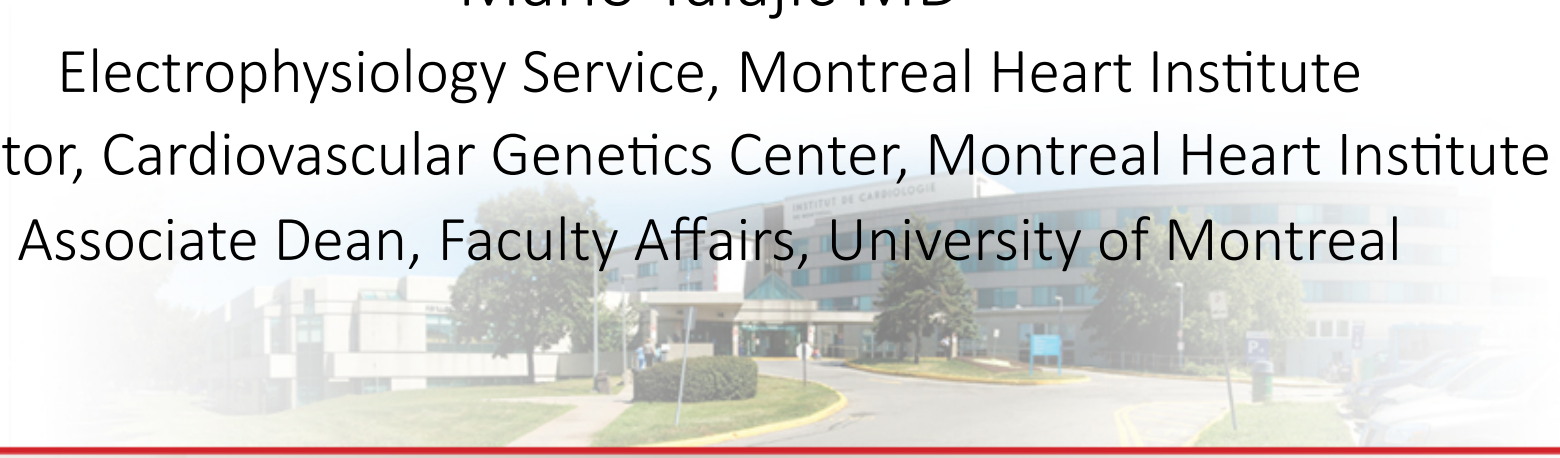
CCS Focused Update on Atrial Fibrillation New Guidelines for 2016

Mario Talajic MD
Electrophysiology Service, Montreal Heart Institute
Director, Cardiovascular Genetics Center, Montreal Heart Institute
Associate Dean, Faculty Affairs, University of Montreal



Conflict Disclosures

The speaker has received fees/honoraria from the following sources:

Research Support/ Advisory Boards/ Speaker

Bristol-Myers-Squibb/Pfizer Alliance

Bayer

.

Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Implementing GRADE and Achieving Consensus

Gillis et al. Canadian Journal of Cardiology 2011;27:27-30

Focused 2012 Update of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines: Recommendations for Stroke Prevention and Rate/Rhythm Control

Skanes et al. Canadian Journal of Cardiology 2012;28:125-36

2014 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation

Verma et al. Canadian Journal of Cardiology 2014;30:1114-30

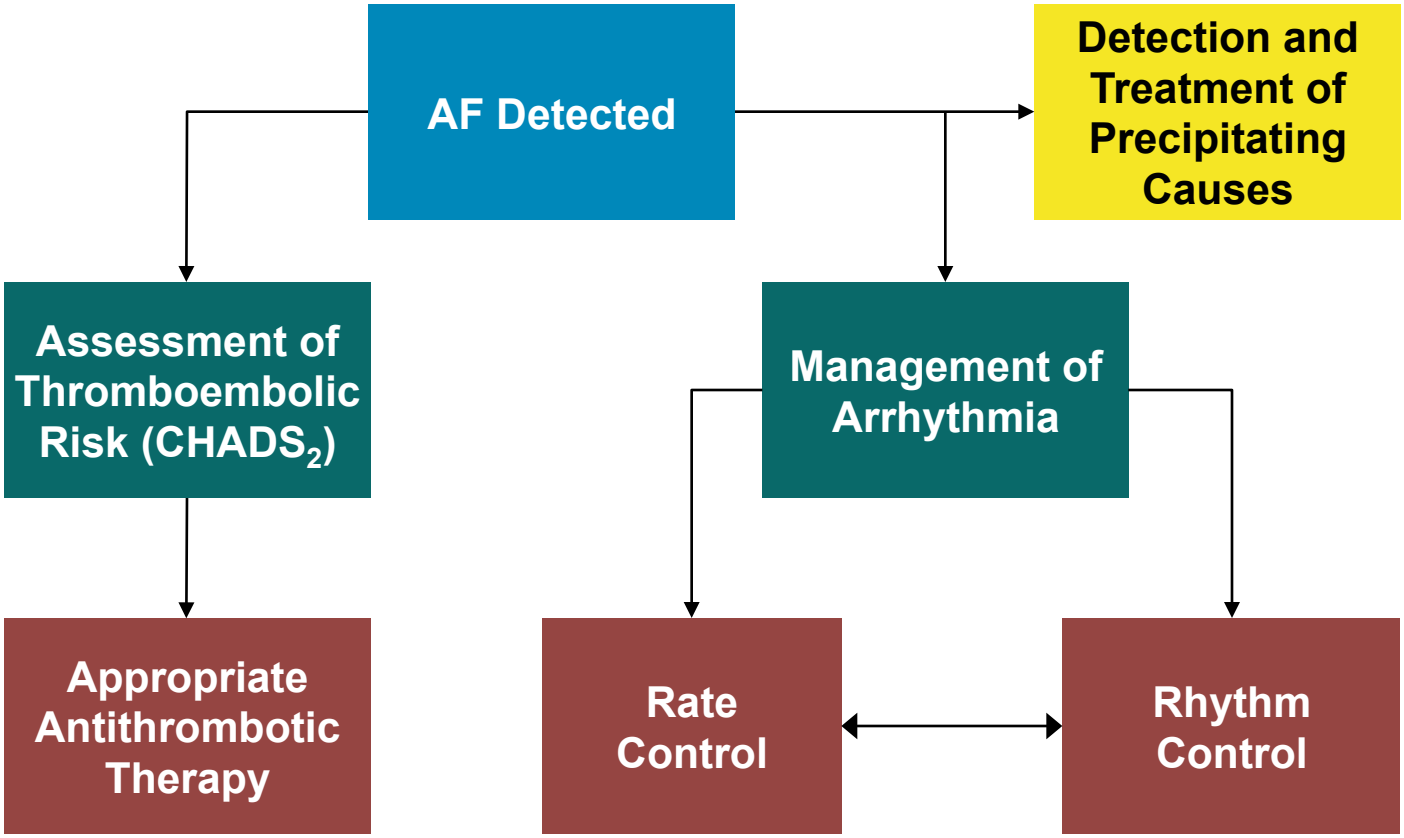
The 2014 Atrial Fibrillation Guidelines Companion: A Practical Approach to the Use of the Canadian Cardiovascular Society Guidelines

Macle et al. Canadian Journal of Cardiology 2015;31:1207-18

2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation

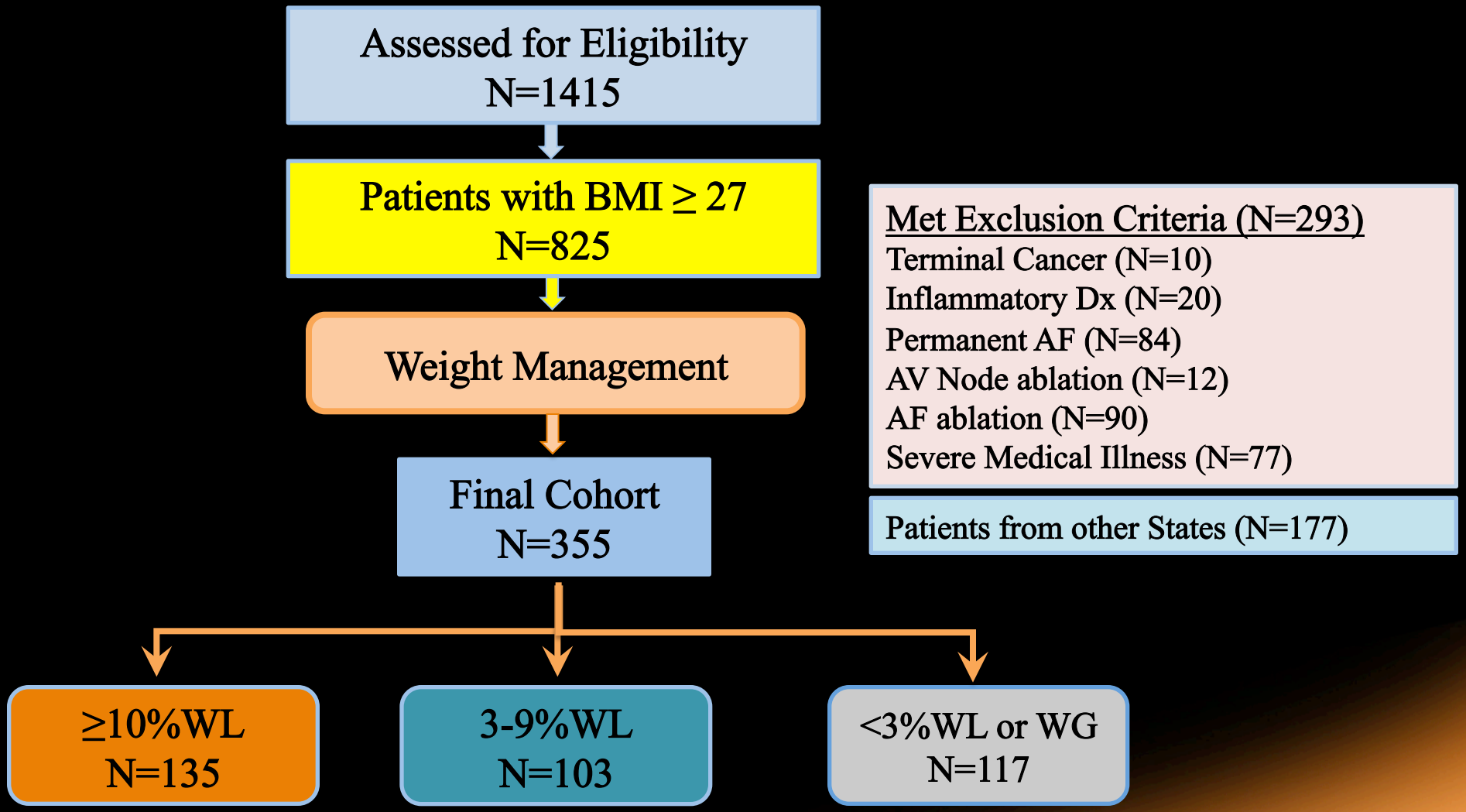
Macle et al. Canadian Journal of Cardiology 2016;32:1170-85

Overview of AF Management



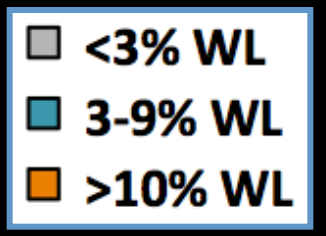
Atrial Fibrillation
Etiology/ 'Reversible'/Actionable Conditions

Age	Hyperthyroidism
Hypertension	Obesity
Structural Cardiac Disease	WPW/SVT
Pulmonary Disease	Unnecessary ventricular pacing
Post Cardiac Surgery	Vagally mediated (over-training)
Familial/Genetic	Alcohol
Sleep Apnea	

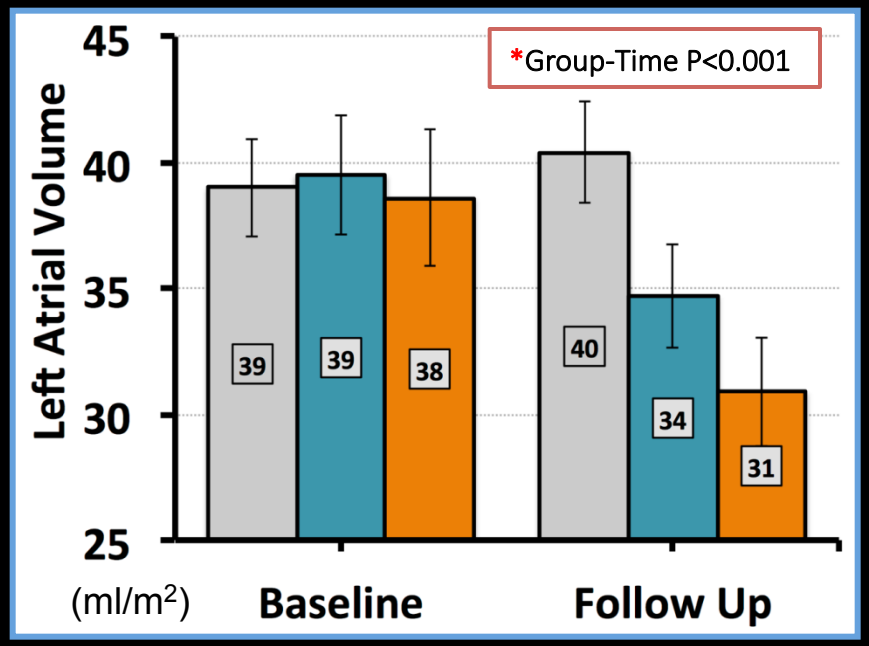


Pathak et al. JACC 2015

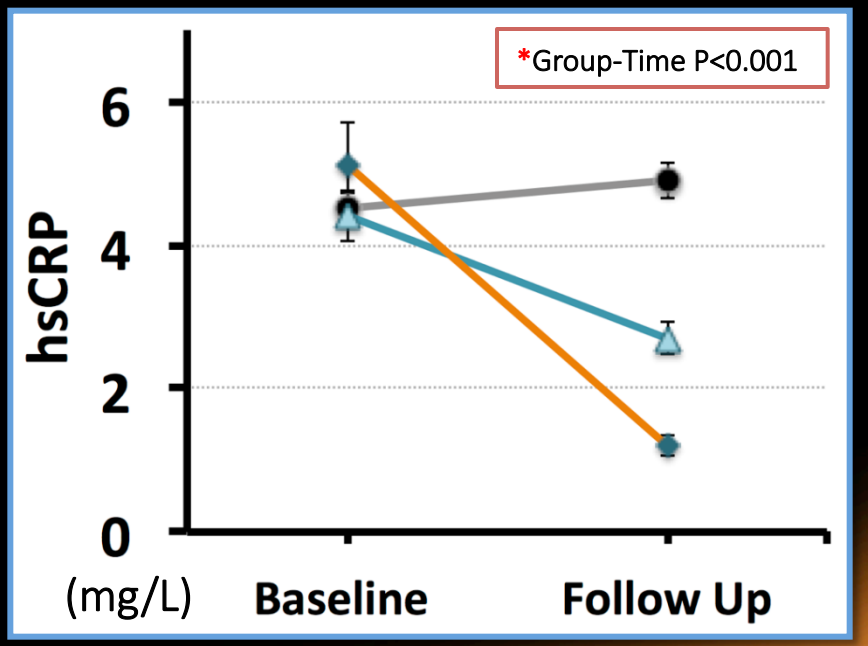
Structural Remodeling



LA Volume (Indexed)



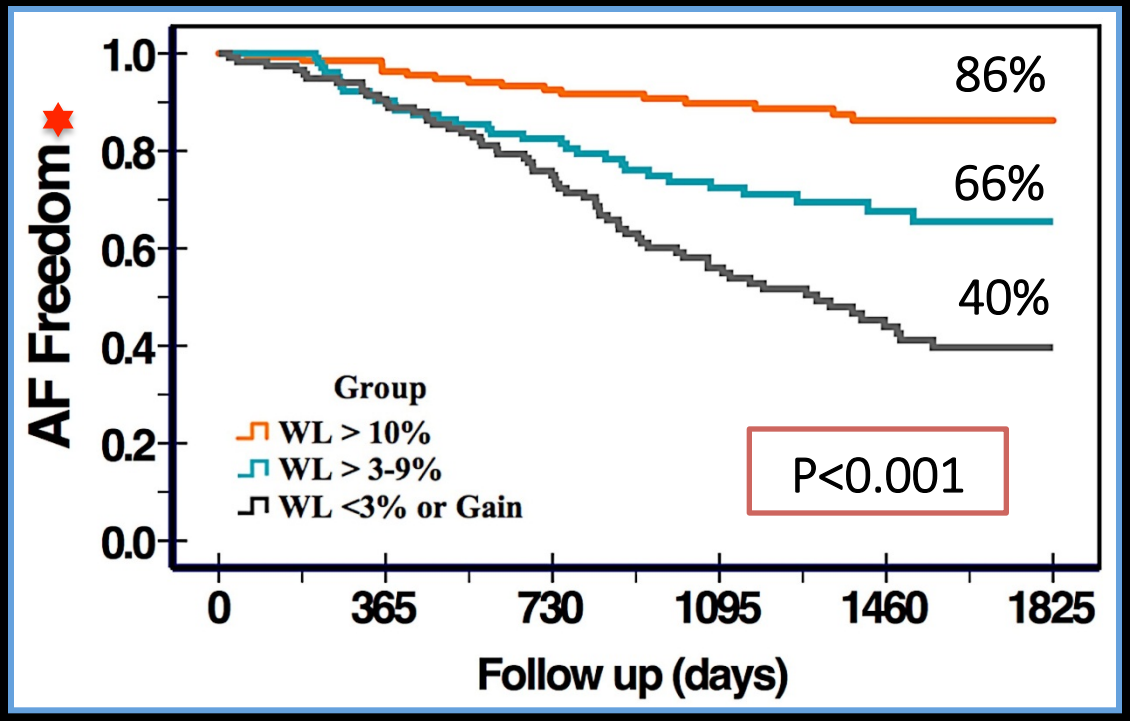
hsCRP Level



Pathak et al. JACC 2015

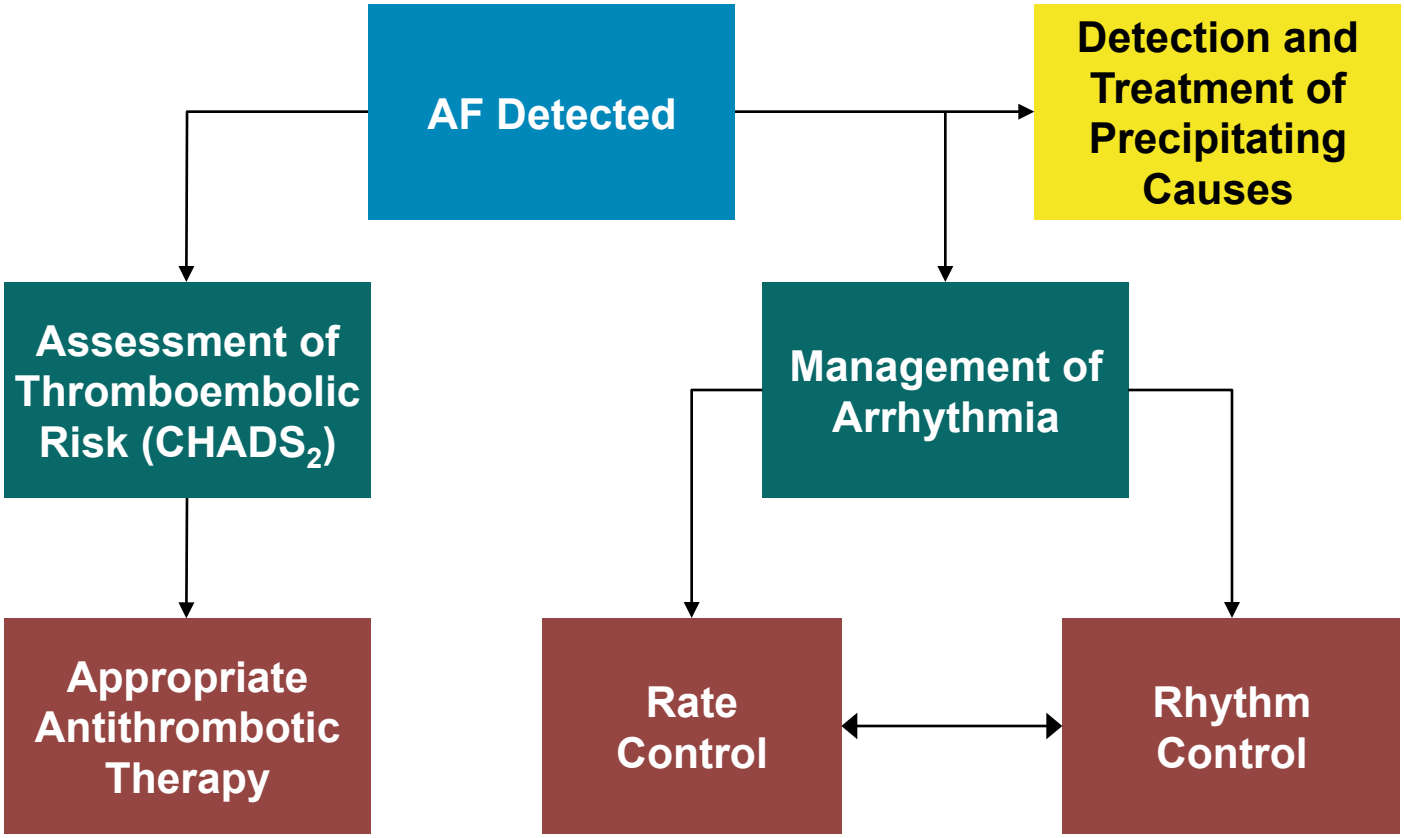
Total Arrhythmia-Free Survival

With AAD and/or ablation



Days	0	365	730	1095	1460	1825
>10%WL	135	130	114	86	67	36
3-9% WL	103	93	83	57	35	22
<3% WL	117	105	85	53	32	22

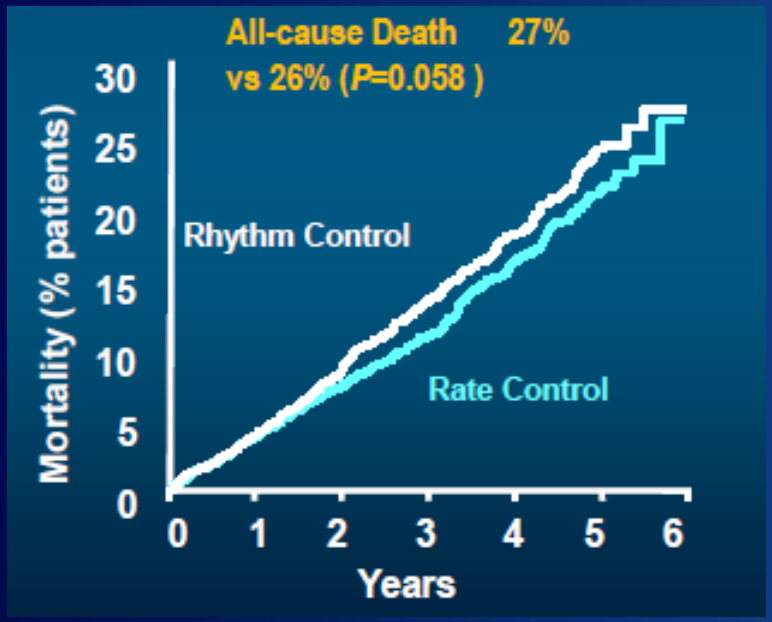
Overview of AF Management



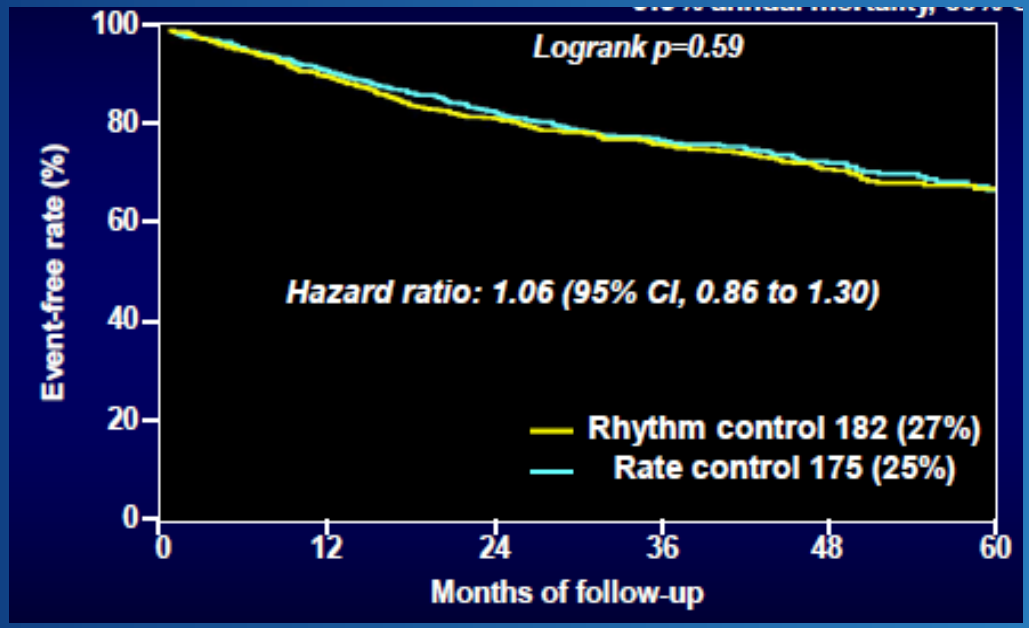
Rate vs Rhythm Trials

No mortality advantages of sinus rhythm

AFFIRM



AF-CHF



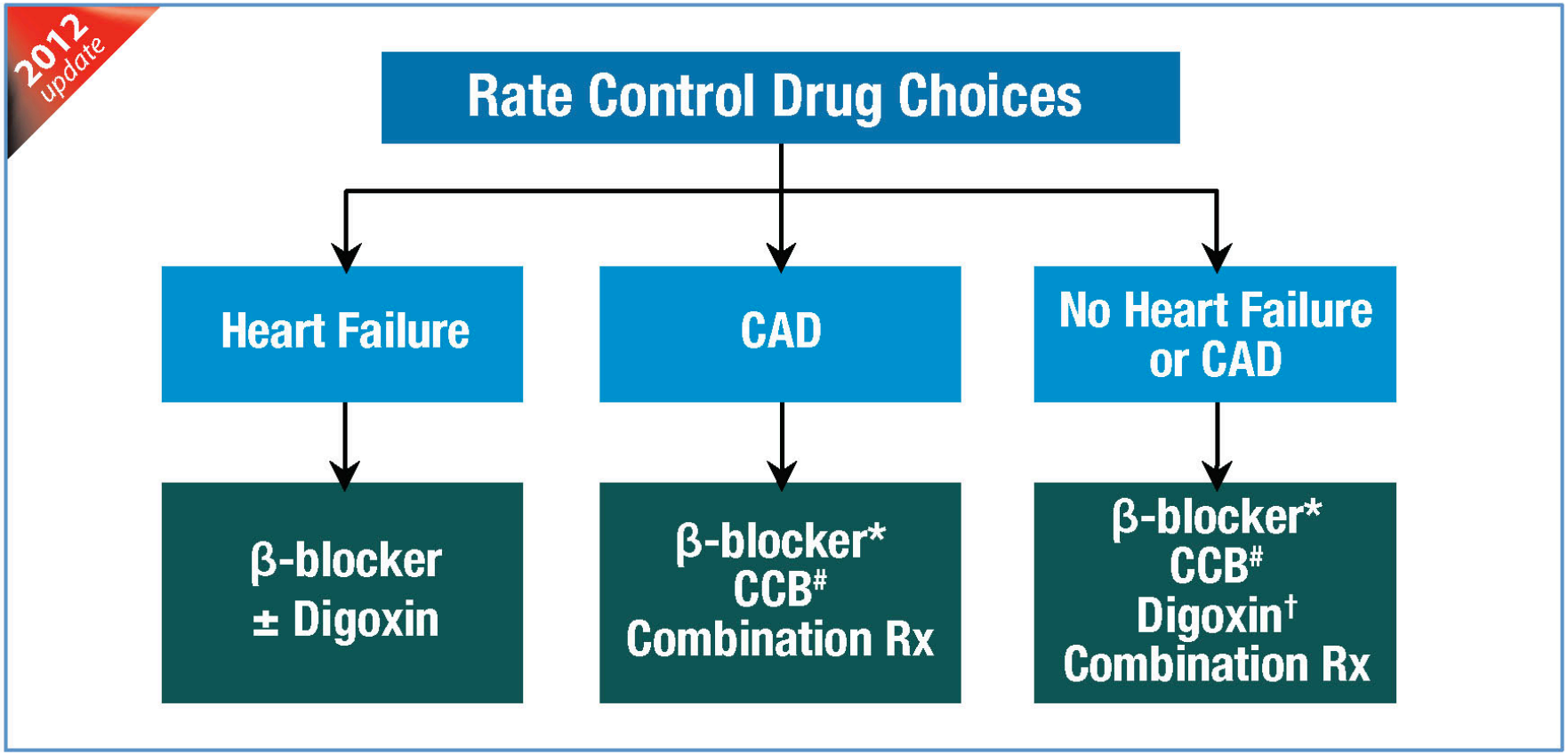
The AFFIRM Investigators. N Engl J Med 2002;347:1825-1833

Roy, Talajic, Nattel et al N Engl J Med 2008; 358: 2667

Rate vs Rhythm Decision

- Is AF (despite controlled rate) causing symptoms?
- What is the likelihood of maintaining sinus rhythm?

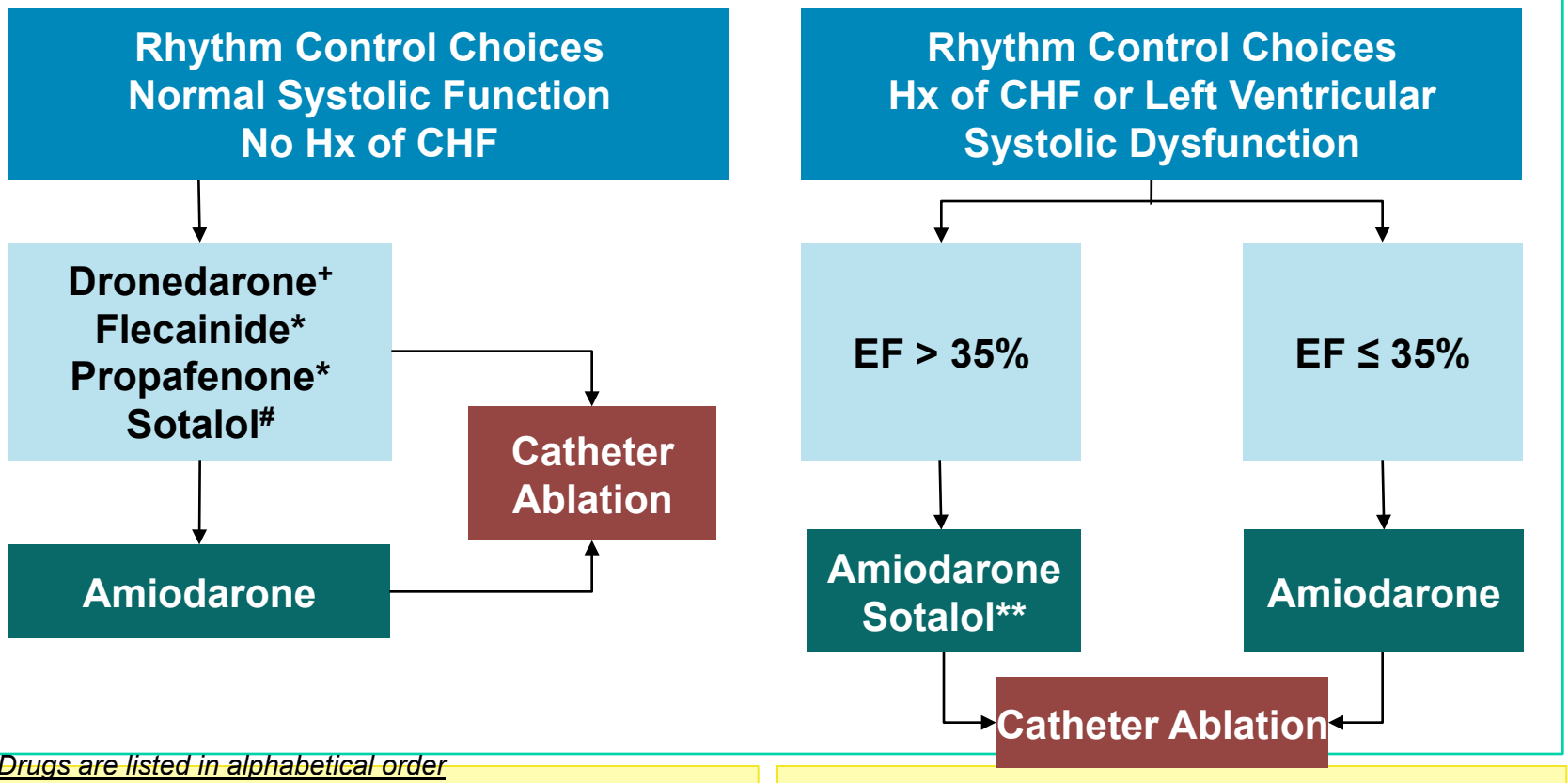
Overview of Rate Management



Drugs are listed in alphabetical order
***β-blockers preferred in CAD**
 # Non-dihydropyridine calcium channel blockers (diltiazem, verapamil)
†Digoxin may be considered as monotherapy only in particularly sedentary individuals

Skanes AC, Healey JS et al., *Can J Cardiol* 2012 Mar;28(2): 125-136

Overview of Rhythm Management



Drugs are listed in alphabetical order

+*Dronedarone should be used with caution in combination with digoxin*

- *Class I agents should be AVOIDED in CAD and should be COMBINED with AV-nodal blocking agents*

#*Sotalol should be used with caution in those at risk for torsades de pointes VT (e.g. female, age > 65 yr, taking diuretics)*

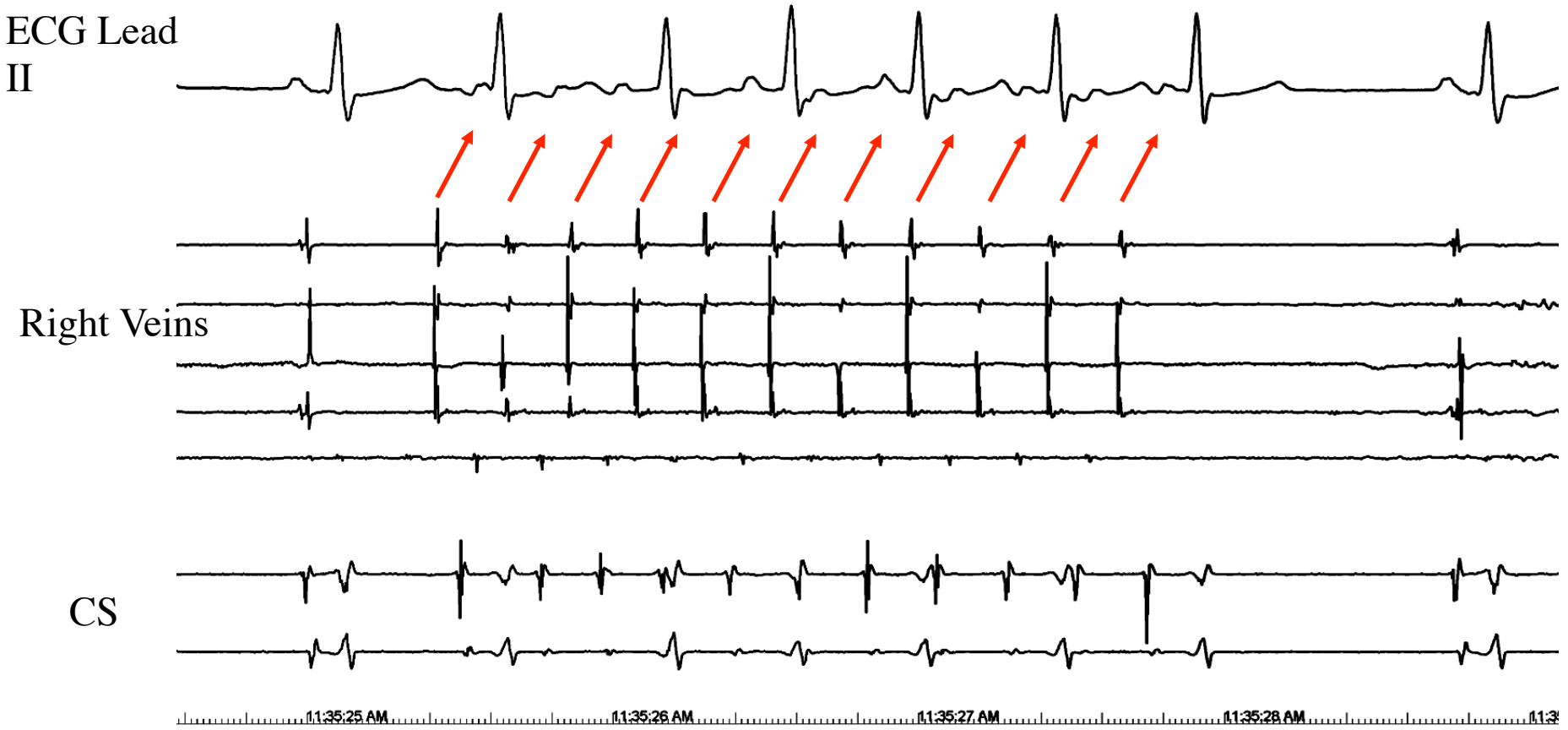
** *Sotalol should be used with caution with EF 35-40% and those at risk for torsades de pointes VT (e.g. female, age > 65 yr, taking diuretics)*

Rhythm Control Does Not Replace Anticoagulation

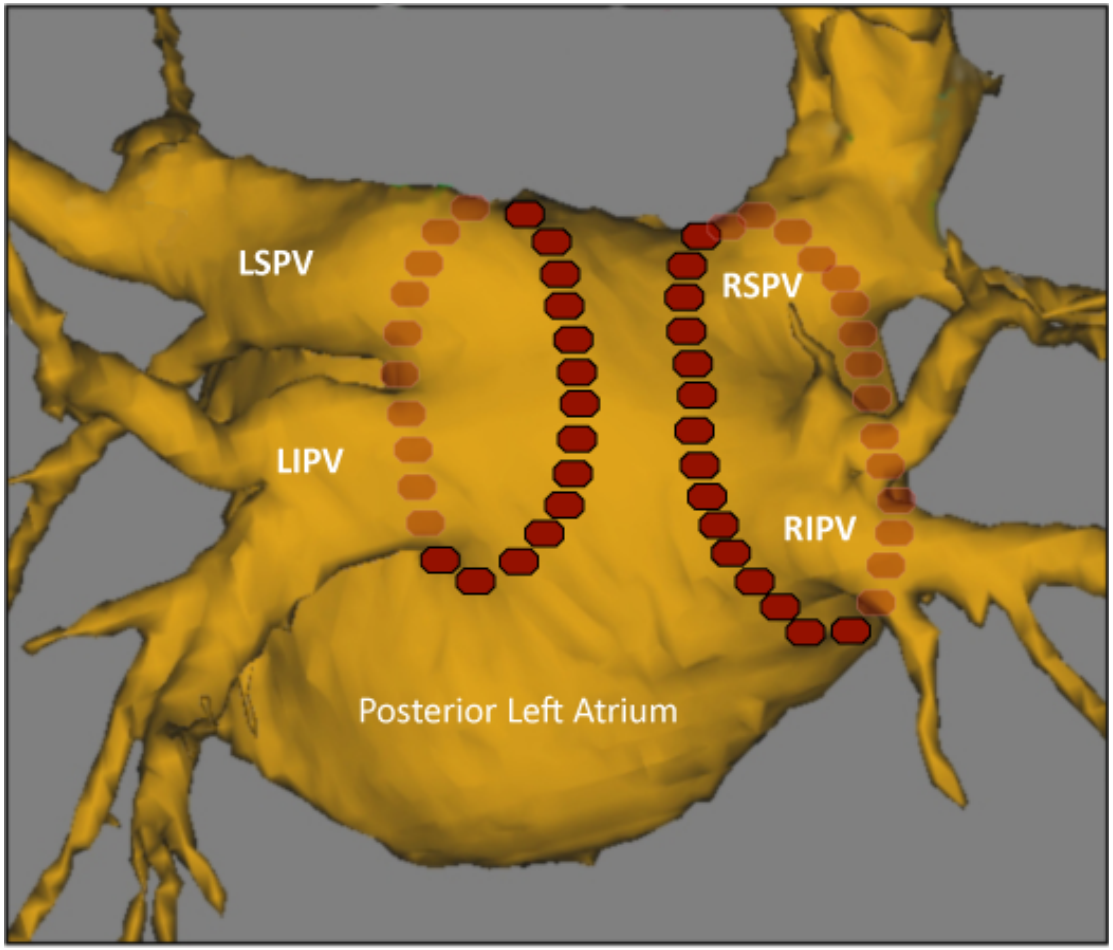
- ***No*** **evidence that AF reduction via antiarrhythmic therapy reduces the risk of stroke/thromboembolism**
- **Patients *must* continue on appropriate anticoagulation according to their individual embolic risk ($CHADS_2$ score)**

Skanes AC, Healey JS et al., *Can J Cardiol* 2012 Mar;28(2): 125-136

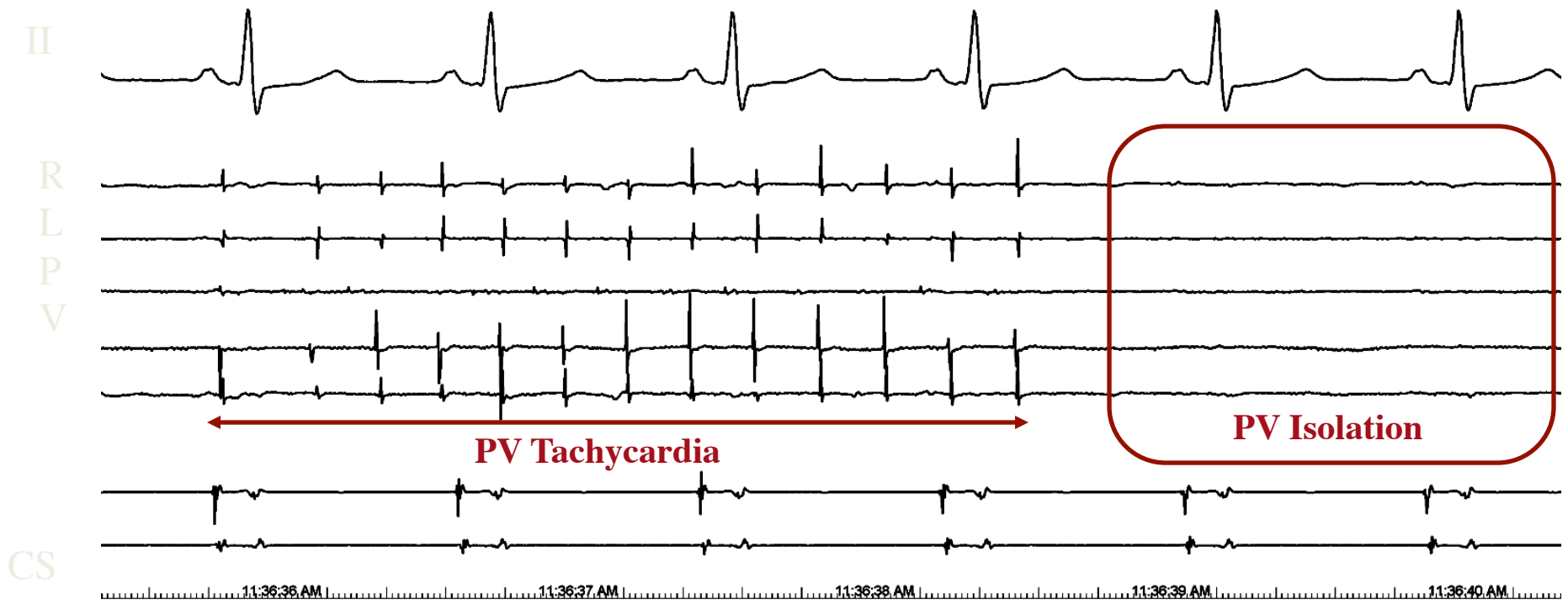
Tachycardia in Right Veins



AF Ablation lesion set



Tachycardia in Right Veins: Behind Fence



Worldwide AF Ablation ('03-'06)

Type of Complication (n=14,218)	No of Pts	Rate%
Femoral pseudoaneurysm	152	0.93
AV fistulae	88	0.54
Pneumothorax	15	0.09
Valve damage/requiring surgery	11/7	0.07
Tamponade	213	1.31
Transient ischaemic attack	115	0.71
PV stenosis requiring intervention	48	0.29
Stroke	37	0.23
Permanent diaphragmatic paralysis	28	0.17
Death	25	0.15
Atrium-esophageal fistulae	3	0.02
TOTAL	**741**	**4.54%**

Cappato R et al. Circ Arrhythm Electrophysiol. 2010;3:32-8

Patient Selection: AF Ablation

(Symptomatic pt refractory to AAD)

Good Patient

- 55 yo
- Paroxysmal AF
- No structural Heart Disease
- Left atrial diameter < 55mm

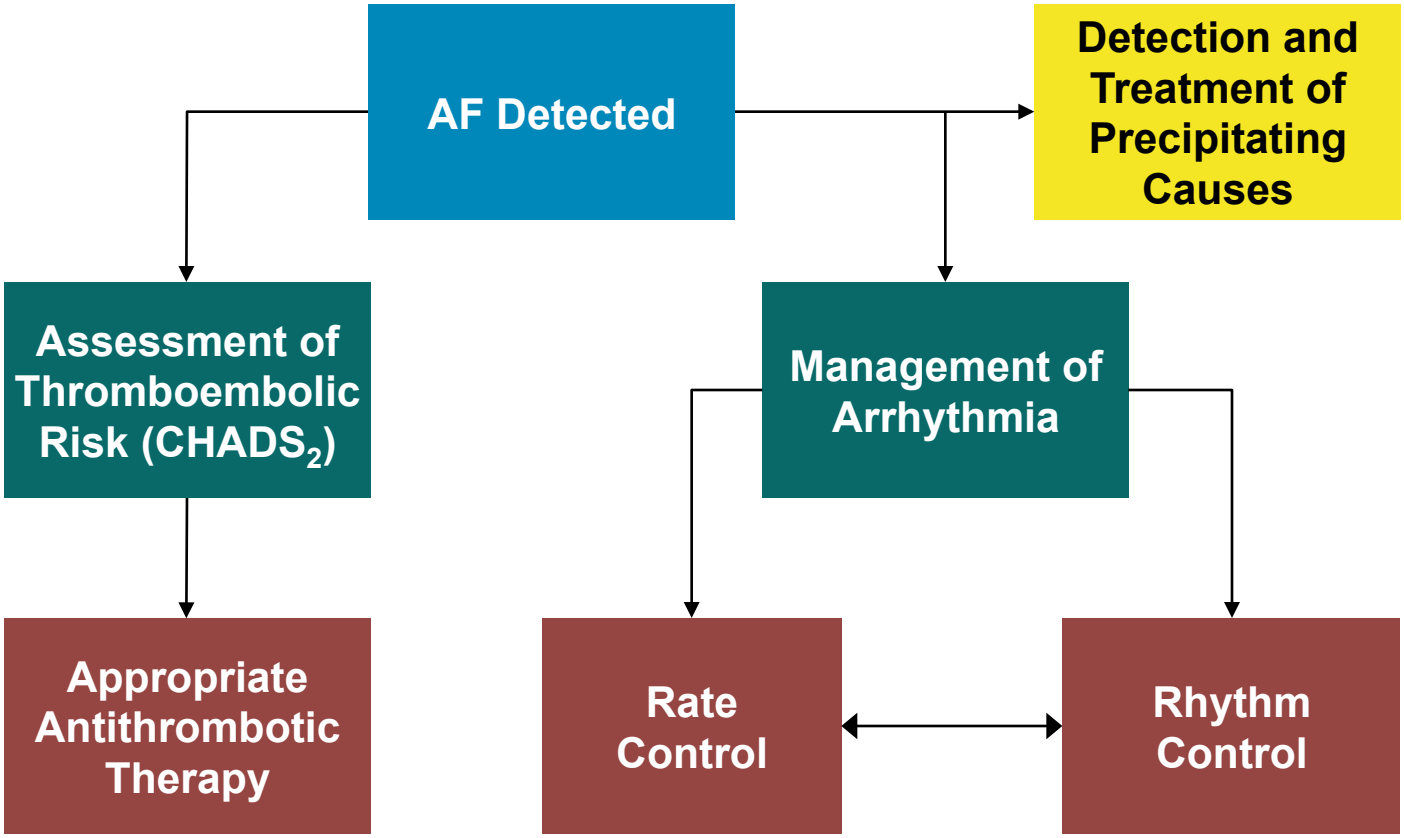
- 80% success rate after 1 ablation

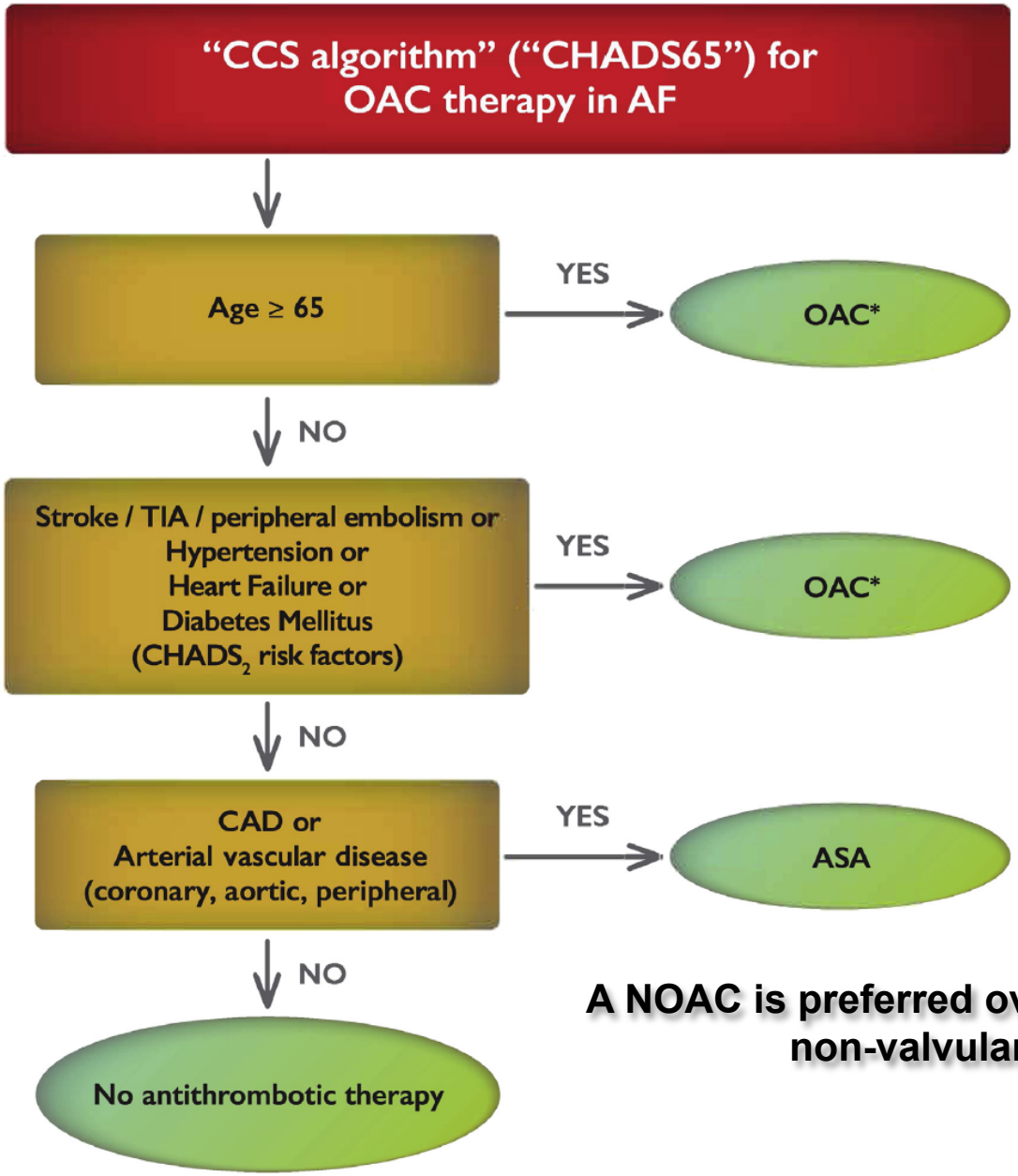
Poor Patient

- 80 yo
- Persistant AF
- Structural Heart Disease present
- Left atrial diameter > 55 mm

- 30% success rate after 1 ablation

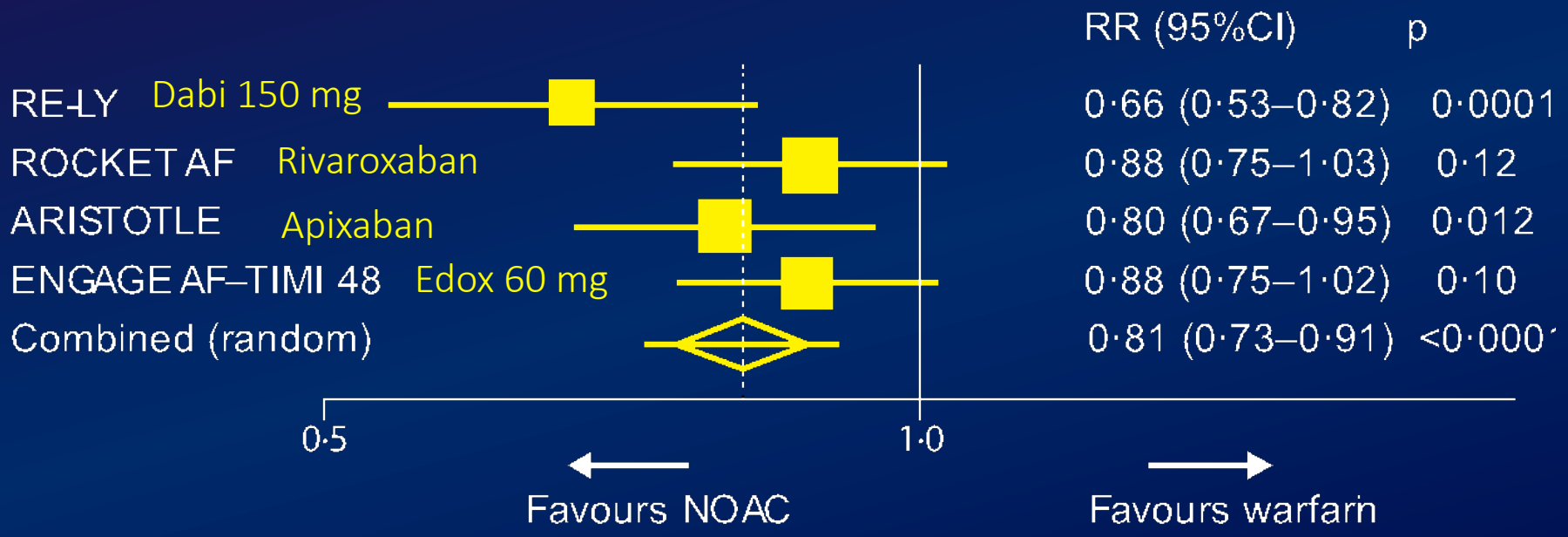
Overview of AF Management





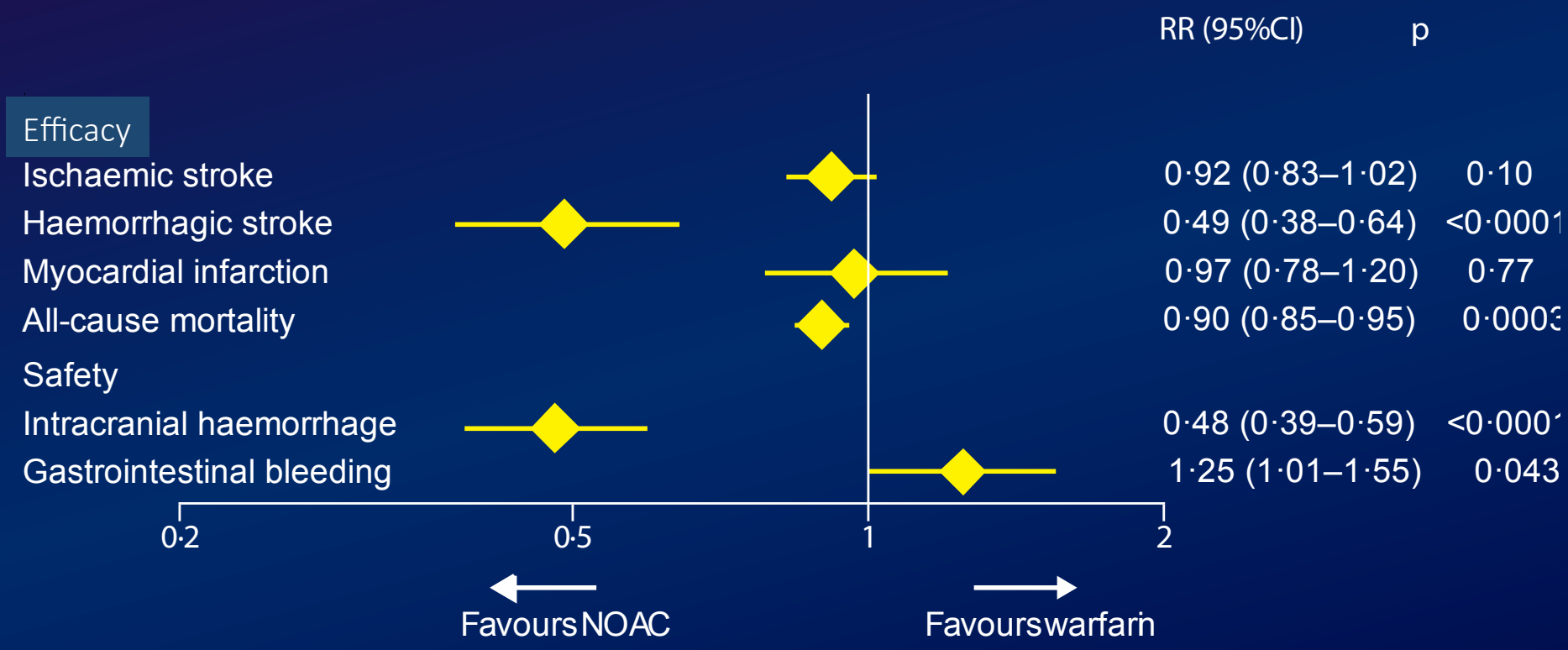
A NOAC is preferred over warfarin for non-valvular AF.

Stroke or systemic embolic events in large NOAC trials, vs warfarin



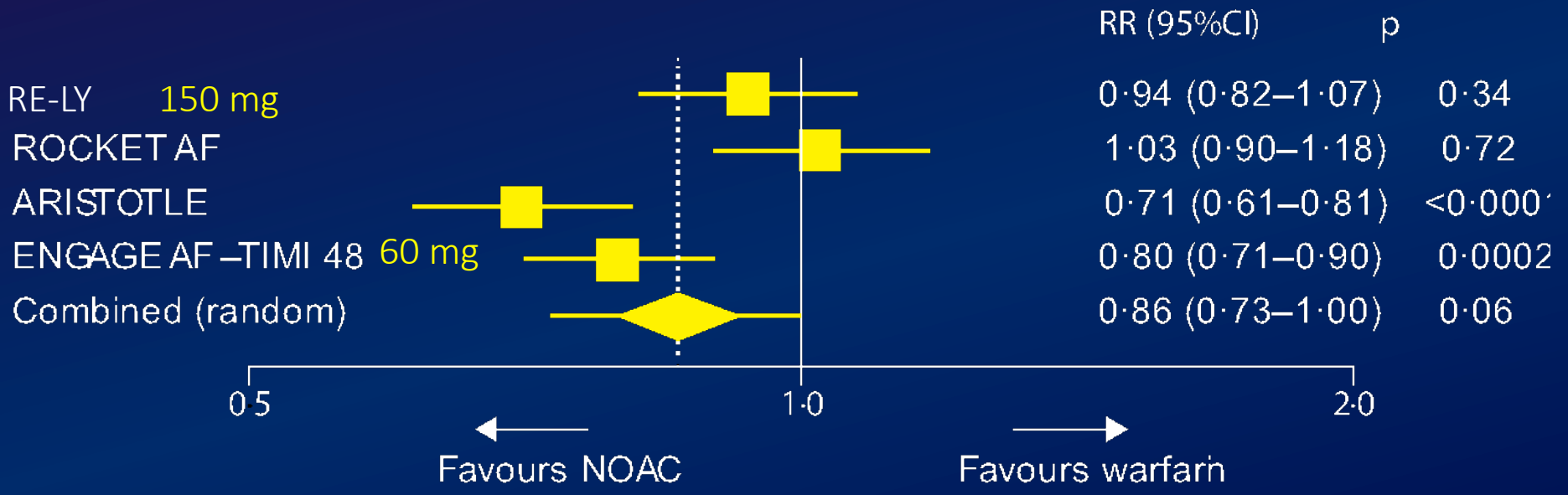
Ruff *et al.*, The Lancet, 2013

Secondary efficacy and safety outcomes in large NOAC trials, vs. warfarin



Ruff *et al.*, The Lancet, 2013

Major bleeding events in large NOAC trials, vs warfarin



Ruff *et al.*, The Lancet, 2013

NOAC preferred over Warfarin because of:

A.Convenience and **ease of use** for patients and physicians

B. All NOACs are **at least as effective and as safe** as Warfarin

-some have greater efficacy for stroke/systemic embolus and mortality
-some have greater safety for major bleeding

Warfarin indicated over NOAC for patients with:

Mechanical prosthetic valves
Rheumatic MS
Severe renal dysfunction

Choice of anticoagulant
Which NOAC?

- No direct comparisons between NOACs
- No specific guidelines
- Moderate renal insufficiency: consider Rivaroxaban, Apixaban, Edoxaban
- Very high stroke risk: consider Dabigatran 150 bid
- High bleeding risk: consider Dabigatran 110, Apixaban, Edoxaban
- Patient preference for QD: Rivaroxaban, Edoxaban

NOACs 2016

- **Management of Complex Disease**

  Choice/Dosing Drug Interactions

  Patients on warfarin Valvular heart disease

  FU/Adherence Peri-operative Management

  Renal Failure Cardioversion

  Bleeding Risk ER management of AF

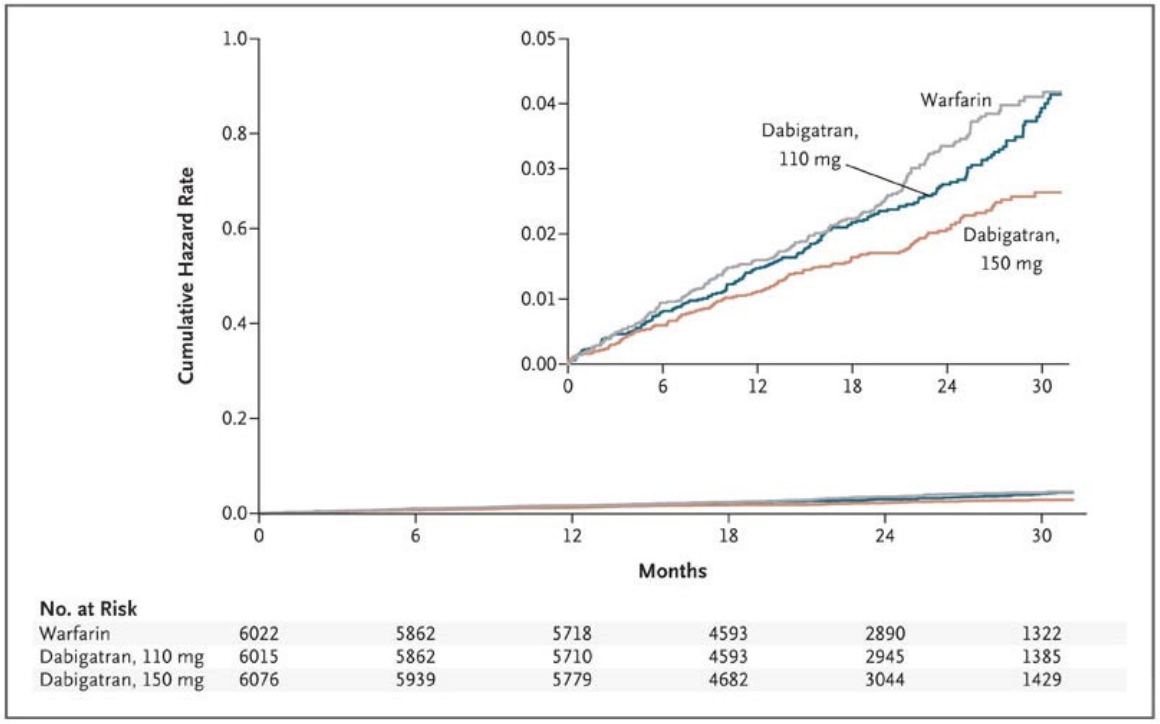
  Concomitant CAD NOAC management after CVA

  Recent Stenting/ACS AF Ablation

  Cryptogenic Stroke

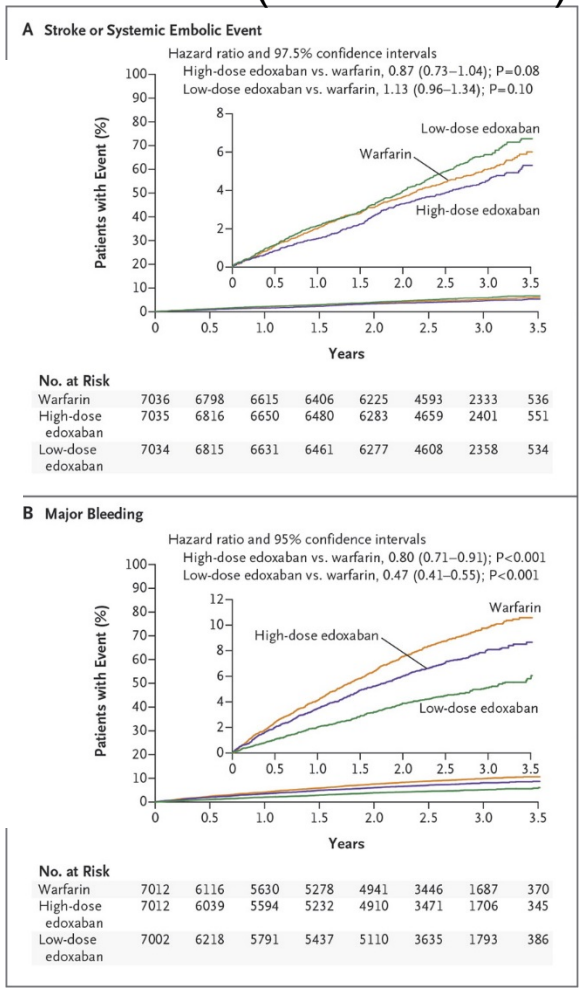
NOAC Dose Matters!!

Dabigatran (RELY)



No. at Risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

Edoxaban (ENGAGE-AF)



NOAC dosing

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban*
Standard Dose	150 mg bid	20 mg die	5 mg bid	60 mg die
Low Dose	110 mg bid	15 mg die	2.5 mg bid	30 mg die
Criteria for low dose	Physician choice (risk bleeding vs risk of stroke)	CrCl 30-49 ml/min	2 of 3 criteria Weight ≤ 60 kg, age ≥ 80, Cr ≥ 133 µM/L	CrCl 15-50 ml/min (FDA rec)
% NOAC pts on low dose in RCT	50% (RELY)	21% (ROCKET)	5% (ARISTOTLE)	50% (ENGAGE-AF)

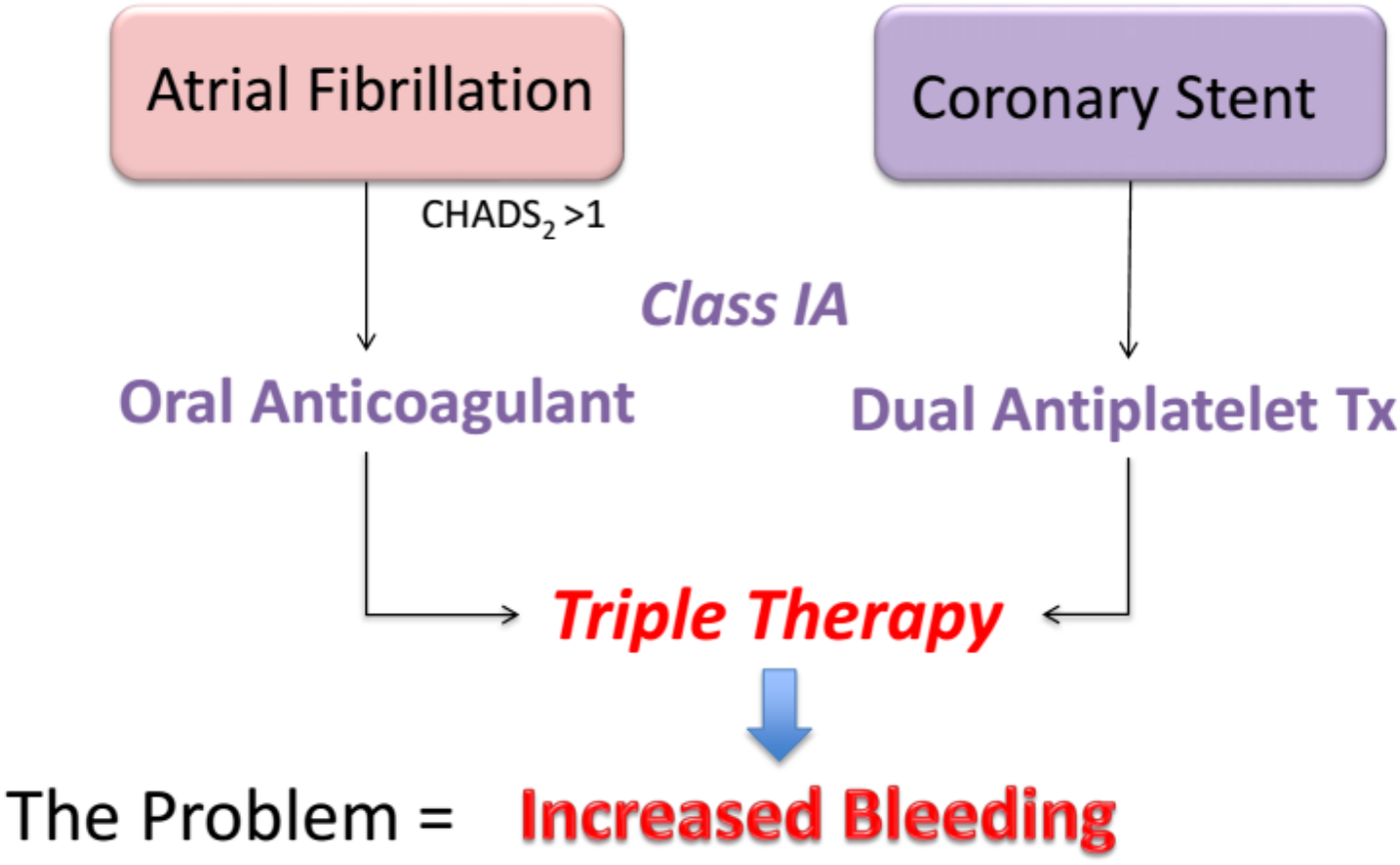
* US monograph SAVAYSA should not be used in patients with CrCL > 95 mL/min because of an increased risk of ischemic stroke compared to warfarin

NOAC Antidotes

- Currently available for clinical use
  - Idarucizumab (Praxbind®)
    - Dabigatran-specific reversal agent

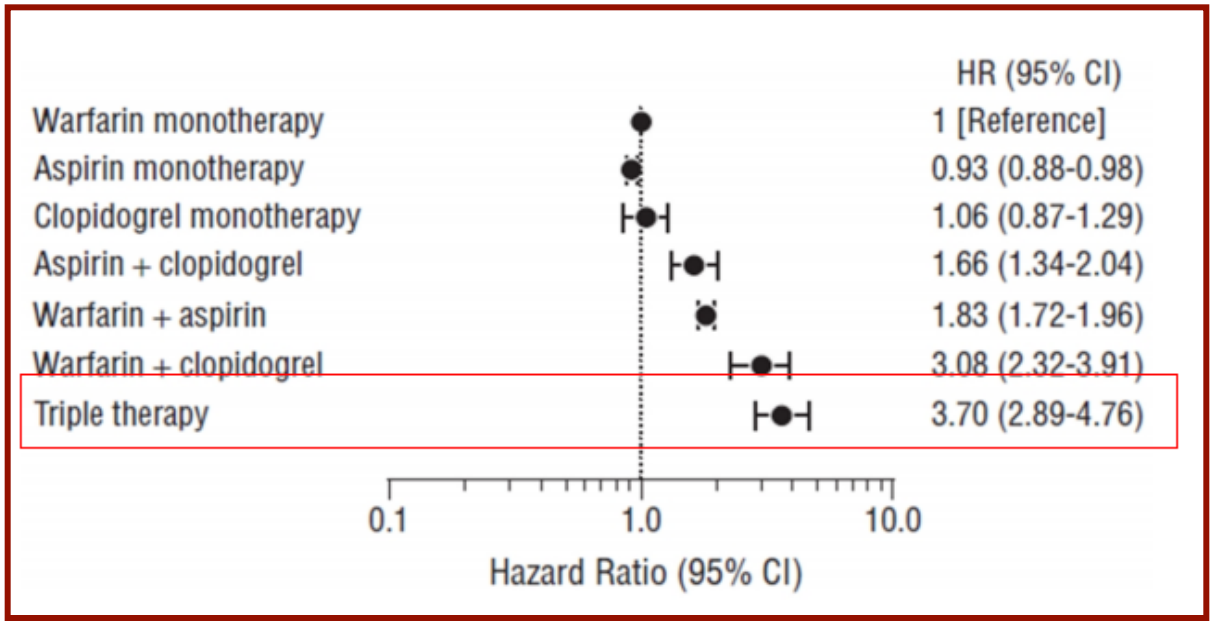
- Not available yet for clinical use
  - Andexanet Alpha
    - Factor Xa reversal agent (e.g apixaban, rivaroxaban, edoxaban)
  - Ciraparantag (PER-977, aripazine)
    - “universal” reversal agent

ACC AHA Guideline Recommended Therapy



Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation

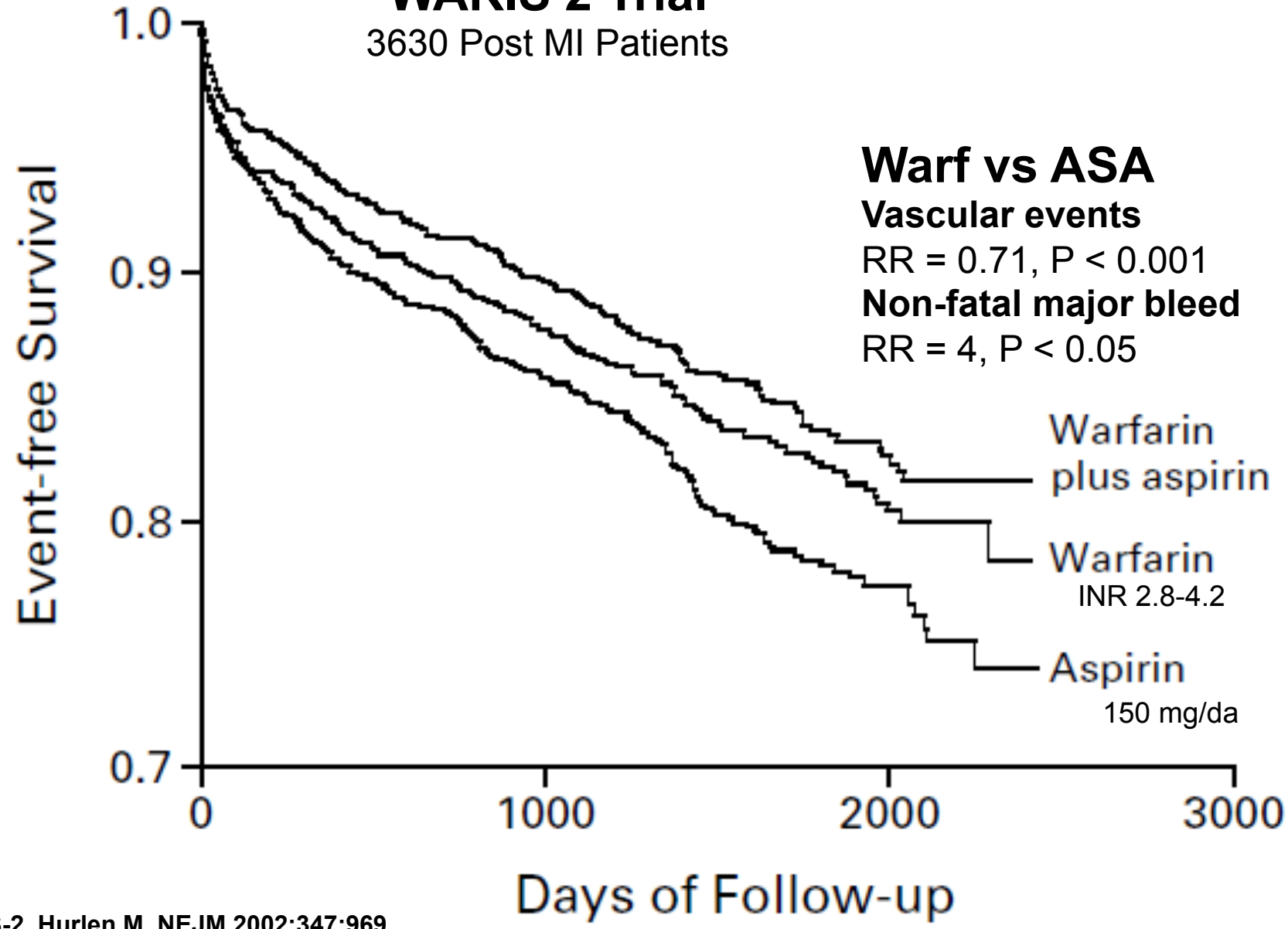
- Registre Danois
- 82k patients
- 1997-2006
- F-up moyen
  - 3.3 ans
- Incidence saignements (non-fatal ou fatal): 11.4%



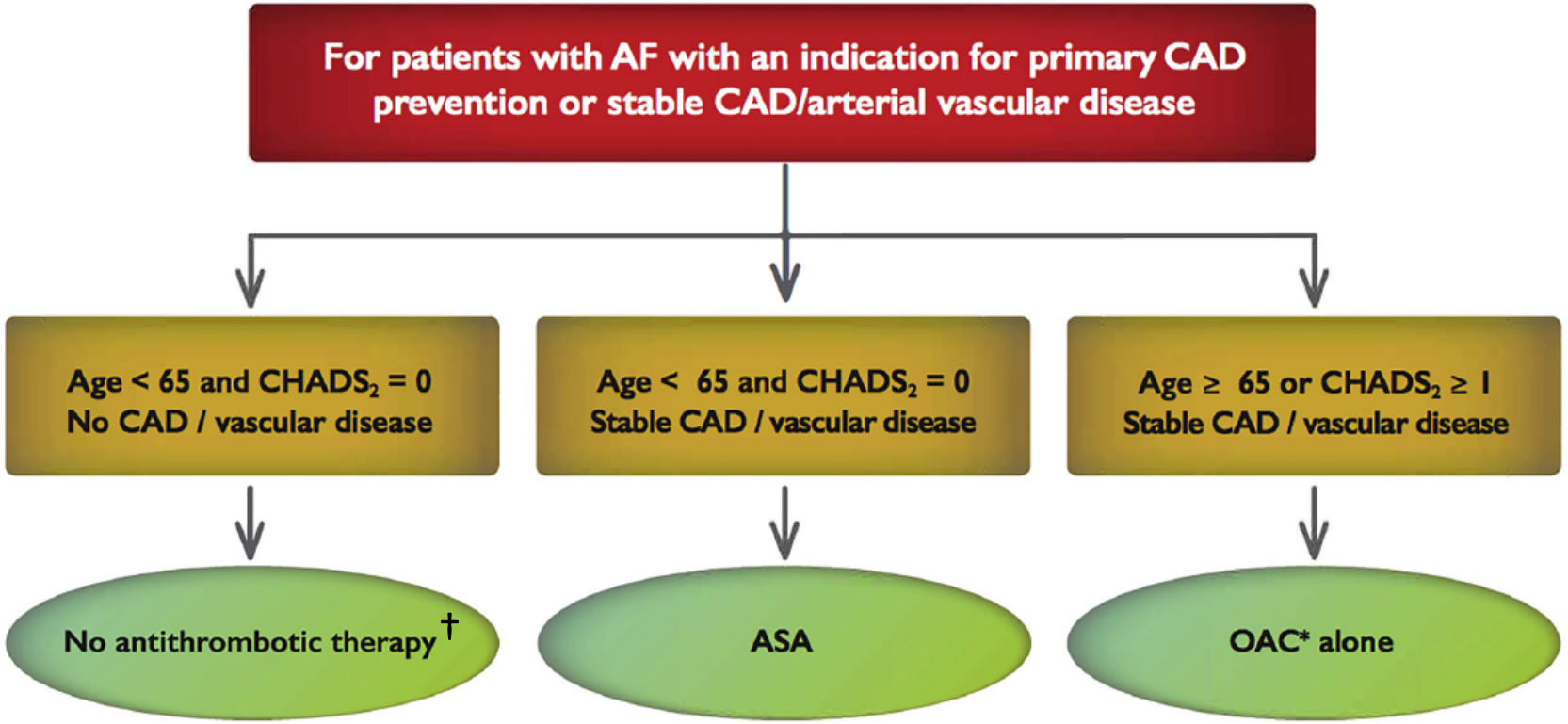
Hansen ML et al. Arch Intern Med 2010;170:1433-41

WARIS 2 Trial

3630 Post MI Patients



WARIS-2. Hurlen M. NEJM 2002;347:969



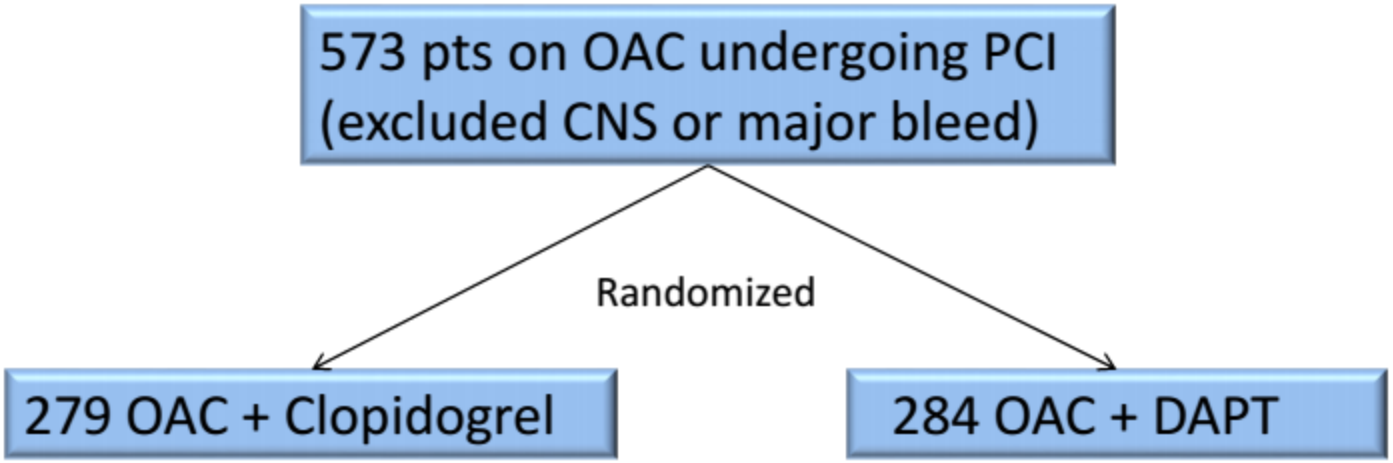
* A NOAC is preferred over warfarin for non-valvular AF

† Primary CAD prevention with ASA may be considered in selected high-risk patients

Concomitant AF and CAD – CCS Guidelines Update 2016

WOEST Trial

Randomized Trial of Triple vs Dual Therapy



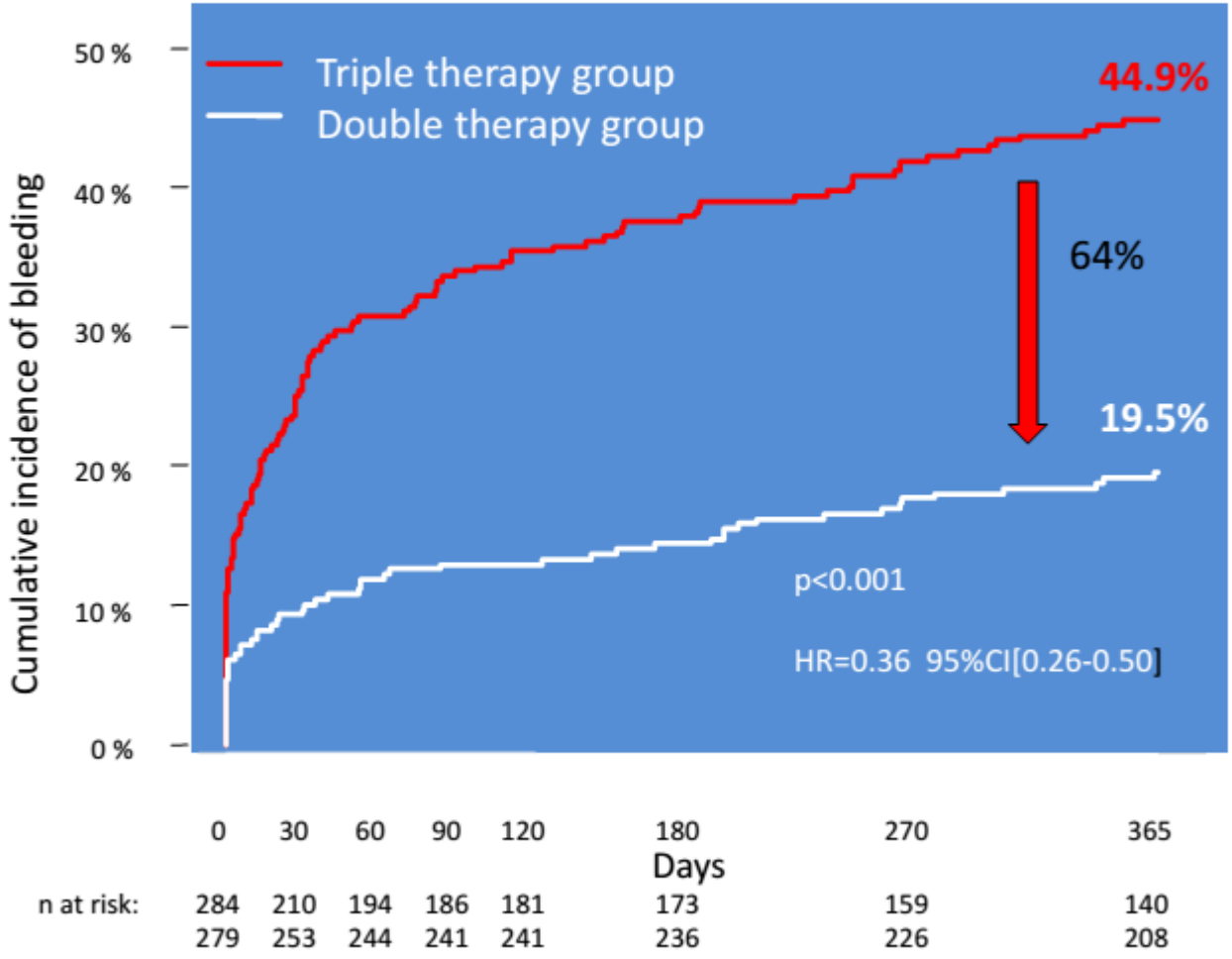
Clopidogrel for 1 month minimum after BMS and 1 y after DES

Primary EP= All bleeding events (TIMI) at one year
Secondary EP= Stroke, death, MI , ST and TVR

Dewilde, Lancet 2013

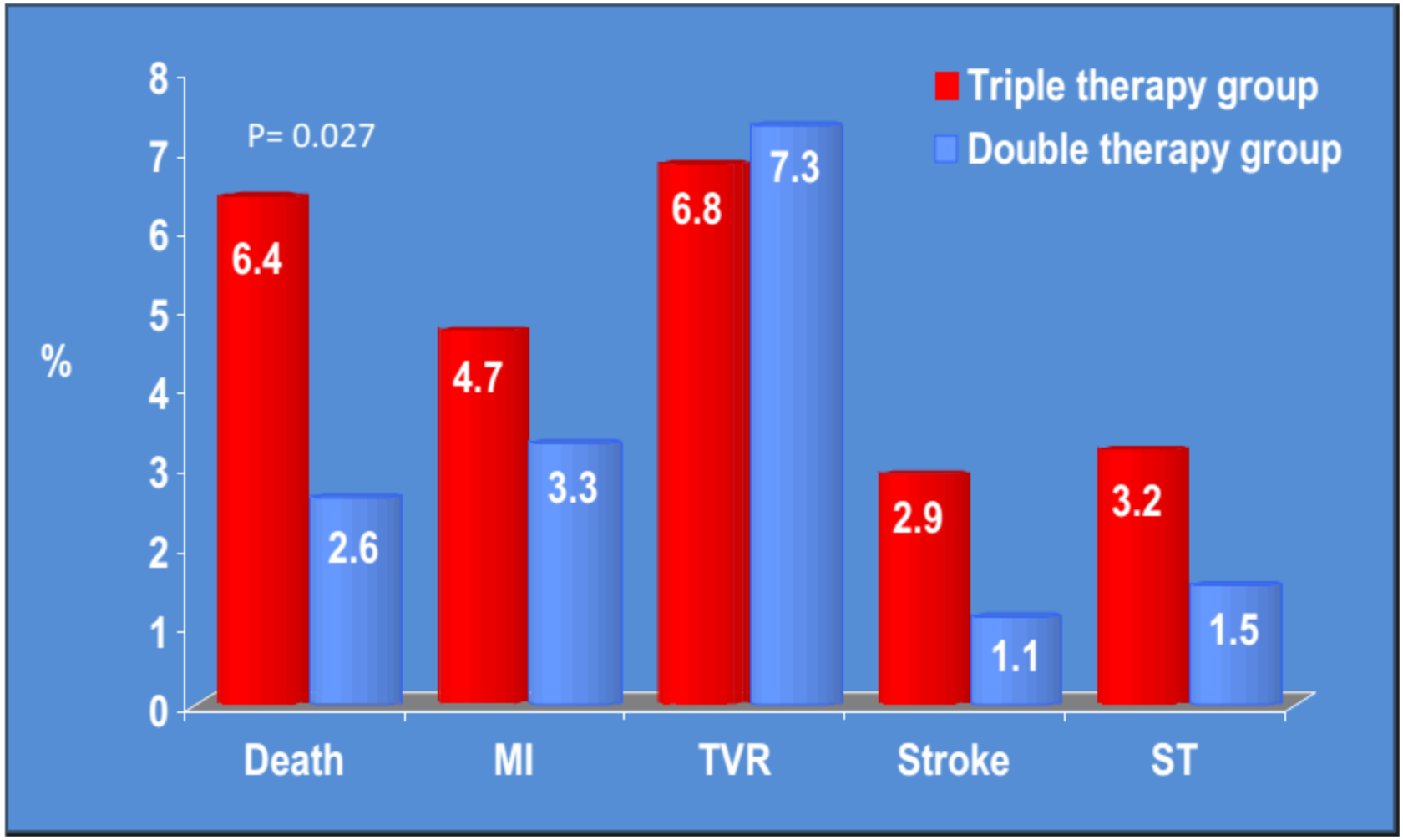
WOEST

Primary Endpoint: *Total* TIMI bleeding events



Dewilde Lancet 2013

WOEST: Secondary endpoints



Dewilde W et al. Lancet 2013

Patients With Atrial Fibrillation Undergoing Coronary Stent Placement: PIONEER AF-PCI

- 2100 patients with NVAF
- Coronary stenting
- No prior stroke/TIA, GI bleeding, Hb<10, CrCl<30

≤72 hours
After Sheath removal

RANDOMIZE

End of treatment 12 months

WOEST Like
Rivaroxaban 15 mg qd*
Clopidogrel 75 mg qd†

1,6, or 12 months
Pre randomization MD Choice

ATLAS Like
Rivaroxaban 2.5 mg bid
Clopidogrel 75 mg qd†
Aspirin 75-100 mg qd‡

Rivaroxaban 15mg QD
Aspirin 75-100 mg qd

1,6, or 12 months
Pre randomization MD Choice

Triple Therapy
VKA$^{\Delta}$ (target INR 2.0-3.0)
Clopidogrel 75 mg qd†
Aspirin 75-100 mg qd

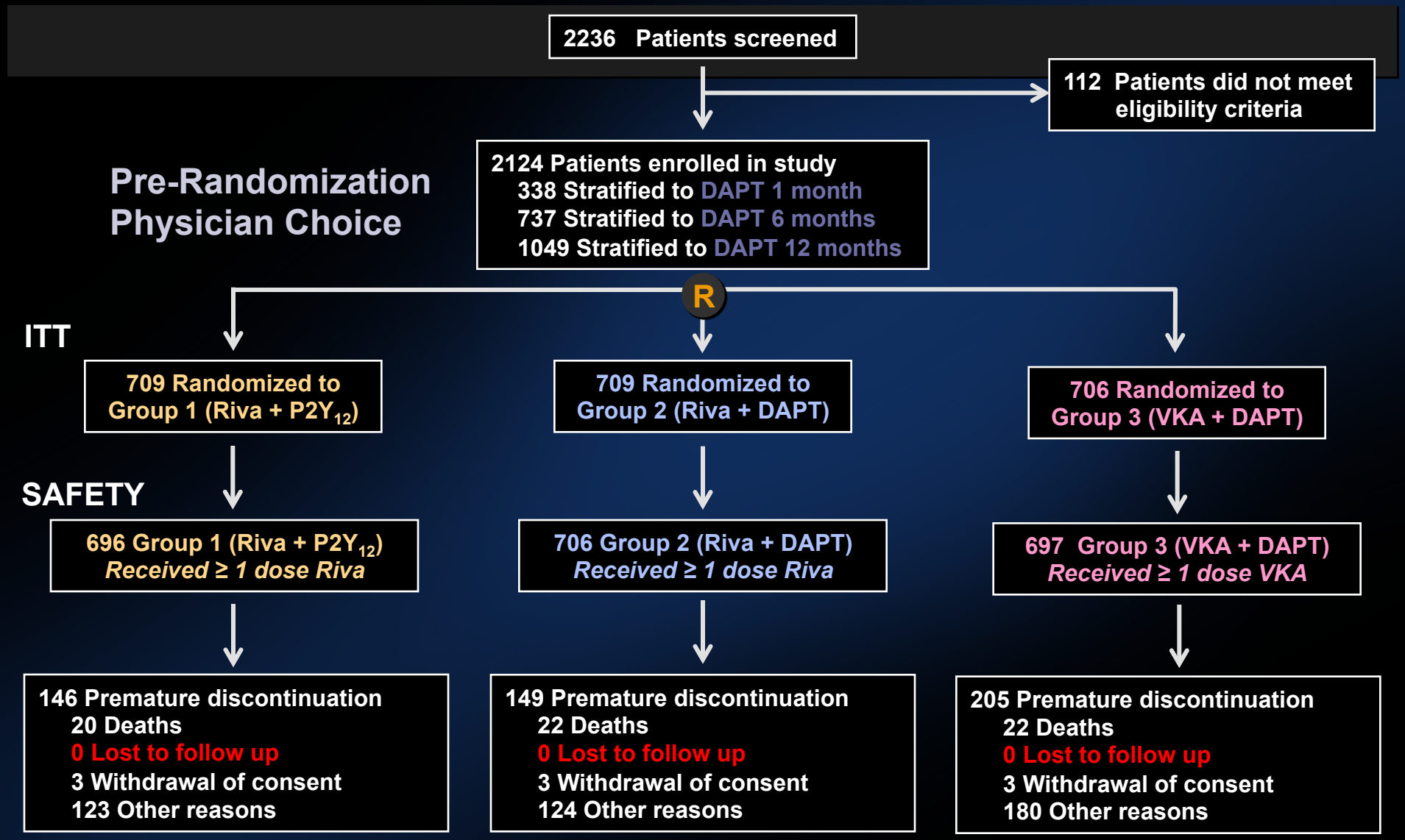
VKA$^{\Delta}$ (target INR 2.0-3.0)
Aspirin 75-100 mg qd

- Primary endpoint: TIMI major + minor + bleeding requiring medical attention
- Secondary endpoint: CV death, MI, and stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

*Rivaroxaban dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.
†Alternative $P2Y_{12}$ inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.
‡Low-dose aspirin (75-100 mg/d). Δ Open label VKA

Gibson et al. AHA 2016

CONSORT Diagram



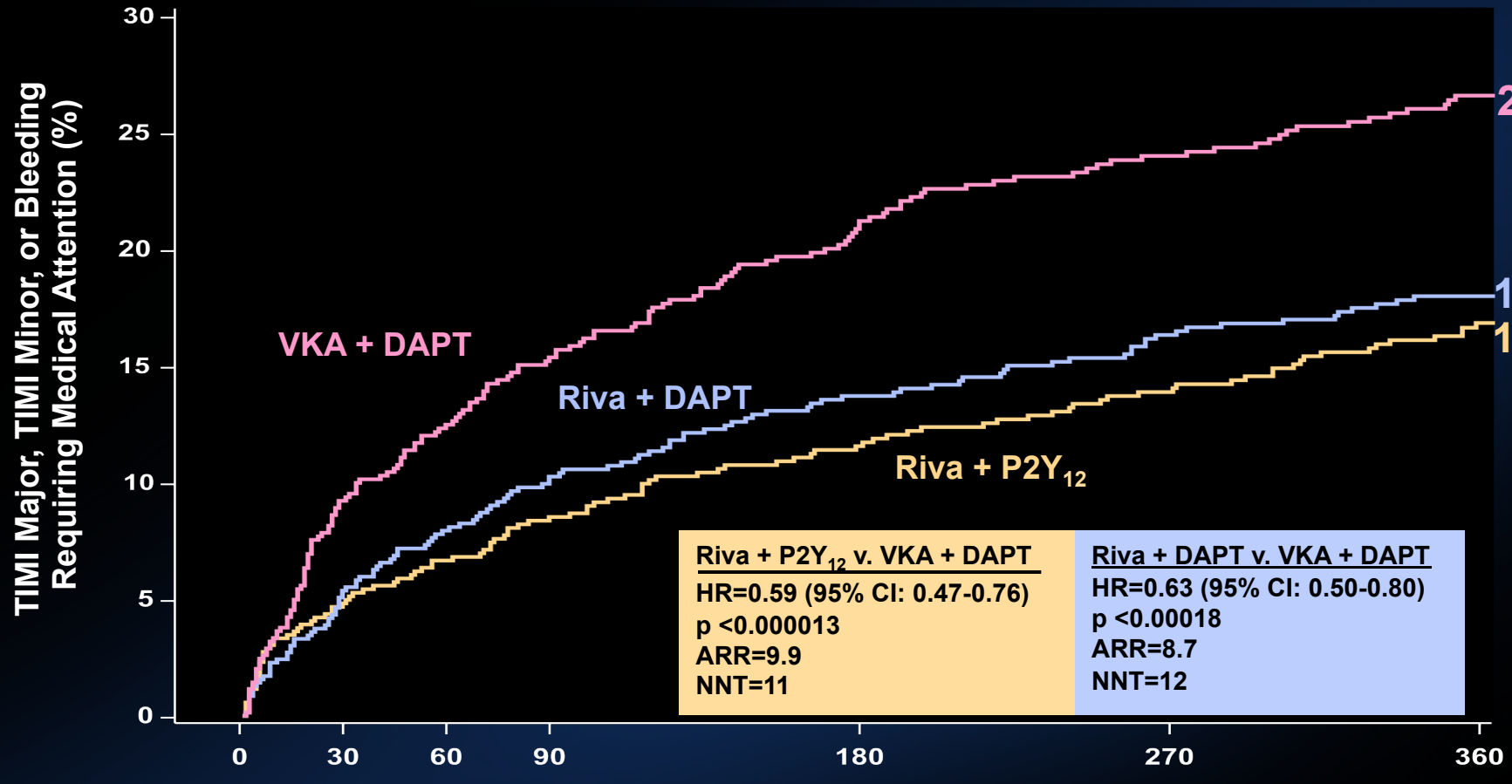
Gibson et al. AHA 2016

Baseline Characteristics

	Riva + $P2Y_{12}$ (N=709)	Riva + DAPT (N=709)	VKA + DAPT (N=706)
Age, mean ± SD	70.4 ± 9.1	70.0 ± 9.1	69.9 ± 8.7
Sex, female, n (%)	181 (25.5%)	174 (24.5%)	188 (26.6%)
Diabetes Mellitus, n (%)	204 (28.8%)	199 (28.1%)	221 (31.1%)
Type of Index Event, n (%)			
NSTEMI	130 (18.5%)	129 (18.4%)	123 (17.8%)
STEMI	86 (12.3%)	97 (13.8%)	74 (10.7%)
Unstable Angina	145 (20.7%)	148 (21.1%)	164 (23.7%)
Stable Angina	340 (48.5%)	329 (46.8%)	330 (47.8%)
Drug-eluting stent, n (%)	464 (65.4%)	471 (66.8%)	468 (66.5%)
Type of Atrial Fibrillation, n (%)			
Persistent	146 (20.6%)	146 (20.6%)	149 (21.1%)
Permanent	262 (37.0%)	238 (33.6%)	243 (34.5%)
Paroxysmal	300 (42.4%)	325 (45.8%)	313 (44.4%)

Gibson et al. AHA 2016

Kaplan-Meier Estimates of First Occurrence of Clinically Significant Bleeding Events



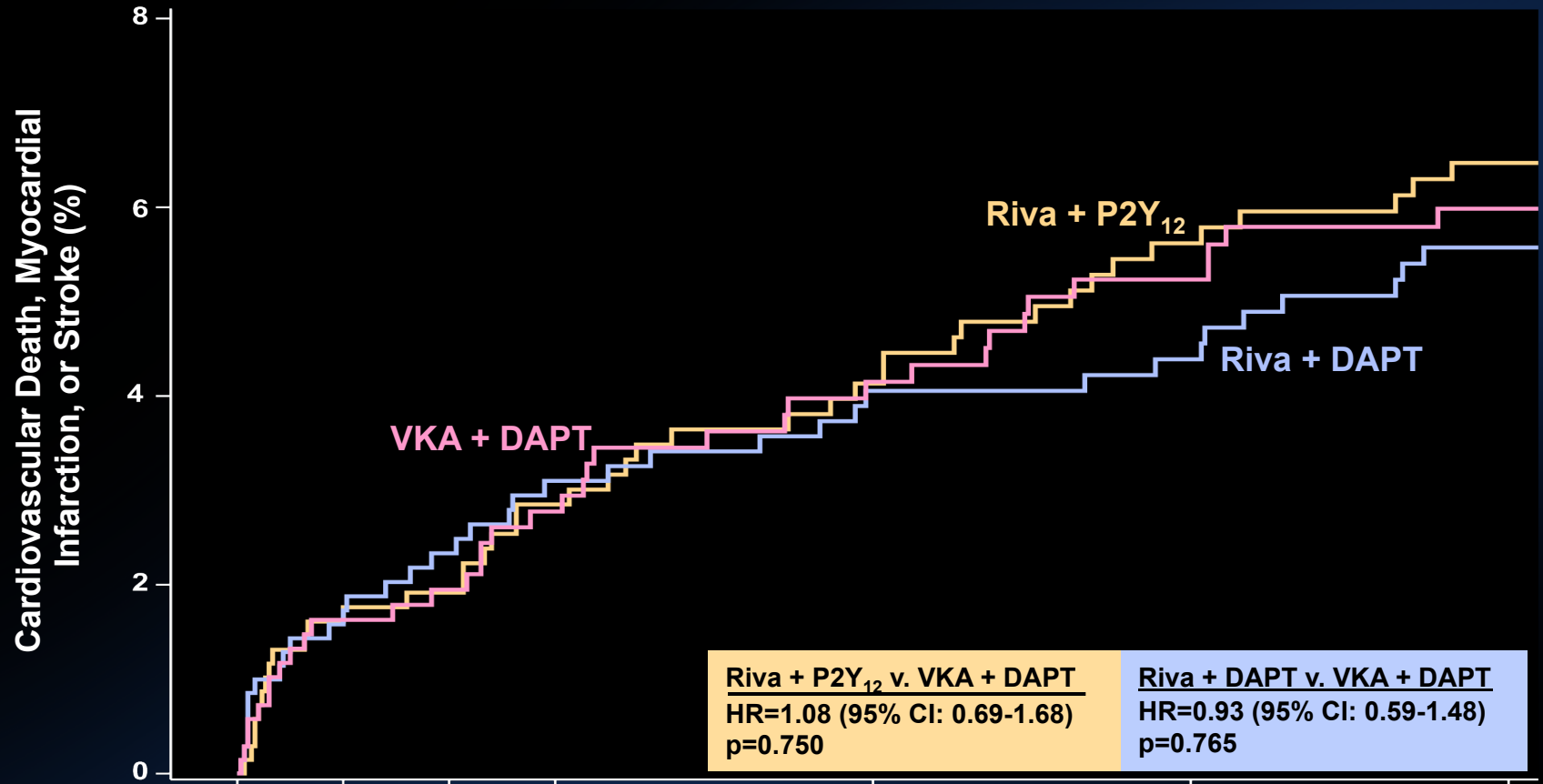
No. at risk

Riva + P2Y$_{12}$	696	628	606	585	543	510	383
Riva + DAPT	695	696	666	579	563	500	409
VKA + DAPT	697	593	555	521	461	426	329

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Clinically significant bleeding is the composite of TIMI major, TIMI minor, and BRMA.
Hazard ratios as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.
Log-Rank P-values as compared to VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) two-sided log rank test.

Gibson et al. AHA 2016

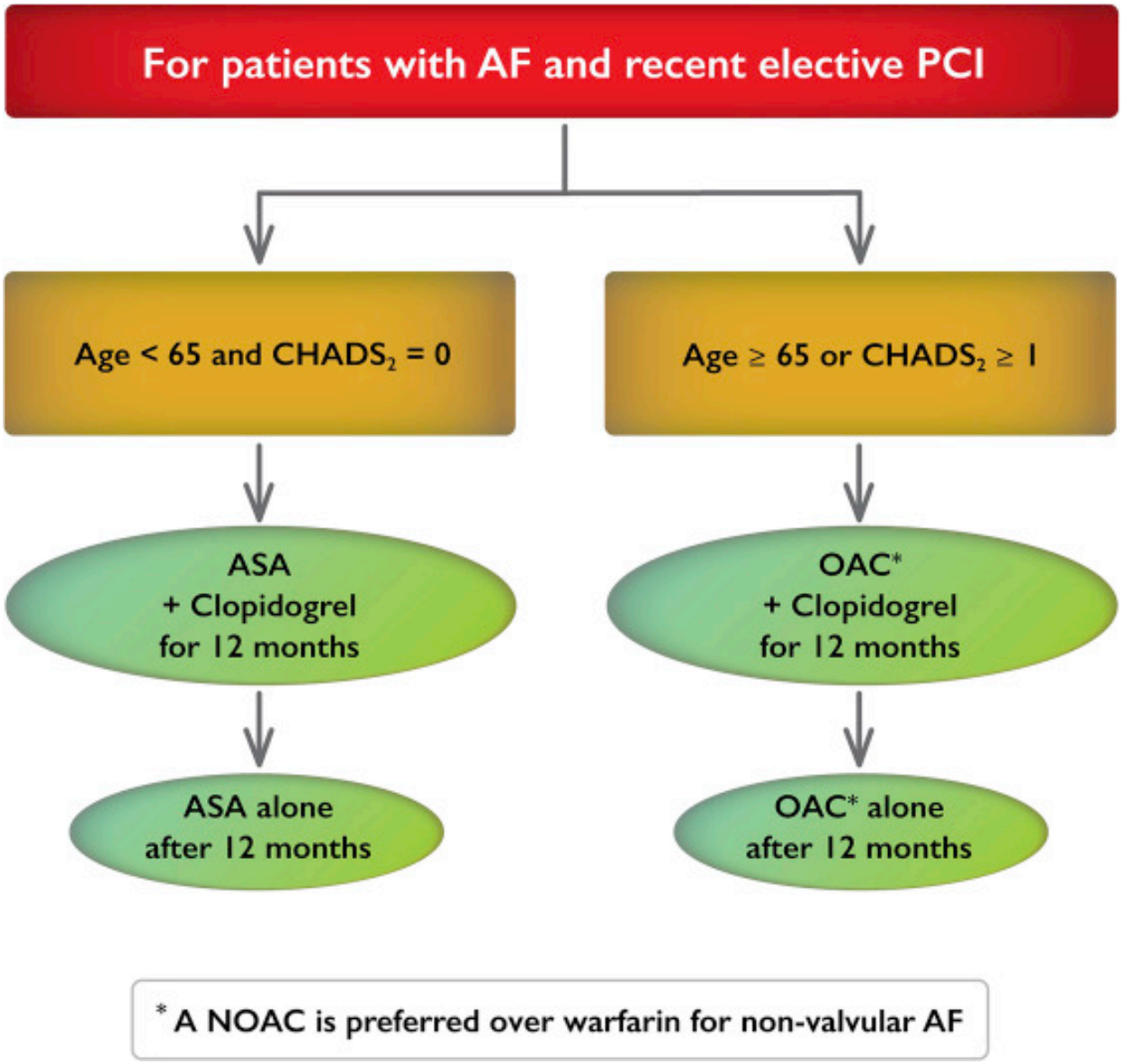
Kaplan-Meier Estimates of First Occurrence of CV Death, MI or Stroke



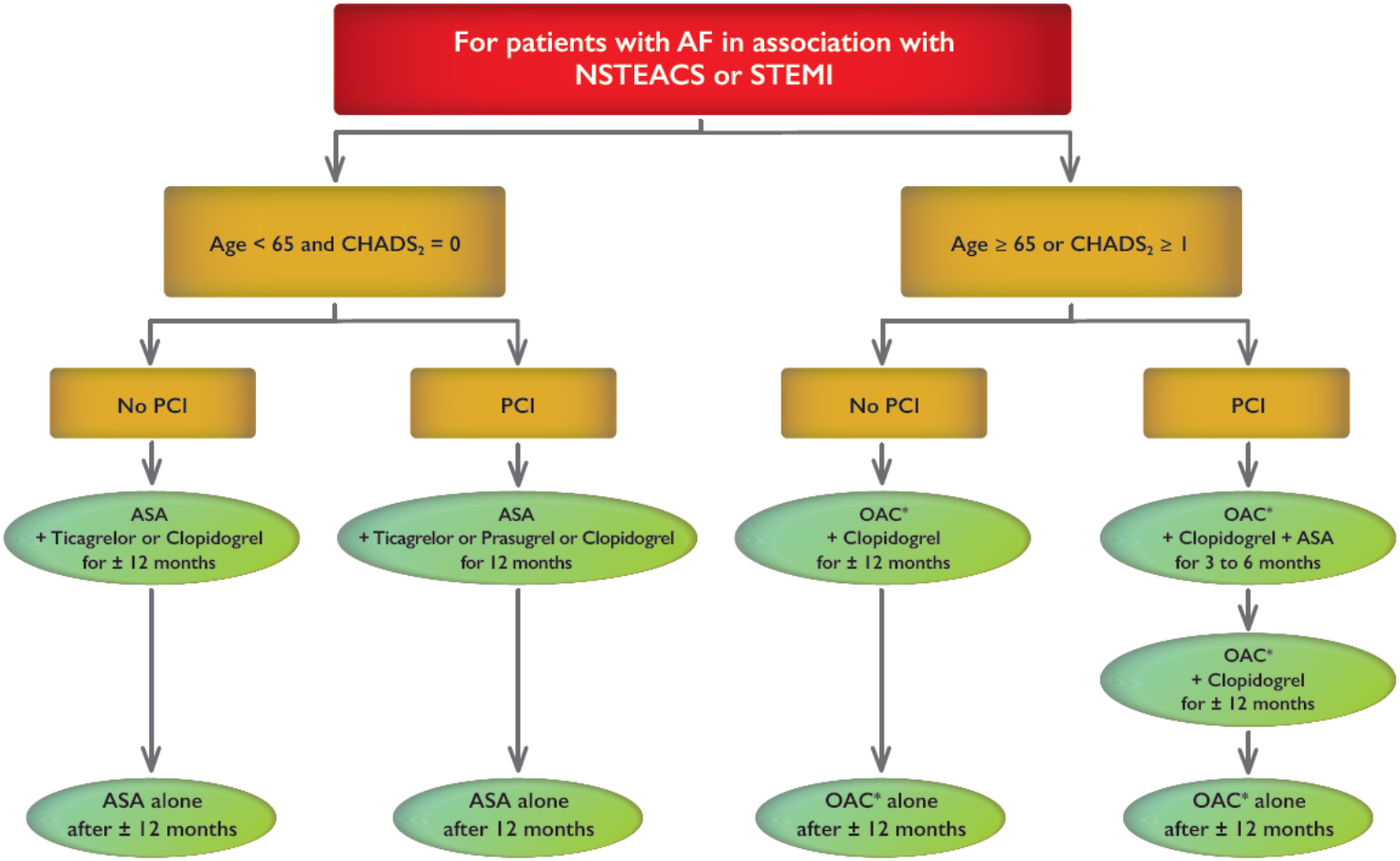
No. at risk							
Riva + P2Y$_{12}$	694	648	633	621	590	562	430
Riva + DAPT	704	662	640	628	596	570	457
VKA + DAPT	695	635	607	579	543	514	408

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Composite of adverse CV events is composite of CV death, MI, and stroke.
Hazard ratios as compared to VKA group are based on the (stratified, only for the Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.
Log-Rank P-values as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/115 mg QD comparing VKA) two-sided log rank test.
6 Subjects were excluded from all efficacy analyses because of violations in Good Clinical Practice guidelines

Gibson et al. AHA 2016

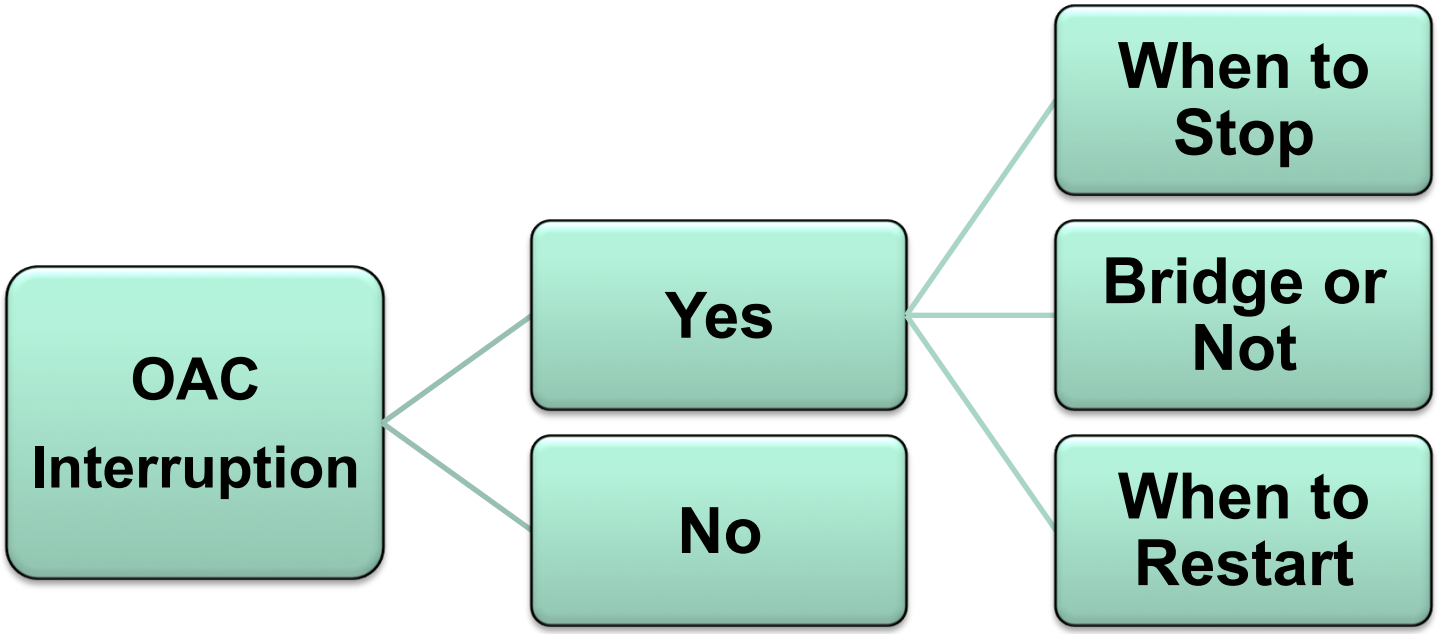


Canadian Journal of Cardiology 2016 32, 1170-1185DOI: (10.1016/j.cjca.2016.07.591)



Concomitant AF and CAD – CCS Guidelines Update 2016

Periprocedural Management of Anticoagulation



Low Risk of Bleeding

Interruption Not Necessary

- Dental extractions (1 or 2 teeth), cleaning, and most dental procedures (including root canal)
- Skin biopsy or skin cancer removal
- Cataract surgery
- Dermatologic procedures (e.g. biopsy)
- Gastroscopy or colonoscopy without biopsy
- Selective invasive procedures: paracentesis, thoracentesis, arthrocentesis
- Coronary angiography
- Cardiac device implantation (pacemaker, ICD)

Practical Tip: http://thrombosiscanada.ca/?page_id=502&calc=perioperativeAnticoagulantAlgorithm

Intermediate Risk of Bleeding

Interruption Necessary

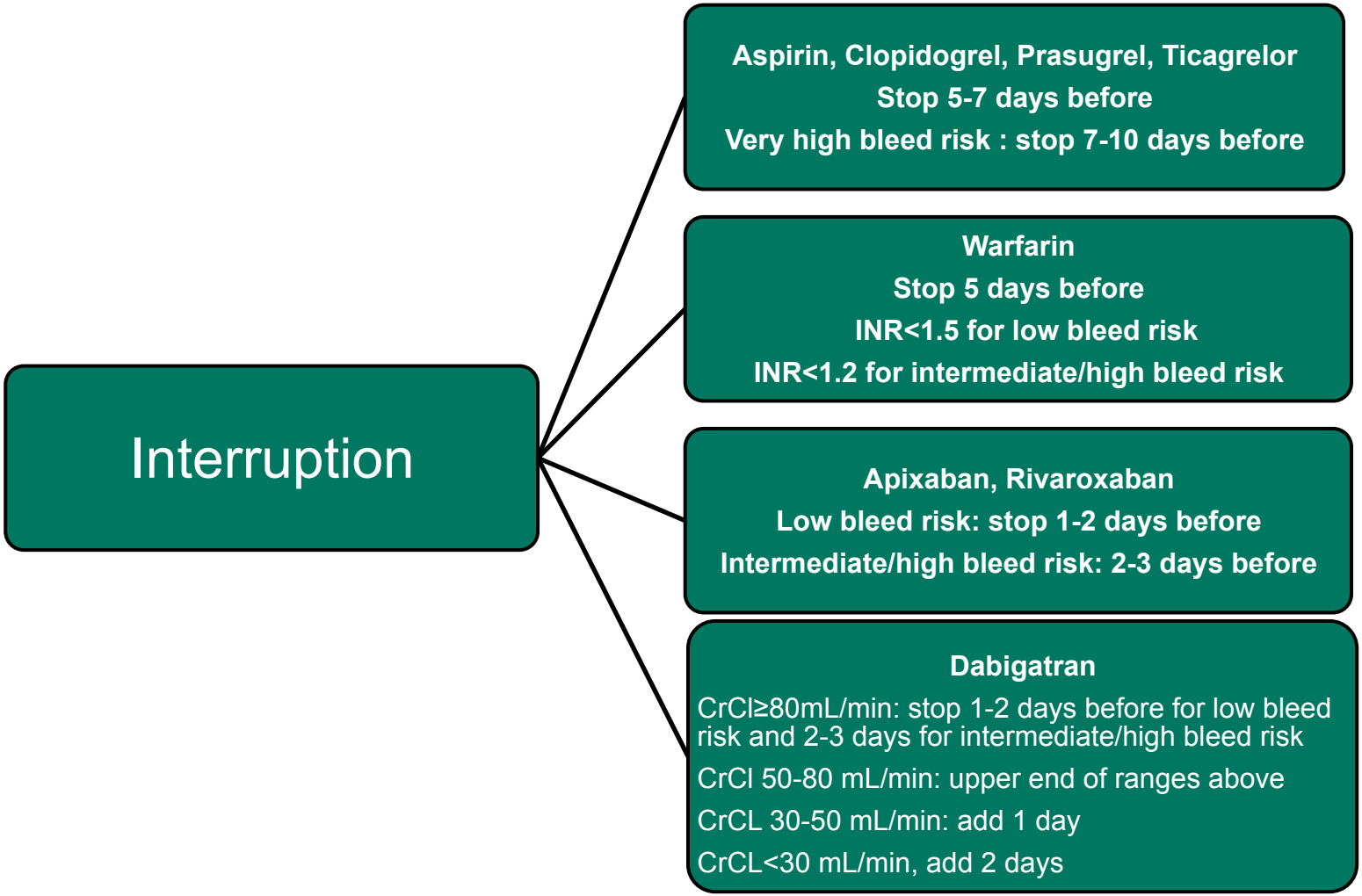
- Certain intraabdominal surgery (including laparoscopic cholecystectomy, and laparoscopic inguinal hernia repair)
- Certain intrathoracic surgery (including breast surgery)
- Bone marrow aspirate and biopsy
- Lymph node biopsy
- Other orthopedic surgery
- Other vascular surgery

High Risk of Bleeding

Interruption Necessary

- Neurosurgery (Intracranial or surgery)
- Neuroaxial procedure (Spinal or epidural anesthesia)
- Cardiac surgery (CABG or heart valve replacement)
- Major vascular surgery (Aortic aneurysm repair, aortofemoral bypass)
- Major urologic surgery (prostatectomy, bladder tumour resection)
- Major lower limb orthopedic surgery (hip/knee joint replacement)
- Lung resection surgery
- Extensive cancer surgery (pancreas, liver resection)
- Intestinal anastomosis surgery
- Selected biopsy procedures (kidney, prostate, and cervical cone)
- Reconstructive plastic surgery
- Pericardiocentesis
- Colonic polypectomy or biopsy

Timing of Antithrombotic Interruption



Bridging for AF / AFL Patients on Warfarin When Is It Recommended?

- **Recommended for patients at high risk of thromboembolic events**
  - CHADS2 ≥4 (was ≥3 in prior guidelines)
  - Mechanical heart valve
  - Stroke, TIA, thromboembolic events <3 months
  - Rheumatic heart disease
- **Pre-procedure**: when INR is below therapeutic, start LMWH or UFH
  - LMWH should be stopped 24 hours prior to the procedure
  - UFH should be stopped 4-6 hours prior to the procedure
- **Post-procedure**: LMWH or UFH restarted when hemostasis is established (~24 hours for a procedure with a low bleeding risk, 48-72 hours for procedures with intermediate/high risk of bleeding). Use prophylactic dosages for the first 24-72 hours and then increase to therapeutic dosages. Continue until INR is therapeutic.

Macle L, et al. 2016 Focused Update of the CCS Guidelines for the Management of Atrial Fibrillation. Canadian Journal of Cardiology, Oct. 2016;32(10): 1170 – 1185.

The Bridge Trial: Outcomes and Conclusions

Table 3. Study Outcomes.

Outcome	No Bridging (N=918)	Bridging (N=895)	P Value
	number of patients (percent)		
Primary			
Arterial thromboembolism	4 (0.4)	3 (0.3)	0.01*, 0.73†
Stroke	2 (0.2)	3 (0.3)	
Transient ischemic attack	2 (0.2)	0	
Systemic embolism	0	0	
Major bleeding	12 (1.3)	29 (3.2)	0.005†
Secondary			
Death	5 (0.5)	4 (0.4)	0.88†
Myocardial infarction	7 (0.8)	14 (1.6)	0.10†
Deep-vein thrombosis	0	1 (0.1)	0.25†
Pulmonary embolism	0	1 (0.1)	0.25†
Minor bleeding	110 (12.0)	187 (20.9)	<0.001†

* P value for noninferiority.
† P value for superiority.

Findings:

1. Arterial thromboembolism
(No bridge 0.4%, bridge 0.3%;
no bridge was non-inferior)
2. Major bleed
(No bridge 1.3%, bridge 3.2%;
p=0.005 in favor of no bridge)
3. Other events
(Death, MI, DVT, PE not significant;
Minor bleeding: no bridge 12%, bridge 20.9%; p<0.001 in favor of no bridge)

Conclusions:

In patients with AF requiring temporary interruption of warfarin treatment for an elective operation or invasive procedure, a strategy of forgoing bridging was non inferior to perioperative bridging for prevention of arterial thromboembolism and is associated with lower risk of major and minor bleeding.

Douketis et al. NEJM 2015; 373: 823-33

No Bridging in Patients on NOACs

Recommendation

We recommend no bridging (LMWH or UFH) for NVAF patients receiving NOACs who undergo elective surgery or invasive procedures requiring interruption of anticoagulation **(Strong Recommendation, Moderate-Quality Evidence).**

Macle L, et al. 2016 Focused Update of the CCS Guidelines for the Management of Atrial Fibrillation. Canadian Journal of Cardiology, Oct. 2016;32(10): 1170 – 1185.

MERCI!

INSTITUT DE CARDIOLOGIE DE MONTRÉAL

AFFILIÉ À Université de Montréal