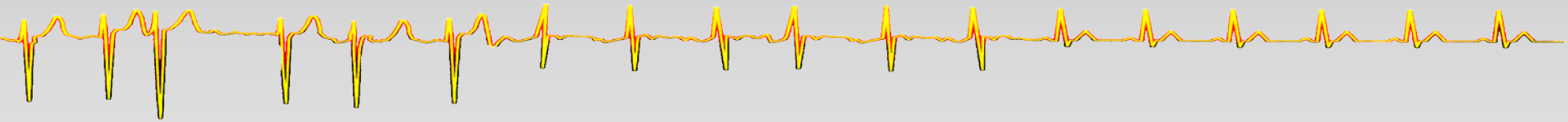
Atrial Fibrillation: Beyond Primary Care



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3/21/14

Disclosures

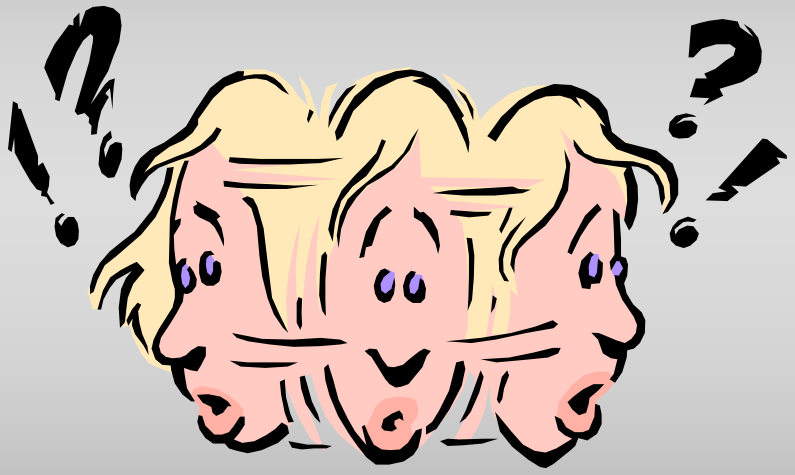
- Mary Eng Huntsinger
  - None
- Stephanie H. Yoakum
  - None

Objectives

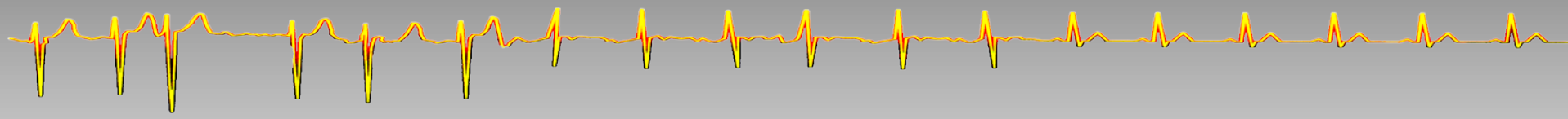
- List the primary etiologies of atrial fibrillation (AF)
- Discuss the difference in management between rate and rhythm control
- Discuss the different anticoagulation options for CVA prophylaxis related to AF

ABC’s of AF

- Who?
- What?
- Why?
- When?
- Where?



ABC’s of AF



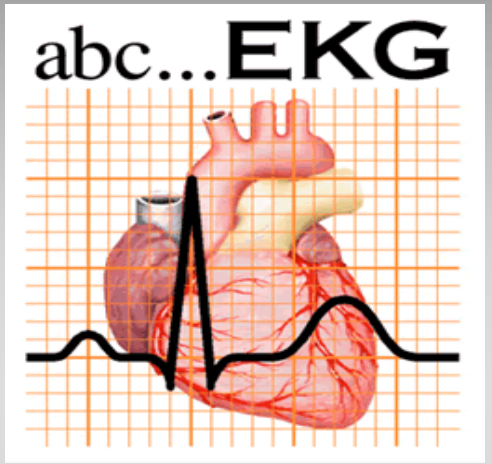
- Definition
- Incidence and prevalence
- Mechanism
- Classification / Types
- Evaluation of patient
- Recommendations for management

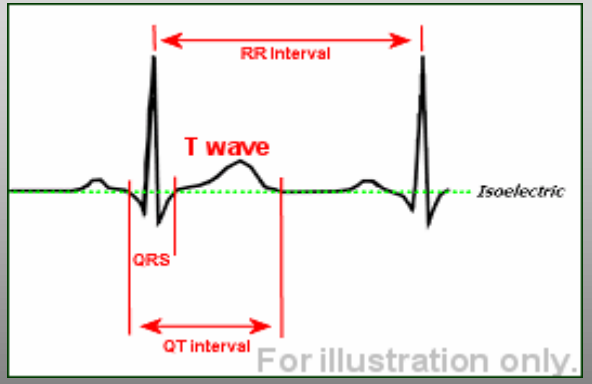
What is AF?

- Definition: a supraventricular tachyarrhythmia with uncoordinated atrial activation resulting in deterioration of atrial mechanical function
- On ECG, P wave is replaced by irregular fibrillatory waves with varying shape & timing
- Irregular ventricular response, depends on AV node, vagal & sympathetic tone, or drugs
- May occur with atrial flutter or other atrial tachycardias

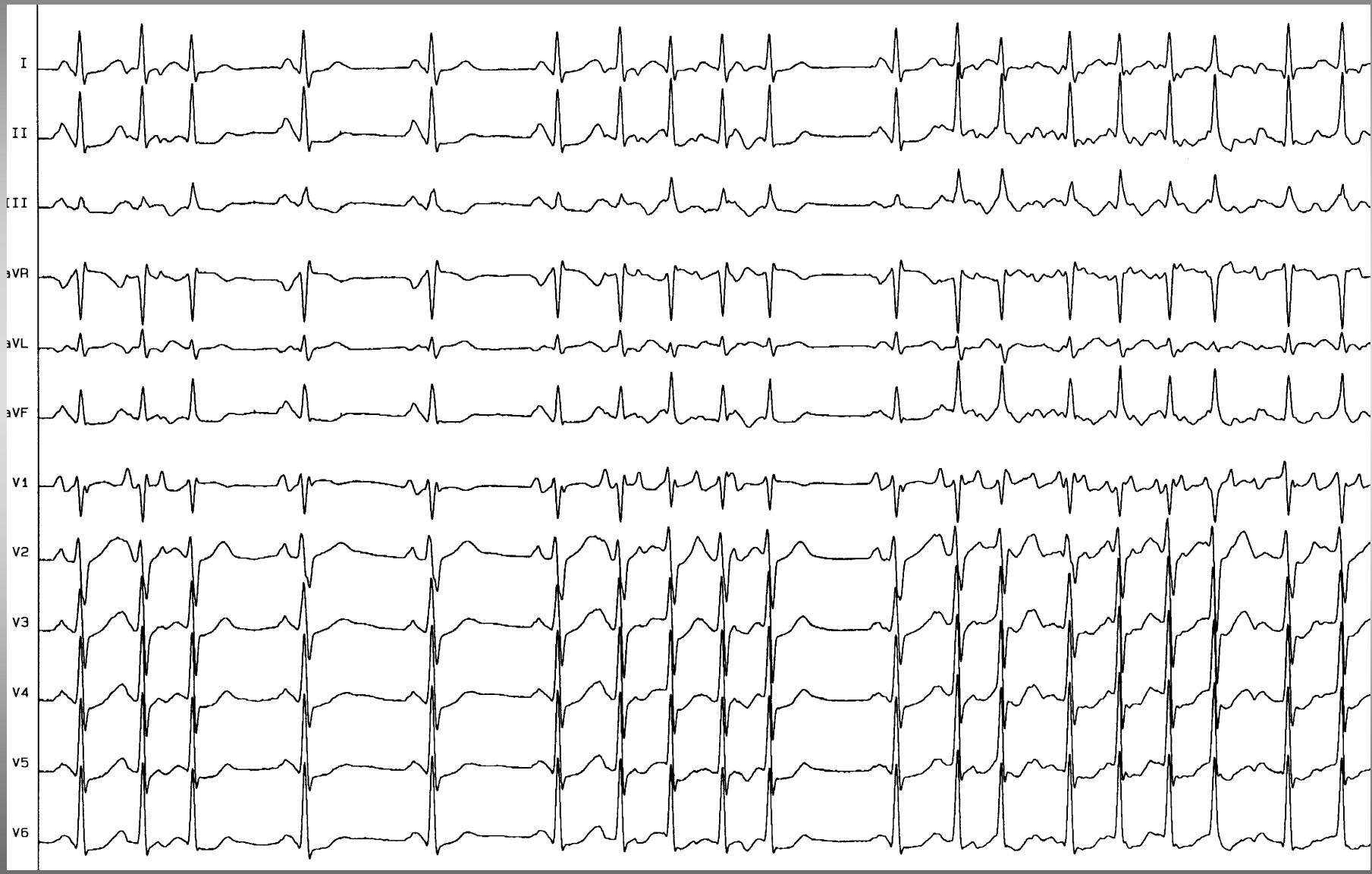
Normal Electrocardiogram (ECG)

- EKG = ECG
- P wave: atrial depolarization
- PR interval: AV conduction
- QRS complex: ventricular depolarization
- T wave: ventricular repolarization
- Normal sinus rhythm: things are regular

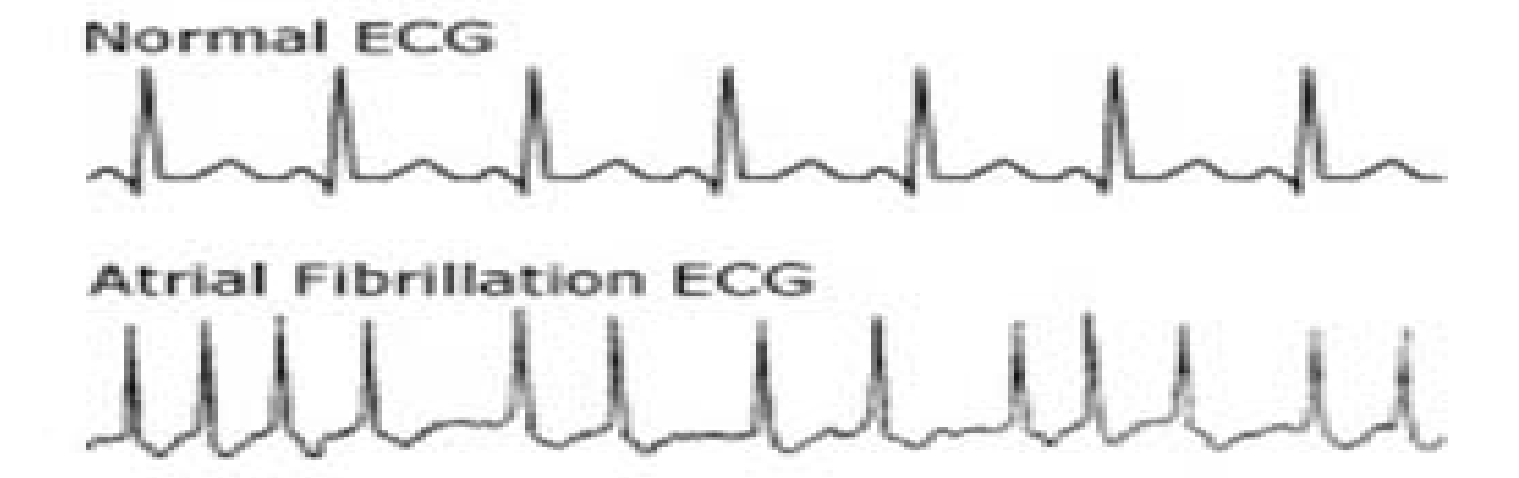




Atrial Fibrillation



AF: “Irregularly Irregular”



- ♥ Normal sinus rhythm (NSR)
  - P waves precedes QRS complexes
  - R-R waves are at regular intervals
- ♥ Atrial Fibrillation (AF)
  - No discernable P waves
  - Irregularly irregular R waves

Incidence & Prevalence

- AF is the most common arrhythmia
- AF accounts for ~ 1/3 of hospitalizations
- Affects ~2.3 million people in North America & 4.5 million in Europe
- Past 20 years, hospital admissions increased by 66%
  - Aging population
  - Rising prevalence of chronic heart disease
  - More frequent diagnosing

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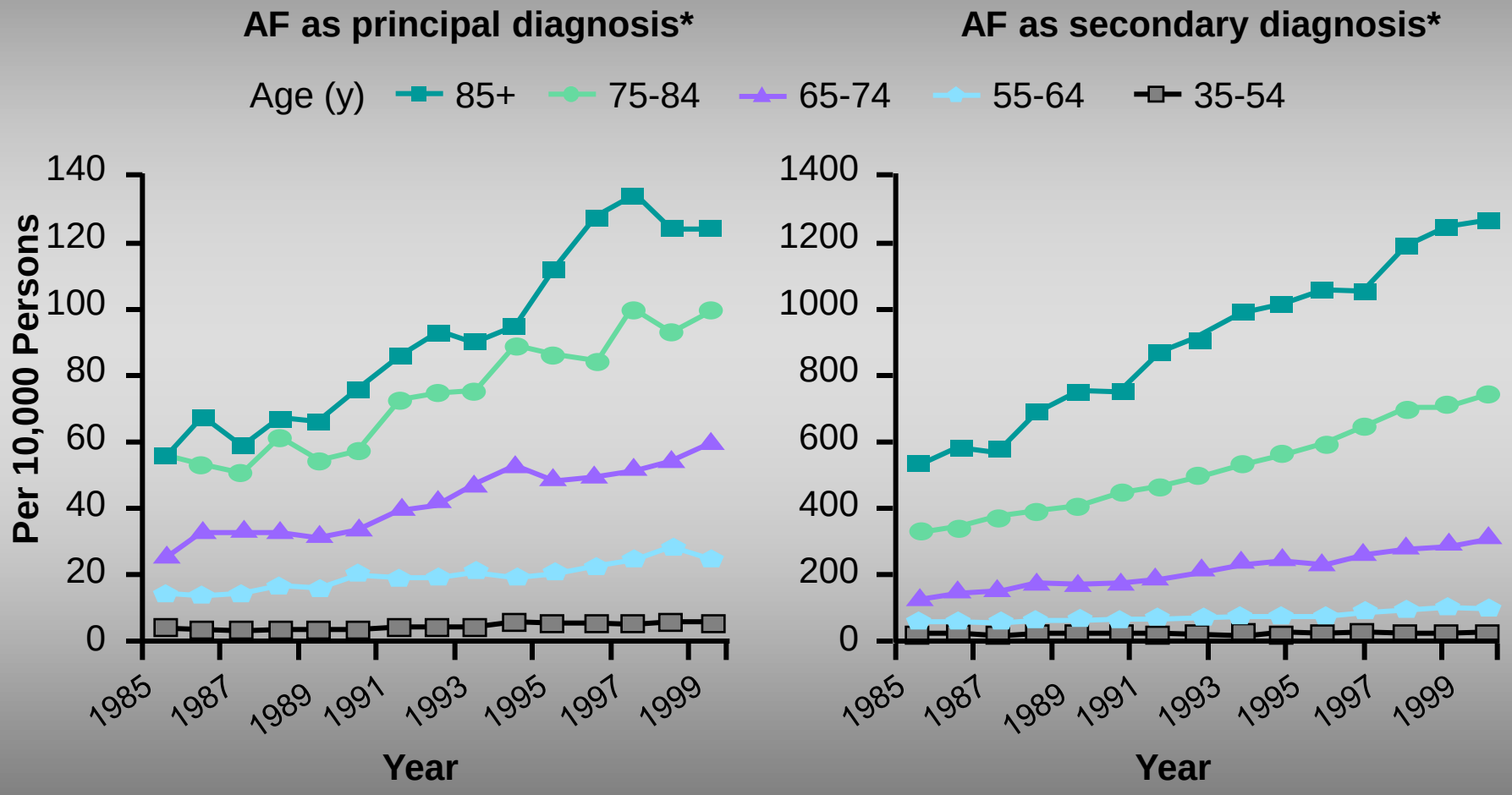
Hospitalizations for AF Are Increasing

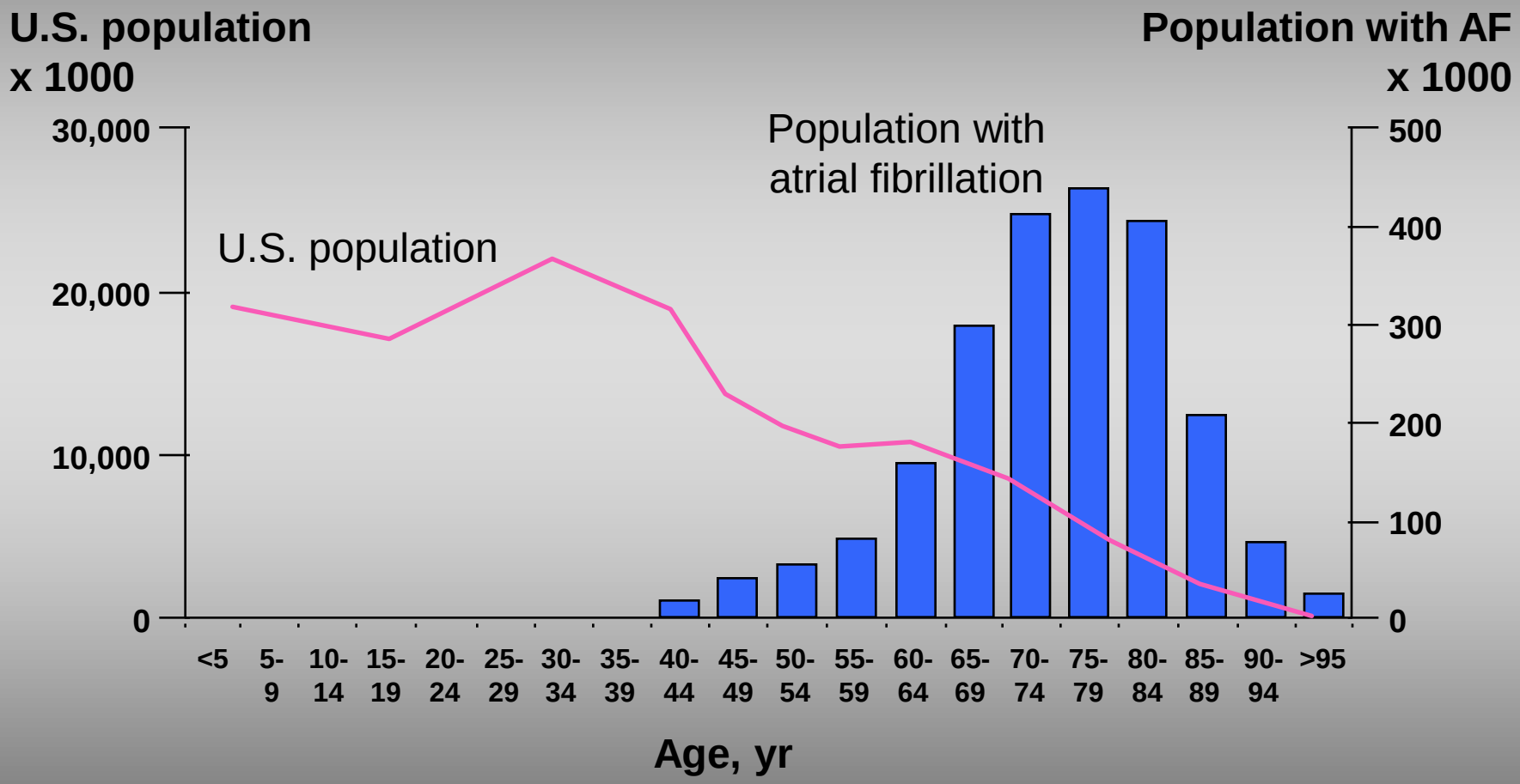
1985-1999: National Hospital Discharge Survey



*Also includes atrial flutter.

Wattigney et al. *Circulation*. 2003;108:711-716.

AF: Prevalence Increases with Age



2.3 million No America, 4.5 million in EU

Adapted from Feinberg WM. Arch Intern Med. 1995;155:469-473.

Costs of Atrial Fibrillation

- Past 20 years, 66% increase in hospital admissions
  - Aging population
  - Rising prevalence of chronic heart disease
  - More frequent diagnosing
- Expensive public health problem
  - $3600 per patient annually
  - Total cost burden, estimated $15.7 billion
- Distribution of cost
  - Hospitalizations (52%)
  - Drugs (23%)
  - Consults (9%)
  - Further investigations (8%)
  - Loss of work (6%)
  - Paramedical procedures (2%)

Heuzy, et al. Cost of Care Distribution in AF pt: The COCAF study, 2004 **AMHeart J** 147(1):121-126.

AF: EPIDEMIOLOGY

AF population predominantly >65 yrs with many co-morbidities

- AF prevalence estimate: 2.44 million and increasing (USA)
- Prevalence by age distribution:
  - 45 – 54 (7%)
  - 55 – 64 (10%)
  - 65 – 74 (24%)
  - 75 – 84 (34%)
  - 85+ (25%)

- AF is associated with other underlying CV conditions:
  - Hypertension (37%)
  - Heart Failure (22.5%)
  - Coronary Artery Disease (18%)
  - Diabetes (15%)
  - AMI (4%)
- Annual hospital admissions for AF in 2001: 384,000

Etiologies & Predisposing Factors

- EP abnormalities:
  - Focal AF
  - AVNRT
- Atrial Pressure Elevations:
  - Valvular disease
  - Myocardial disease leading to systolic or diastolic dysfunction
- Atrial Ischemia
- Inflammatory Atrial disease
- Sleep Apnea
- Primary or Metastatic disease
- Congenital HD

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Etiologies & Predisposing Factors, p.2

- ♥ Drugs:
  - Alcohol or/or caffeine
- ♥ Endocrine Disorders
  - Hyperthyroidism
- ♥ Neurogenic
- ♥ Post-operative: ⇑ in Autonomic tone
- ♥ Idiopathic (lone AF)
- ♥ Familial AF

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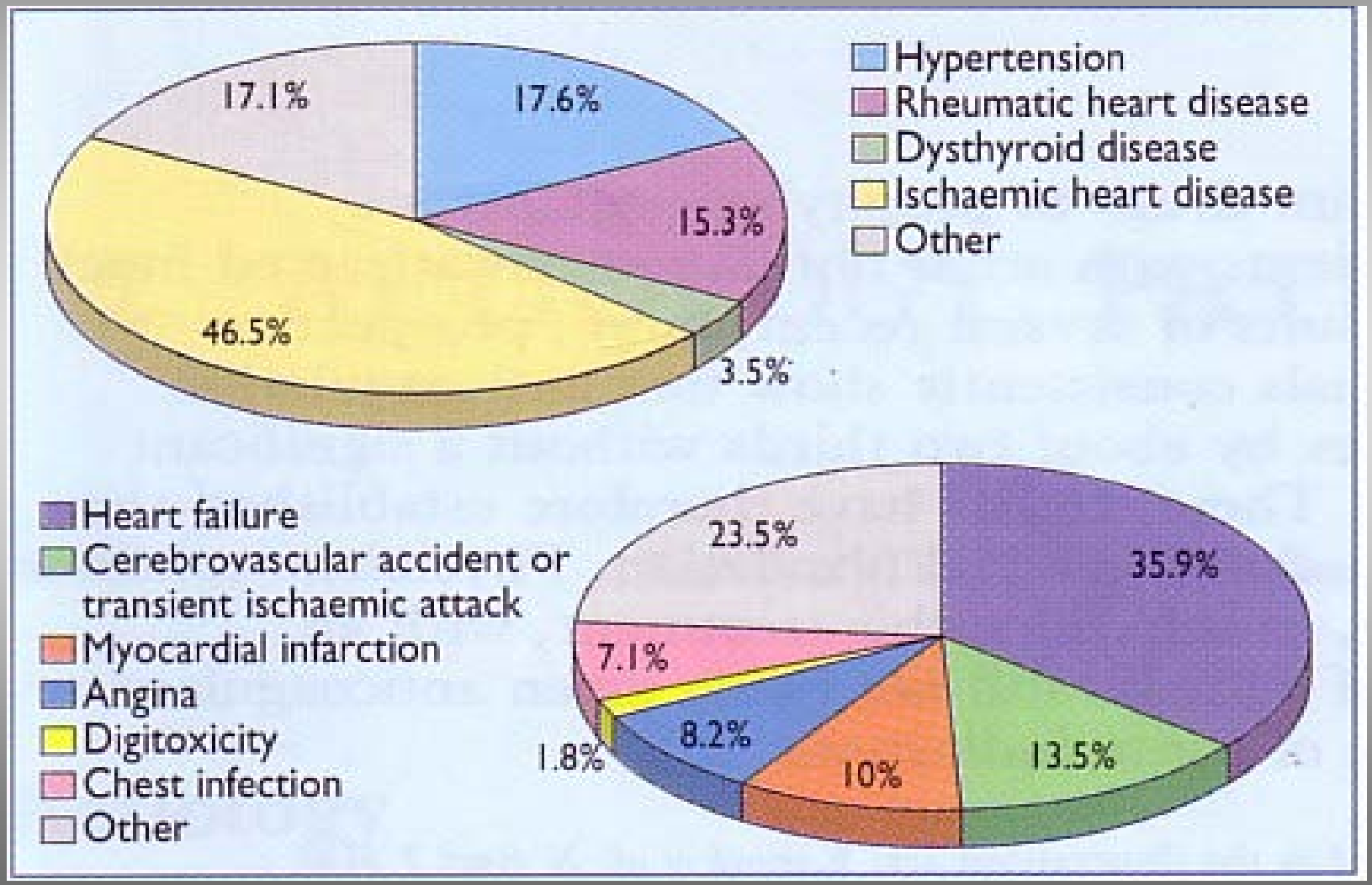
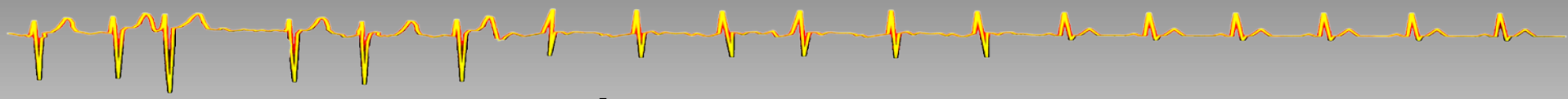
Causes of AF Among Emergency Admission to Hospital



Lip, GY, DG Beevers, 1996 UK.

AF Risk Factors



- Age
- Hypertension
- Heart disease
- Sleep apnea
- Other chronic conditions
- Alcohol use
- Drug use
- Family history
- Obesity

Clinical Consequences of AF

- Arrhythmia-associated symptoms: palpitations, dizziness, dyspnea, chest pain, fatigue
- Reduction in LV function, exercise tolerance, and QOL
- Tachycardia-mediated cardiomyopathy and CHF
- 2-fold ↑ in cardiac mortality
- 5-fold ↑ in risk of stroke
- Over 75,000 AF-strokes in US yearly
- Risk: 5 - 8% per year in high-risk patients; accounts for 15% of all strokes
  - Presumably due to LAA clot (95%)
- Significant burden to healthcare system

Clinical Presentation

- Asymptomatic
  - Found incidentally on exam
- Symptomatic
  - Palpitations
  - Chest pain
  - Dyspnea
  - Fatigue
  - Lightheadedness or syncope
  - CVA presentation

Clinical Evaluation

Basic & Minimum Evaluation

- History
- Physical Examination
- Electrocardiogram (12L ECG)
- Echocardiogram (transthoracic)
- Blood Tests
  - Thyroid, renal and hepatic functions
  - CBC

Clinical Evaluation

Additional Testing

- Six-minute walk
- Exercise Testing
- Holter Monitoring or Event Monitor
- Transesophageal Echocardiogram (TEE)
- Electrophysiology Study (EPS)
- Sleep Study
- Chest radiograph (CXR)

Management of Patients with AF

ACC/AHA/ESC Practice Guidelines

ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation—Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation)

Developed in Collaboration With the European Heart Rhythm Association and the Heart Rhythm Society

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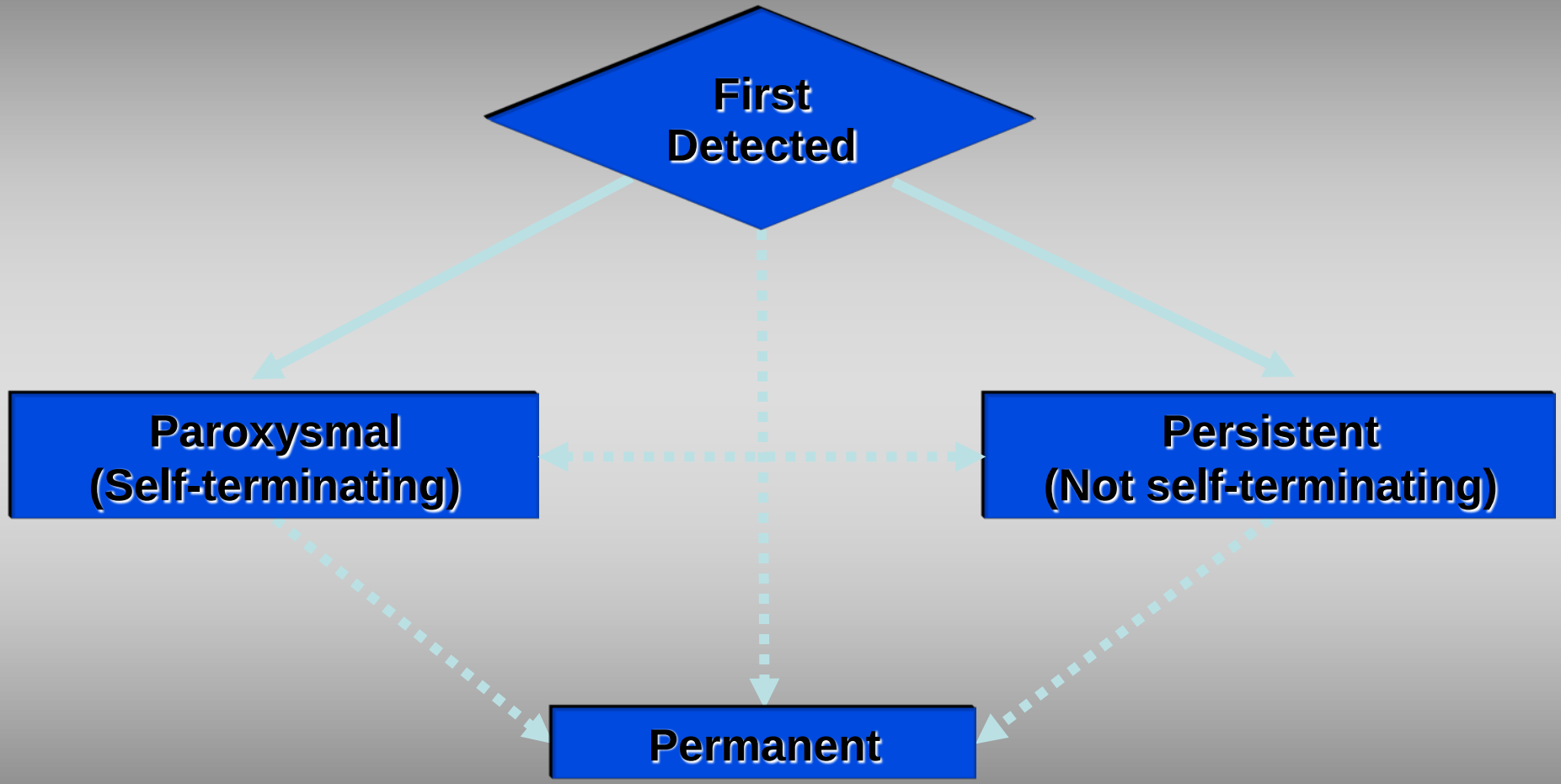
Classification of AF: 2006 *ACC/AHA/ESC Guidelines*



Fuster et al. *J Am Coll Cardiol*. 2006;48:854-906.

Classification

- Paroxysmal Atrial Fibrillation **(23%)**
  - Self terminating
  - Episodes lasts < 24-48 hours (most), & ≤ 7 days
  - May be recurrent episodes
- Persistent Atrial Fibrillation **(38%)**
  - Episodes lasts > 7 days, < 6 months
  - Does not self terminate
- Permanent Atrial Fibrillation **(37%)**
  - Cardioversion failed or not attempted
  - Usually > 30 days without reversible cause
- "Lone" Atrial Fibrillation **(< 12%)**
  - No identifiable cardiopulmonary abnormality
  - No RF of >75, Htn, HF, structural heart disease

Rx: Classifications & Levels

- Classification of recommendations:
  - Class I: Favorable evidence of benefit of treatment
  - Class II: Conflicting evidence/opinion
    - Class IIa: More likely to be of benefit/effective
    - Class IIb: Efficacy is less well established
  - Class III: Not useful, treatment may even be harmful
- Weight or level of evidence:
  - Level A: Data is derived from multiple clinical trials
  - Level B: Data derived from a limited # of trials
  - Level C: Expert consensus was the basis of recommendation

Treatment of AF

- Strategic objectives to management:
  - Rate control
    - Control ventricular rate before you try to change the rhythm
  - Correction of rhythm disturbance
    - Rhythm control is strategy attempts restoration or maintenance of sinus rhythm
  - Prevention of thromboembolism
    - Antithrombotic therapy
- Pharmacological & non-pharmacological treatment options

Therapeutic Approaches

- Pharmacologic
  - Rate Control: control ventricular rate
  - Rhythm control: pharmacologic cardioversion
  - Thromboembolic prevention: anticoagulation
- Nonpharmacologic
  - Direct current cardioversion
  - Surgical ablation (“MAZE”)
  - Catheter ablation
    - Pulmonary vein isolation and rotors
    - AV node ablation & pacemaker implantation
  - Pacemakers & Implantable Cardioverter-Defibrillators
    - Suppression of AF through pacing
    - Internal cardioversions for AF through ICDs

Rate vs Rhythm Control

- Rate control is to control ventricular response rate & anticoagulate
- Rhythm control is to restore sinus rhythm
- Which is better?

AFFIRM TRIAL 1995-1999

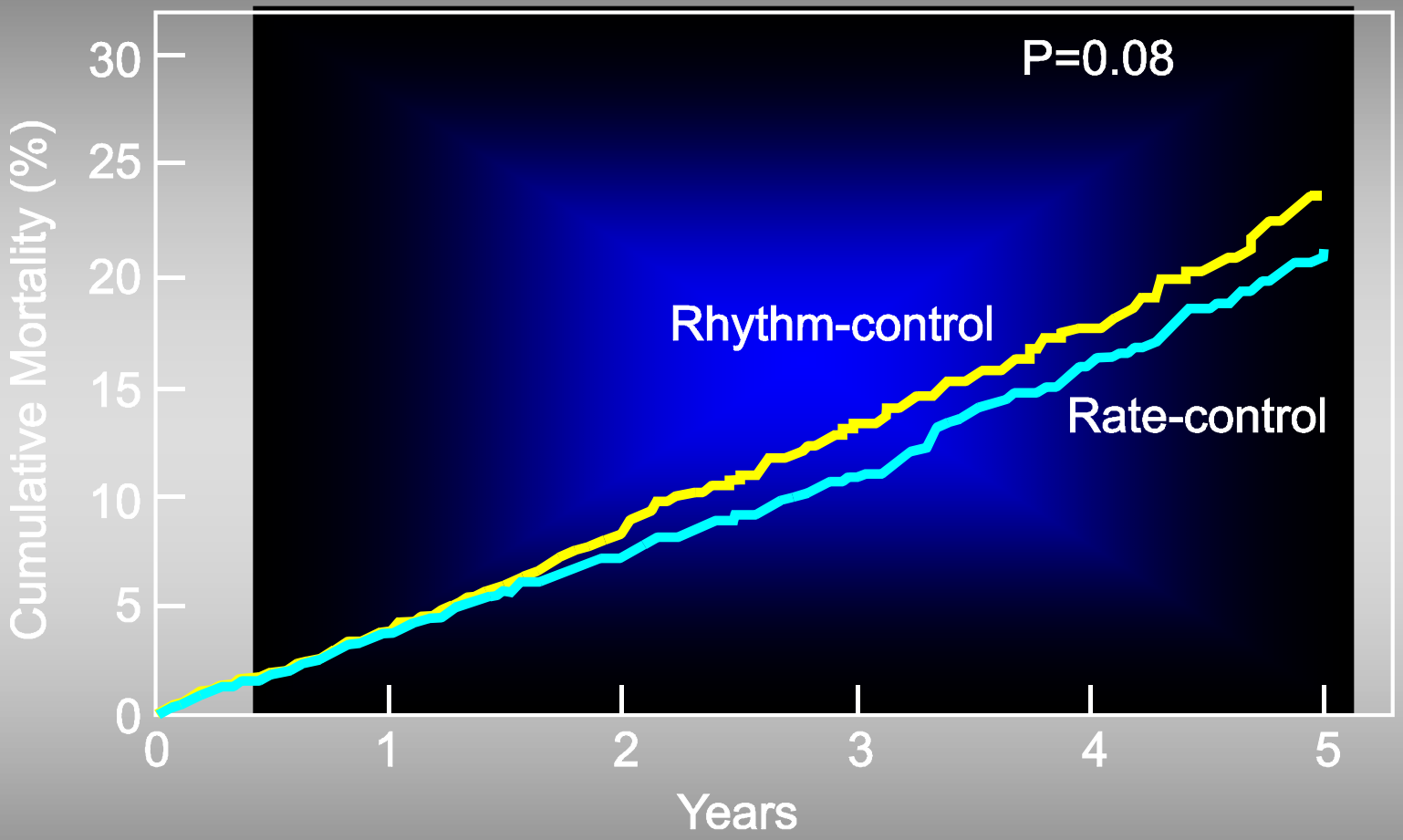
The New England
Journal of Medicine

A COMPARISON OF RATE CONTROL AND RHYTHM CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION

THE ATRIAL FIBRILLATION FOLLOW-UP INVESTIGATION OF RHYTHM MANAGEMENT (AFFIRM) INVESTIGATORS

- Rhythm control no better than rate control: mortality, stroke, quality of life
- Rate control should be the first approach to Rx
- Anticoagulation is warranted in ALL patients with Afib (and Aflutter) and CVA risks

Cumulative Mortality in Rhythm-Control vs Rate-Control



No. of Deaths		number (%)				
Rhythm control	0	80 (4)	175 (9)	257 (13)	314 (18)	352 (24)
Rate control	0	78 (4)	148 (7)	210(11)	275 (16)	306 (21)

NEJM 2002: 347;23

AF Rx: Rate Control

- **Class I**
  - Control HR w/ β-blocker or nondihydropyridine CCB (B)
  - In acute setting: slow HR w/ β-blocker or NDH CCB (B)
  - IV digoxin or amiodarone if no accessory pathways (B)
  - If symptomatic w/ activity, check HR control with exercise and adjust therapy (C)
- **Class IIa**
  - Digoxin + β-blocker or Digoxin + NDH CCB for rate control (B)
  - Ablate AV node or accessory pathway if cannot control or tolerate w/ drugs (B)
  - IV amio if other measures fail or is contraindicated (C)
  - If DCCV is not necessary in pts w/ accessory pathway, can give IV procainamide or ibutilide as alternative (C)

AF Rx: Rate Control, cont.

- **Class IIb**
  - Oral amio if inadequate rate control w/ β-blocker , NDH CCB, dig alone or in combo @ rest & exercise (C)
  - Hemodynamically stable & w/ accessory pathway: can give IV procainamide, disopyramide, ibutilide or amio (B)
  - If cannot control w/ drugs or suspect tachycardia induced CM, can ablate AV node (C)
- **Class III**
  - Dig should not be used alone as sole agent (B)
  - AV node ablation should not be done prior to trial of medications (C)
  - Decompensated HF & AF, IV CCB can worsen hemodynamic compromise (C)
  - Pts w/ pre-excitation syndrome & AF may have accelerated ventricular response w/ IV dig or NDH CCB, so do not give. (C)

Agents for Rate Control of AF

Acute Setting

AGENTS	MAJOR SIDE EFFECTS
Patients Without Accessory Pathway	
Esmolol	⇓ BP, Heart Block, ⇓ HR, asthma, HF
Metoprolol	⇓ BP, Heart Block, ⇓ HR, asthma, HF
Propranolol	⇓ BP, Heart Block, ⇓ HR, asthma, HF
Diltiazem	⇓ BP, Heart Block, Heart Failure
Verapamil	⇓ BP, Heart Block, Heart Failure
Patients With Accessory Pathway	
Amiodarone	⇓ HR, ⇓ BP, hypothyroidism, pulmonary toxicity, corneal deposits & optic neuropathy
Patients With Heart Failure & Without Accessory Pathway	
Digoxin	Digitalis toxicity, Heart Block, ⇓ HR
Amiodarone	⇓ HR, ⇓ BP, hypothyroidism, pulmonary toxicity, corneal deposits & optic neuropathy

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Agents for Rate Control of AF

Non-acute setting

AGENTS	MAJOR SIDE EFFECTS
Heart rate control	
Metoprolol	⇓ BP, Heart Block, ⇓ HR, asthma, HF
Propranolol	⇓ BP, Heart Block, ⇓ HR, asthma, HF
Diltiazem	⇓ BP, Heart Block, Heart Failure
Verapamil	⇓ BP, Heart Block, Heart Failure
HR control, pts with HF & without accessory pathway	
Digoxin	Digitalis toxicity, Heart Block, ⇓ HR
Amiodarone	⇓ HR, ⇓ BP, hypothyroidism, pulmonary toxicity, corneal deposits & optic neuropathy

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Classification of Antiarrhythmic Drugs

- ♥ Type I: Sodium Channel Blockers
  - Type IA
    - Disopyramide *(Norpace®)*
    - Procainamide *(Pronestyl®)*
    - Quinidine (*generic*)
  - Type IB
    - Lidocaine *(generic)*
    - Mexiletine *(Mexitil®)*
  - Type IC
    - Flecainide (*Tambocor®*)
    - Propafenone *(Rythmol®)*
- ♥ Type II: Beta Blockers

Antiarrhythmic Classification

- ♥ Type III
  - Amiodarone *(Cordarone®)*
  - Bretylium *(generic)*
  - Dofetilide (*Tikosyn®*)
  - Ibutilide *(Corvert®)*
  - Sotalol *(Betapace®)*
- ♥ Type IV: Ca+ Channel Blockers
  - Nondihydropyridine CCB (NDH CCB)
    - Verapamil
    - Diltiazem
- ♥ Type V
  - Adenosine, digoxin, mg sulfate

Cardioversion (Rhythm Control)

PHARMACOLOGIC

- Efficacy for some at least initially < 50%
- Low initial cost, Noninvasive
- Drug toxicity, potential proarrhythmia, interaction
- Thromboembolism prophylaxis recommended

DC CARDIOVERSION

- More effective : ~75%
- High cost, require anesthesia, sedation
- Thromboembolism risk : 1-7%
- Defibrillation threshold, biphasic energy better
- Complications: arrhythmia, cutaneous

Guideline Recommendations: Pharmacological Cardioversion

- **Class I**
  - Flecainide, dofetilide, propafenone, or ibutilide (A)
- **Class IIa**
  - Amiodarone (A)
  - Single oral dose of propafenone or flecinide. Use β-blocker or CCB first (C)
  - Outpatient amio for PAF or persistent AF (C)
- **Class IIb**
  - Quinidine or procainamide (C)
- **Class III**
  - Dig and/or sotalol (A)
  - Quinidine, procainamide, disopyramide and dofetilide should NOT be started outside of the hospital (B)

Guideline Recommendations: Direct Current Cardioversion

- **Class I**
  - When RVR does not respond promptly to medications in pts w/ ongoing MI, symptomatic hypotension, angina or HF (C)
  - AF w/pre-excitation & very rapid techy or hemodynamic instability (B)
  - Symptoms of AF are unacceptable to pt., can repeat DCCV after giving meds should AF return (C)
- **Class IIa**
  - Restore SR as along term management strategy (B)
  - Infrequent repeat DCCV if pts wants for symptomatic or recurrent AF (B)
- **Class III**
  - Frequent repeat DCCV for pts w/ short periods of sinus between relapses despite medication enhancements (C)
  - Dig toxicity or hyopkalemia, DCCV is contraindicated (C)

Guideline Recommendations: Pharmacological Enhancement of Cardioversion

- **Class IIa**
  - Pretreat w/ amio, flecainide, ibutilide, propafenone or sotalol (B)
  - In pt who relapse after successful DCCV, repeat w/ medications (B)
- **Class IIB**
  - β-blocker, disopyramide, diltiazem, dofetilide, procainamide or verapamil (C)
  - Can start meds as an outpatient if no heart disease (C)
  - Can start meds as outpatient if pt has heart disease, once drug safety has been established (C)

Agents for Pharmacologic CV of AF

Potential Adverse Effects

DRUG	ADVERSE EFFECTS
Amiodarone **(Pacerone®)**	**⇓ HR, ⇓ BP, QT prolongation, Toxicities: thyroid, pulmonary, hepatic; GI, eye complications, torsades**
Dofetilide **(Tikosyn®)**	**QT prolongation, torsades de pointes, dose adjusted for renal function, body size & age**
Flecainide **(Tambacor®)**	**Ventricular tachycardia, heart failure, conversion to Atrial flutter with rapid conduction**
Ibutelide **(Corvert®)**	**QT prolongation, Torsades de pointes**
Propafenone **(Rythmol®)**	**Ventricular tachycardia, heart failure, conversion to Atrial flutter with rapid conduction**
Sotalol **(Betapace®)**	**Torsades de pointes, Heart Failure, Bradycardia, COPD exacerbation**

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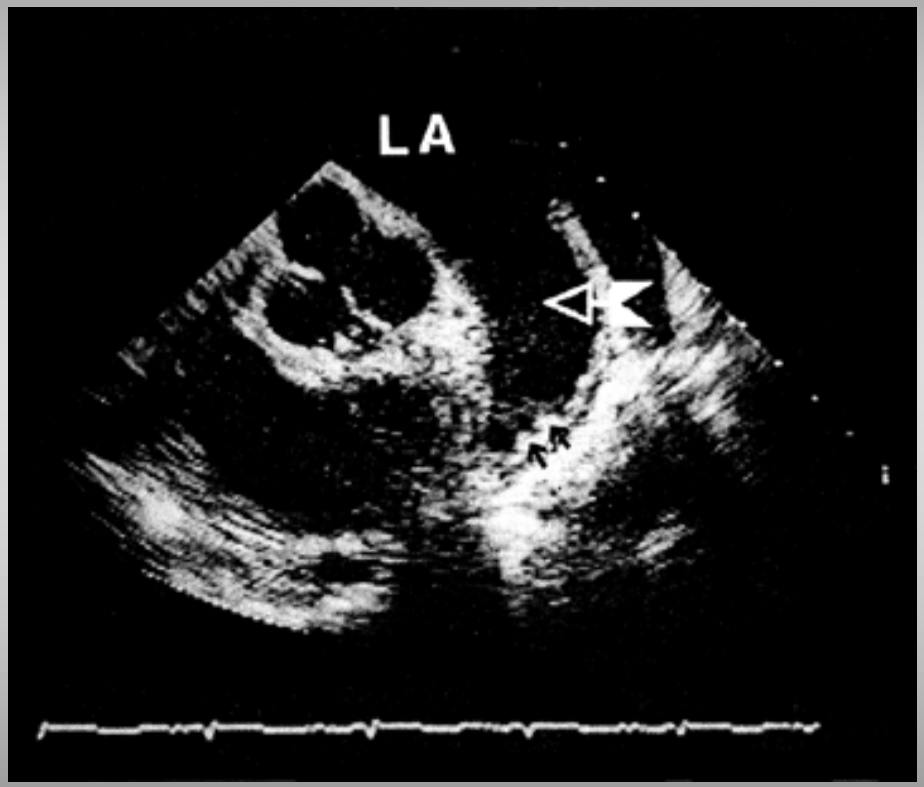
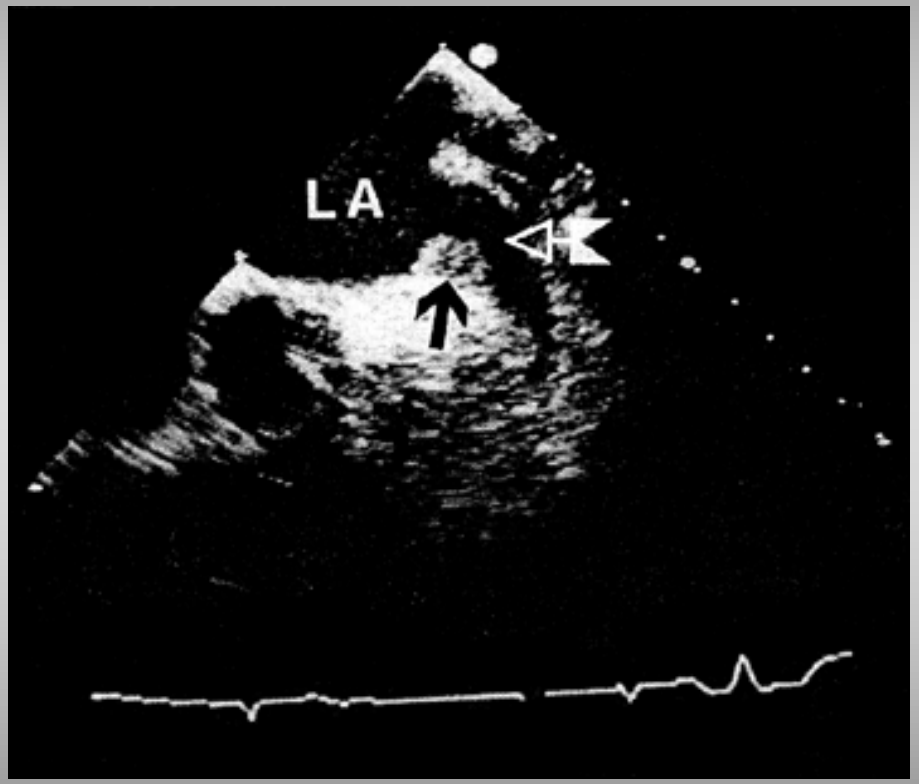
Clinical Aspects of Cardioversion

- Pre-procedure preparation: TEE?, electrolytes
- Safe in patients with pacemakers/ICD
- Indications: (Class 1A-C recommendations)
- Unresponsive to pharmacologic measures
- Symptomatic or unstable: angina, CHF, ↓ BP
- Pre-excitation with rapid tachycardia
- AF symptoms unacceptable to patient following antiarrhythmic therapy
- Complications: thromboembolism, more lethal arrhythmias, complications of anesthesia

TEE in Atrial Fibrillation



A Left Atrium



B Left Atrial Appendage Clot

Specificity - 98% Sensitive – 92%

Manning WJ. N Engl J Med. 1993;328:750-755.

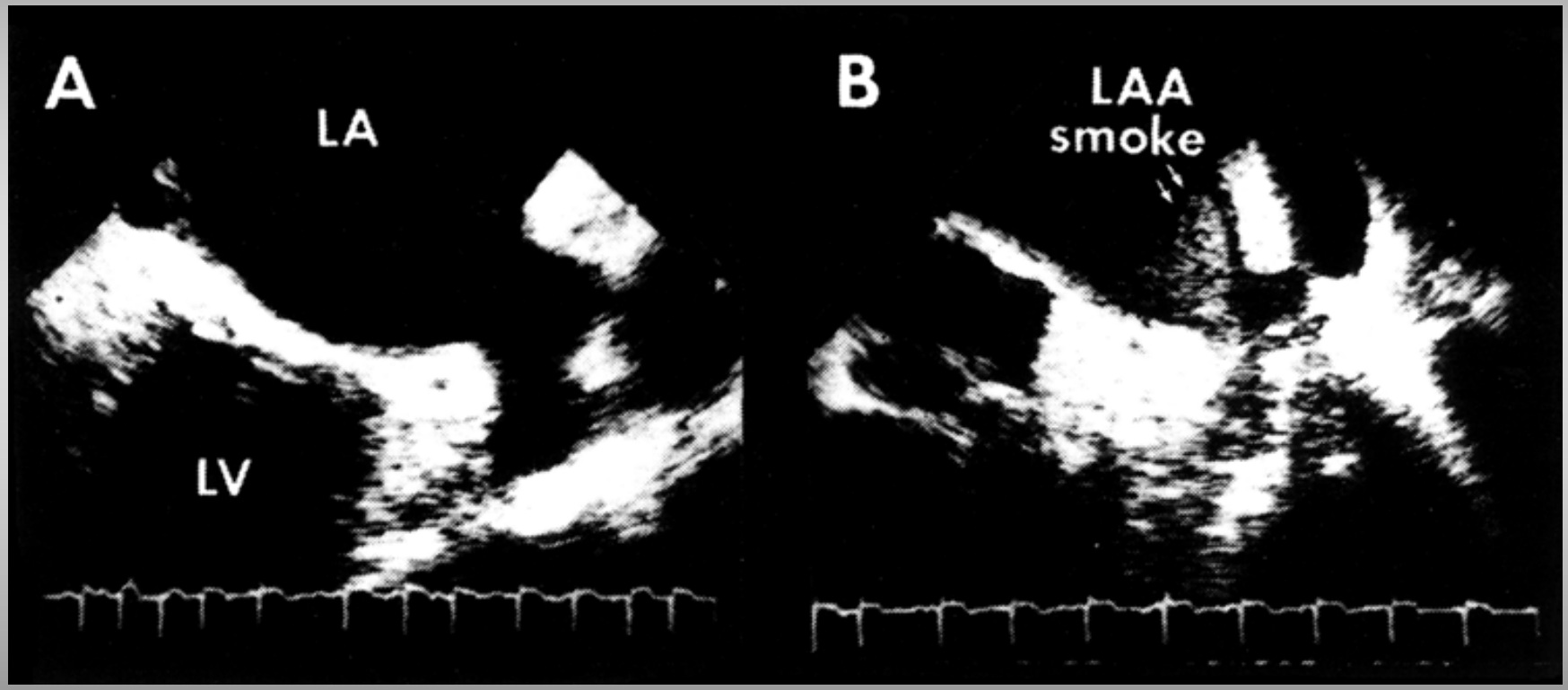
Atrial Thrombi in Patients With New AF

TEE Studies

Study	No. of Patients	No. (%) With Atrial Thrombi
Stoddard (1995)	206	37 (18%)
ACUTE Pilot (1997)	56	7 (13%)
Weigner (2001)	539	70 (13%)
ACUTE, Klein (2001)	619	76 (12%)
Corrado (1999)	123	11 (9%)

Corrado et al. *Chest.* 1999;115:140-143; Klein et al. *Ann Intern Med.* 1997:126:200-209; Klein et al. *N Engl J Med.* 2001;344:1411-1120; Stoddard et al. *Am Heart J.* 1995;129:1204-1215; Weigner et al. *Am J Med.* 2001;110:694-702.

Increase in Spontaneous Echo Contrast ("Smoke") Following Electrical Cardioversion



Left atrial appendage (LAA) before (A) and after (B) cardioversion

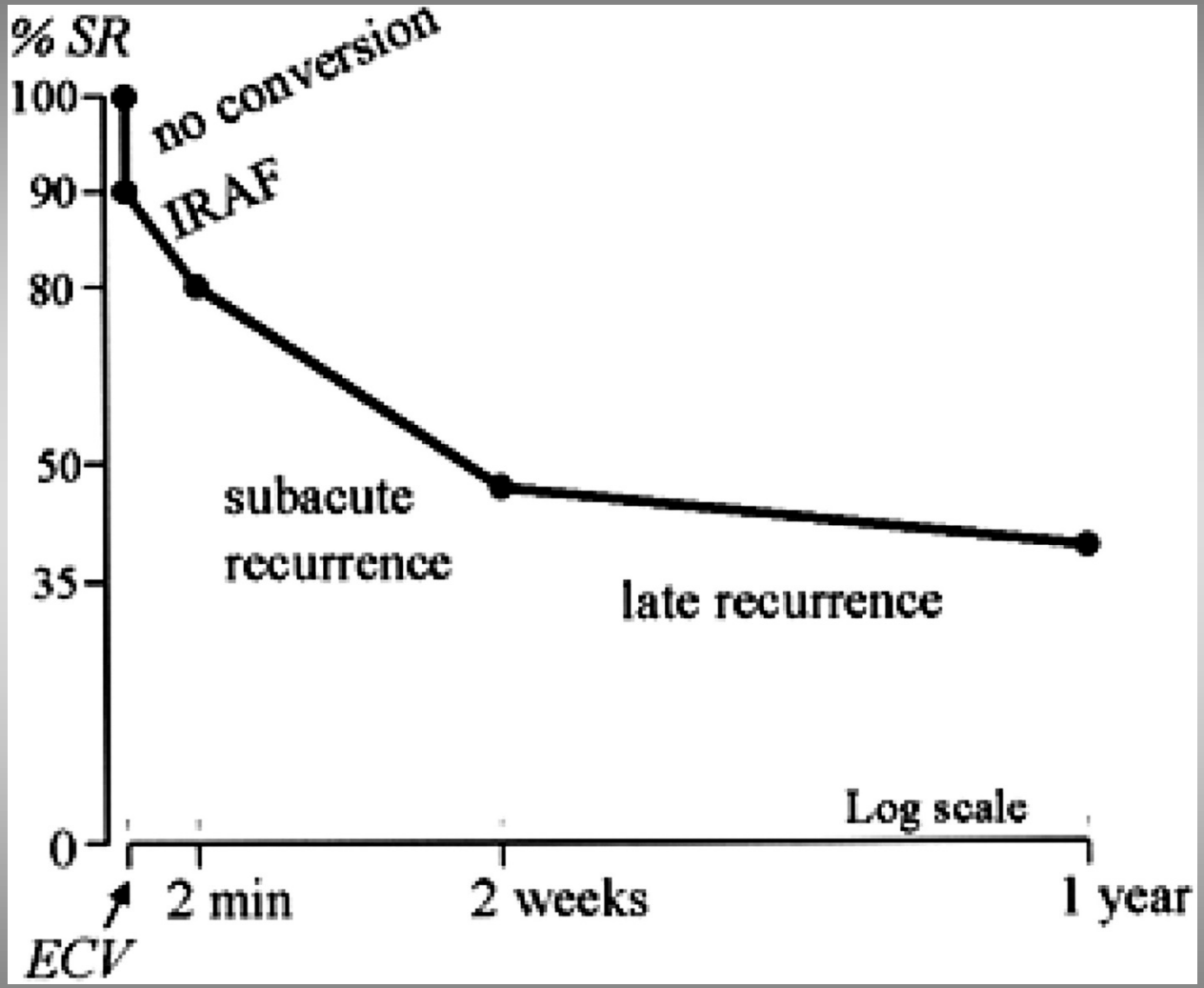
Grimm RA. J Am Coll Cardiol. 1993;22(5):1359-1366.

Direct Current Cardioversion

Success rate varies:

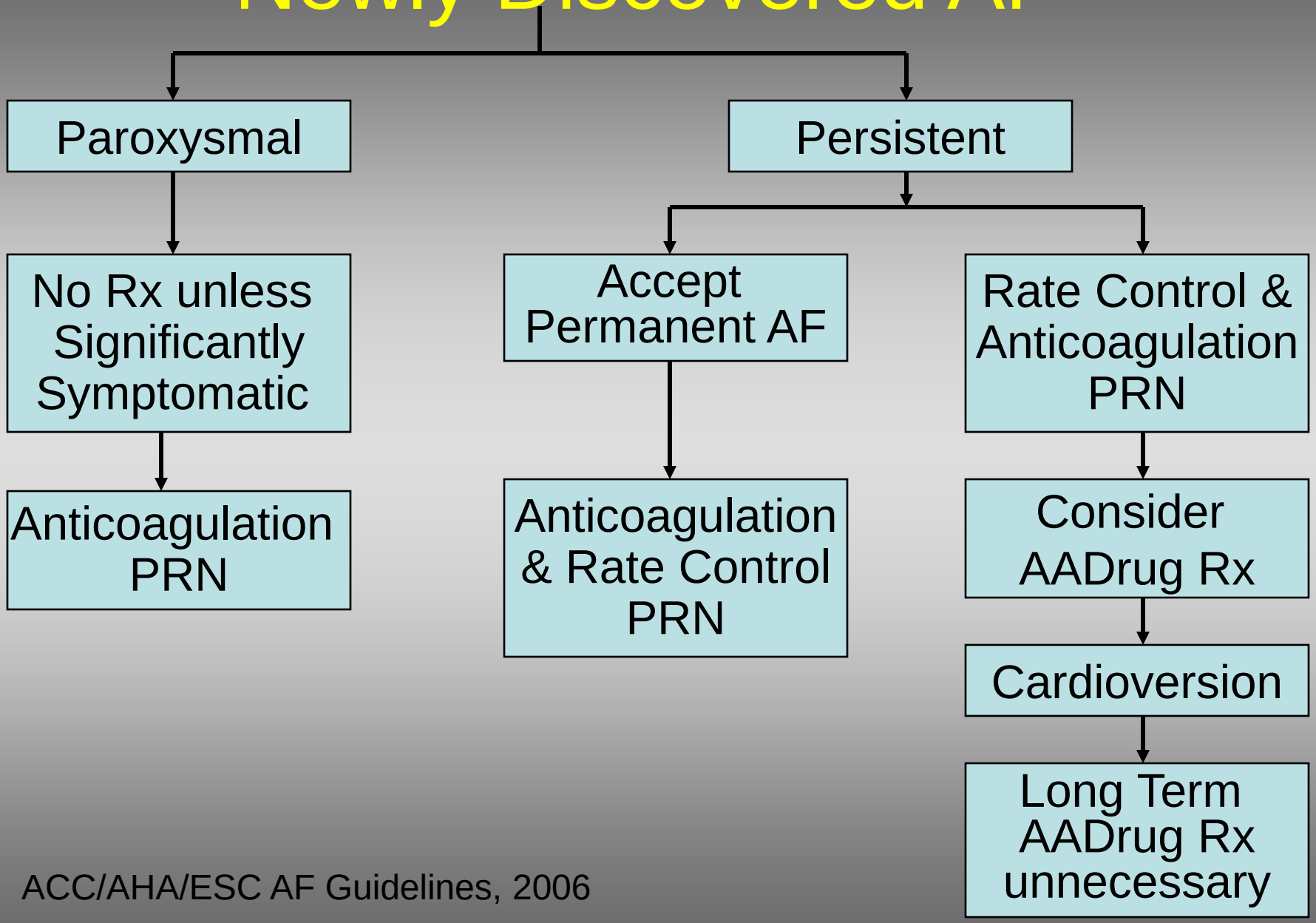
- Defibrillation threshold
- Duration of AF, underlying heart disease
- Immediate success 70 – 99%
  - AFib: 70-80%, A flutter: >95% success rates
  - Varies with duration of AF, LA size
- Complete shock failure & immediate recurrence 25%
- Recurrence up to 25% within 2 weeks
- Pre-treatment or Concomitant AAD therapy enhances success & suppresses recurrence
- Repeated CV after 2nd attempt following relapse is of no value

Hypothetical illustration of cardioversion failure.

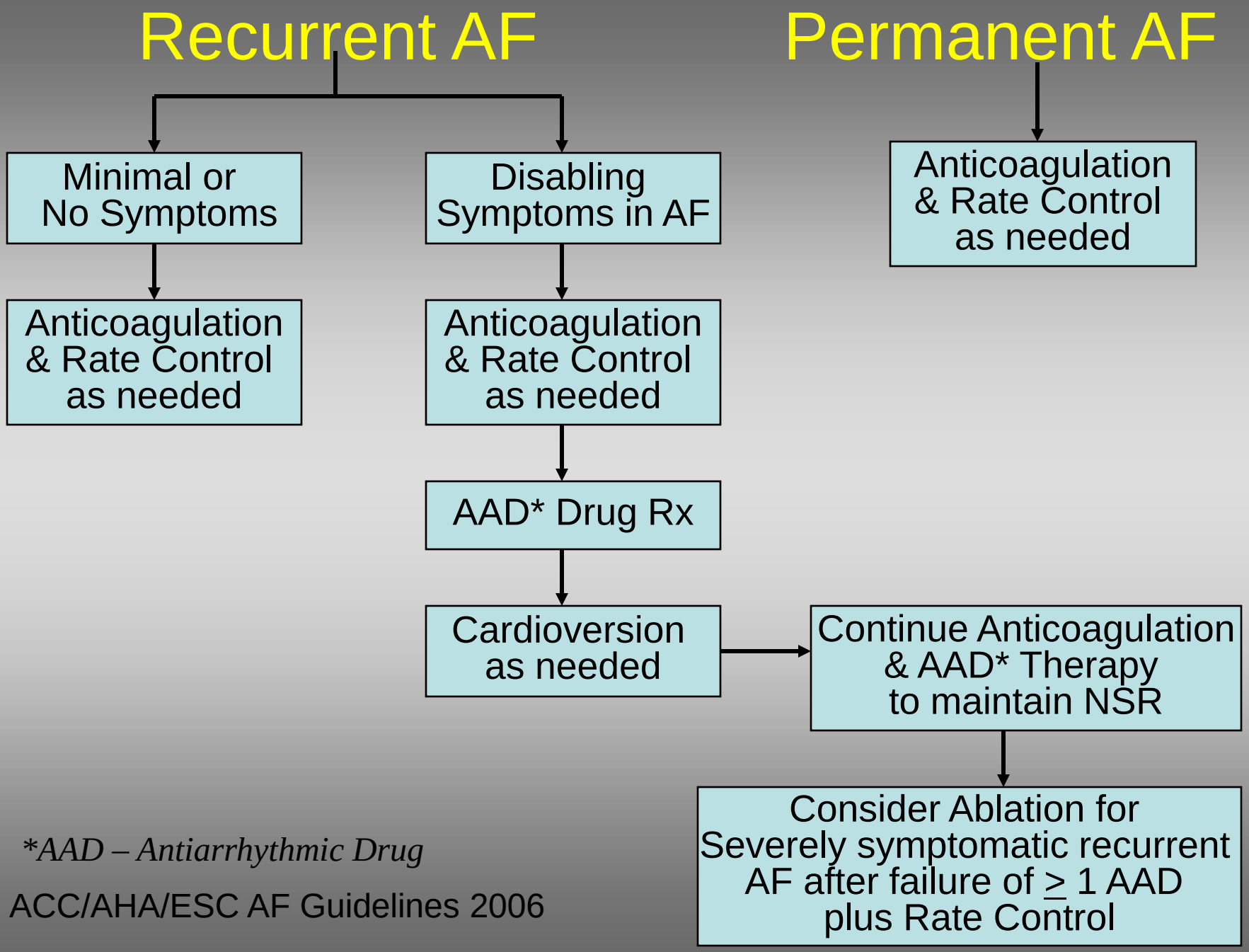


Fuster V et al. Circulation 2011;123:e269-e367

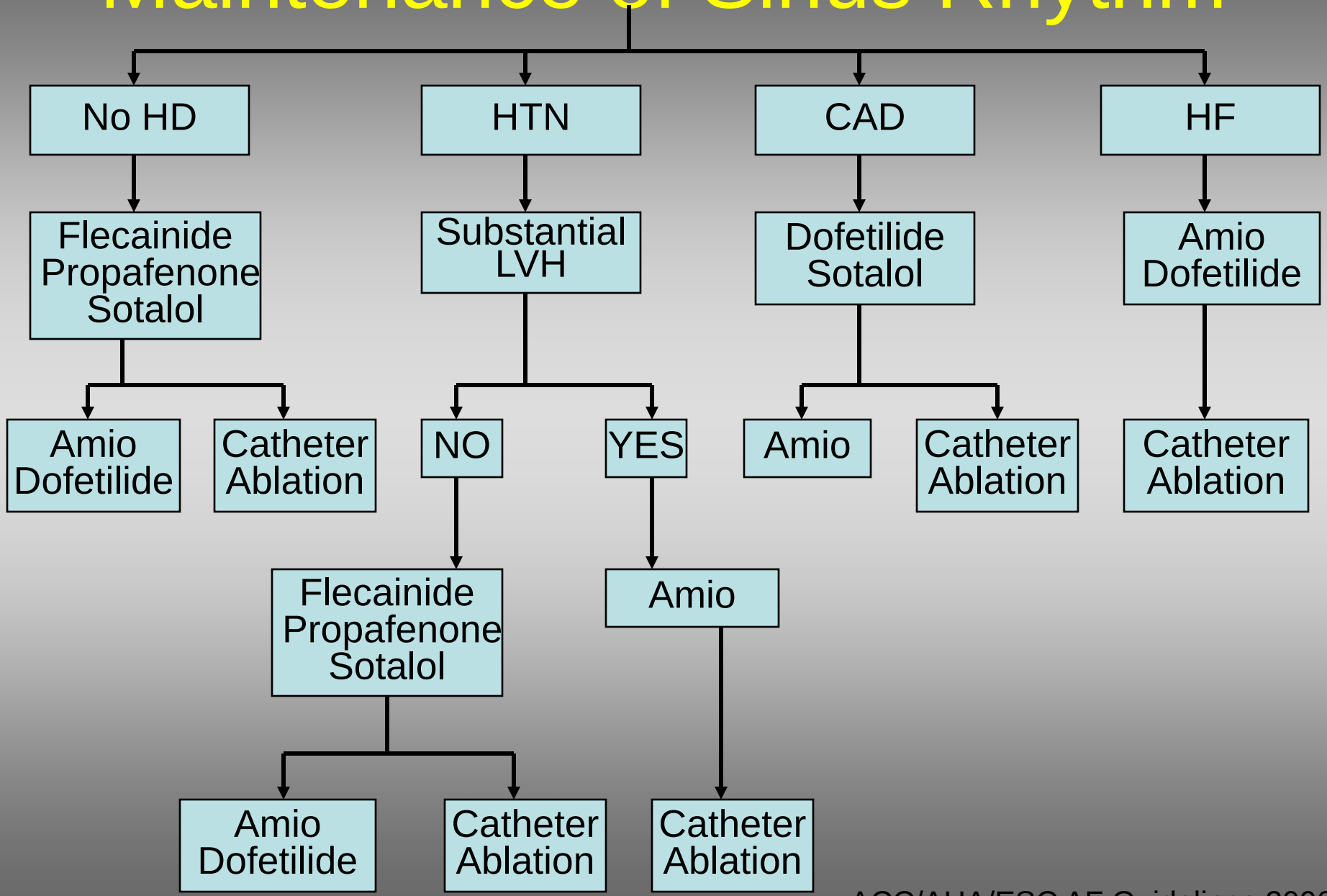
Newly Discovered AF



ACC/AHA/ESC AF Guidelines, 2006


Recurrent AF
Permanent AF
Minimal or No Symptoms
Disabling Symptoms in AF
Anticoagulation & Rate Control as needed
Anticoagulation & Rate Control as needed
AAD* Drug Rx
Cardioversion as needed
Continue Anticoagulation & AAD* Therapy to maintain NSR
Consider Ablation for Severely symptomatic recurrent AF after failure of ≥ 1 AAD plus Rate Control
*AAD – Antiarrhythmic Drug
ACC/AHA/ESC AF Guidelines 2006

Maintenance of Sinus Rhythm



ACC/AHA/ESC AF Guidelines 2006

Guideline Recommendations: Maintenance of Sinus Rhythm

- **Class I**
  - Before treating w/ anti-arrhythmics, treat reversible causes of AF (C)
  - Ablation OK over meds to prevent recurrent AF in symptomatic pts with little or no LAE and normal EF (A)
- **Class IIa**
  - Use meds to maintain SR & prevent tachy-induced CM (C)
  - Infrequent, well tolerate recurrence is a reasonable outcome of medical Rx (C)
  - Initiate meds as outpatient, if pt has no associated heart disease (C)
  - Lone AF + no structural heart dz, can start propafenone or flecainide as outpatient, as long as in SR at time (B)
  - Sotalol in outpatients for PAF if QT < 460ms, normal lytes and no contraindication for class III's (C)
  - Dronedarone- decrease recurrent of PAF, can start outpatient (B)
- **Class III**
  - Antiarrhythmics are not recommended for maintaining SR or pts w/ RF for proarrhythmia with that specific agent (A)
  - Meds not recommended for advanced sinus node or AV node dysfunction in absence of pacemaker (C)

Initiation of Antiarrhythmic Agents (AAD)

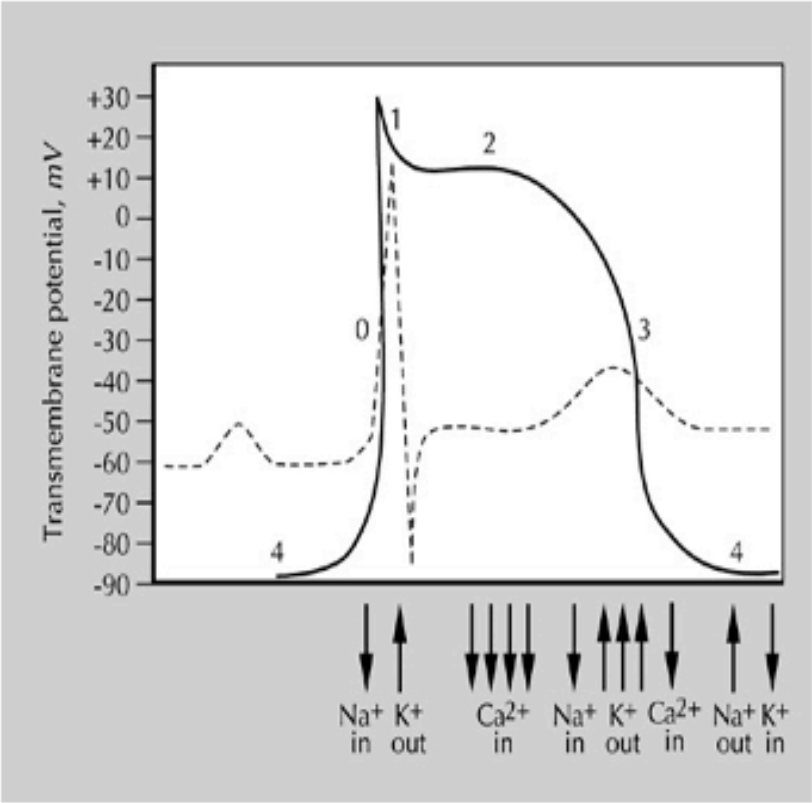
- Main risk – Proarrhythmia, tachy and brady
- Screen for proarrhythmia risks – LV dysfunction, prolonged PR, QRS, QT, or repolarization abnormalities, ischemia
- Flecainide, Propafenone, Sotalol, Amiodarone, and Dronedarone are safe for outpatient initiation
- Quinidine, Procainamide, Disopyramide, and Dofetilide should be started in in-patient setting

Vaughan-Williams Classification

Class	Agents	Automaticity	Conduction Velocity	Refractory Period
Ia	Quinidine Procainamide Disopyramide	↓	↓	↑
Ib	Lidocaine Tocainide Mexiletine	↓	-	-↓
Ic	Propafenone Flecainide/Morizicine	↓	↓	-
II (nodal tissue)	Propranolol Metoprolol Esmolol	↓	↓	↑
III	Amiodarone/Dronedarone Sotalol Ibutilide/Dofetilide Azimilide Vernakalant	-	-	↑
IV (nodal tissue)	Verapamil Diltiazem	↓	↓	↑
Misc	Digoxin Magnesium Adenosine			

Electrophysiology: Cardiac Action Potentials

- Depolarization
- Repolarization
- Refractory period
- Conduction velocity
- Automaticity



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AAD: Flecainide

- Class IC agent, Na channel blocker
- Contraindicated in patients with CAD per CAST trial
- Must be used in conjunction with AV nodal blocking agent to prevent atrial flutter 1:1 conductions
- Can prolong QRS duration
- Recommend follow-up ECG after 5 doses; some providers perform ETT due to “use dependence”
- Daily dosing, BID
- “Pill-in-the-pocket”
  - Self administration of a single oral dose of drug shortly after the onset of symptomatic AF

AAD: Propafenone

- Class IC agent, Na channel blocker
- Contraindicated in patients with CAD per CAST trial
- Must be used in conjunction with AV nodal blocking agent to prevent atrial flutter 1:1 conductions
- Can prolong QRS duration
- Recommend follow-up ECG after 5 doses; some providers perform ETT
- Daily dosing, BID
- Beta blocker side effects

AAD: Sotalol

- Class III agent, K channel blocker
- Beta blocker properties: slow HR and decrease BP, similar side effects in some people
- Contraindicated with LVH, baseline QTc interval > 460 ms
- Can prolong QTc interval
  - QTc acceptable up to 500 ms or 550 ms with paced rhythm or bundle branch block
  - If QTc prolongs > 15% need to decrease dose
- Renal dosing
- ECG monitoring practices

AAD: Dofetilide/Tikosyn®

- Class III agent, K^+ channel blocker
- Contraindicated with LVH, baseline QTc interval > 460 ms
- Will not slow HR
- Can prolong QTc interval
  - QTc acceptable up to 500 ms or 550 ms with paced rhythm or bundle branch block
  - If QTc prolongs >15% need to decrease dose
- FDA mandates inpatient initiation
  - 5 doses with ECG 2 hours after each dose
  - One night in hospital post cardioversion
- Renal dosing
- Have to be a certified provider to prescribe

AAD: Amiodarone

- Class III agent, blocks Na, K, Ca, Beta, Alpha
- Properties of all 4 classes
- Can prolong QTc interval
  - However QTc prolongation not associated with increase in morbidity and mortality
- Can be used for ventricular arrhythmias as well
- Should use loading dose prior to cardioversion
  - 6 grams is goal load
- Many potential adverse reactions
  - Liver, thyroid, pulmonary fibrosis, corneal deposits, skin discoloration/photosensitivity
- Because of toxicities, the LOWEST effective maintenance dose is always targeted for chronic therapy.

AAD: Amiodarone

- Monitoring
  - ECG: baseline and every 6 months
  - LFT's, TFT's: baseline, 6 months, annually
  - PFT's with DLCO: baseline, 6 months, annually
  - CXR
  - Eye exam: baseline, annually
- Encourage patients to avoid direct sun exposure, use sunscreen
- If patients develop hypothyroidism can treat with replacement. Hyperthyroidism requires immediate discontinuation of amiodarone and referral to Endocrine

AAD: Dronedarone/Multaq®

- Class III agent, blocks Na, K, Ca, Beta, Alpha
- Has properties of all 4 classes
- Non-iodinated analog of amiodarone; “amiodarone without all the side effects”
- Contraindicated in patients with bradycardia HR <50 bpm, moderate to severe heart failure, Permanent AF, Hepatic or pulmonary toxicity previously on amiodarone
- 400 mg BID

Patient Education

- Explanation of symptoms
- Self monitoring: HR, BP, symptoms
- Signs and symptoms to report
- Medication compliance
- Anticoagulation
- Food-drug & drug-drug interactions
- Follow-up
- Written handouts helpful

Patient Monitoring

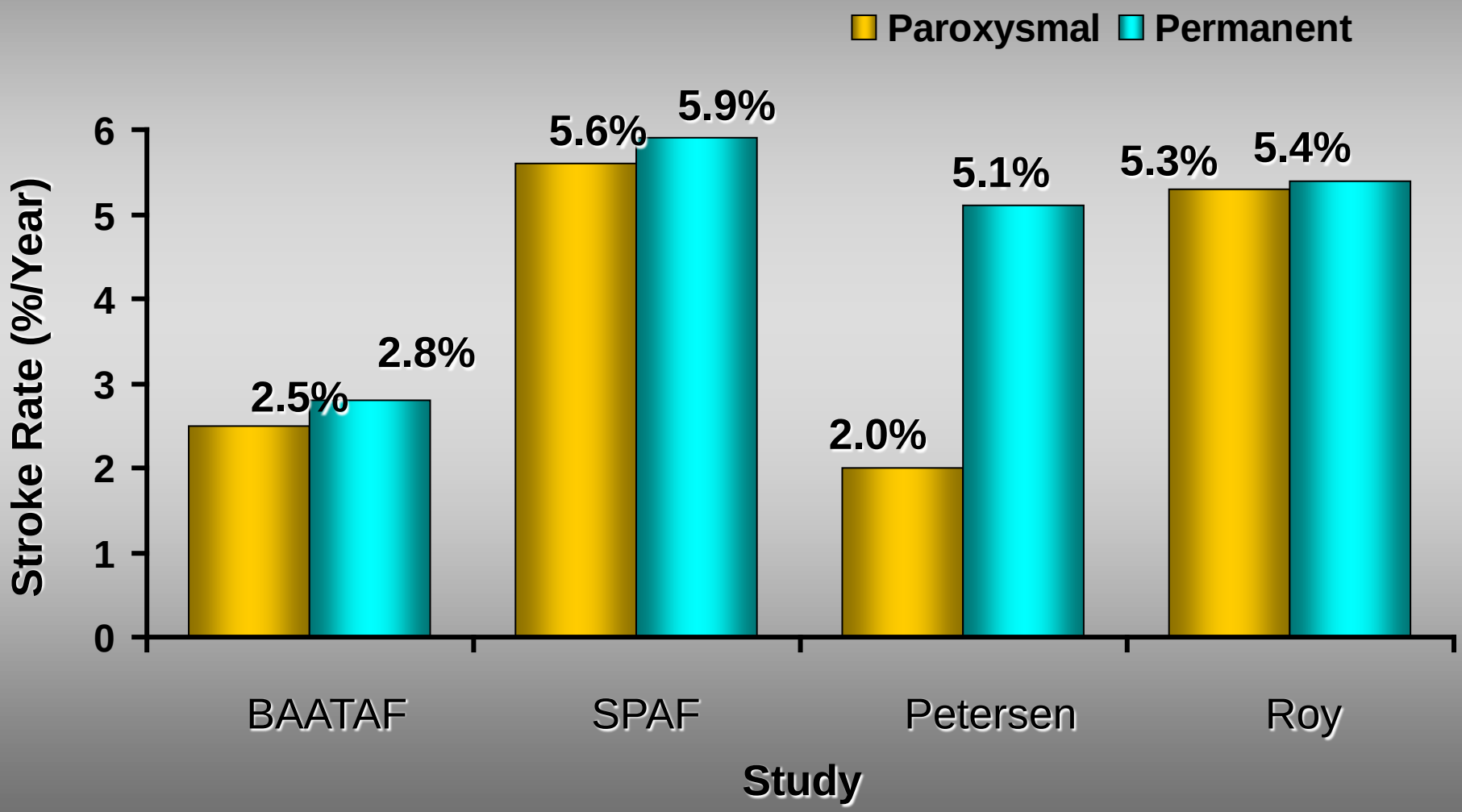
- Vital signs
- Pt symptoms
- Side effects
- Risk identification
- Labs
  - Serum electrolytes (K+, Mg)
  - Digoxin level
  - Renal and liver function
- ECG
- Echo
- PFT (drug dependent)

Atrial Fibrillation and Stroke

- Risk: 5 - 8% per year in high-risk patients; accounts for 15% of all strokes
- Presumably due to LAA clot (95%)
- Meta-analysis showed that adjusted dose oral anticoagulation is highly efficacious
- Data revealed a risk reduction of 61-70% versus placebo
- Evaluate patient for risk stratification

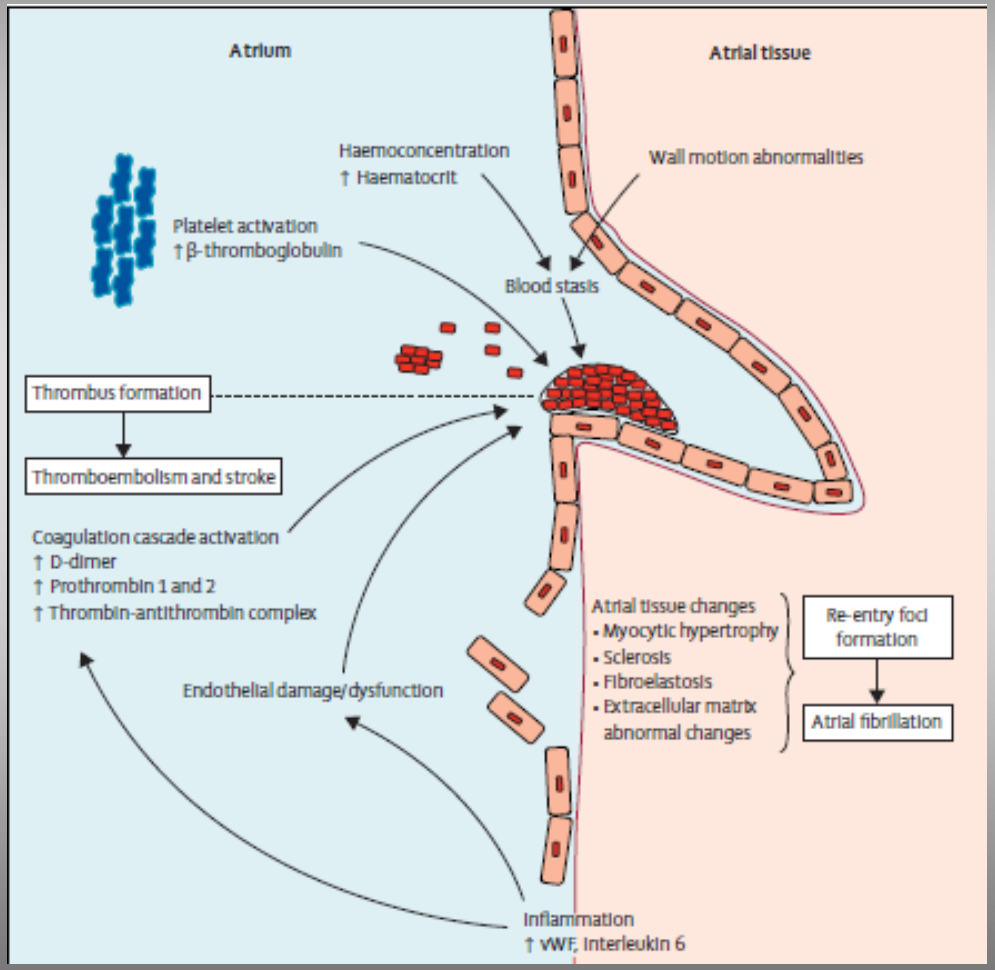
Stroke in AF

Paroxysmal vs Permanent



Scheidt. *CVR&R*. February 1997:23-43.

Clot Formation in AF



Antithrombotic Strategies:
Prevention of Ischemic CVA & Systemic Embolism

- Anticoagulation with Vitamin K Antagonist agents (VKA = warfarin)
- Aspirin
- Combining anticoagulation and platelet-inhibitor therapy
- Novel Antithrombotic Agents
- Low-molecular weight heparins
- Nonpharmacologic approaches
  - Obliteration or occlusion of the LAA
  - Surgical amputation or amputation or truncation of the appendage

Guideline Recommendations: Preventing Thromboembolism

- **Class I**
  - Anticoagulate all AF pts except those w/ lone AF or contraindications (A)
  - Choose anticoagulate based on absolute risks of stroke vs bleeding (A)
  - INR goal 2.0-3.0 w/ warfarin (without mechanical valve) (A)
  - Warfarin if > 1 risk factor (A)
  - Warfarin: check INR weekly when initiating, then monthly (A)
  - ASA 81-325mg daily in low risk pts w/ contraindications to warfarin (A)
  - AF w/ mechanical valves, adjust per valve, INR at least 2.5 (B)
  - Treat atrial flutter as AF (C)

Guideline Recommendations: Preventing Thromboembolism

- **Class IIa**
  - ASA alone or warfarin for AF if just one: age > 75, htn, CHF, EF < 35%, DM (A)
  - ASA alone or warfarin for AF IF ≥ 1: age 65-74, female, CAD (B)
  - Same recommendations for anticoagulation: PAF, persistent & permanent AF (B)
  - If no mechanical valve, can interrupt warfarin for up to one week w/o heparin for surgery/procedures (C)
  - Reasonable to re-evaluate as needed for anticoagulation at regular intervals (C)

Guideline Recommendations: Preventing Thromboembolism

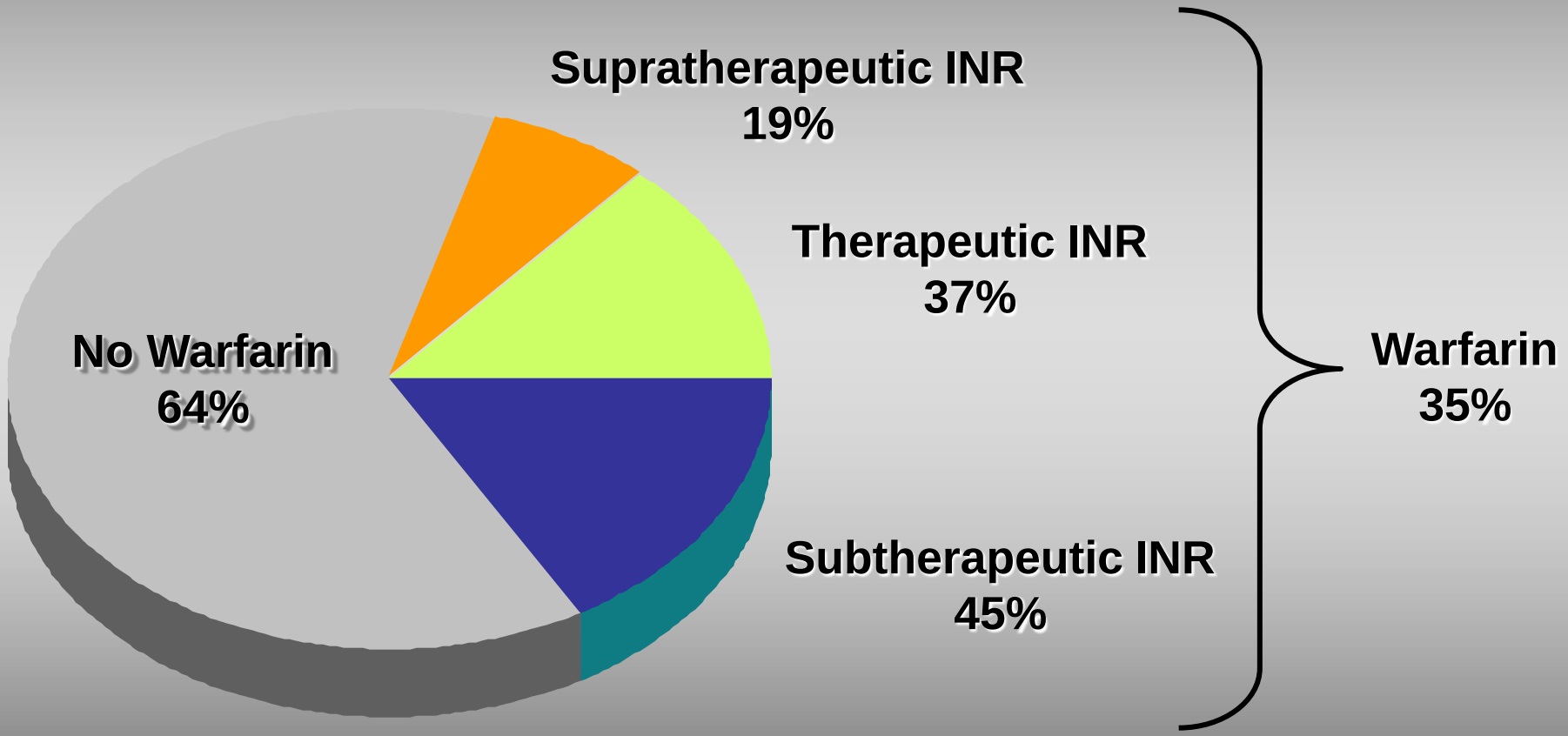
- **Class IIb**
  - > 75 yo + ⇑risk of bleeding: lower INR goal to target 2.0; range 1.6-2.5 (C)
  - LMWH if surg/procedures require interruption of anticoagulation for > 1 week in high risk pts (C)
  - After PCI: OK to give ASA 81mg, plavix & warfarin (C)
  - Can hold warfarin for PCI, but restart ASAP.
  - Lone AF: risk of embolism is low, no need for ASA (C)
  - If CVA in AF pt while on warfarin w/ INR 2.0-3.0, can increase to 3.0-3.5 instead of adding anti-platelet (C)
- **Class III**
  - Long term warfarin for primary CVA prevention in pts < 60, no CAD, no RF for embolus (C)

Predictors of Thromboembolic Risk in Atrial Fibrillation

Weaker Risk Factors	Moderate Risk Factors	High Risk Factors
Female Gender	Age ≥ 75 years	Prior CVA, TIA
Age 65 to 74 years	Hypertension	Mitral Stenosis
Coronary Artery Disease	Heart failure	Prosthetic Heart Valve
Thyrotoxicosis	LVEF < 35% or Diabetes Mellitus	Prior Embolism

ACC/AHA/ESC AF Guidelines 2006

Use and Adequacy of Anticoagulation on Hospital Admission in AF Patients



n-1085 patients admitted to a tertiary care facility

Bungard et al. *Pharmacotherapy.* 2000;20:1060-1065.

CHADS2

♥ Conditions	♥ Score, points
• CHF	• yes- 1
• Hypertension	• yes-1
• Age	• ≥ 75- 1
• Diabetes	• yes- 1
• Stroke/TIA	• Yes- 2

Score and recommendations:
Max score: 6
Score 0: aspirin
Score 1: aspirin or oral anticoagulation
Score 2 or more: oral anticoagulation

Stroke risk factors –$CHADS_2$

Risk Factor	Points
Congestive heart failure	1
Hypertension	1
Age ≥ 75	1
Diabetes mellitus	1
Stroke or TIA history	2

Points	% stroke per year	Therapy
0	1.9	No anticoagulation
1	2.8	Aspirin 75 – 325mg or oral anticoagulant
2	4	Oral anticoagulant
3	5.9	
4	8.5	
5	12.5	
6	18.2	

Gage *JAMA* 2001
EACTS *Eur Heart J* 2010

Stroke risk factors – CHA_2DS_2VASc

Table 8 CHA_2DS_2VASc score and stroke rate

(a) Risk factors for stroke and thrombo-embolism in non-valvular AF	
'Major' risk factors	**'Clinically relevant non-major' risk factors**
Previous stroke, TIA, or systemic embolism Age ≥75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF ≤40%) Hypertension - Diabetes mellitus Female sex - Age 65–74 years Vascular disease[a]

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc
(Note: maximum score is 9 since age may contribute 0, 1, or 2 points)

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

(c) Adjusted stroke rate according to CHA_2DS_2-VASc score

CHA_2DS_2-VASc score	Patients (n=7329)	Adjusted stroke rate (%/year)[b]
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

EACTS *Eur Heart J* 2010
Lip *Stroke* 2010

CHA_2DS_2 -VASc

- Conditions
  - CHF
  - Hypertension
  - Age
  - Diabetes
  - Stroke/TIA/Thrombo
  - Vascular disease
  - Age
  - Sex category
- Score
  - Yes- 1
  - Yes- 1
  - <65- 0, 65-74-1, ≥75- 2
  - Yes- 1
  - Yes- 2
  - Yes- 1
  - ≥ 65-74- 1
  - Female- 1, male- 0

Stroke Prophylaxis in AF

- ♥ $CHAD_2DS_2$-VASc score = 0
  - Asa 81 – 325mg daily
- ♥ CHAD2DS2-VASc score = 1
  - Asa or oral anticoagulant
- ♥ CHAD2DS2-VASc score = $\geq$ 2
  - Oral anticoagulant

Current Options

- Vitamin K Antagonist → Warfarin
- Unfractionated Heparin → Heparin
- Low Molecular Weight Heparin (LMWH)
  - Dalteparin, Enoxaparin
- Direct Thrombin Inhibitor
  - Dabigatran, Argatroban, Bivalrudan
- Factor Xa Inhibitor
  - Rivaroxaban, Apixaban, Endoxaban, Fondaprinux (Arixtra)

Warfarin

- Interferes with hepatic synthesis of vitamin K dependent clotting factors II, VII, IX & X as well as proteins C and S
- Antidote is Vitamin K
- Therapeutic Range: PT/INR
  - Target INR is 2.5 with a range of 2.0 – 3.0 for most indications for warfarin therapy.
  - Target INR is 3.0 with a range of 2.5 – 3.5 for the following indications
    - Mechanical heart valves in mitral position

Duration of Warfarin Therapy

- AF: based on CHA2DS2 VASc score
- Mechanical cardiac valves: indefinitely
- Bioprosthetic cardiac valves: varies
- Surgery provoked DVT or PE: 3 months
- First unprovoked DVT or PE: 3 months
- Second unprovoked DVT or PE: extended treatment
- LV thrombus: ~3 months, repeat echo

Limitations with warfarin

- Narrow therapeutic range
- Slow onset of action
- Slow offset of action
- Multiple drug and dietary interactions
- Monitoring required to maintain therapeutic range
- PROS: Not a lot of data on procedures to restore sinus rhythm on other anticoagulants

Dabigatran- Pradaxa®

- Direct thrombin (factor IIa) inhibitor
- Approved to prevent stroke and systemic embolism for nonvalvular AF
- Dosage 150 mg BID, one dose fits all
- Half life: 7-17 hours
- Elimination: renal (80%)
  - Consider 75 mg BID with CrCl 30-50 ml/m2
  - Contraindicated in patients with CrCl <30 ml/m2
- Increased risk of GI bleeding in patients >75 years of age
- Trials: RE-LY (AF), RE-NOVATE (THA), RE- MODEL (TKA), RE-COVER (acute VTE)

Dabigatran- Pradaxa®

- No drug-food interactions
- No antidote
- Dialyzable
- Unstable if not stored in original bottle (dessicant in lid)
- Must be used within 4 months
- Main side effect dyspepsia 10%

Rivaroxaban- Xarelto®

- Factor Xa inhibitor
- Approved to prevent stroke and systemic embolism for nonvalvular AF and postoperative thromboprophylaxis for knee and hip replacement
- Dosage 10- 20 mg daily with evening meal
  - AF: CrCl > 50 ml/m2: 20 mg daily, CrCl 15-50 ml/m2: 15 mg daily, CrCl <15 ml/m2 avoid use
  - Post-op VTE: 10 mg daily
- Half life: 5-9 hours
- Elimination: renal 2/3 fecal 1/3
- Trials: ROCKET AF (AF) RECORD 1, 2 (THA), RECORD 3,4 (TKA), EINSTEIN (acute VTE)

Rivaroxaban- Xarelto®

- Metabolism: oxidation via CYP3A4 and CYP2J2
- Drug Interactions: Ketoconazole, ritonavir, clarithromycin, erythromycin, rifamipin
- Recommend to be taken with food
- Not readily available for AF at VA

Apixaban- Eliquis®

- Factor Xa inhibitor
- Half-life 5-6 hours
- Metabolism: oxidation via CYP3A4
- Dosage: 5 mg BID
  - Decreased to 2.5 mg BID if age ≥ 80 years, ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dl
- Not dialyzable
- Excretion: 25% renal, 75% fecal
- Trials: ARISTOTLE (AF), ADVANCE 3 (THA), ADVANCE1,2 (TKA), AMPLIFY(acute VTE)

Timing of Antithrombotic Rx & Cardioversion for AF

- Stable AF of unknown duration or > 48 hours

  Therapeutic warfarin levels for 3 weeks prior ➔ Cardioversion

  Therapeutic warfarin levels for 4 weeks after cardioversion

- Unstable AF

  Unfractionated Heparin or LMWH

TEE-guided
- NO CLOT → **CV then warfarin**
- CLOT → **warfarin X 3 wks repeat TEE →CV**

Interruption of Anticoagulation

Elective Procedures

- Mechanical Valves and High Risk Patients
  - Self administered LMWH or IV UFH (Class IIb)
  - Held before procedure
  - Resumed when possible with LMWH SQ or Unfractionated Heparin IV
  - Oral anticoagulation restarted and heparin/LMWH discontinued when INR goal is achieved
- Non mechanical valves patients
  - May be interrupted for 1 week without heparin substitution

ACC/AHA/ESC AF Guidelines 2006

Surgical Consideration

- Warfarin
  - Discontinue warfarin ~ 5 days prior to surgery
  - Resume warfarin 12-24 hours after surgery
- Dabigatran
  - Discontinue 1-2 days (CrCl ≥ 50 ml/min) or 3-5 days (CrCl < 50 ml/min)
  - Resume as soon as adequate hemostasis is established
- Rivaroxaban
  - Discontinue at least 24 hours before surgery
  - Resume as soon as adequate hemostasis is established
- Apixaban
  - Stop 24-48 hours before surgery/procedure

Anticoagulation for AF

Major Contraindications

- Intracranial hemorrhage
- Unstable gait, fall risk or syncope
- Poor compliance
- Poor memory
- ETOH Abuse
- Psychosis

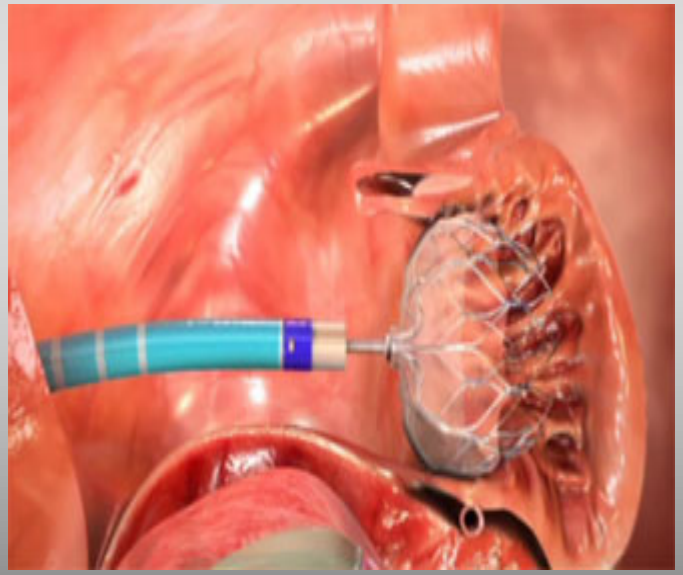
Adverse Effects

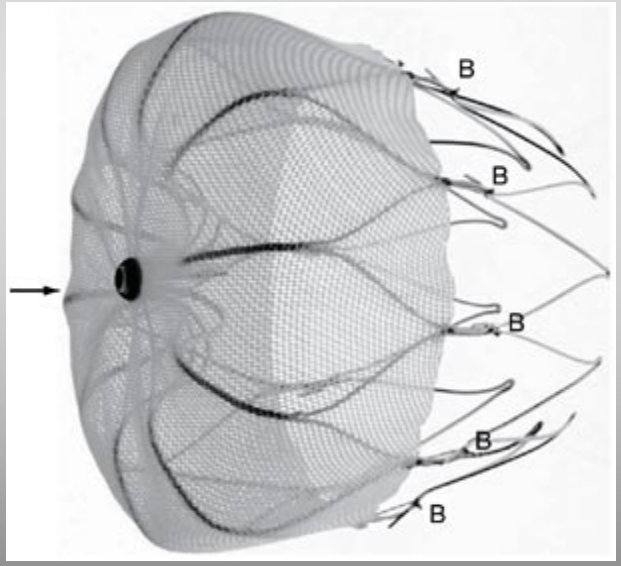
- Bleeding: ICH (0.1-0.8%)
- Intracranial hemorrhage
- GI Bleeding
- Cutaneous
- Drug-drug interactions
- Food-drug interactions

Non-Pharmacologic Therapies

- Direct Current Cardioversion (DCCV)
  - External synchronized cardioversion
- Catheter Ablation
  - Radiofrequency
  - Cryoballoon
- Left atrial appendage closure
  - Percutaneous
    - Watchman, Amplatzer Cardiac Plug
    - Lariat
  - Surgical LAA ligation and amputation
- Surgical Procedures
  - Maze Procedure
  - Thorascopic surgical maze
- AV Node Ablation & Pacemaker

Left Atrial Appendage Exclusion





Catheter Ablation for AF

Appropriate for Patients

(Class IIa -> Class I Recommendation)

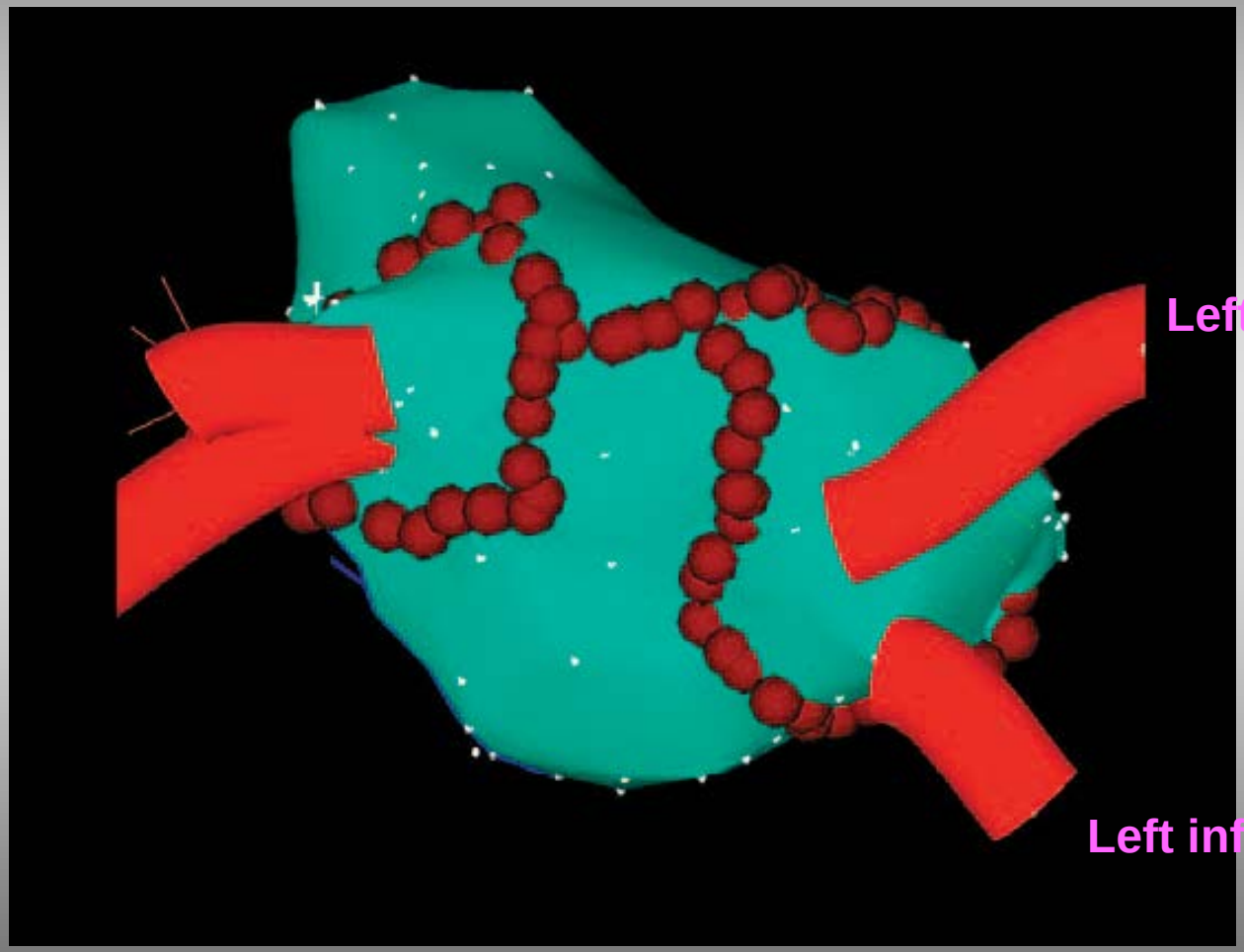
- With recurrent symptomatic paroxysmal or persistent AF
- Who are intolerant or failed AAD therapy
- Who have frequent ambient atrial ectopic activity with little or no LA enlargement
- Who have tachycardia-mediated cardiomyopathy

AF “Trigger” Sites

Extensions of Cardiac Myocytes Found In:

- **Pulmonary veins**
- Superior vena cava
- Coronary sinus/ligament of Marshall
- Crista terminalis
- **Left atrial free wall**

AF Ablation Burn Sites



Oral, H. et al, NEJM, 2006

CATHETER ABLATION

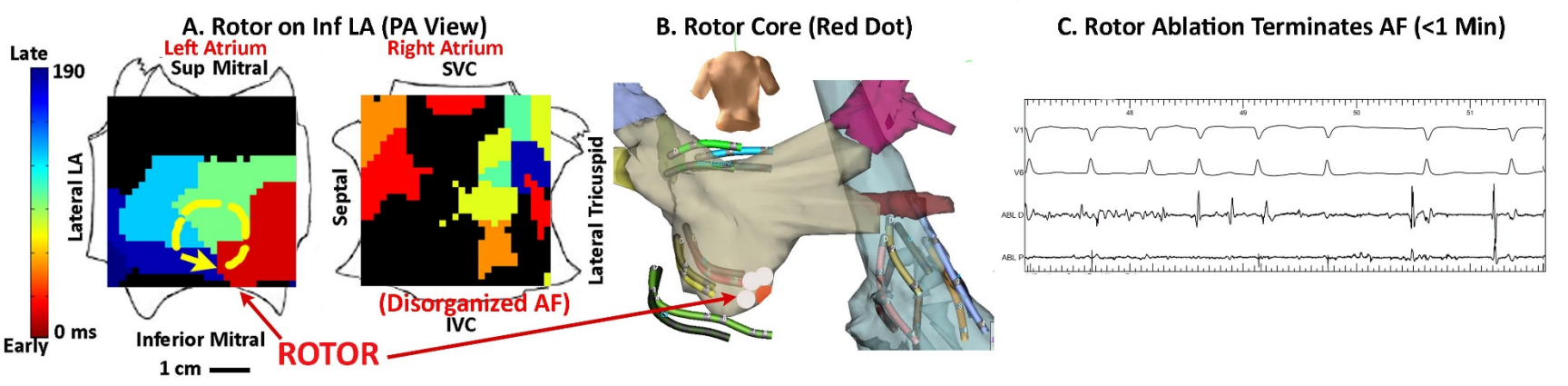
Success rates vary:

- Ablation Techniques
  - Early techniques with success rate 40-50%
  - New mapping technology and catheters
  - Operator technical experience
  - RFA techniques wider anatomical targets ⇑ 60-90%
- Patient variables
  - Lower in persistent AF vs PAF
  - Lower in presence of concurrent heart disease
  - Success rate may be dependent on Pt's ability to recognize symptoms of AF
  - Structural changes: dilated LA
  - Sleep apnea

FIRM Catheter Ablation

- Focal Impulse and Rotor Modulation
- Hypothesis proposes that organized and fast reentrant circuits (rotors) or focal impulses are discrete and disorganize into fibrillatory waves at their periphery
- RhythmView™ mapping system using a 64 pole basket catheter
- Targeting a focal source
- Performed with or without PVI
- Less ablation time (average 5 minutes), possible higher success rates

FIRM Catheter Ablation

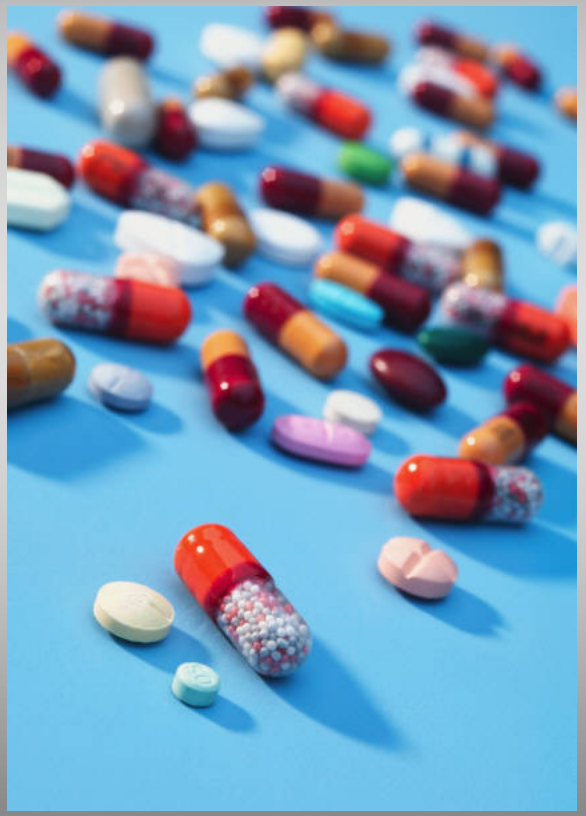


Catheter Ablation Complications

- Complications
- PV stenosis
- Thromboembolism
- Atrio-esopohageal fistula
- LA flutter
- Phrenic nerve or diaphragm paralysis
- Cardiac Tamponade
- Hematoma
- Mild pericarditis symptoms
- Fluid overload
- Radiation burns from fluoroscopy

Post Ablation Care

- ♥ Anticoagulate
  - Warfarin or novel agent
- ♥ Antiarrhythmic
  - AAD class Ic or III
- ♥ GI prophylaxis
  - PPI: pantoprazole bid
  - Sucralfate qid
- ♥ Monitor rhythm



AV Node Ablation & Pacemaker Implantation

Indications

(Class IIa Recommendation)

- Permanent atrial fibrillation with RVR
- Recurrent symptoms; CHF/CM despite medical therapy
- Intolerant of drug therapy for rate control or SR maintenance therapy

Implications

- Irreversible, lifetime pacemaker dependency & anticoagulation
- Improvement in cardiac symptoms, QOL, clinical status
- Inferior atrial AV node modification optional to avoid PPM

LVEF Following AV Node Ablation

			LVEF %		
Study	Pts	F/U (m)	Pre	Post	P
Kay	156	12	31	41	0.0001
Manolis	46	6	42	50	NS
Twidale	44	1	35	44	0.01
Rodriguez	12	14	43	54	0.0001
Edner	14	12	32	45	0.001

A Meta-analysis

AF: Surgical Ablation (MAZE)

- Surgical incisions in the atria (geographical “maze”) to create electrical barriers to conduction & prevention of sustained AF
- Success rate around 70% - 95% over 15 years
- May be combined with LAA obliteration or amputation
- Requirements: thoracotomy, general anesthesia & coronary bypass
- Risks: death (<1%), may need permanent pacing, bleeding, impaired atrial transport function, delayed atrial arrhythmias

Implications of Age for Ablation

Study	N	Age, y	Parox, %	SHD, %	AF free, %*
Ouyang et al., 2004	41	63 ± 9	100	NA	76
Haisaguerre et al., 2004	70	53 ± 8	NA	43	79
Mansour et al., 2004	40	55 ± 10	80	13	75
Marrouche et al., 2003	259	54 ± 11	51	21	87
Oral et al., 2003	40	54 ± 11	100	3	88
Pappone et al., 2003	580	65 ± 9	69	6	79
Total	1039				81.0

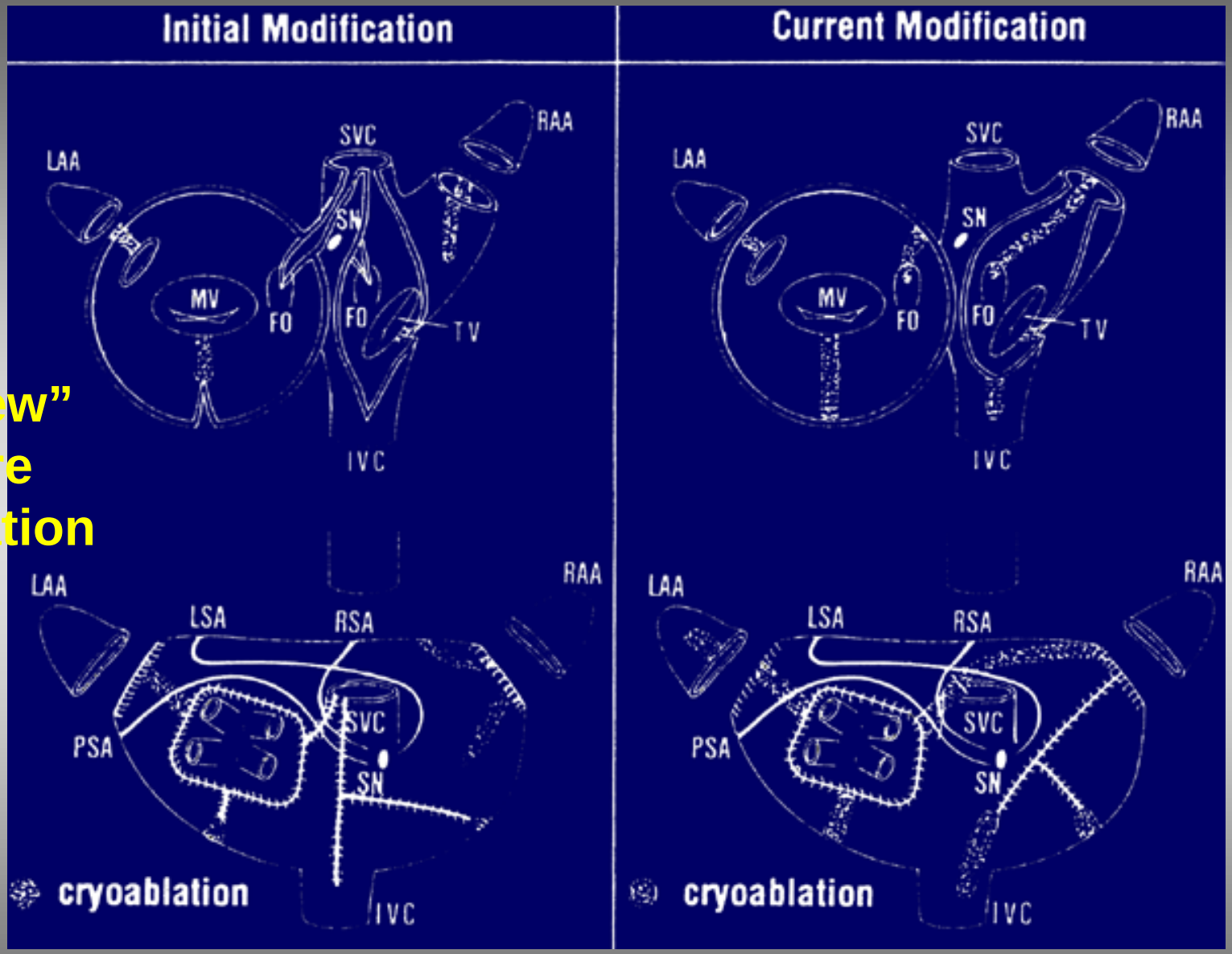
"Ablation may particularly benefit younger patients with lone AF who are frequently symptomatic and for whom very-long-term antiarrhythmic and anticoagulation pose higher risks and lifestyle costs."

*Off drugs

Verma et al. *Circulation.* 2005.

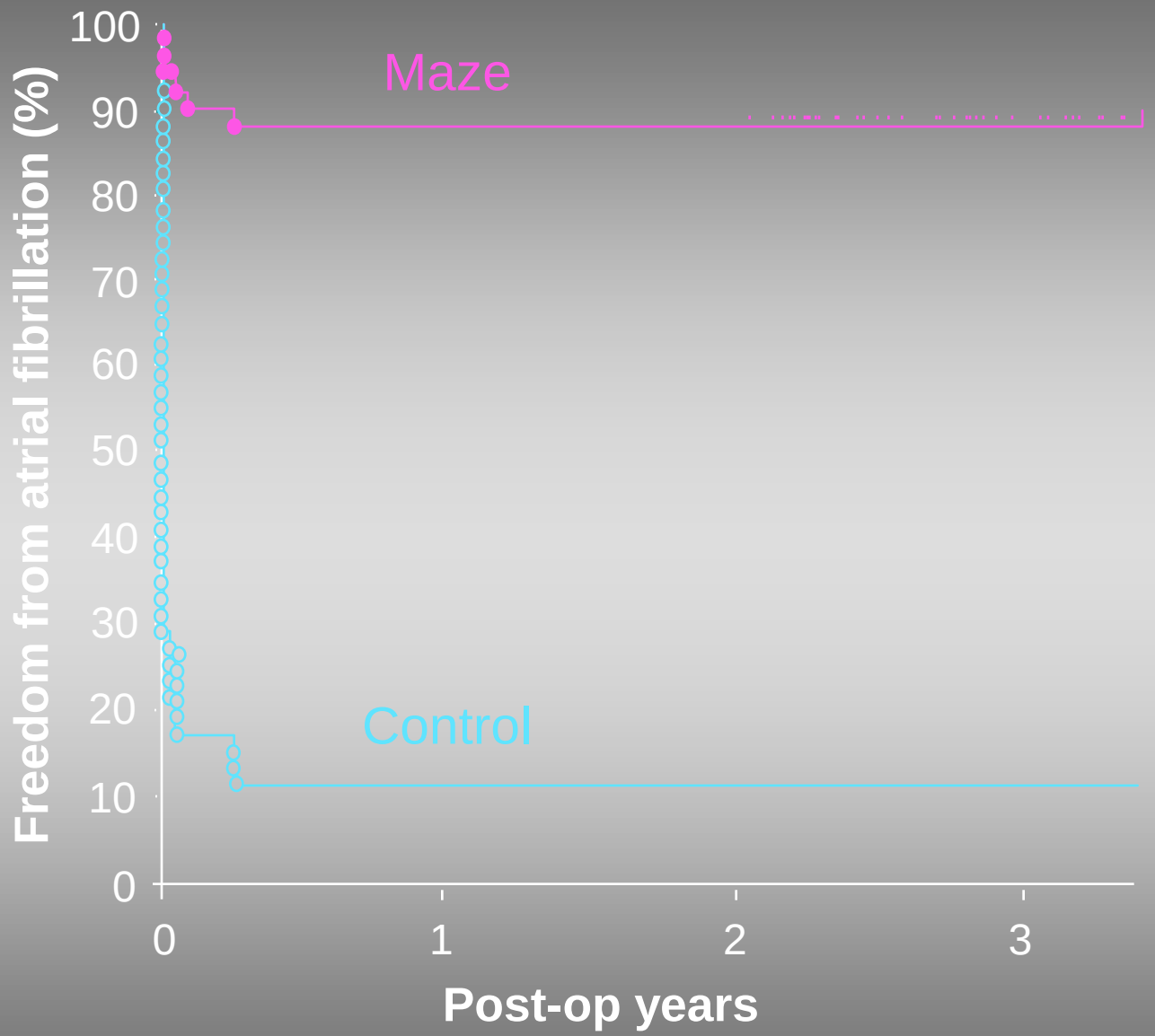
Atrial Fibrillation Curative Procedures: Surgical Maze

“cut & sew” procedure with ablation



Kawaguchi AT. J Am Coll Cardiol. 1996;28:985-990.

Efficacy of Surgical Maze Procedure for Atrial Fibrillation



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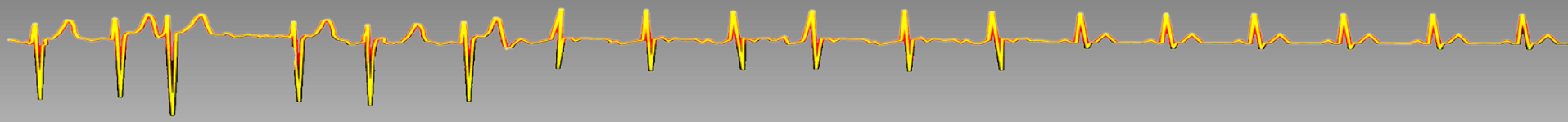
Approach to the AF Patient:

- ✓ What is the etiology of the AF? First time? Recurrent? Reversible?
- ✓ Is patient symptomatic?
- ✓ Has patient had any work-up?
- ✓ Has anticoagulation been considered or implemented?
- ✓ Will the patient benefit from cardioversion? Or Sinus Rhythm maintenance?
- ✓ Has the patient failed drug therapy?
- ✓ Has percutaneous or catheter based strategy been considered for pharmacologic failures?

Conclusions



- Diverse invasive therapies becoming more widespread
- Accurate patient assessment is important to guide therapy
- Pharmacologic agents can be effective but require monitoring
- Ultimately, “curing” atrial fibrillation may require a combination of approaches