Atrial Fibrillation Update…

"Hot" / Controversial Journal Articles

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Overview

- Modifiable Risk Factors for AFib
- Ethnicity as an AFib Thromboembolic Risk Factor
- Is Anti-platelet Therapy Effective in AFib…
- Anticoagulation in Patients with AFib / CKD
- Anticoagulation Post ICH w/ AFib
- Management of Patients on Amiodarone

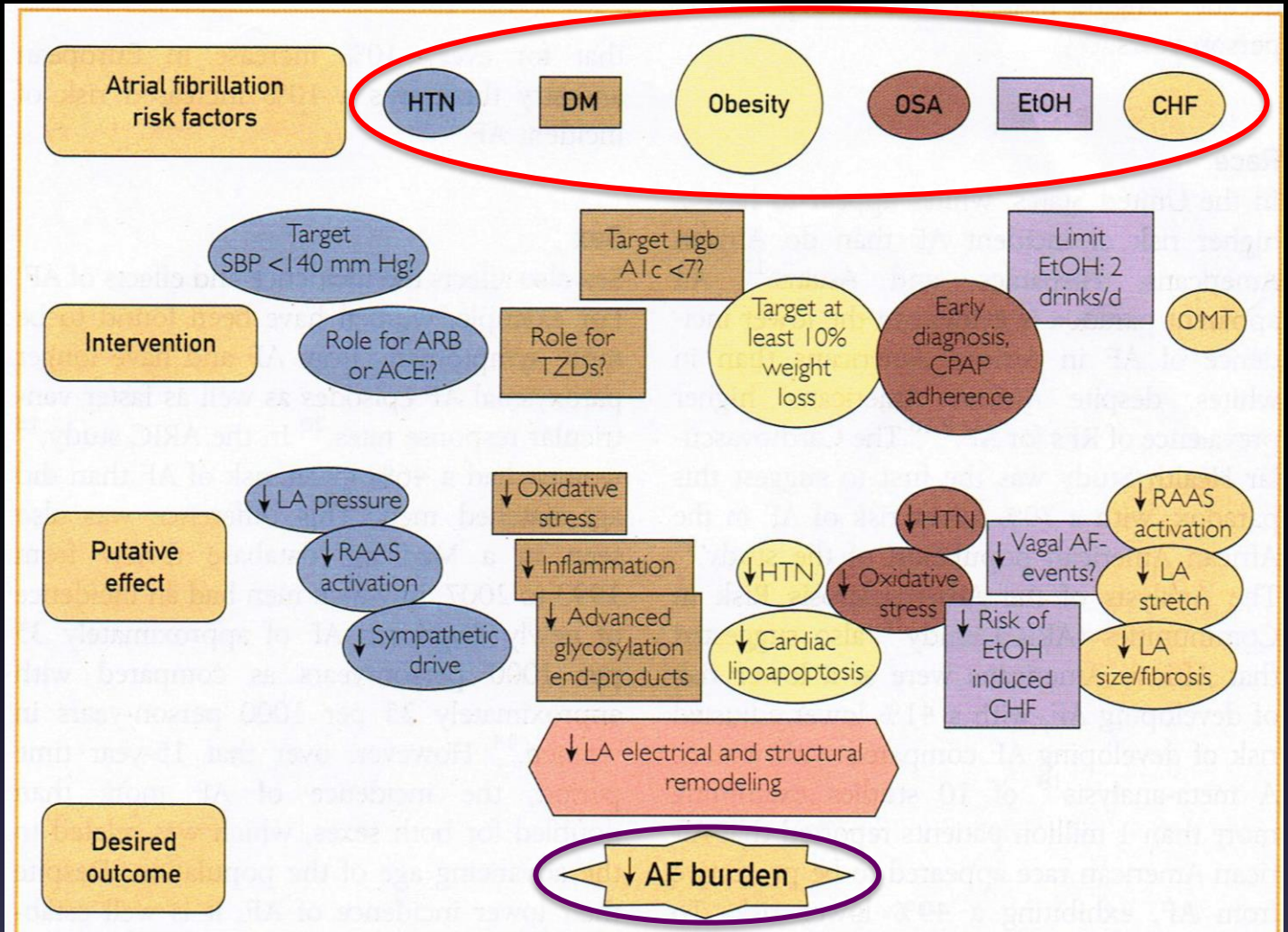


FIGURE 1. Atrial fibrillation risk factor modification and its putative effects. ACEi = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CHF = congestive heart failure; CPAP = continuous positive airway pressure; DM = diabetes mellitus; EtOH = ethyl alcohol consumption; Hgb A1c = hemoglobin A_{1c}; HTN = hypertension; LA = left atrial; OMT = optimal medical therapy; OSA = obstructive sleep apnea; SBP = systolic blood pressure; TZD = thiazolidinedione; RAAS = renin-angiotensin-aldosterone system.

Morin et al. (Mayo Clin Proc.) 2016;91(12):1778-1810

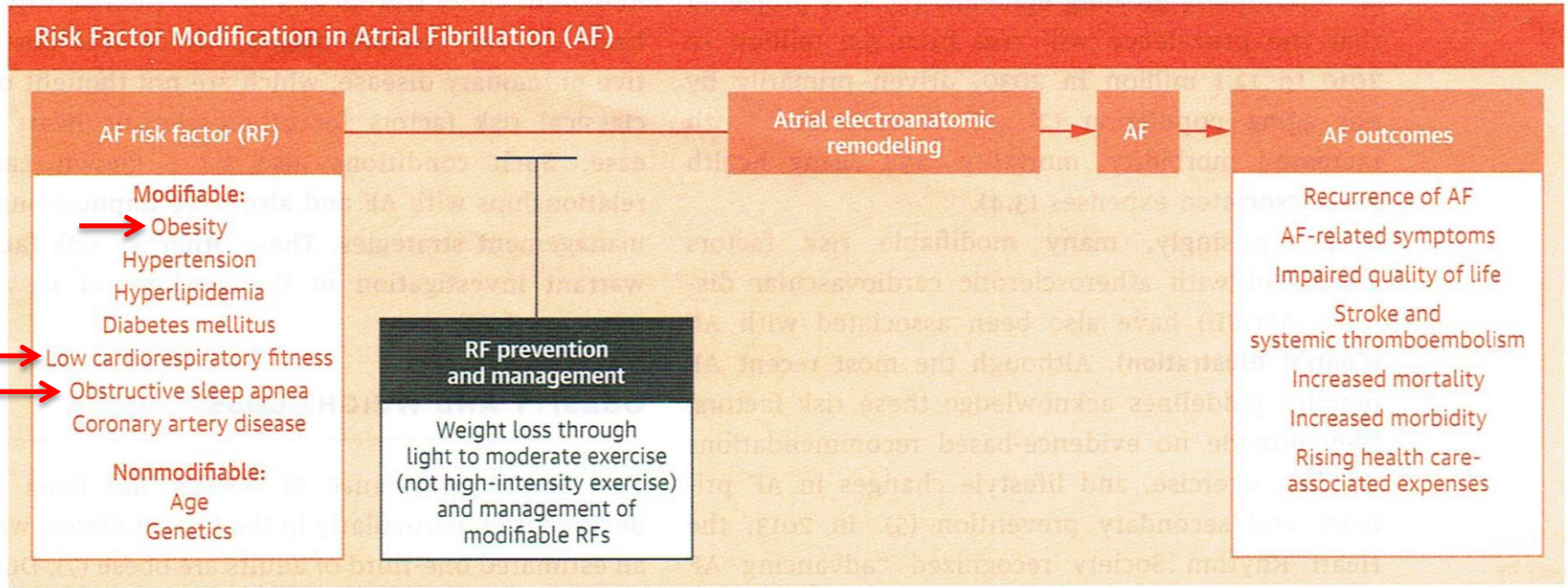
Obesity, Exercise, OSA, and Modifiable ASCVD Risk Factors in AFib

- AFib: Most Common Sustained Arrhythmia
- Prevalence: 5.2 M 2010 … 12.1 M 2030
- Incr Morbidity / Mortality / Health Care Costs
- HRS recognized "advancing AF prevention efforts by focusing on RF modification" (2013)

Miller et al. (JACC) 2015;66:2899-906

Association Between MRFs & AFib

CENTRAL ILLUSTRATION **RFM in AF: The Associations Between Cardiometabolic RFs and AF**



Miller, J.D. et al. J Am Coll Cardiol. 2015; 66(25):2899-906.

Cardiometabolic risk factors contribute to the development and consequences of atrial fibrillation (AF) and can be modified by weight loss, exercise, and management of comorbid cardiac risk factors. RF = risk factor; RFM = risk factor modification.

Obesity / Exercise in AFib Risk

- ARIC (n=14,598): 17% AFib Risk Attributed to Obesity / Overweight Status
- Higher Levels of Exercise Shown to Attenuate Risk in Post Menopausal Females (WHI)
- LAE / Fibrosis / Inflammation / Lipids / NH
- 3 Studies (n=654) Showed Decr Afib Burden (Frequency / Duration) w/ Weight Reduction

Exercise / AFib Risk

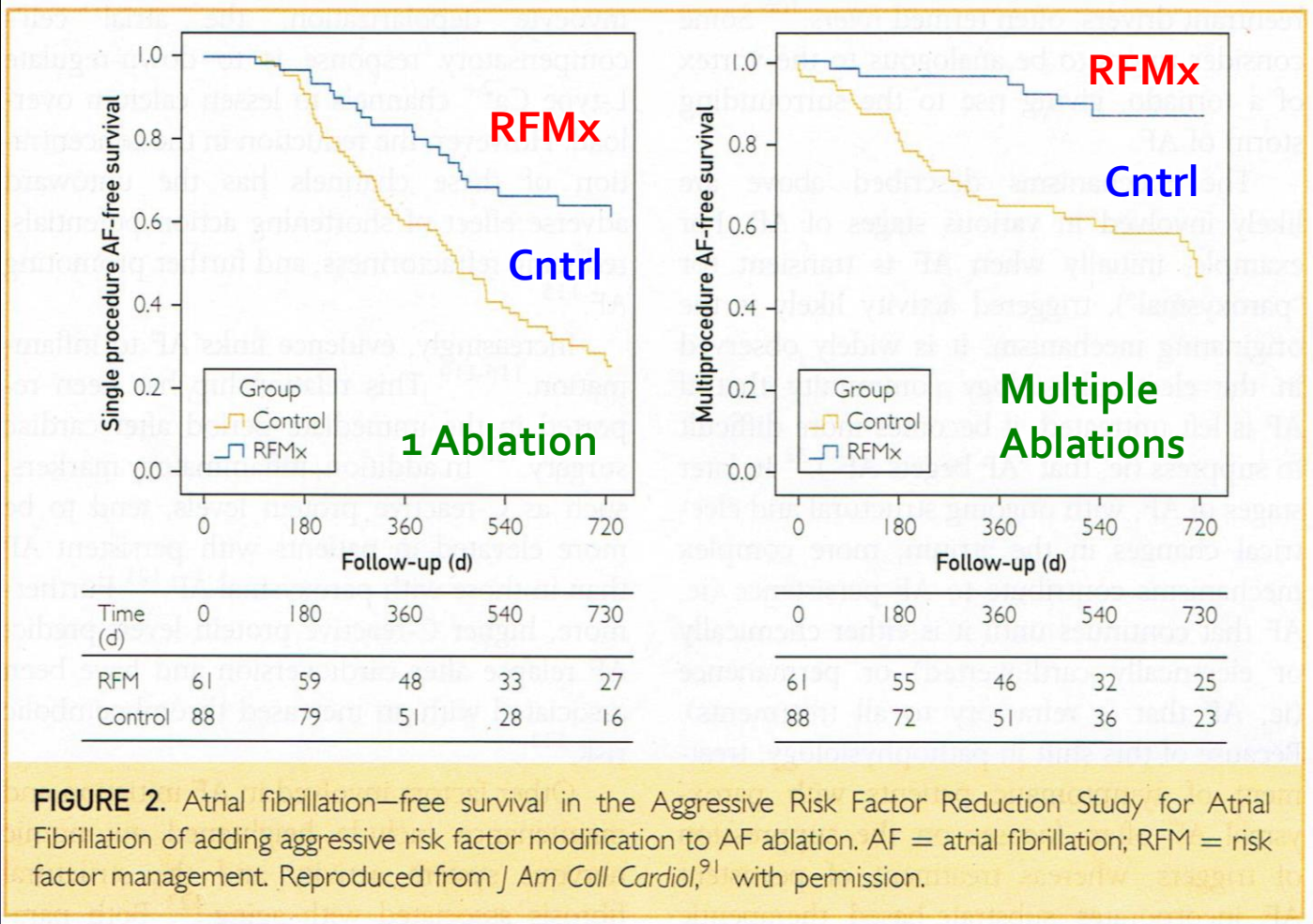
- Incr Risk of AFib in Young Endurance Athletes
- Several Studies Show Decr AFib w/ Light to Moderate Exercise vs None
- Cohort of 64,561 showed for every 1 MET on EST … 7% Decr of Developing AFib (5 yr f/u)
- CARDIO-FIT (n=308 BMI ≥27)…those w/ High CV Fitness / Incr ≥ 2 METs had Less AFib

OSA / AFib Risk

- Prospective Study(Gami 2004): 49% AFib pts (n= 151) had OSA vs 32% of "Controls" (n=312)
- Hypoxia / Hypercapnia / Sympathetic Tone / Inflammation…? Lead to Remodeling
- Prospective Study: Arrhythmia Free @ 1 yr 71.9% Compliant w/ PPTx vs 36.7% NOT Compliant
  - PVI Ablation Appears to Ameliorate this Difference

ARFRS s/p Ablation

(Single Center / Observational: Weight Loss / Exercise / PPT)



Time (d)	0	180	360	540	730
RFM	61	59	48	33	27
Control	88	79	51	28	16

0	180	360	540	730
61	55	46	32	25
88	72	51	36	23

FIGURE 2. Atrial fibrillation—free survival in the Aggressive Risk Factor Reduction Study for Atrial Fibrillation of adding aggressive risk factor modification to AF ablation. AF = atrial fibrillation; RFM = risk factor management. Reproduced from *J Am Coll Cardiol*,[91] with permission.

Pathak et al (JACC) 2014;64(21):2222-2231

Refining Stroke Prediction in Afib Pts by Addition of African-American Ethnicity to CHA2DS2VASc Score

- Afro-Americans > Stroke Risk vs Whites
- *Retrospective* Study of Medicare Claims

  2010-2012 Newly Dx Atrial Fibrillation

  – n=460,417 / 85% non-Hispanic White /

    7% non-Hispanic African American / 8% other

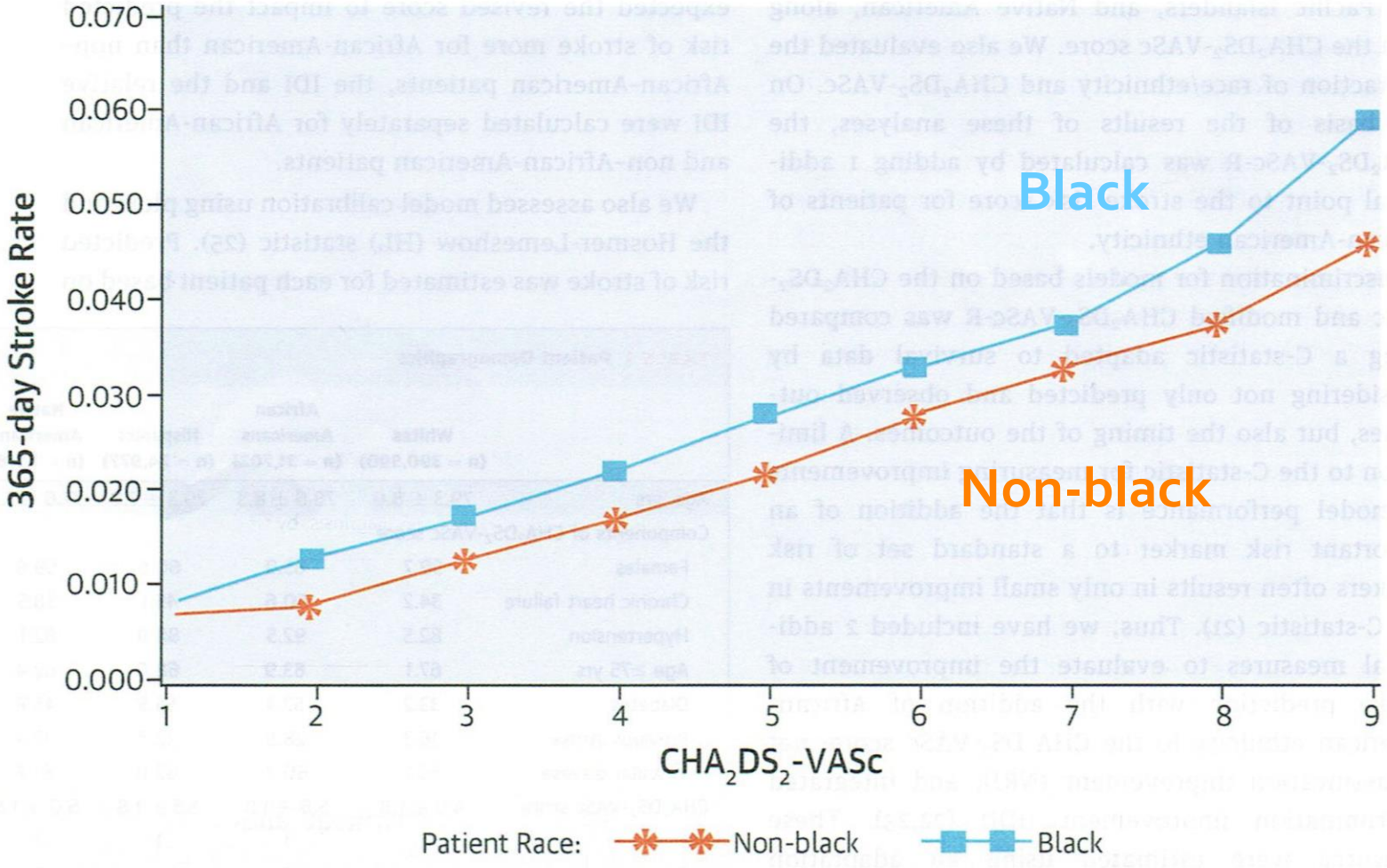
  – Mean age 79 ± 8 / 60% Female / 16,703 Strokes

Kabra et al. (JACC) 2016;68:461-70

Ethnicity / Stroke Prediction Model

- CHAS2DS2-VASc vs CHAS2DS2-VASc-R
- African-American Ethnicity ADD 1 point
- Adding -R Improved Prediction Significantly ($p < 0.001$) in Pts > 65 yrs of Age
- Only Hx of CVA / Age ≥ 75 / Female Sex were Stronger Predictors of Stroke than Ethnicity

CENTRAL ILLUSTRATION CHA_2DS_2-VASc Score for Stroke Prediction in AF: Stroke Rates for All Patients



Kabra, R. et al. J Am Coll Cardiol. 2016;68(5):461-70.

Stroke rate at 365 days after atrial fibrillation (AF) diagnosis, by race/ethnicity and CHA_2DS_2-VASc score for all patients. CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke, vascular disease, age 65 to 74, and female sex.

Background Comments on Aspirin for TE Prophylaxis in AFib

- ASA Recommendation for TE Prophylaxis Based on 7 Trials (1989-2006)
- Only 1 of these (SPAF) w/ "Modest" Effect of ASA
- Meta Analysis: 22% Relative Risk Reduction with ASA vs Placebo
  - Mainly TIAs and "Minor" Strokes
  - Disabling Strokes Only Reduced by 13%

Background on ASA for TE Prophylaxis in Afib(2)

- Data from 12 Placebo-controlled Trials showed Effect of AGE on ASA Effectiveness
  - Relative Efficacy Decreases with AGE
  - By age 75 Effect is Insignificantly Negative
- 2012 European Guidelines NO Longer Recommend Monotherapy with ASA
  - Also Removed from Asian / Canadian Guidelines

Atrial Fibrillation patients do not benefit from acetylsalicylic acid

- Retrospective Analysis of Pts w/ Dx AFib (7/1/05-1/1/09) Ntl Sweedish Patient Registry
- n=115,185 (58,671 ASA / 56,514 NO Tx)
- Mean AGE: 80.34 ±10.07 ASA / 75.12 ±13.78 NO
- Mean Follow Up: 1.5 yrs

Sjalander et al. (Europace) 2014;16:631-638

ASA vs NO TX

ALL P ≤ 0.024 / MOST < 0.001

- Older (80 vs 75)
- F > M (52% vs 48%)
- Prior TIA / Stroke
- Vascular Disease
- Hypertension
- Diabetes
- Renal Failure
- Heart Failure
- CHA2DS2-VASc Sc (4 vs 3.3)
- HAS-BLED Score (2.92 vs 1.92)

ASA vs NO Tx: *Results*

- Pts Treated with ASA Showed NO Reduction in Ischemic Stroke / TE when Related to CHA2DS2-VASc Score
- Trend Toward Higher Incidence of Ischemic Stroke / TE Treated with ASA
- Rates of ICH / Major Bleeding were Similar when Related to CHA2DS2-Vasc Score

Annualized Incidence of Outcome Events

(Propensity Score Matched)

Table 4 Annualized incidence (95% CI) of outcome events in relation to treatement strategy, according to propensity score matching

	ASA	No antithrombotic treatment	P
Ischaemic stroke	7.37% (7.11–7.63)	6.61% (6.37–6.86)	<0.001
Thrombo-embolic event	10.60% (10.29–10.92)	9.53% (9.24–9.83)	<0.001
Intracranial haemorrhage	0.95% (0.87–1.05)	1.00% (0.91–1.10)	0.46
Major bleeding	3.85% (3.67–4.03)	4.06% (3.87–4.25)	0.12

AFib and TE in Patients with CKD

State of the Art Review

- Pts with AFib have > Incidence of CKD and CKD Predisposes to AFib
- Incidence of AFib as High as 12.1/1000 with ESRD vs 5.0/1000 in Controls
- The Presence of Both (AFib / CKD) Increase Risk of Hemorrhagic Events as Well

Lau et al. (JACC) 2016;68;1452-64

TE Pathophysiologic Interaction Between AFib and CKD

- AFib is Prothrombotic (Virchow's Triad)
  - Worsening GFR Causes Reduced LAA Flow
  - CKD Related Endothelial Damage / Dysfunction
  - Increased Plt / Coag Abnormalities in CKD
- CKD Associated with Activation of RAS / Inflammation / Vascular Calcification

Hemorrhagic Tendency in CKD

- CIRCS: Incr Incidence of Hemorrhagic CVA (4x in M / 7 x in F) w/ GFR <60 ml/min/1.73m^2
- Japanese Study(1993): Dialysis Pts (n=1,609) RR = 10.7 of ICH vs Controls…
- Incr GI Bleeding with CKD / Dialysis
- Plt Dysfunction / Impaired Adhesion / Impaired Plt GP IIb / IIIa Receptor Function / Altered VW Factor Function / Nitric Oxide Metabolism

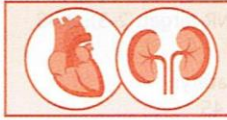
AFib / CKD / TE Risk: Issues

- Some Studies Show Incr Ischemic CVA with VKA and patients on Hemodialysis…
- Non-dialysis Patients Do Better with VKA…
- In Pts with CKD (NOT ESRD) there was a Lower Risk of Bleeding and CVA w/ NOACs vs VKA in a Meta-analysis
- Small Group / Pharmacokinetic Model "suggest" that Apixaban 5mg BID is Effective / Safe w/ ESRD

AFib / CKD / TE Risk: *Author Comments*

- CHA2DS2-Vasc Helpful in CKD … Adding Renal Dysfunction (-R2) does NOT Appear to Help
- "A high HAS-BLED should not lead to withdrawing OAC, but a high HAS-BLED score among those with CKD should flag the patients potentially at risk for bleeding for more careful review or f/u and the correction of modifiable risk factors…"

CENTRAL ILLUSTRATION **Proposed Algorithm for Oral Anticoagulant Choices in Patients With Atrial Fibrillation and Chronic Kidney Disease**



Patient with atrial fibrillation and chronic kidney disease

Determine stroke risk (CHA_2DS_2-VASc Score)
Consider oral anticoagulation if score is ≥ 1 in males / ≥ 2 in females

Determine bleeding risk (HAS-BLED Score)

Estimate creatinine clearance (CrCl) to determine appropriate oral anticoagulant (OAC)

OAC options:	CrCl < 15 ml/min or ESRD on RRT	CrCl 15–29 ml/min	CrCl 30–49 ml/min	CrCl ≥ 50 ml/min
Vitamin K antagonist	When time in therapeutic range >70%	When time in therapeutic range >70%	When time in therapeutic range >70%	When time in therapeutic range >70%
Apixaban	5 mg, b.i.d.*	2.5 mg, b.i.d.	5 mg, b.i.d.†	5 mg, b.i.d.†
Dabigatran	✖	75 mg, b.i.d.‡	150 or 110 mg, b.i.d.§	150 mg, b.i.d.‖
Edoxaban	✖	30 mg, o.d.	30 mg, o.d.	60 mg, o.d.¶
Rivaroxaban	✖	15 mg, o.d.	15 mg, o.d.	20 mg, o.d.

Address bleeding risk factors, frequent follow up, and closely monitor renal function in NOAC users

Lau, Y.C. et al. J Am Coll Cardiol. 2016;68(13):1452-64.

Afib: CVA / Anticoagulation / ICH
General Comments

- AFib Most Common Sustained Arrhythmia
  - 1-2% General Population
- AFib: 5 Fold Incr Stroke Risk / 20% of Strokes
- OAT w/ Warfarin Considered "Standard of Care"*
- Pts on Warfarin Account for 25% of ICH
  - Warfarin Worsens Severity of ICH / Incr Mortality
- Trials w/ NOACS have Shown Lower Rates of ICH

Anticoagulation Therapy in Afib after ICH

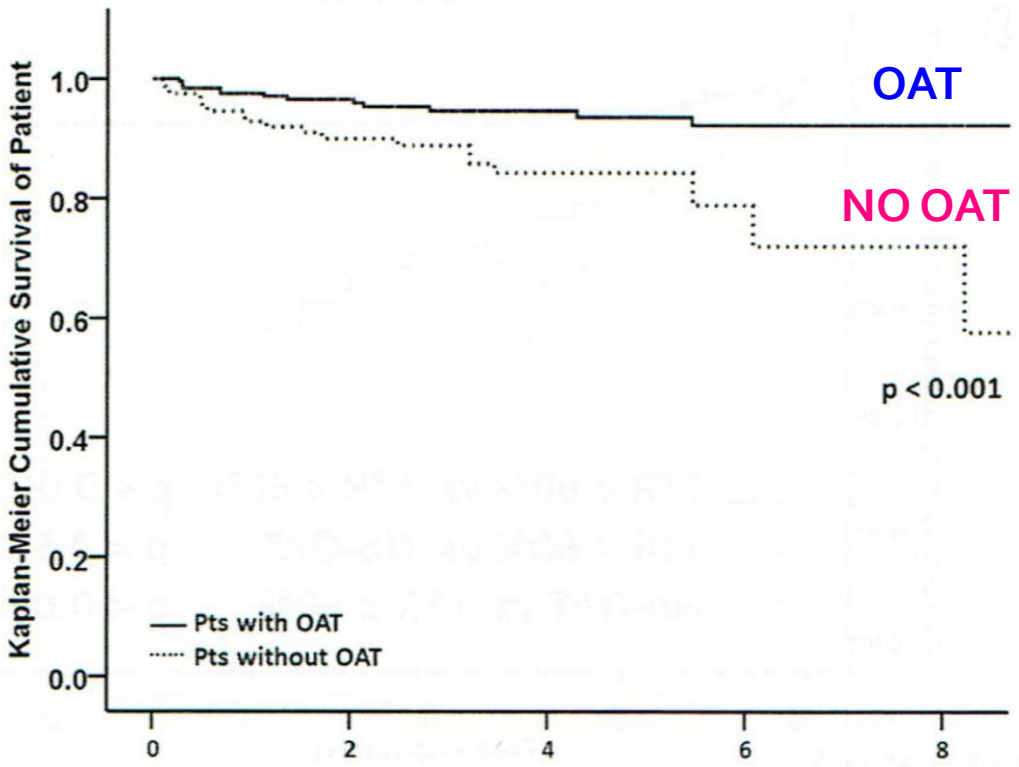
- Retrospective Analysis
- 428 pts with AFib and History of ICH
  - OAT n= 254 (21.7 % Trauma Related)
  - no-OAT n=174 (42% Trauma Related)
- CHA2DS2-VASc / HAS-BLED Scores Evaluated
- Composite Endpoint: Thromboembolism / Major Bleeding / All-cause Mortality

Park et al. (Heart Rhythm) 2016;13:1794-1802

Anticoag Tx / AFib s/p ICH (2)

- Mean Follow Up 39.5 + 31.9 mos
- CHA2DS2VASc / HAS-BLED Scores Similar
- TE: 2.4 OAT / 8.3 no-OAT 100 pt yrs ($p<0.001$)
- Composite: 11.5 OAT / 7.9 no-OAT ($p=0.154$)
- Better Composite End Point if TTR $\geq$ 60%
- Early (< 2 weeks) OAT s/p ICH did NOT have Lower Composite End Point (Incr Major Bleeds)

Cumulative Survival



Number at risk					
OAT	254	140	86	52	25
No-OAT	174	75	38	14	4

Figure 5 Kaplan-Meier cumulative survival free of all-cause mortality. Patients without OAT had a lower cumulative survival than those with OAT ($P < .001$). OAT = oral anticoagulation therapy.

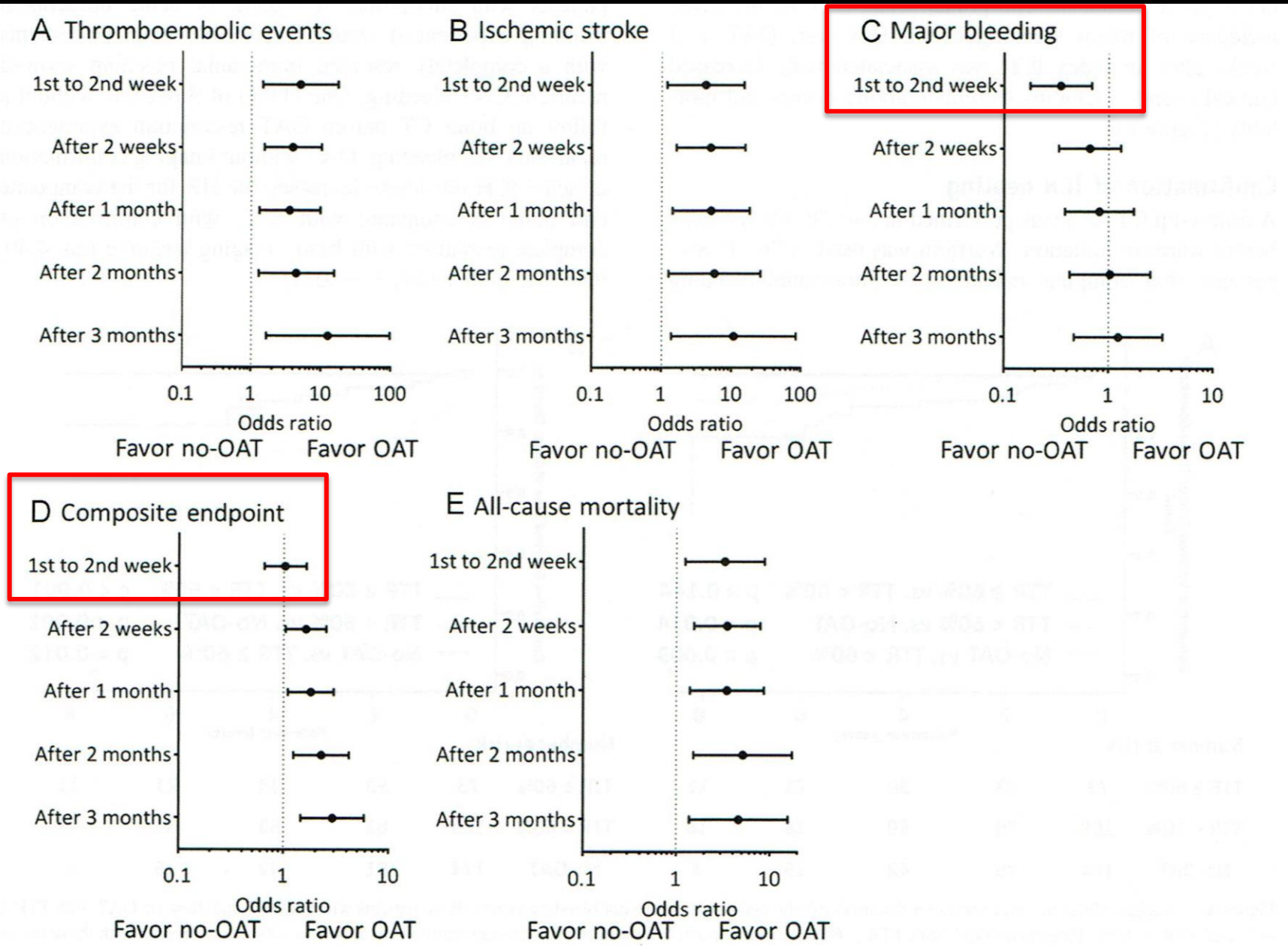


Figure 6 Hazard ratio according to the timing of warfarin initiation after an index intracranial hemorrhage event: (**A**) thromboembolic events; (**B**) ischemic stroke; (**C**) major bleeding events; (**D**) composite end point; and (**E**) all-cause mortality. OAT = oral anticoagulation therapy.

FDA Warning re: Amio 12/04

- "…can cause serious side effects that can lead to death including: lung damage, liver damage and worse heart beat problems…"
- Approved only for the treatment of ventricular arrhythmias, but most of its use occurs for unapproved conditions.
- More than 2,000,000 Rx / year for afib or other off-label conditions.
- "…should only be used in adults with life threatening heart beat problems…"

Practical Management Guide for Clinicians Who Tx Patients w/ Amio

- Amiodarone is MOST Commonly Used AAA
- Amiodarone is ***NOT*** FDA Approved for Afib !!
- NSR: 65% Amio vs 37% Sotalol / Propafenone
  - CTAF / n=403 / mean f/u 16 mos
- Side Effects: Up to 15% 1st yr / 50% Lifetime
- Rarely Fatal (Liver / Lung)

Epstein et al. AJM (2016) 129,468-475

Amiodarone Toxicity

- Pulmonary: 2% Cough / Dyspnea (Refer)
- Gastrointestinal
  - 30% Nausea / Anorexia / Constipation
  - 15-30% Incr AST or ALT … IF > 2 x Normal (STOP)
  - < 3% Hepatitis / Cirrhosis (STOP)
- Thyroid: 4-22% Hypo / 2-12% Hyper (STOP)*

Amiodarone Toxicity (2)

- Skin: < 10% Blue Skin / 25-75% Photosensitive
- CNS: 3-30% Ataxia / Neuropathy / Tremor
- Ocular: < 5% Halo / > 90% Corneal Deposits / ≤ 1% Optic Neuritis (STOP)*
- Cvasc: 5% Brady or AV Block / <1% TDP
  - Prolonged QTc (Even > 500) NOT Indication to DC
- GU: < 1% Epididymitis / ED

Amiodarone: Pulmonary Issues

- No Data that Amio Worsens Lung Disease*
- *Very* Rarely ARDS / Acute Pneumonitis
- Meta analysis of 65,000: about 2% Lung Toxicity
  - More in Elderly / Dose & Duration Dependent
- Decr D_LCO / Restrictive Pattern / Ground Glass
  - Bronchoscopy w/ Lavage ± Bx May Help (Risky)
- STOP Drug / Steroids / Mortality *maybe* 10% ??

Amiodarone: Liver Issues

- Occurs in Up to 1% Treated Annually
- Resembles ETOH Histo but AST / ALT Equal
- Some Elevation "Normal" … ≤ 2 times
- Liver may be "Bright" on CT w/o Toxicity
- Usually Resolves after Stopping…but has been Fatal

Table 3 Recommended Laboratory Testing in Patients Receiving Amiodarone

Type of Test	Time When Test is Performed*
Liver function tests	Baseline and every 6 mo
Thyroid function tests	TSH, free T4, and total or free T3 at baseline with a follow-up TSH every 6 mo
Chest x-ray study	Baseline and then yearly
Ophthalmologic evaluation	At baseline if visual impairment or for symptoms
Pulmonary function tests (with D_LCO)	Baseline and for unexplained cough or dyspnea, especially in patients with underlying lung disease, if there are suggestive x-ray film abnormalities, and if there is a clinical suspicion of pulmonary toxicity
High-resolution CT scan	If clinical suspicion of pulmonary toxicity
Electrocardiogram	Baseline and when clinically relevant

D_LCO = diffusion capacity of carbon monoxide; Free T4 = free thyroxine; TSH = thyroid stimulating hormone.

*If clinical circumstances warrant, more frequent follow-up will be necessary.

AFib Topics Summary

- Controlling MRFs may Help Control AFib
- Ethnicity may Improve TE Risk Prediction
- Anti-platelet Tx does NOT Appear Helpful
- Complex Interaction of CKD / AFib (TE / ICH)
- ?? Re-anticoagulate > 2 weeks After ICH
- Be Vigilant with Amiodarone Risk Surveillance