gastrointestinal Bleeding	25% increase	RR 1.25, 95% CI 1.01-1.55; p<.04
Major Bleeding when TTR < 66%	24% reduction	RR 0.69 vs RR 0.93; p=.022

Lancet 2014; 383:955-962.

Need for a Randomized Clinical Trial

Several trials are ongoing or in review

- **CMB-NOW-** MB with anticoagulation therapy for AF, Japan
- **Apache AF** – Apixiban vs Antiplatelets vs No therapy, Netherlands, 2018
- **NASPAF-ICH-** NOAC for AF with prior ICH, Canada, 2020
- **Prestige AF-** modeling personalized risk prevention tool, Europe, 2022

- **STATICH-** evaluating treatment for AF after ICH, Norway, 2021
- **SoStart-** Start or Stop Anticoagulants, Edinburgh, 2023

- **LAA Occlusion trials**