Disclosure slide

- Nothing to disclose
- Currently accepting ideas for things to disclose

Atrial Fibrillation:

Why a Cardiologist is Better Than a Lie Detector Test

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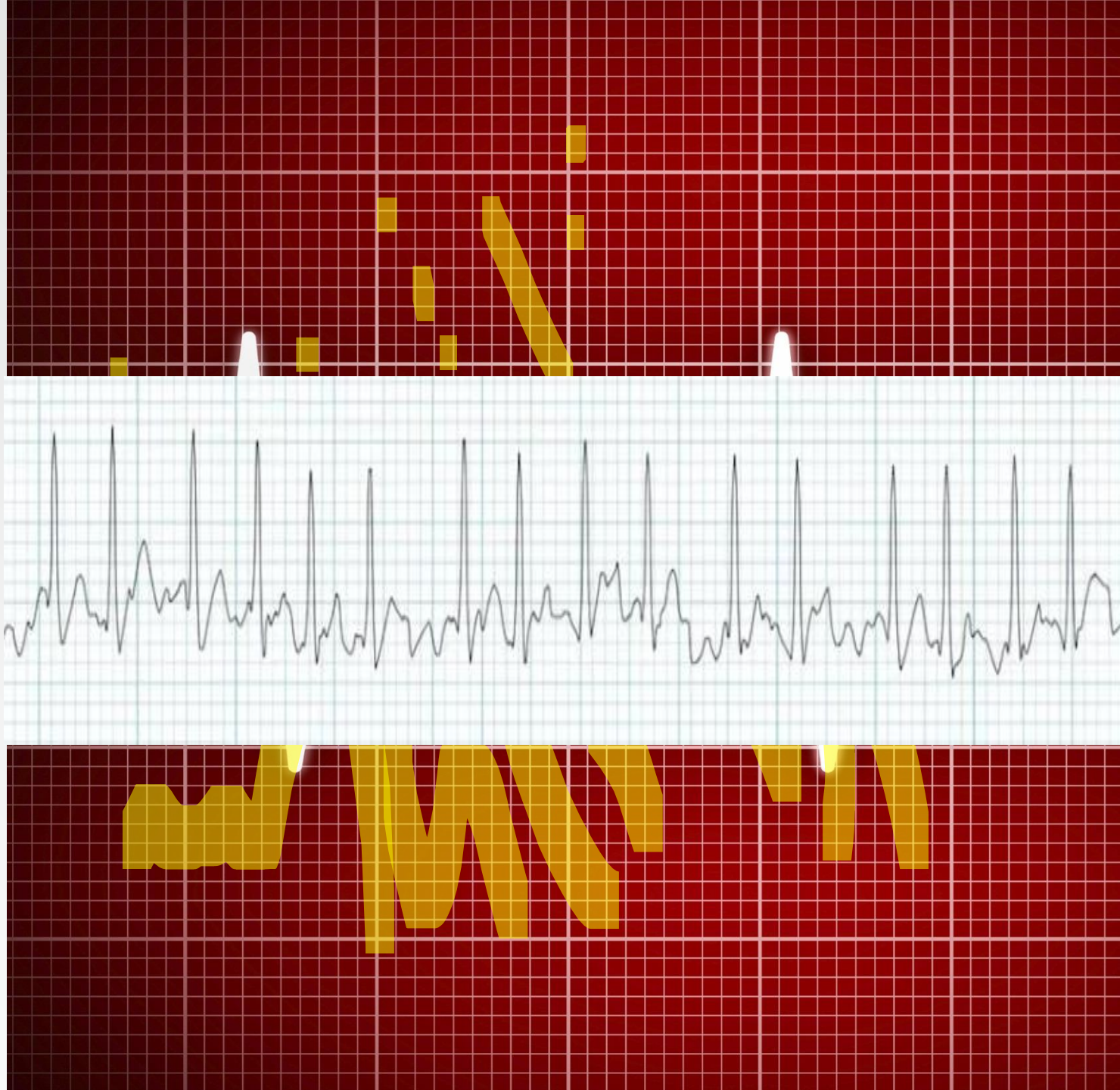
OCTOBER 6, 2022

VERMONT CARDIAC NETWORK



1. True or False

- Rate control is equivalent to rhythm control in AF treatment

2. AF that lasts for more than 7 consecutive days but converts in less than 30 days is called:

- A. Paroxysmal atrial fibrillation
- B. Long standing persistent AF
- C. Lone AF
- D. Persistent AF
- E. Annoying AF

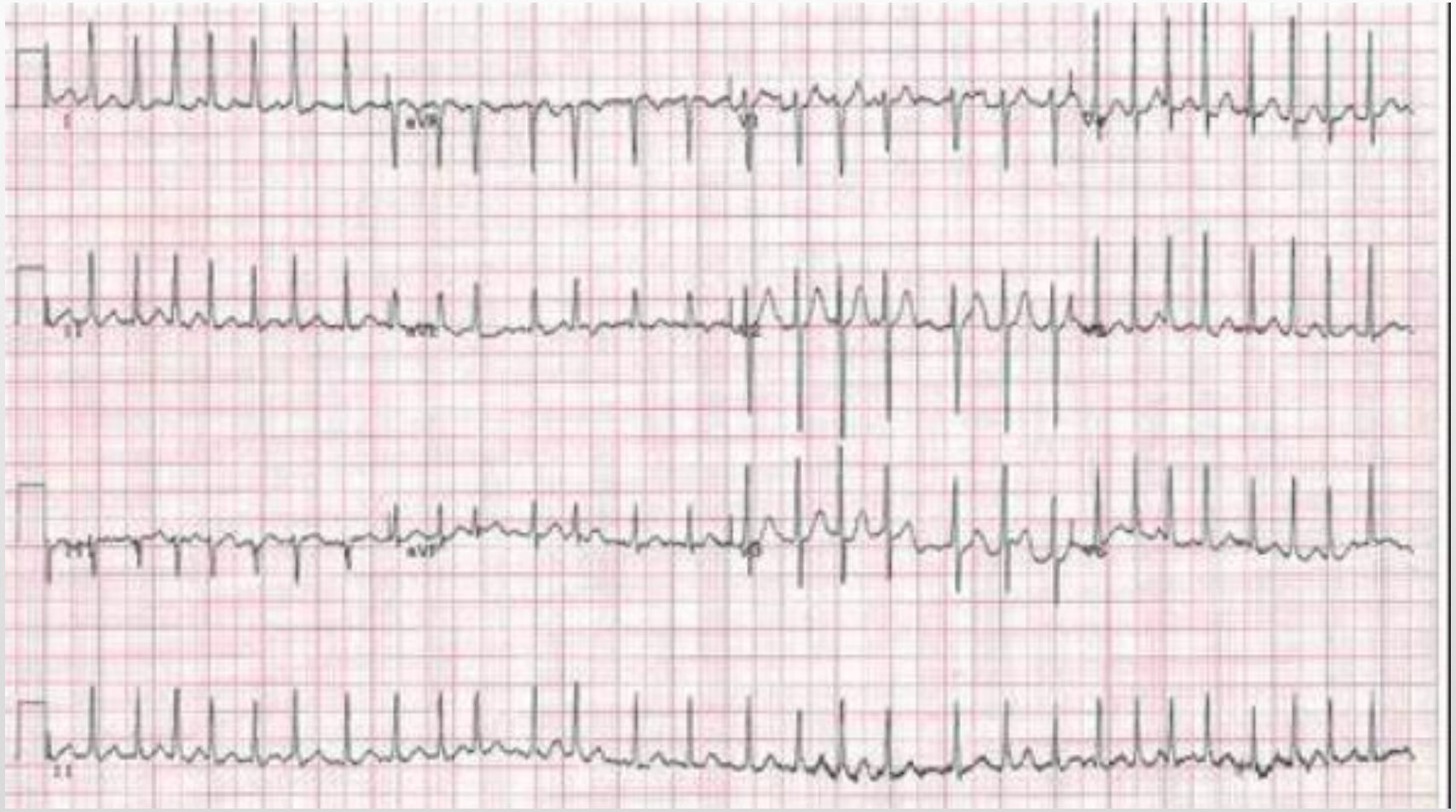
3. The decision for rhythm control over rate control in a patient with AF is based on which the following:

- A. Age
- B. Symptoms
- C. AF burden
- D. Patient preference

4. The ideal antiarrhythmic drug for a 68yo woman with CAD, mild HFrEF and highly symptomatic pAF who wishes to avoid invasive therapy:

- A. Flecainide
- B. Sotalol
- C. Amiodarone
- D. Dofetilide
- E. Ivabridine

5. This EKG demonstrates:



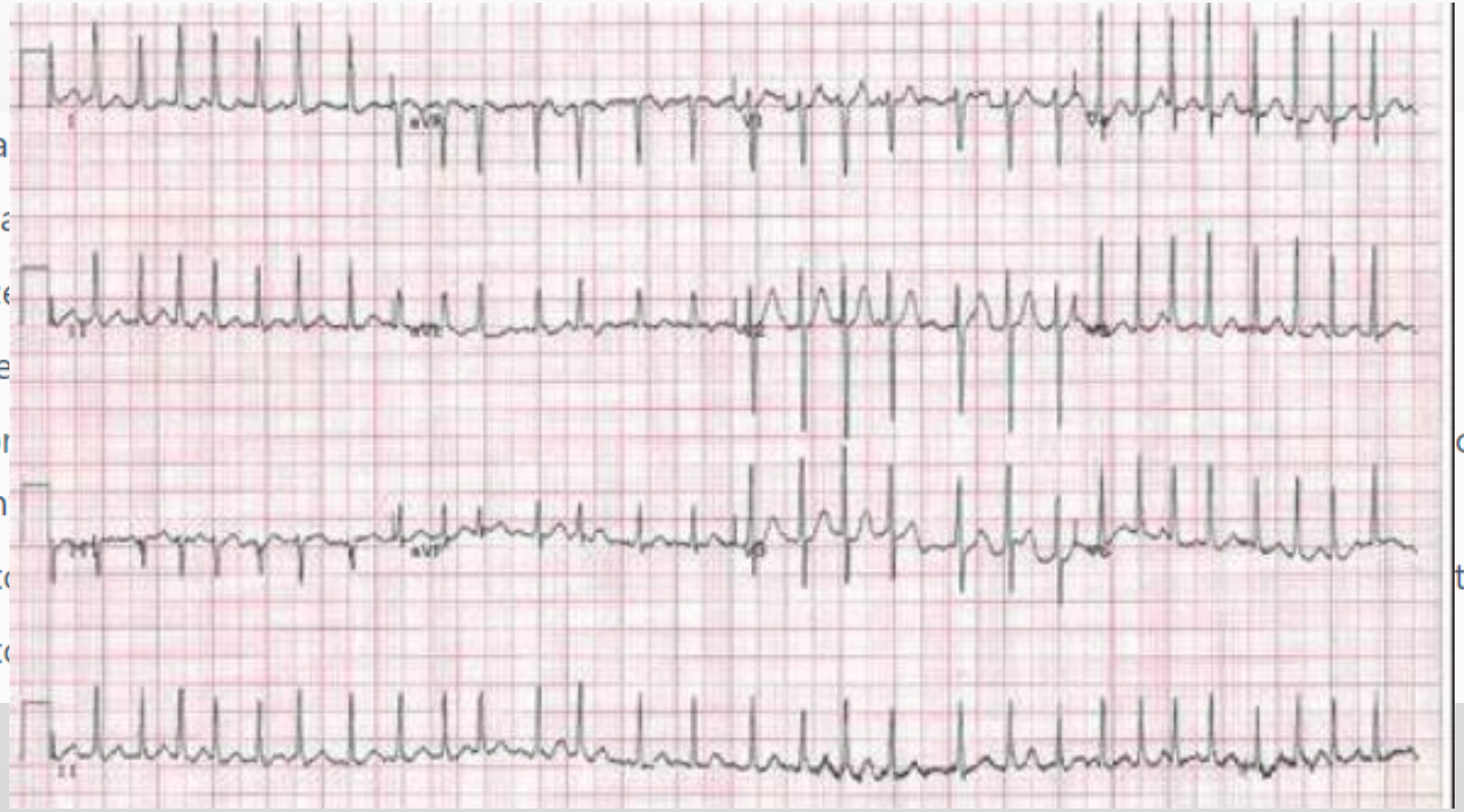
Areas covered in this presentation

- AF Basics
- Pathophysiology & Epidemiology of AF
- Risk factors for AF
- Diagnosis
- Treatment of AF
  - Lifestyle modification
  - Drug therapy: rate v rhythm
- Population considerations
  - Sex and racial disparities in AF management and outcomes
  - AF in the elderly
- To be covered elsewhere:
  - OAC for AF
  - LAAO
  - Invasive approaches to rhythm control (percutaneous RFA/cryoablation, surgical ablation, MAZE)
  - Role of device-based therapy

- Alfred Vulpian
- In 1874
- First to observe & describe chaotic rhythm of the heart in dog hearts
- “fibrillation” ~”fremissement fibrillaire”

Recognizing AF

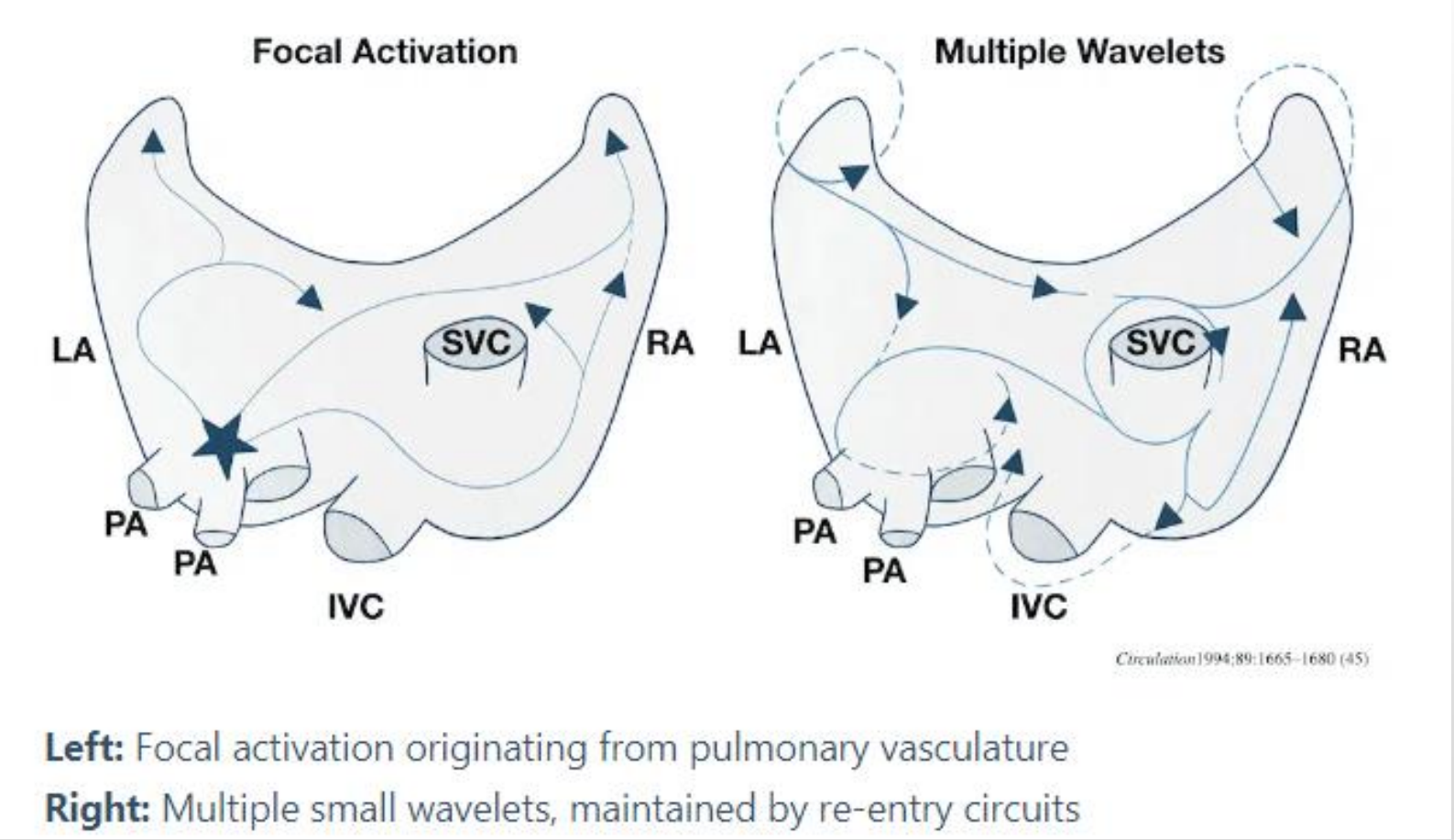
- Irregula
- No P wa
- Absence
- Variable
- QRS co
  aberran
- Fibrillat
- Fibrillat



or rate-related

tude > 0.5mm)

Mechanisms of AF



Left: Focal activation originating from pulmonary vasculature

Right: Multiple small wavelets, maintained by re-entry circuits

Causes & Comorbidities

- Ischaemic heart disease
- Hypertension
- Valvular heart disease (esp. mitral stenosis / regurgitation)
- Acute infections
- Electrolyte disturbance (hypokalaemia, hypomagnesaemia)
- Thyrotoxicosis
- Drugs (e.g. sympathomimetics)
- Alcohol
- Pulmonary embolus
- Pericardial disease
- Acid-base disturbance
- Pre-excitation syndromes
- Cardiomyopathies: dilated, hypertrophic.
- Phaeochromocytoma

Causes & Comorbidities

- Older age
- DM2
- Obesity
- Sleep apnea
- Tobacco, alcohol, THC, illicit drug use

AF Classification

AF category	Defining characteristics
First detected	only one diagnosed episode
Paroxysmal	recurrent episodes that stop on their own in less than seven days
Persistent	recurrent episodes that last more than seven days
Longstanding Persistent	recurrent episodes that last more than twelve months
Permanent	AF that has been accepted, and for which a solely rate control strategy has been decided upon.

Why do we care about AF?

- It is the most common arrhythmia in adults
- Population estimates suggest up to 44 million are affected worldwide
- Future burden: 1 in 4 adults can expect to experience AF in their lifetime
- Affects nearly 15% of people over the age of 80
- Significant cause of morbidity, particularly stroke
- Those suffering from AF report decreased quality of life, increased utilization of healthcare services

Pathophysiology: Inflammation

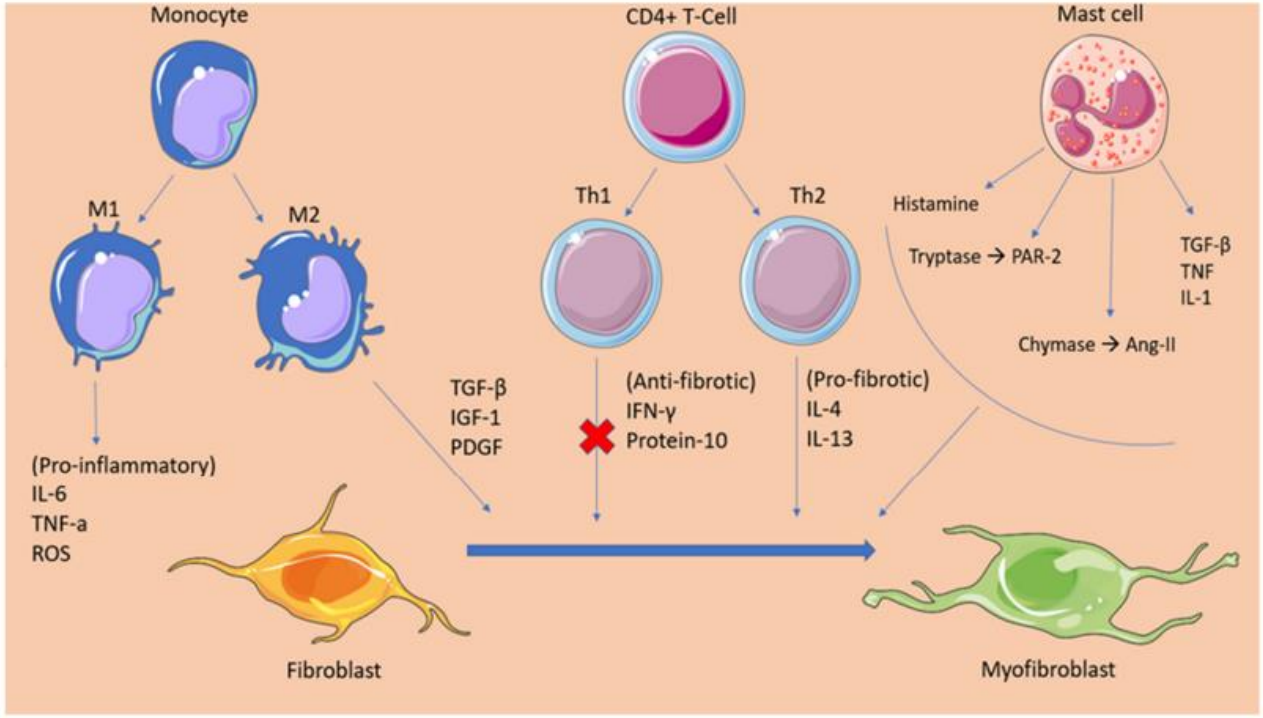
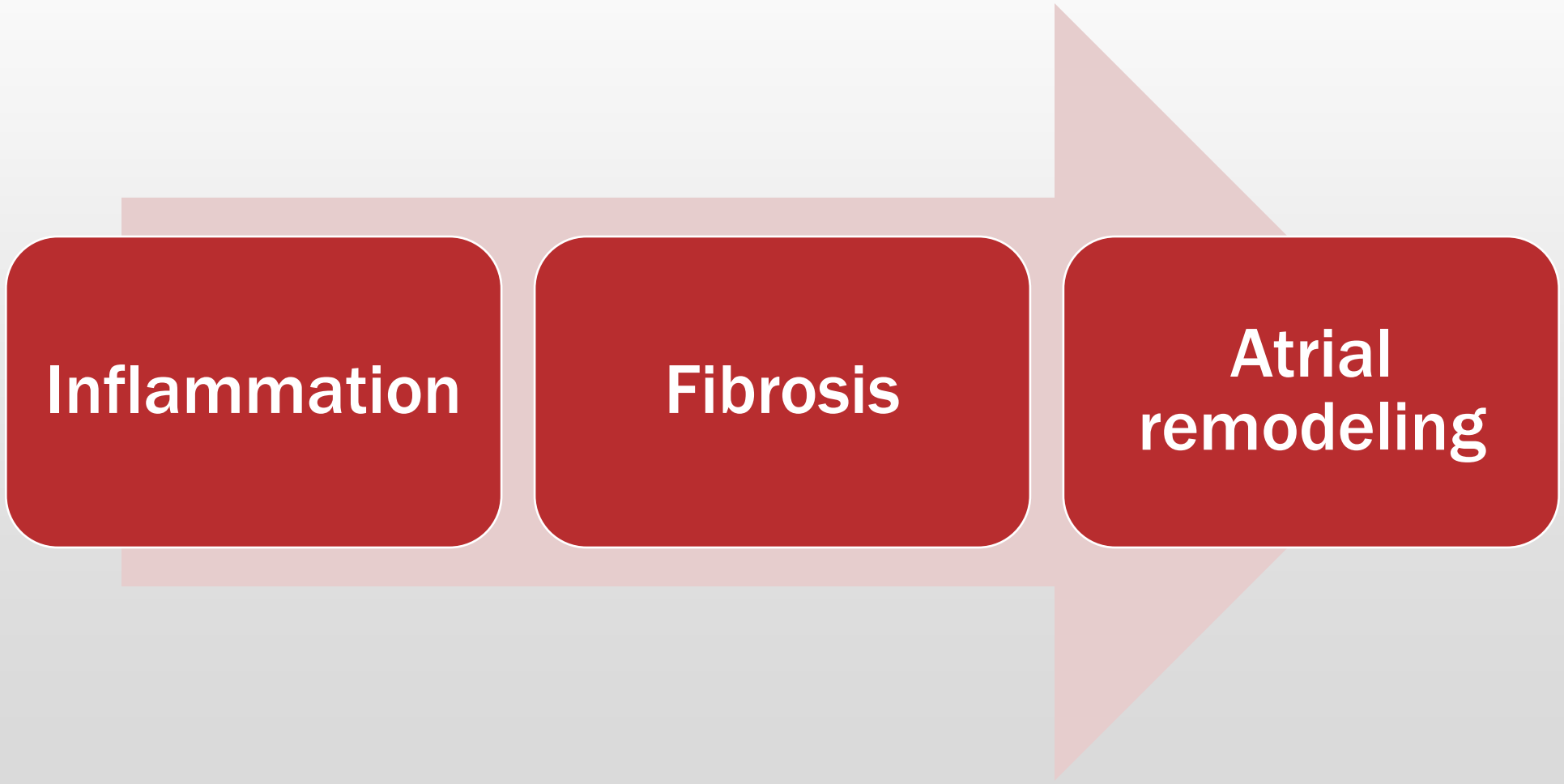


Figure 1. This graphical abstract summarizes the cellular mediators of atrial fibrosis. Following an insult, inflammatory mediators signal immune cells such as monocytes, CD4+ T-cells, and mast cells to infiltrate the atrial myocardium. These cells promote tissue fibrosis by secreting pro-fibrotic factors and regulatory molecules that enhance the activation and differentiation of fibroblasts to myofibroblasts. Additionally, the figure depicts the anti-fibrotic mediators that are secreted by Th1 cells in the early-insult stage and that are gradually overhauled by the products of pro-fibrotic Th2 cells. TGFβ, transforming growth factor beta; TNFα, tumor necrosis factor alpha; PDGF, platelet-derived growth factor; IL-1, interleukin 1; IL-4, interleukin 4; IL-6, interleukin 6; IL-10, interleukin 10;


Inflammation
Fibrosis
Atrial remodeling

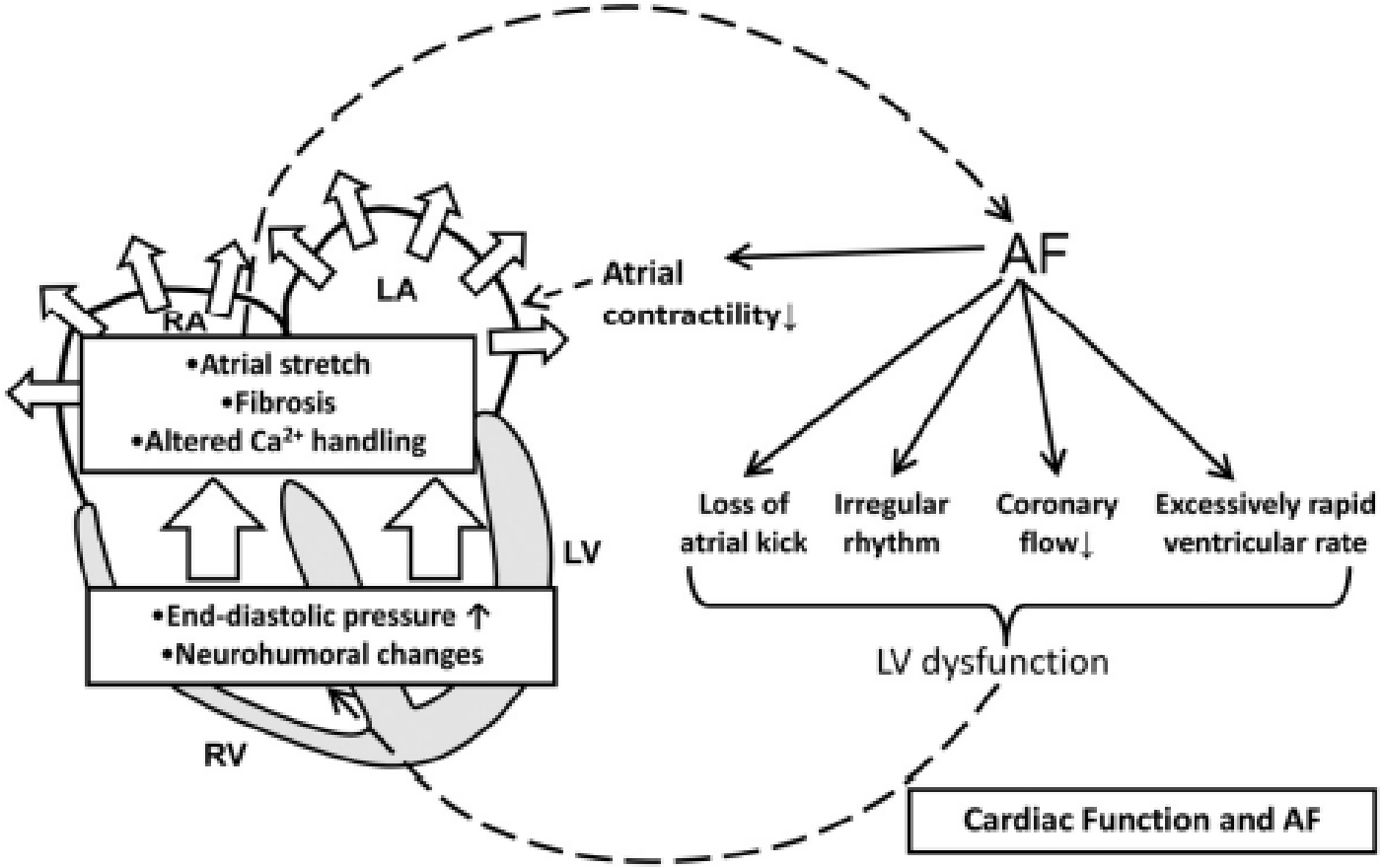


Figure 7. Dynamic interactions between atrial and ventricular function during atrial fibrillation (AF). LV indicates left ventricular.

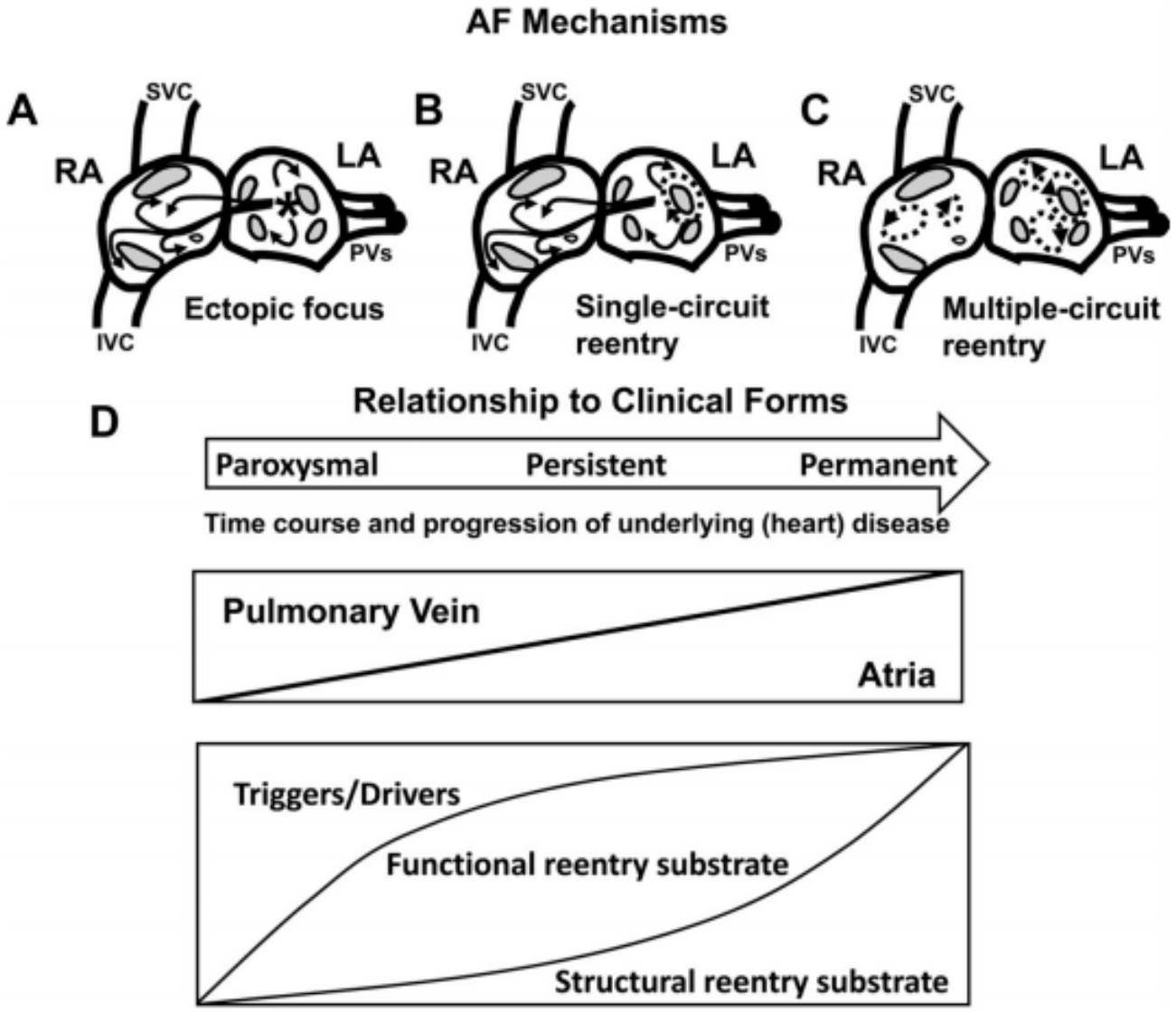


Figure 1. Principal atrial fibrillation (AF)–maintaining mechanisms. **A,** Local ectopic firing. **B,** Single-circuit reentry. **C,** Multiple-circuit reentry. **D,** Clinical AF forms and relation to mechanisms. Paroxysmal forms show a predominance of local triggers/drivers, particularly from pulmonary veins (PVs). As AF becomes more persistent and eventually permanent, reentry substrates (initially functional and then structural) predominate. RA indicates right atrium; SVC, superior vena cava; LA, left atrium; and IVC, inferior vena cava.

Inflammatory markers and AF

Table 1. Differences in concentrations of inflammatory proteins in patients with and without atrial fibrillation.

Protein	Protein Serum Levels Difference	Atrial Tissue Levels Difference	Predictor for AF
CRP	NA	NA	Yes
MCP-1	+	+	No
MPO	NA	+	No
TGF-β	NA	+	No
TNF	NA	+	No
HSP-27	+	+	NA
HSP-70	-	-	NA
IL-1	NA	NA	NA
IL-6	NA	+	No
IL-8	+	+	NA
IL-10	NA	+	NA

Abbreviations: AF = atrial Fibrillation, IL = interleukin, CRP = C-reactive protein, TNF = tumor necrosis factor, HSP = heat shock protein, TGF = transforming growth factor, MPO = myeloperoxidase, MCP-1 = monocyte chemoattractant protein, NA = not applicable, (+) = There is a difference in concentration; (-) = There is no difference in concentration.

Genetic factors

Table 2. Genetic mutations that are implicated in atrial fibrillation.

Gene of	Polymorphism-Mutation	Action
ABCC9 (I KATP)	Potassium (K^+) channel genes	The increased K^+ current abbreviates refractoriness and promotes re-entry, while tending to reduce automaticity
KCNA5 (I Kur)		
HCN4 (I f)		
KCND3 (I Ks)		
KCNE1 (IKs)		
KCNE2 (IKs)		
KCNE3 (IKs)		
KCNE4 (IKs)		
KCNE5 (IKs)		
KCNH2 (IKr)		
KCNJ2 (I K1)		
KCNJ5 (I KAch)		
KCNJ8 (I KATP)		
KCNN3 (IAHP)		
KCNQ1 (IKs)		

Genetic factors

Table 2. *Cont.*

Gene of	Polymorphism-Mutation	Action
SCN1B **SCN2B** **SCN3B** **SCN4B** **SCN5A** **SCN10A**	Sodium (Na^+) channel genes	Delay repolarization and promote Ca^{+2} mediated after depolarization
GJA5	Mutations in the gap junctional protein	Re-entry mechanism
NUP155	Nuclear pore complex (nucleoporin) Nup155	Re-entry mechanism
E169K	Junctophilin mutation	Delay repolarization and promote Ca^{+2} mediated after depolarization enhancing RyR2 Ca^{+2} leak
CASR	rs1801725	Delay repolarization and promote Ca^{+2} mediated after depolarization
PITX2	rs2200733 rs10033464 rs2634073	PITX2 deficiency results in electrical and structural remodelling
NURL1	rs6584555 rs6584555	Undefined
PRRX1	rs593479	Undefined
CAV1	rs1177384	Undefined
CUX2	rs649002	Undefined
ZFHX3	rs12932445	Undefined

Epidemiology

- AF correlates:
- Increasing age
- Arterial HTN
- Obesity
- Diabetes mellitus
- Genetic factors “family clusters”

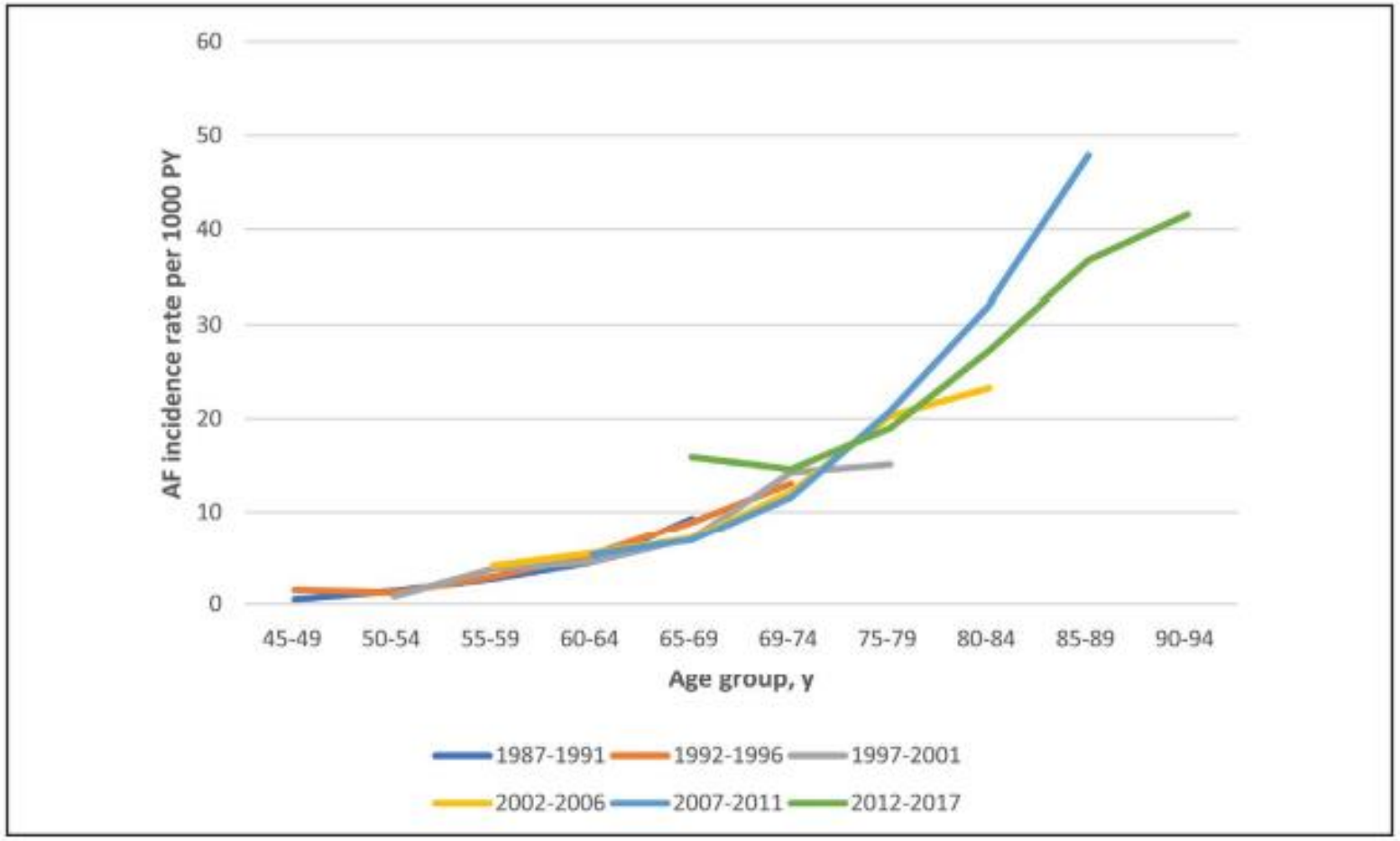


Figure 2. Age-specific incidence rates of atrial fibrillation (AF) by period in the ARIC (Atherosclerosis Risk in Communities) cohort, 1987 to 2017.
PY indicates person-years.

J Am Heart Assoc. 2022;11:e023583. DOI: 10.1161/JAHA.121.023583

Risk Factors

Alcohol

- Depresses cardiac function
- Cardiac conduction delay
- 34% increased risk in FHS if >3 drinks/day
- Another cohort study found 39% increased risk if >14 drinks/week
- 10% increase in RR for each single drink over current daily recommendations

OSA

- Prevalence up to 81% in patients with persistent AF
- Associated with higher AF recurrence after ECV
- Lowers response rate to AAD
- Increases short term recurrence after PVI

Risk Factors

Diabetes

- Found in up to 20% of AF pts
- Hyperglycemia contributes to oxidative stress, inflammation, fibrosis->result is electrical and structural remodeling of LA
- TZD and SGLT2i agents have shown promise in AF risk reduction
- Population-based studies: 2 have shown lower adjusted risk of new AF as well as higher rates of maintenance of SR in AF pts with these Rxs/better DM control

Obesity

- Closely linked to AF risk: in ARIC, Women's Health Study and FHS
- Durable weight loss of ≥10% led to 6-fold increase in probability of AF-free survival
- Epicardial fat – link to increase in AF; higher volume of epicardial fat in persistent vs pAF

Risk Factors continued: HTN

Increase sympathetic output- > increased LA pressure & volume -> active RAAS ->atrial fibrosis & remodeling

FHS and WHS: HTN, even pre-HTN increased risk of AF, up 1.5X in men, 1.4X in women

Aggressive BP tx with targets <120/80 in appropriate candidates may lower incidence of AF

Lifestyle choices and AF prevention

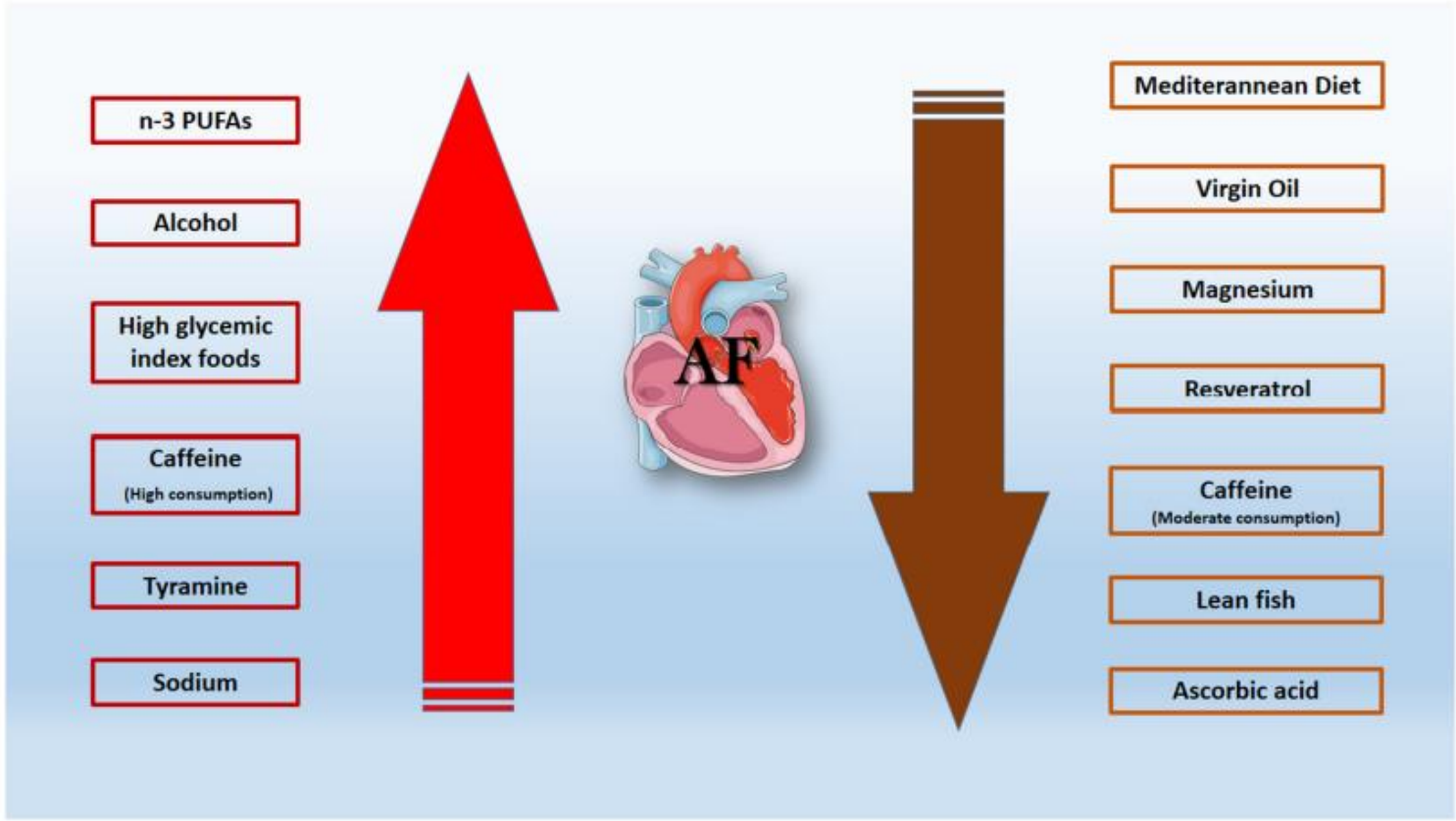


Figure 2. Graphical illustration of daily dietary habits that reduce (brown arrow) or increase (red arrow) the incidence of atrial fibrillation. n-3 PUFAs; polyunsaturated fatty acids.

Using Prediction for Prevention

Table 3 Calculation of the SHARP-D Score for AF prediction in PDD cohort

Variables	Scores	
Sex	Male	1
	Female	0
Hypertension	No	0
	Yes	2
Age (years)	20 to < 30	−2
	30 to < 40	−1
	40 to < 50	0
	50 to < 60	1
	60 to < 70	2
	70 to < 80	3
	80 to < 90	4
	≥90	5
Race	White	0
	Black	−2
	Hispanics	−2
	Others	−3
PAD	No	0
	Yes	2
Diabetes	No	0
	Yes	1

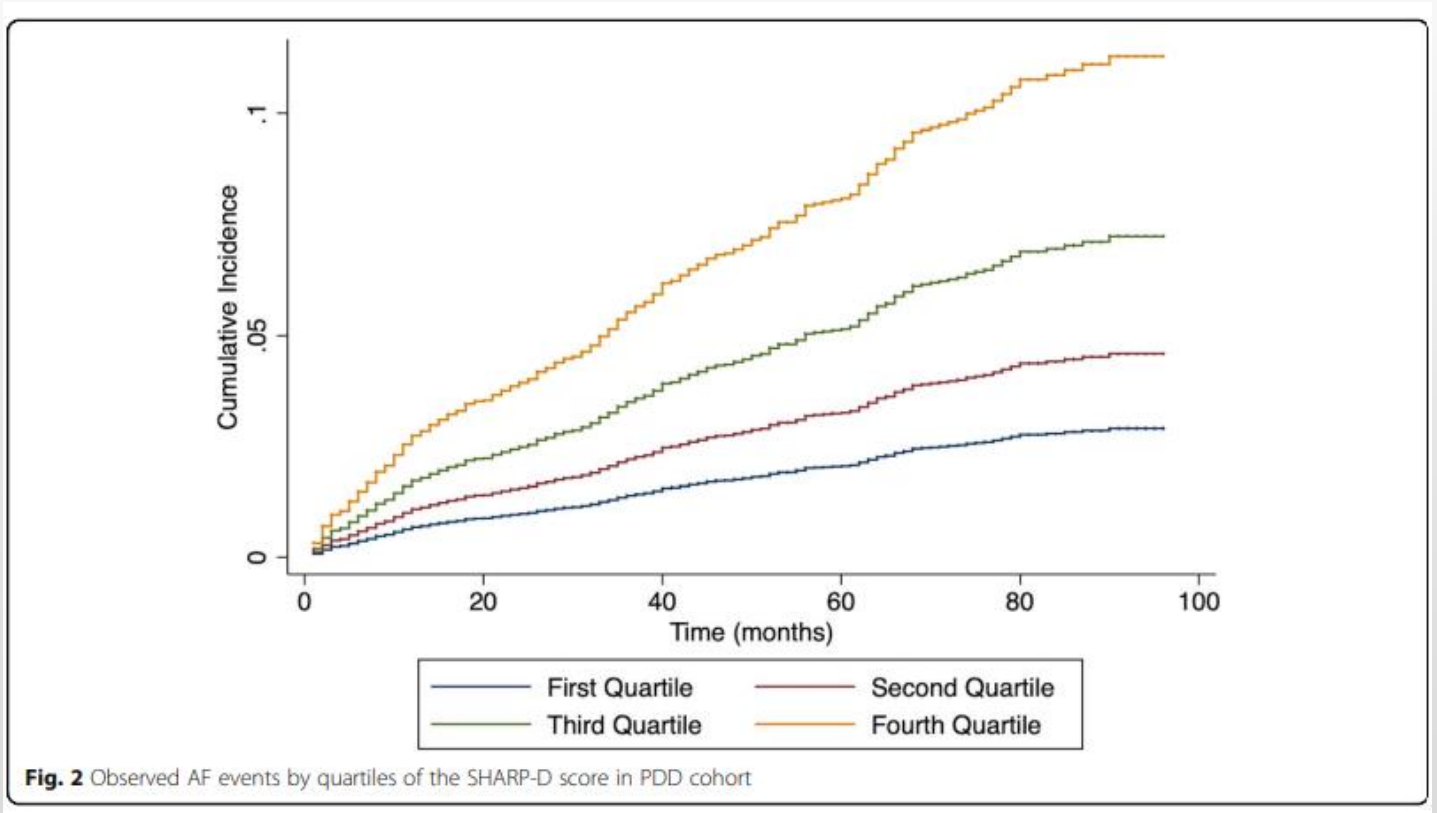


Fig. 2 Observed AF events by quartiles of the SHARP-D score in PDD cohort

Li *et al. BMC Cardiovascular Disorders* (2019) 19:47
https://doi.org/10.1186/s12872-019-1024-4

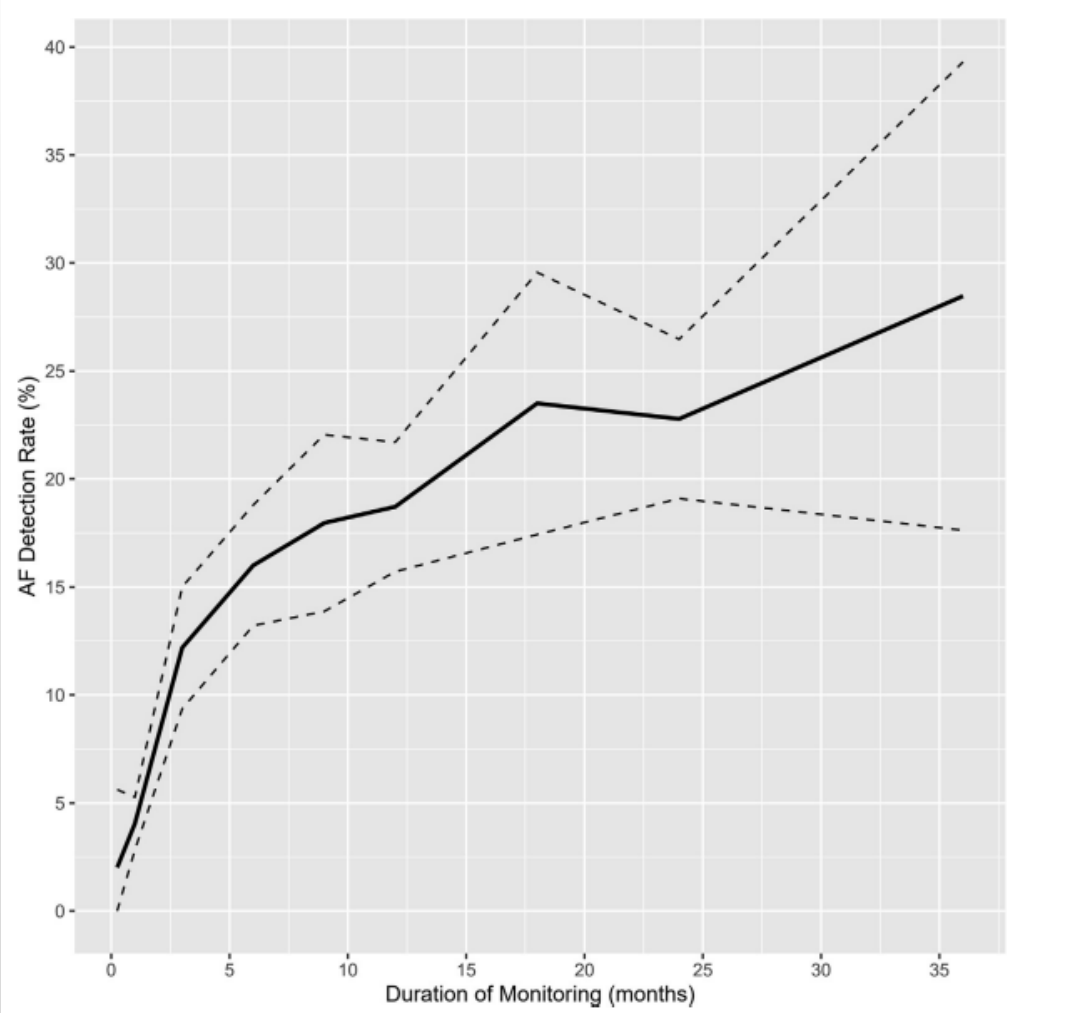
Tailoring Rx for Prevention of AF

- In conjunction with lifestyle changes aimed at reducing inflammation, fibrosis, structural and electrical remodeling…
- Pharmacologic therapies that partner in the fight:
  - ACEi
  - ARB
  - MRA
  - SGLT2i

Challenges of AF Detection after Stroke

- Ischemic stroke is a leading cause of disability and death
- 1/3 of cases are cryptogenic
- 1/3 of those are due to AF…suspected to be even higher
- Stroke from AF is associated with higher mortality and disability
- CRYSTAL-AF study was the first to demonstrate effective role of implantable cardiac monitors (ICMs) in this setting
  - AF detection (12% in the 1st year)

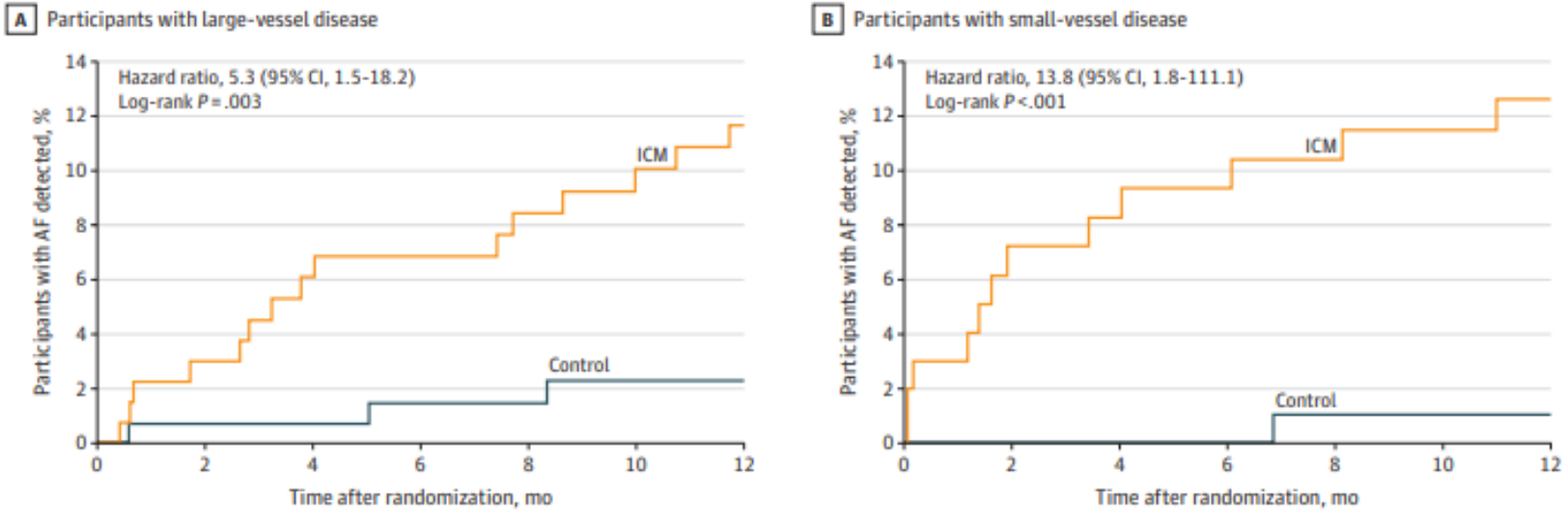
AF Detection After Cryptogenic Stroke



IJC Heart & Vasculature 34 (2021) 100780

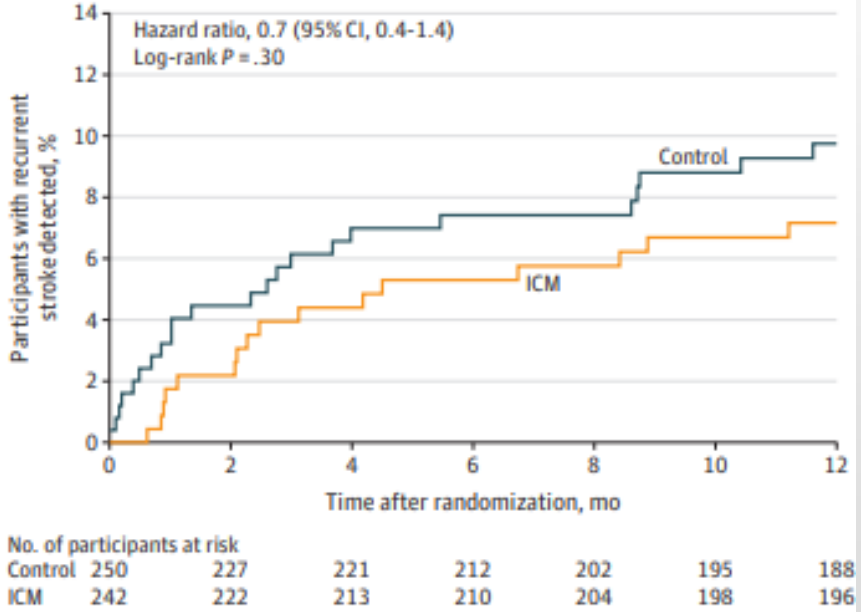
Diagnosis: Stroke-AF Trial

Figure 3. Time to First Detection of Atrial Fibrillation at 12 Months in a Study of Long-term Continuous Cardiac Monitoring vs Usual Care in Patients With Stroke Attributed to Large- or Small-Vessel Disease



The median (interquartile range) observation time was 365 (365-365) days for all randomized patients for each group. ICM indicates insertable cardiac monitor.

Figure 4. Rate of Recurrent Stroke at 12 Months in a Study of Long-term Continuous Cardiac Monitoring vs Usual Care on Detection of Atrial Fibrillation in Patients With Stroke Attributed to Large- or Small-Vessel Disease



The median (interquartile range) observation time was 365 (365-365) days for all randomized patients for each group. ICM indicates insertable cardiac monitor.

Correlates of AF detection on ICMs

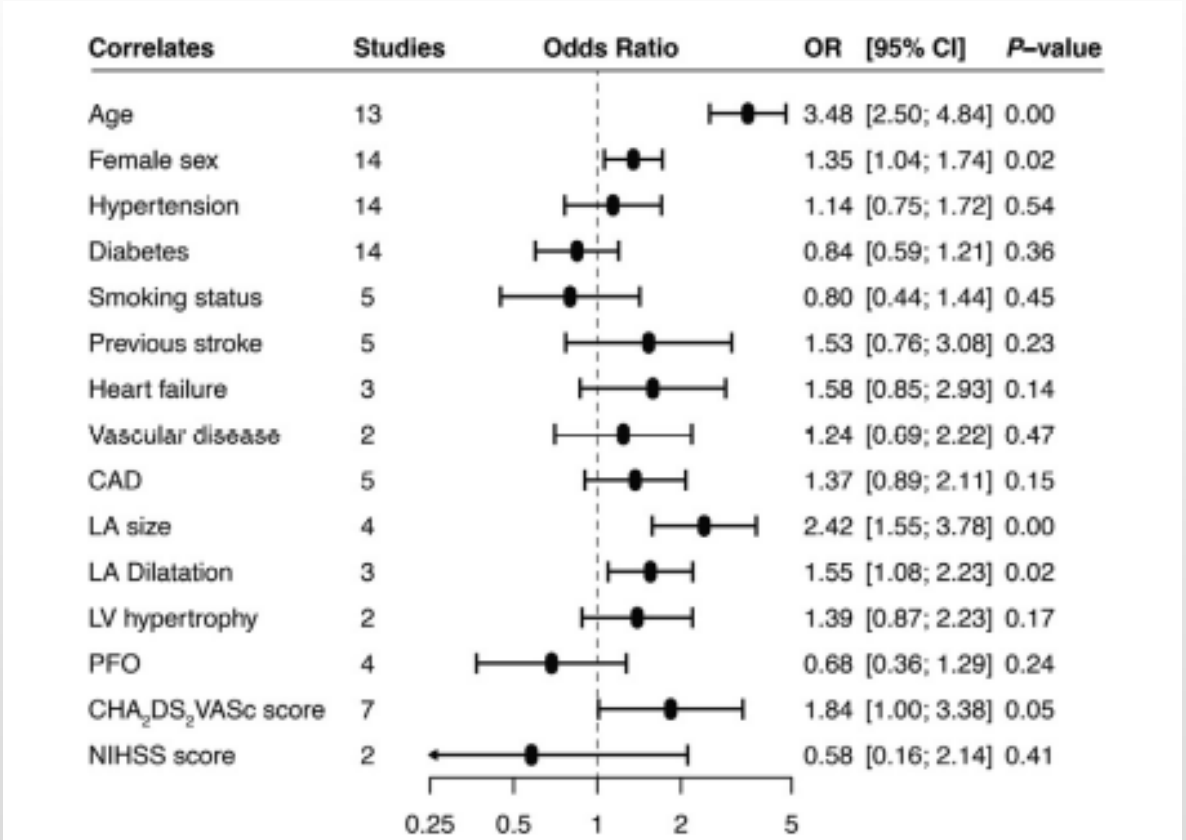


Fig. 3. Univariable correlates of atrial fibrillation detection on implantable cardiac monitors in patients with cryptogenic stroke.

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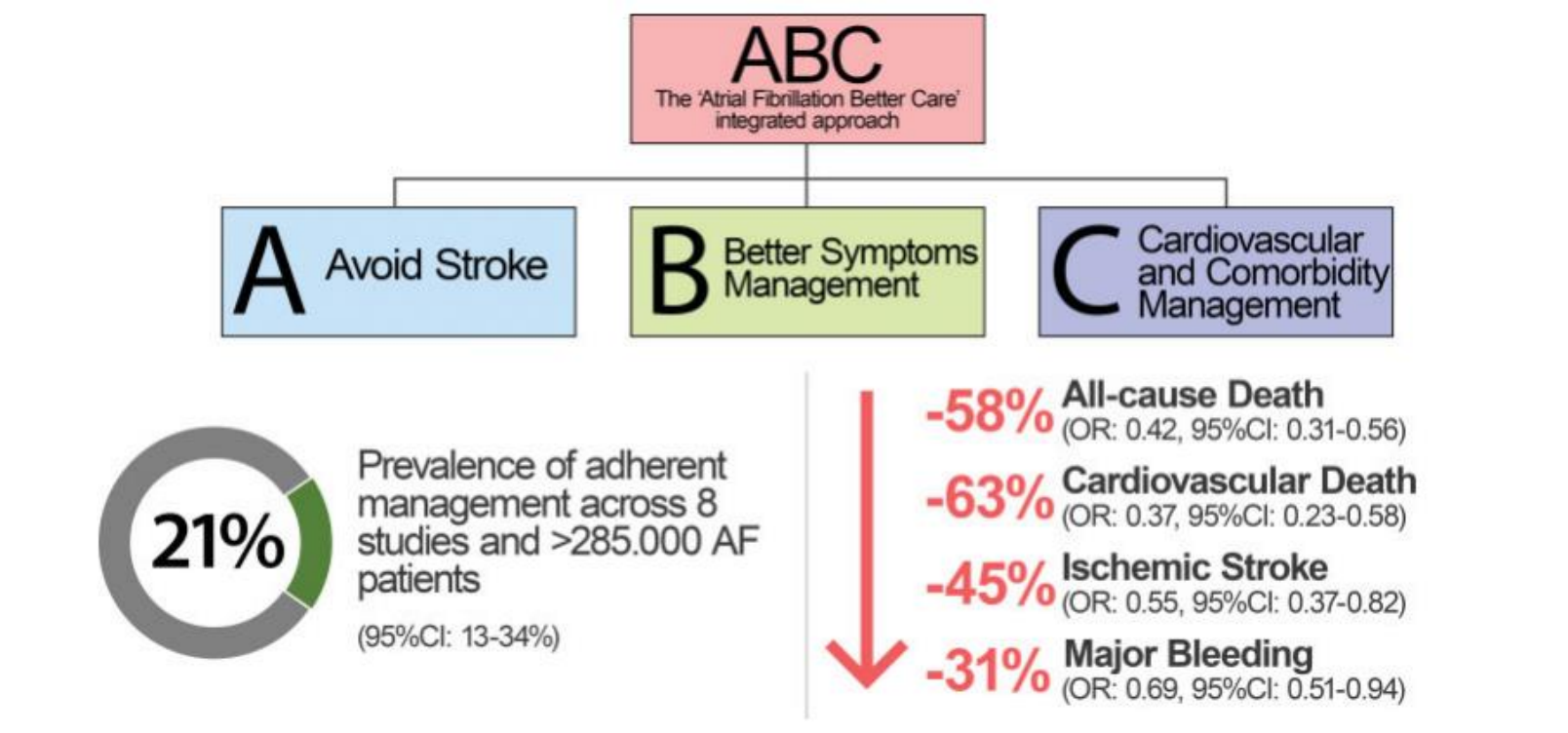
Other tools for AF detection

- Wearables:
  - Kardia mobile
  - Watches

Atrial Fibrillation Better Care pathway

- ABC approach decreased all-cause death, cv death, stroke and bleeding in AF patients

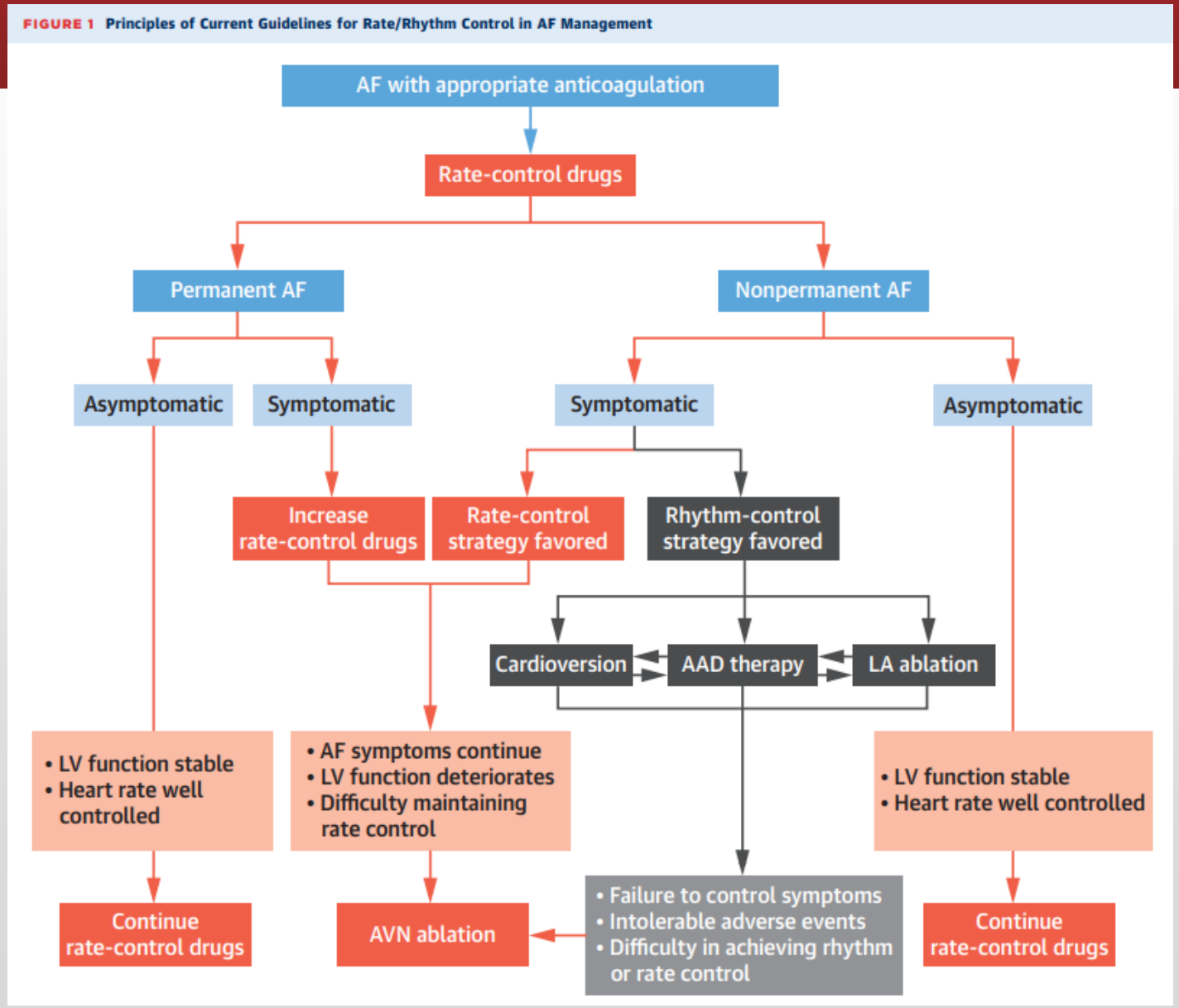


Rate versus Rhythm

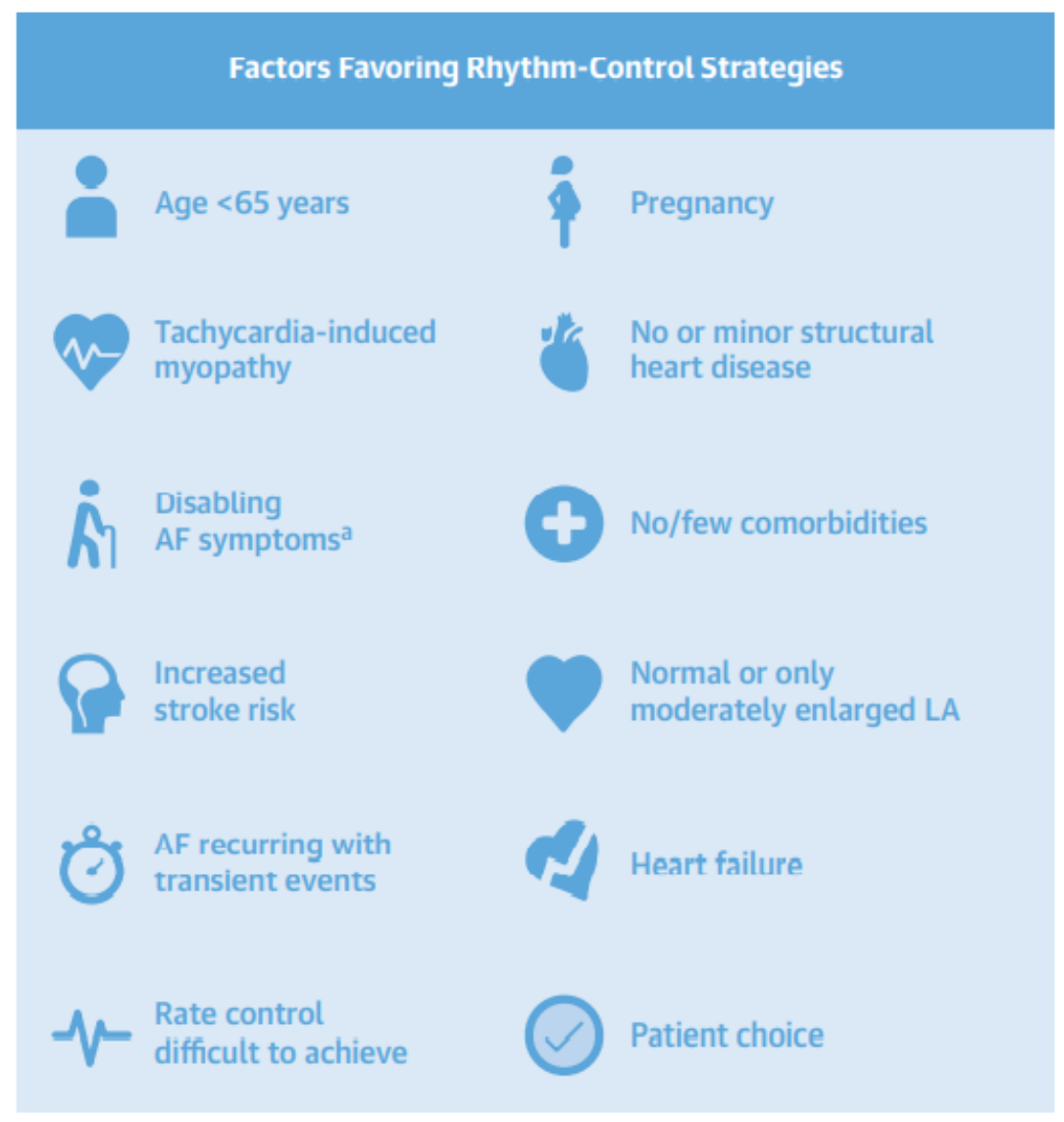
TABLE 2 Key Outcomes of Trials Using Rhythm- and Rate-Control Strategies in Treatment of AF

Trial	Primary Endpoint	Primary Endpoint Result	Patients in SR
PIAF[17]	Improvement in AF-related symptoms (palpitations, dyspnea, and dizziness)	No significant difference between treatment arms	Rhythm control: 56% at study end Rate control: 10% at study end
AFFIRM[18]	Overall mortality	Rhythm control: 24% at 5-y follow-up Rate control: 21% at 5-y follow-up (NS across follow-up period)	Rhythm control: 62.6% at 5-y follow-up Rate control: 34.6% at 5-y follow-up
RACE[19]	Composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, the need for a pacemaker, or severe AEs	Rhythm control: 22.6% at study end Rate control: 17.2% at study end (noninferior, approaching superior)	Rhythm control: 39% at study end Rate control: 10% at study end
STAF[147]	Composite of death, stroke or transient ischemic attack, systemic embolism or cardiopulmonary resuscitation	Rhythm control: 5.54%/y Rate control: 6.09%/year (NS)	Rhythm control: 38% at last follow-up Rate control: 9% at last follow-up
AF-CHF[20]	Death from cardiovascular causes	Rhythm control: 27% at study end Rate control: 25% at study end (NS)	Rhythm control: 73% at 4-y follow-up Rate control: 30% to 41% during follow-up[b]
J-RHYTHM[22]	Composite of total mortality, symptomatic cerebral infarction, systemic embolism, major bleeding, hospitalization for heart failure[a] and physical/psychological disability requiring strategy alteration	Rhythm control: 15.3% at study end Rate control: 22.0% at study end (HR: 0.664; $P = 0.0128$)	Rhythm control: 72.7% at 3 y Rate control: 43.9% at 3 y

Rate versus rhythm



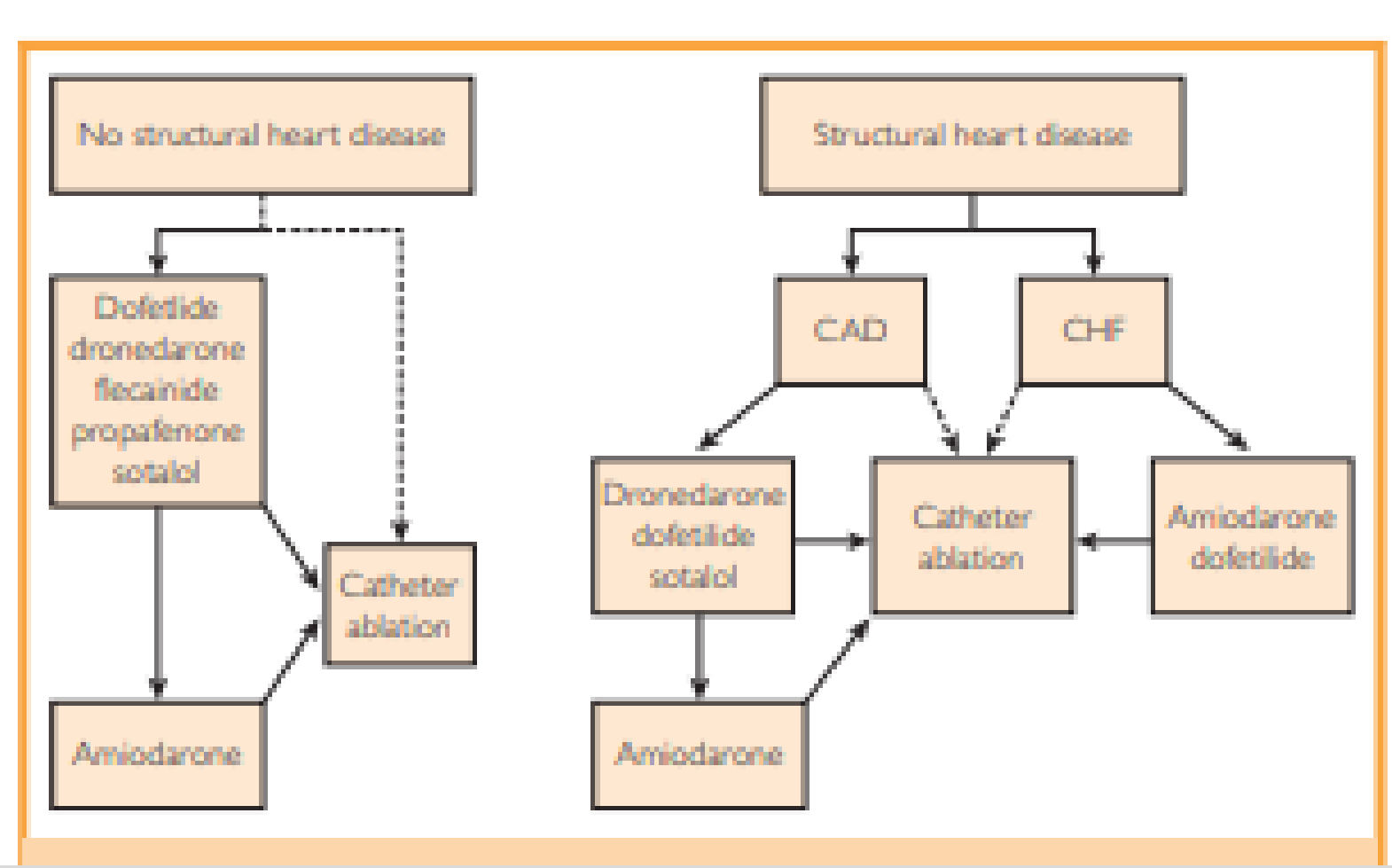
Rate versus rhythm



Considerations for rhythm control

- Symptoms, patient preference, compliance
- Other contributing factors to AF burden
  - Obesity
  - OSA, treated or untreated
  - HTN
  - DM
  - EtOH use
  - Anxiety
- Cardiac parameters
  - structural heart disease/valvular disease/LA size (LAVI)
- Age
- Renal function
- QRS duration, QT duration, evidence of underlying conduction disease

Rhythm control



The Rise of Rhythm Control

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 1, 2020 VOL. 383 NO. 14

Early Rhythm-Control Therapy in Patients with Atrial Fibrillation

P. Kirchhof, A.J. Camm, A. Goette, A. Brandes, L. Eckardt, A. Elvan, T. Fetsch, I.C. van Gelder, D. Haase, L.M. Haegeli, F. Hamann, H. Heidbüchel, G. Hindricks, J. Kautzner, K.-H. Kuck, L. Mont, G.A. Ng, J. Rekosz, N. Schoen, U. Schotten, A. Suling, J. Taggeselle, S. Themistoclakis, E. Vettorazzi, P. Vardas, K. Wegscheider, S. Willems, H.J.G.M. Crijns, and G. Breithardt, for the EAST-AFNET 4 Trial Investigators*

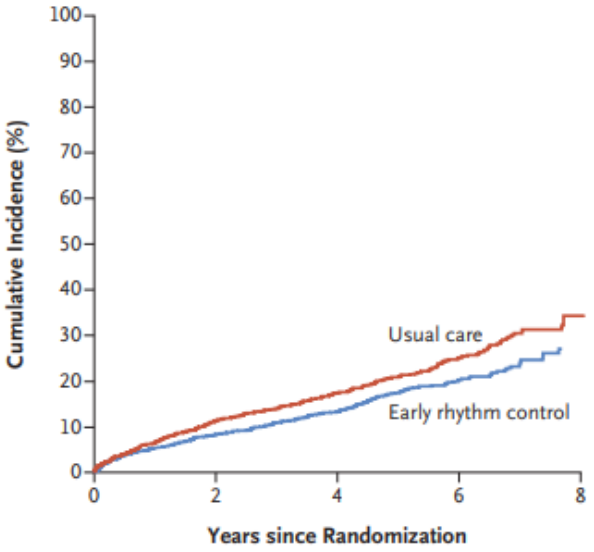
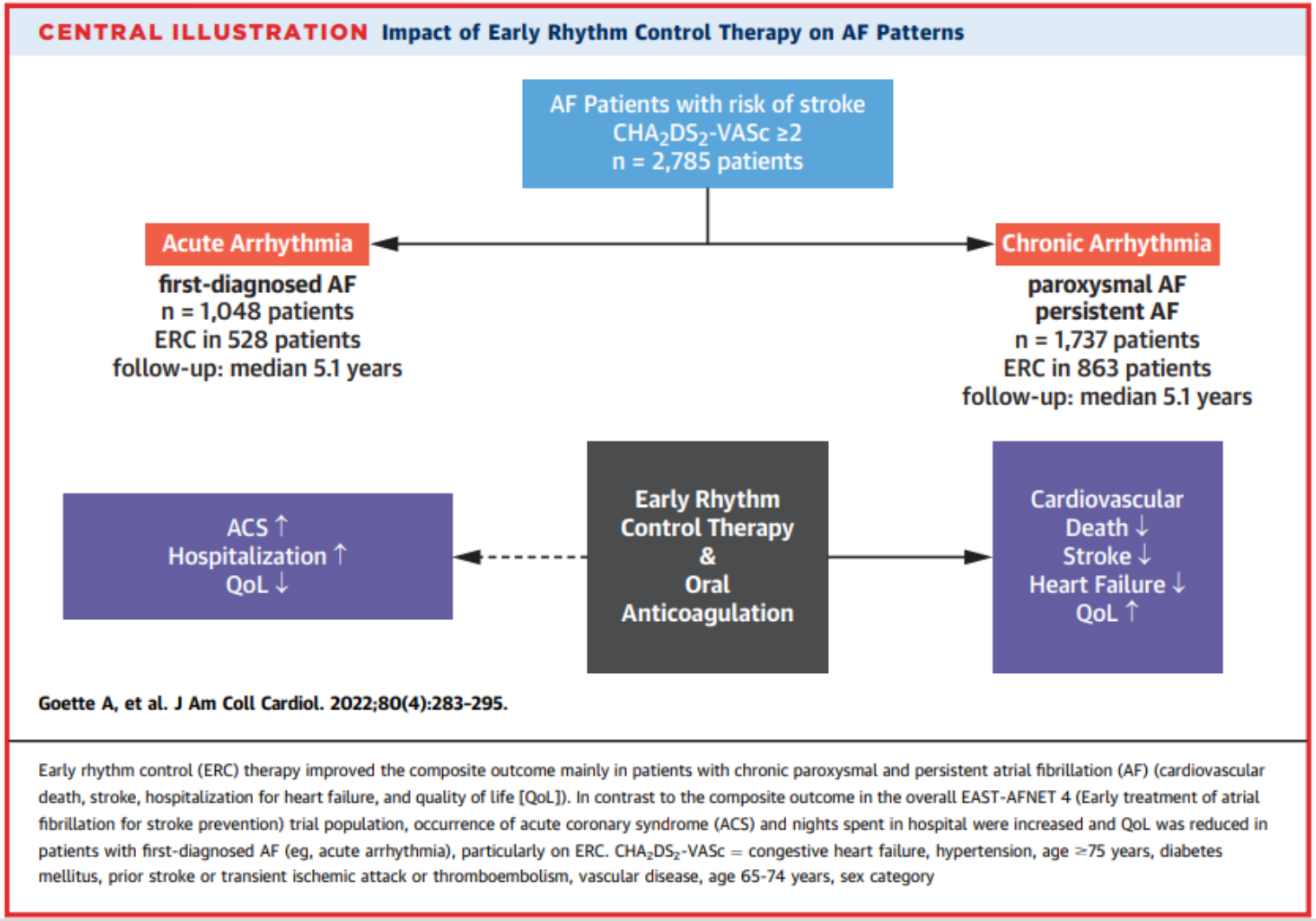


Figure 2. Aalen–Johansen Cumulative-Incidence Curves for the First Primary Outcome.

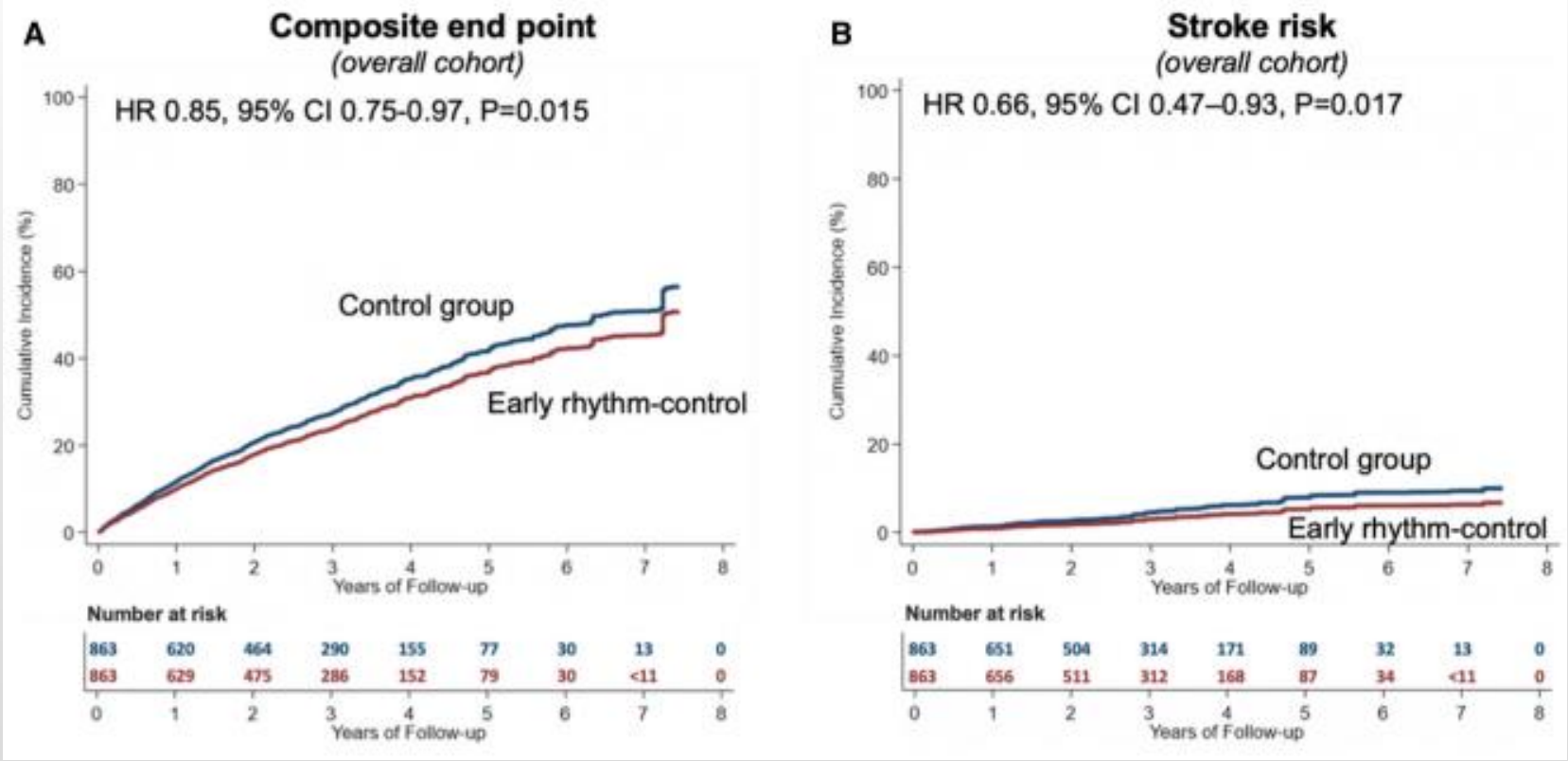
The first primary outcome was a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome.

Timing is Everything…



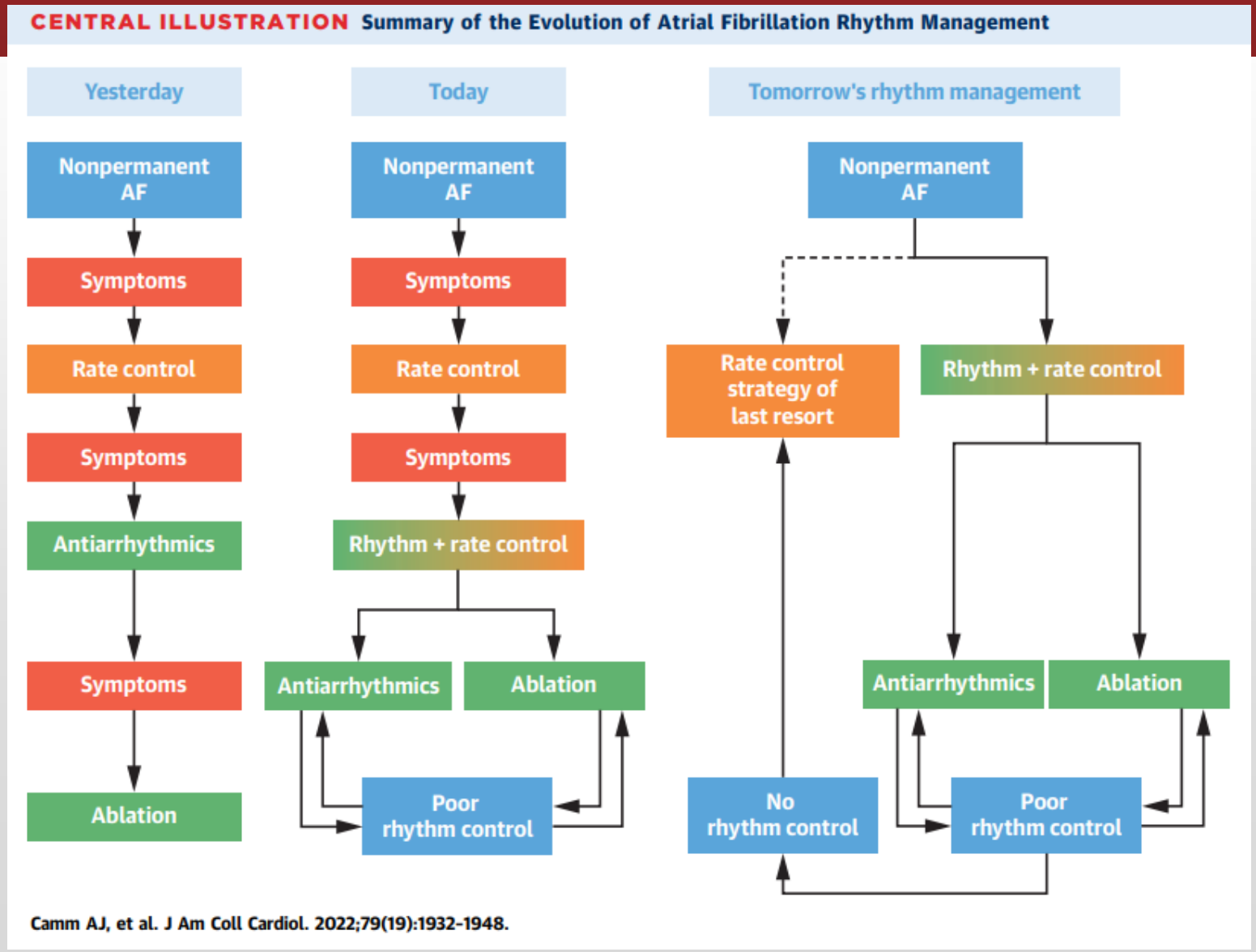
Is EAST-AFNET 4 Generalizable?

This is the largest comparison of patients treated with ERC and controls, including >100 000 patients. The strengths of the study are the close modeling of the EAST-AFNET 4 inclusion criteria and the well-documented information on events. The estimate for eligibility thus should be robust. Taken together with the main findings from the EAST-AFNET 4 randomized clinical trial and with a recent analysis in the Korean Health Data showing lower event rates in Korean patients treated with ERC (early rhythm control 7.42 events per 100 patient-years, controls 9.25 events per 100 patient-years; HR, 0.81 [95% CI, 0.71–0.93]),[21] our data support the inclusion of ERC in the management of all patients with recently diagnosed AF and concomitant conditions to avoid missing positive effects, calling for an update of international guidelines.[22,23]



J Am Heart Assoc. 2022;11:e024214. DOI: 10.1161/JAHA.121.024214

Treatment Directions



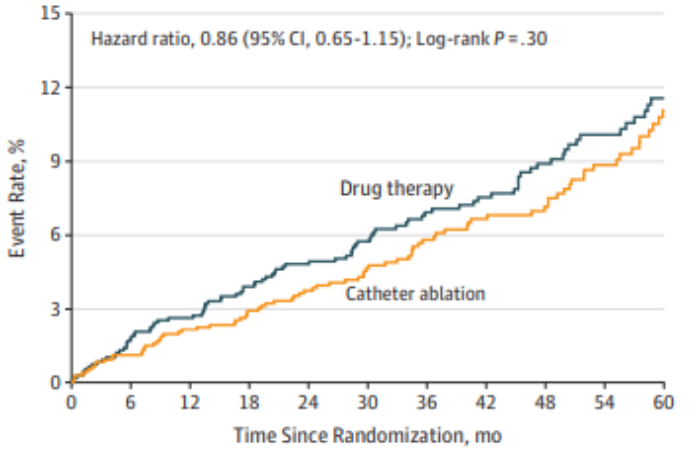
Camm AJ, et al. J Am Coll Cardiol. 2022;79(19):1932-1948.

JAMA | Original Investigation

Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation

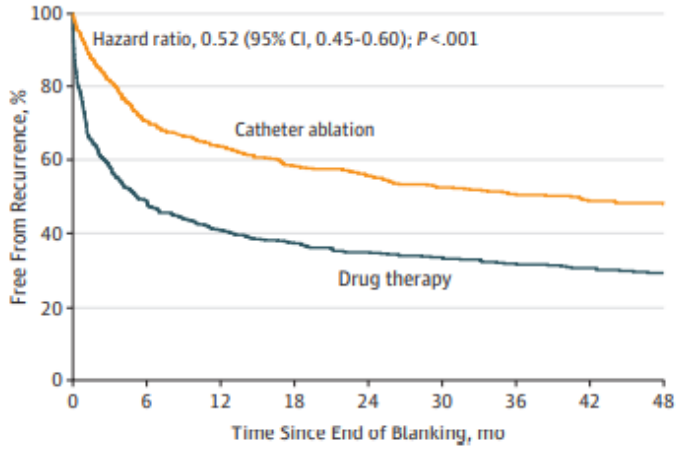
The CABANA Randomized Clinical Trial

Figure 2. Kaplan-Meier Estimates of the Incidence of the Primary End Point



No. at risk											
Drug therapy	1096	1036	1006	970	880	763	652	578	499	418	312
Catheter ablation	1108	1045	1021	996	915	793	700	614	535	432	309

Figure 6. Recurrent Atrial Fibrillation After Blanking by Intention-to-Treat Analysis



No. at risk									
Drug therapy	629	304	252	212	181	157	131	115	94
Catheter ablation	611	432	381	328	291	241	201	163	134

CONCLUSIONS AND RELEVANCE Among patients with AF, the strategy of catheter ablation, compared with medical therapy, did not significantly reduce the primary composite end point of death, disabling stroke, serious bleeding, or cardiac arrest. However, the estimated treatment effect of catheter ablation was affected by lower-than-expected event rates and treatment crossovers, which should be considered in interpreting the results of the trial.

Location, location, location

- Clinic
- ER
- ICU
- General Cardiology unit

Cardioversion: To shock or not to shock

- Everyone deserves a chance at normal sinus rhythm
- Predictors of failure to maintain sinus rhythm
- AF-CVS
  - Prior AF within 30 days
  - Older age
  - Any previous AF history
  - HF
  - Vascular disease

Don't be "shocked" if it fails when…
Comorbid conditions are not optimized:
Untreated OSA
Ongoing EtOH use
Electrolyte derangements, thyroid abns
Severe morbid obesity
Volume overload
Structural: LAVI>40

Cardioversion: When and How

'Diagnostic electrical cardioversion'—a possible new indication

In some patients with persistent AF, e.g. those with heart failure both with reduced and with preserved ejection fraction but also others, the relationship between symptoms and arrhythmia may be unclear. In those patients, a 'diagnostic ECV' may be performed to show improvement of symptoms (or not) when in stable sinus rhythm. To enhance such assessment, the period in sinus rhythm may be lengthened by using temporary amiodarone or flecainide.[23,30] Studies are needed in this area to show usefulness of such an approach.

Key points

- Predictors of successful ECV of persistent AF are AF duration, patient age, better function class, and pre-treatment with AADs.

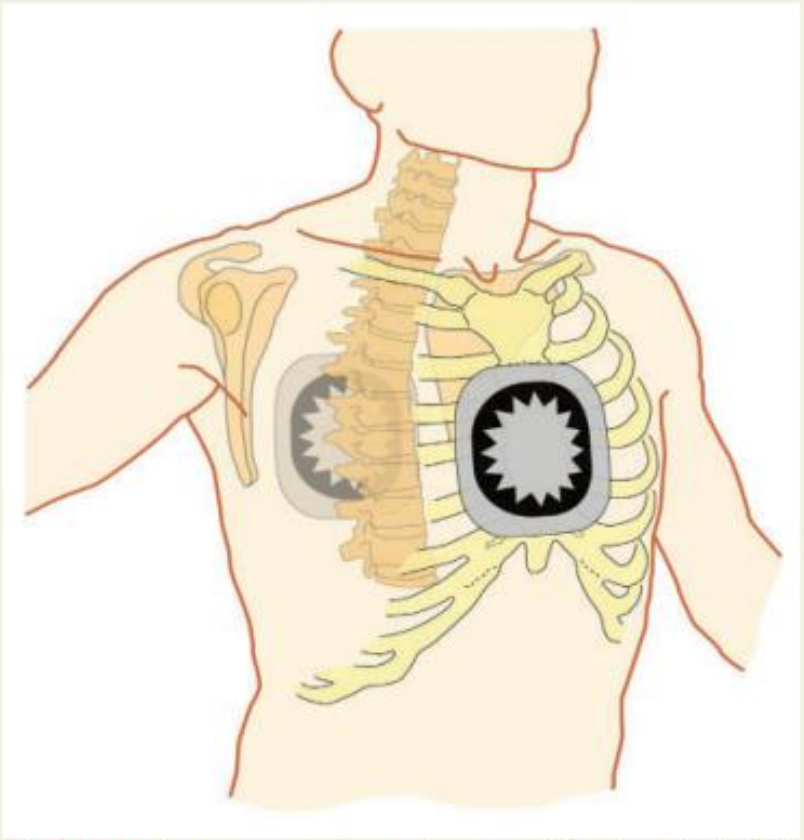


Figure 1 Antero-posterior electrode position for ECV. ECV, electrical cardioversion. Modified after Kirchhof *et al.*[15] with permission.

Key points

- Electrical cardioversion terminates AF in over 90% of cases and is the treatment of choice in haemodynamically compromised patients.
- Pharmacological cardioversion mainly converts recent-onset AF of <48 h duration.
- Electrical cardioversion with an antero-posterior electrode position restores sinus rhythm better than with an antero-apical position.
- Complications of ECV and PCV are generally rare.

Europace (2020) **22**, 1149–1161

PCV, Pharmacologic cardioversion

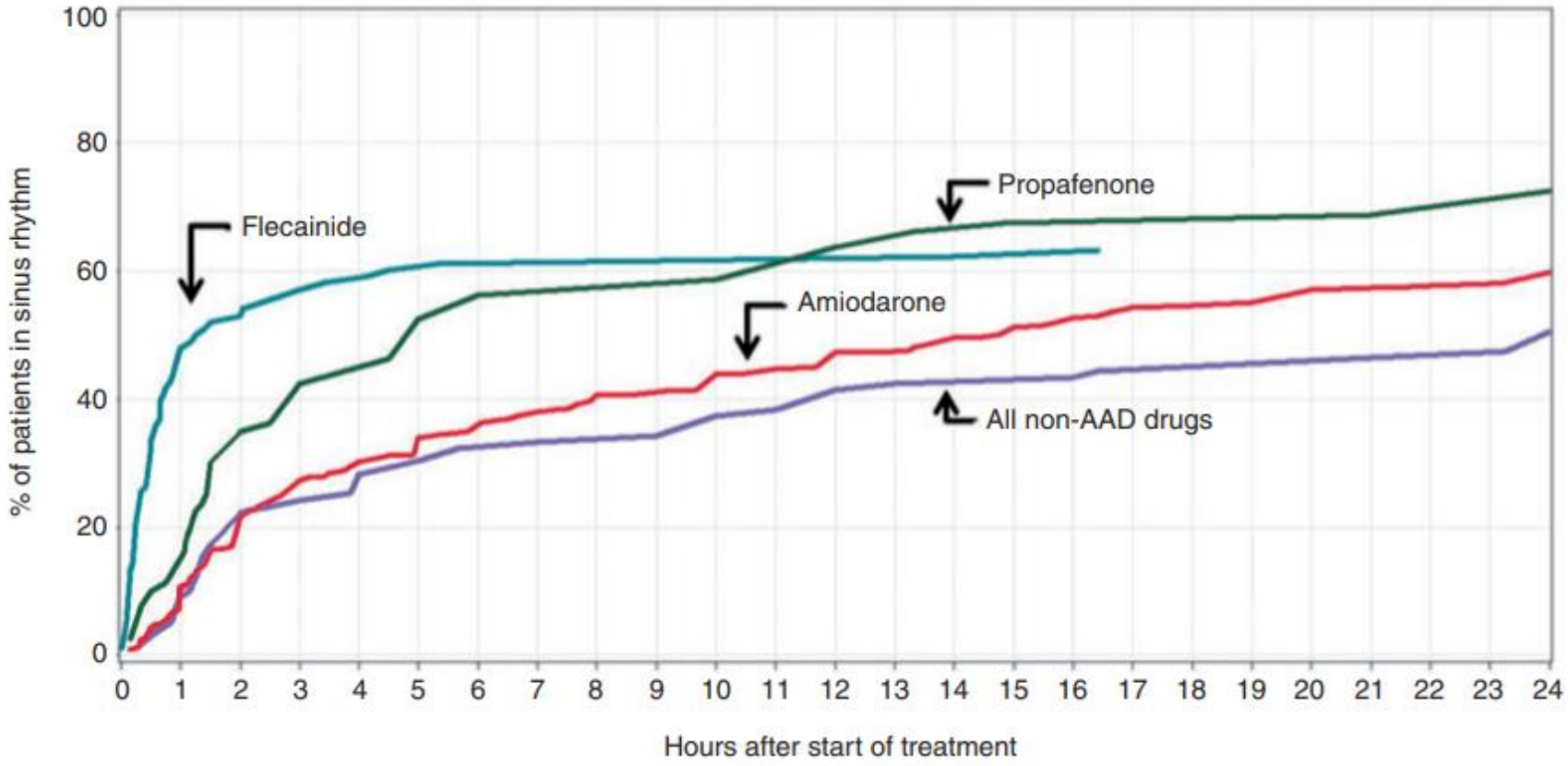


Figure 3 Conversion to sinus rhythm over time after start of drug therapy for recent-onset AF. Class Ic AADs foreshorten time to sinus rhythm significantly. Amiodarone and non-AAD (rate control drugs) are associated with spontaneous conversion, with minimal conversion action of amiodarone discernable from 6 h on. At the end of the day around 60–70% of patients reached sinus rhythm. Modified after Crijns *et al.*,[10] with permission. AAD, antiarrhythmic drug; AF, atrial fibrillation.

To anticoagulate or not for DCCV?

Key points

- Reported peri-cardioversion thromboembolic event rates are between 1.1% and 2% in patients not or insufficiently anticoagulated and between 0.28% and 0.8% in patients sufficiently anticoagulated.
- In patients with AF lasting <48 h the thromboembolic event rate without anticoagulation is around 0.7% and increases with CHA_2DS_2-VASc score. It is significantly reduced with anticoagulation.

Key points

- Almost all thromboembolic events with cardioversion occur within 10 days after the procedure.
- Therefore, anticoagulation up to 4 weeks after cardioversion is recommended.

Image-guided cardioversion

Risk factors for thromboembolism: clinical factors and information from transoesophageal echocardiography

A recent meta-analysis showed that left atrial (LA) thrombus is ob-

LAA flow velocities, TOE may also help identifying other predictors of thromboembolism, e.g. complex aortic plaques. An algorithm detailing echocardiographic evaluation of LAA prior to cardioversion has previously been provided (*Figure 5*).[63]

Key points

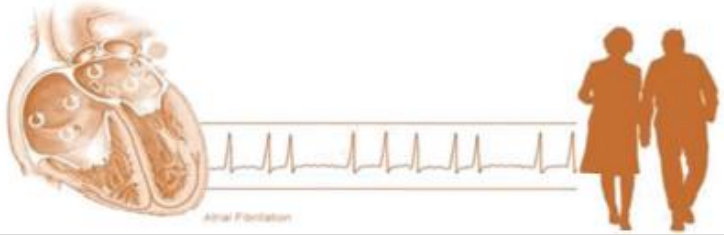
- A left atrial thrombus is observed in about 10% of non-valvular AF.
- Thrombus formation is most frequently observed in the LAA.
- Transoesophageal echocardiography is the gold standard to rule out left-atrial thrombus formation.
- Low flow in the LAA is associated with SEC, LAA thrombi, and thromboembolic events.

Europace (2020) **22**, 1149–1161

Population considerations

Sex Differences in Atrial Fibrillation

SUMMARY OF FINDINGS	
Epidemiology and risk	
Greater total population	Women
Higher age-adjusted prevalence of AF	Men
Prevalence and Incidence of AF increasing over time	Equal
Higher lifetime risk of AF in whites	Men
Higher lifetime risk of AF in blacks	Equal
Higher risk of stroke from AF	Women
Higher risk of death from AF	Women
Symptoms and quality of life	
Longer duration of symptoms	Women
Higher functional impairment and limitation of ADLs	Women
Worse quality of life scores	Women
Risk and Prevention of Stroke	
Higher risk for AF-related stroke	Women
Strokes from AF more severe and disabling	Women
More likely to receive anticoagulation for AF	Men
More time in TTR when on warfarin for AF	Men
Risk from rate and rhythm control	
Higher use and risk of mortality from cardiac glycoside for AF	Women
Higher risk of CV events from antiarrhythmic drugs for AF	Women
Higher risk of proarrhythmia with antiarrhythmic drugs for AF	Women
Higher risk of adverse events with catheter ablation for AF	Women



J Cardiovasc Electrophysiol. 2021 October ; 32(10): 2793–2807.

Gender and Race

Epidemiology and risk	
Higher incidence	White Men
Higher age adjusted prevalence	Women
Higher lifetime risk in whites	Men
Higher lifetime risk in blacks	Same in women and men
Higher risk of death from AF	Women and blacks†
Symptoms and quality of life	
Longer duration of symptoms	Women and blacks
More functional impairment and limitation of ADLs	Women and blacks
Worse quality of life scores	Women and blacks
Risk and Prevention of Stroke	
Higher risk for AF-related stroke	Women and blacks
Less likely to receive anticoagulation	Women, blacks and Hispanics
Rate and rhythm control	
More rate control than rhythm control including drugs, cardioversions, and catheter ablations	Women, blacks and Hispanics

JACC VOL. 74, NO. 22, 2019
DECEMBER 3, 2019:2812–5

Racial differences in comorbidities & stroke

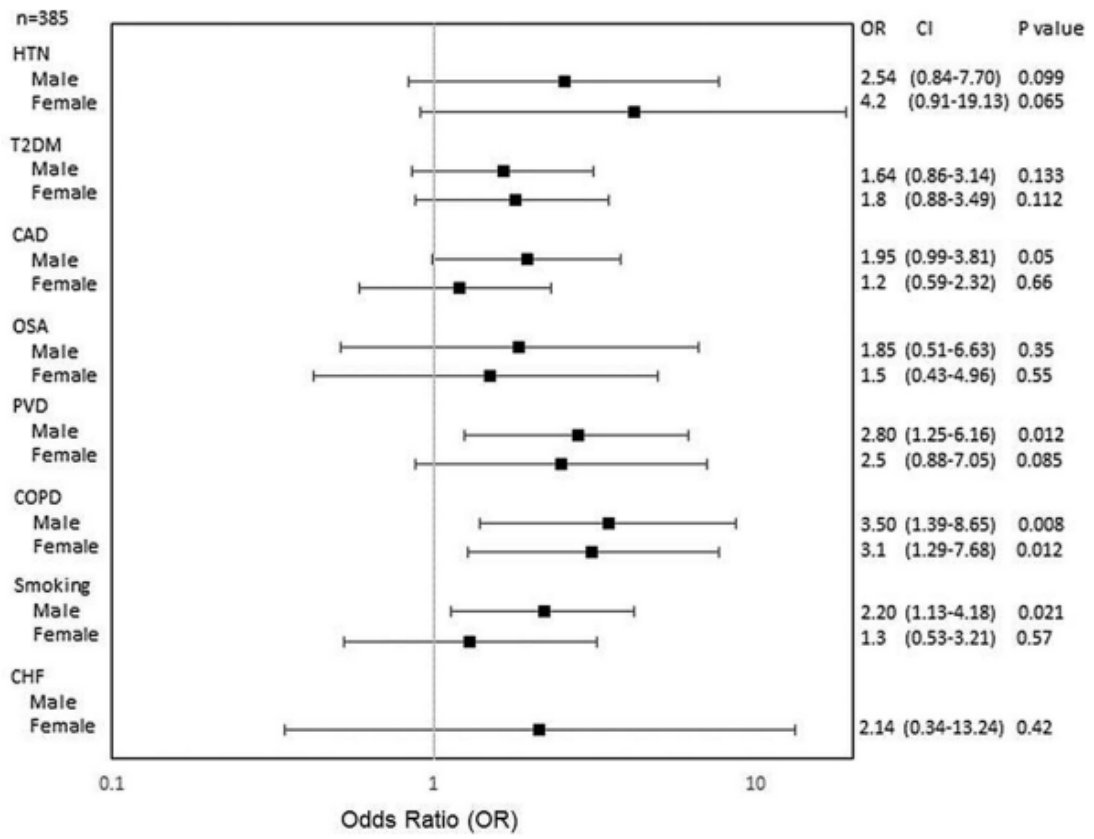


Fig. 2b. Impact of age-adjusted AF risk factors on stroke in Hispanics/Latinos (H/Ls). Abbreviations as in Fig. 2a.

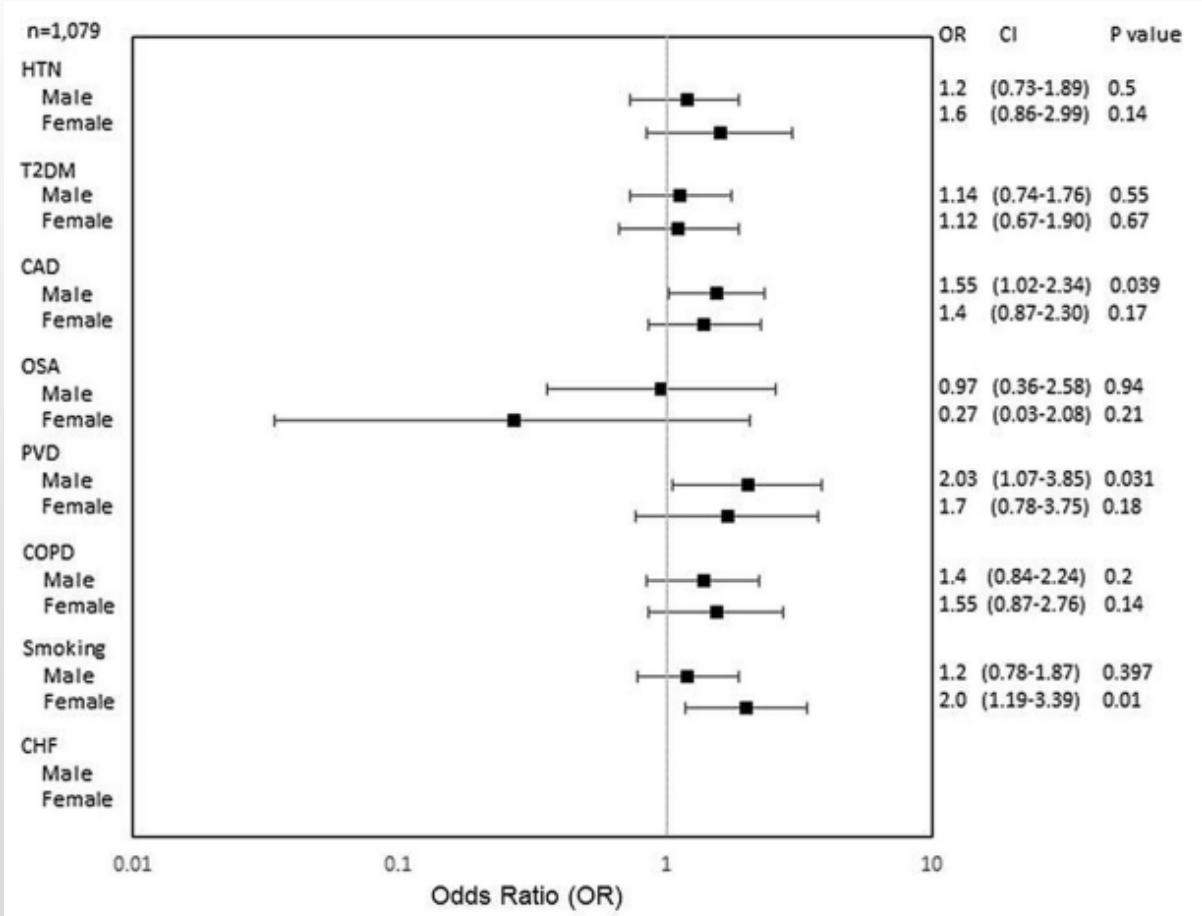


Fig. 2c. Impact of age-adjusted AF risk factors on stroke in Non-Hispanic Whites (NHWs). Abbreviations as in Fig. 2a.

Highest incidence of stroke from AF occurs in American Indians

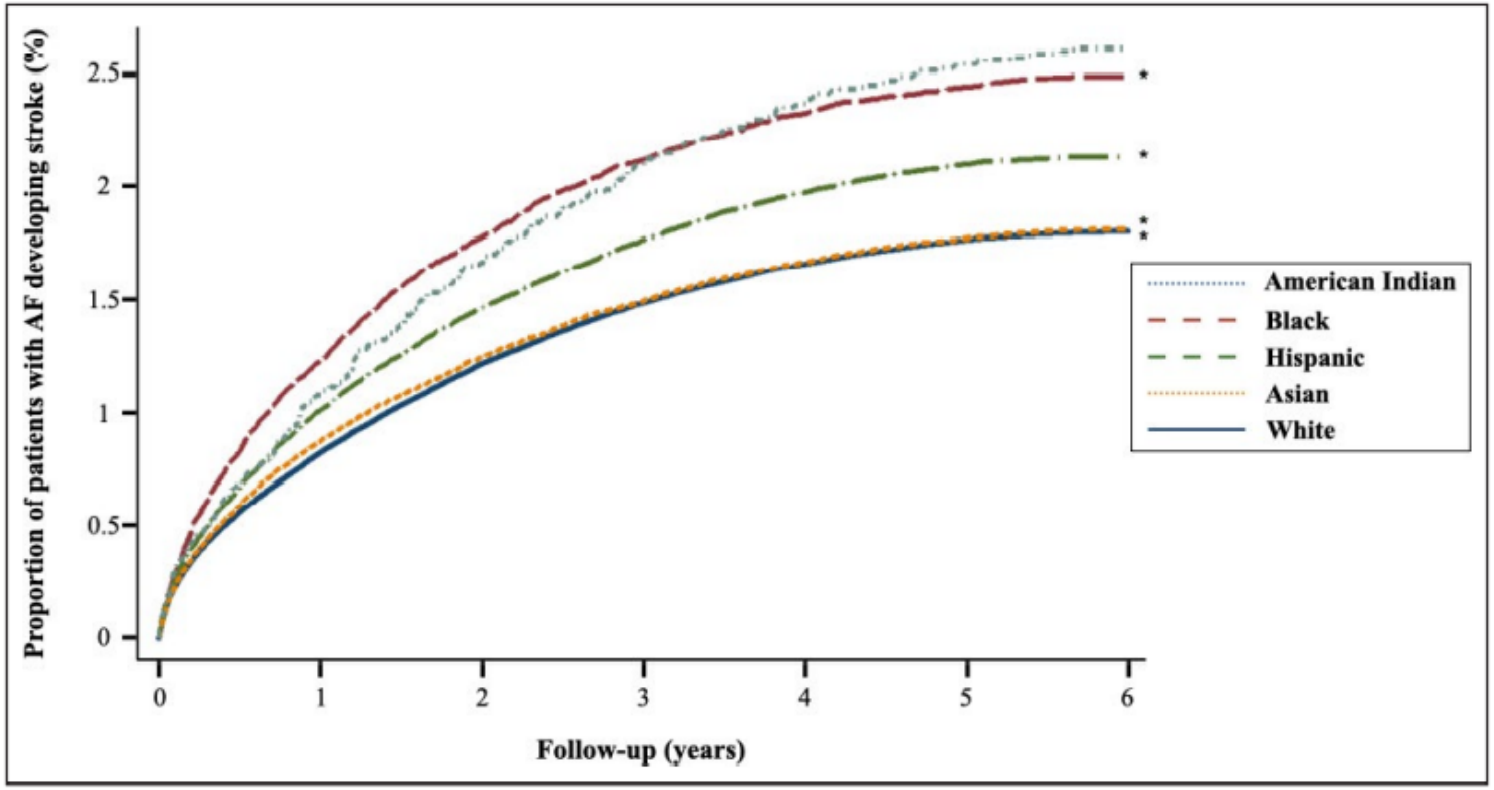


Figure 2. Adjusted Kaplan-Meier curves for incident stroke in American Indian, White, Black, Hispanic, and Asian patients with atrial fibrillation.

The curves are adjusted for age, sex, income level, insurance payer, hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, valvular heart disease, chronic kidney disease, smoking, obstructive sleep apnea, pulmonary disease, and alcohol use. *Comparison between American Indian individuals to each individual race and ethnicity, *P* value<0.0001. AF indicates atrial fibrillation.

CLINICAL PERSPECTIVE

What Is New?

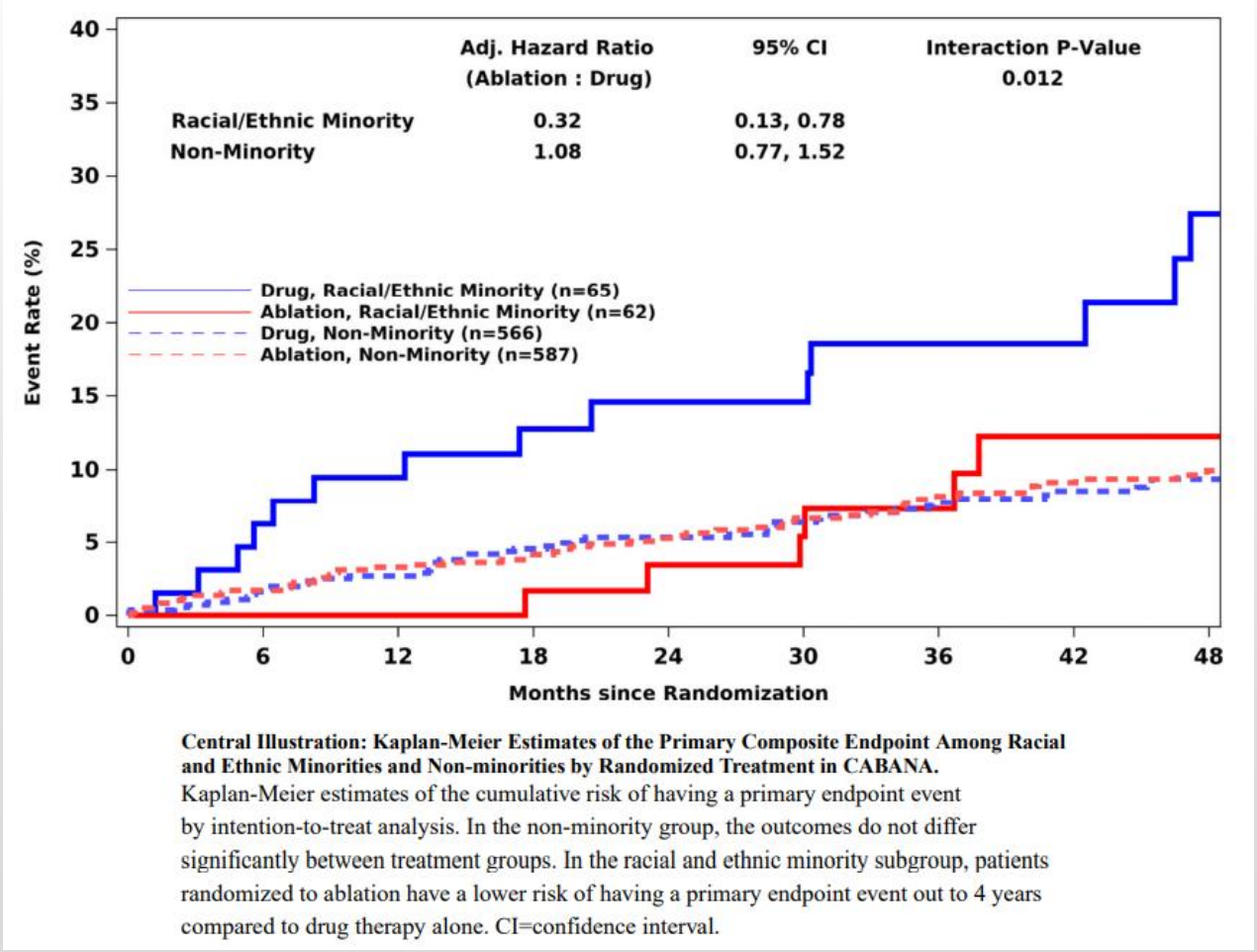
- American Indian individuals experience the highest risk of stroke when compared with other racial and ethnic groups, whether in the presence or absence of atrial fibrillation, and despite multivariable adjustment.

What Are the Clinical Implications?

- Our study highlights the significant health risks accrued by American Indian individuals and their vulnerability to stroke and suggests that unaccounted-for factors are driving these observations.
- This may help guide community efforts aimed at cardiovascular risk factor prevention.

J Am Heart Assoc. 2021;10:e019581. DOI: 10.1161/JAHA.120.019581

CABANA Subanalysis: Rhythm Control in Minorities



Central Illustration: Kaplan-Meier Estimates of the Primary Composite Endpoint Among Racial and Ethnic Minorities and Non-minorities by Randomized Treatment in CABANA.
Kaplan-Meier estimates of the cumulative risk of having a primary endpoint event by intention-to-treat analysis. In the non-minority group, the outcomes do not differ significantly between treatment groups. In the racial and ethnic minority subgroup, patients randomized to ablation have a lower risk of having a primary endpoint event out to 4 years compared to drug therapy alone. CI=confidence interval.

J Am Coll Cardiol. 2021 July 13; 78(2): 126–138.

AF in >75

- Patients has on average 3 additional comorbidities with HTN being the most common
- This led to worse outcomes
  - Higher incidence of HF, stroke, bleeding

Multimorbidity and disease complexity, particularly in the elderly AF population, are markers for increased morbidity and mortality

The American Journal of Medicine, Vol 133, No 10, October 2020

Pearls

Atrial fibrillation is the most common arrhythmia

Risk factor modification is key

Comorbid conditions and control matter

Age is the one risk factor we can't change

Protection from stroke…don't let age or bias about frailty/falls fool you

Early rhythm control, talk about it with your patients regardless of race/sex

Review Questions if time

Questions revisited...

1. True or False

- Rate control is equivalent to rhythm control in AF treatment

2. AF that lasts for more than 7 consecutive days but converts in less than 30 days is called:

- First episode – initial detection of AF regardless of symptoms or duration
- Recurrent AF – More than 2 episodes of AF
- Paroxysmal AF – Self terminating episode < 7 days
- Persistent AF – Not self terminating, duration > 7 days
- Long-standing persistent AF – > 1 year
- Permanent (Accepted) AF – Duration > 1 yr in which rhythm control interventions are not pursued or are unsuccessful

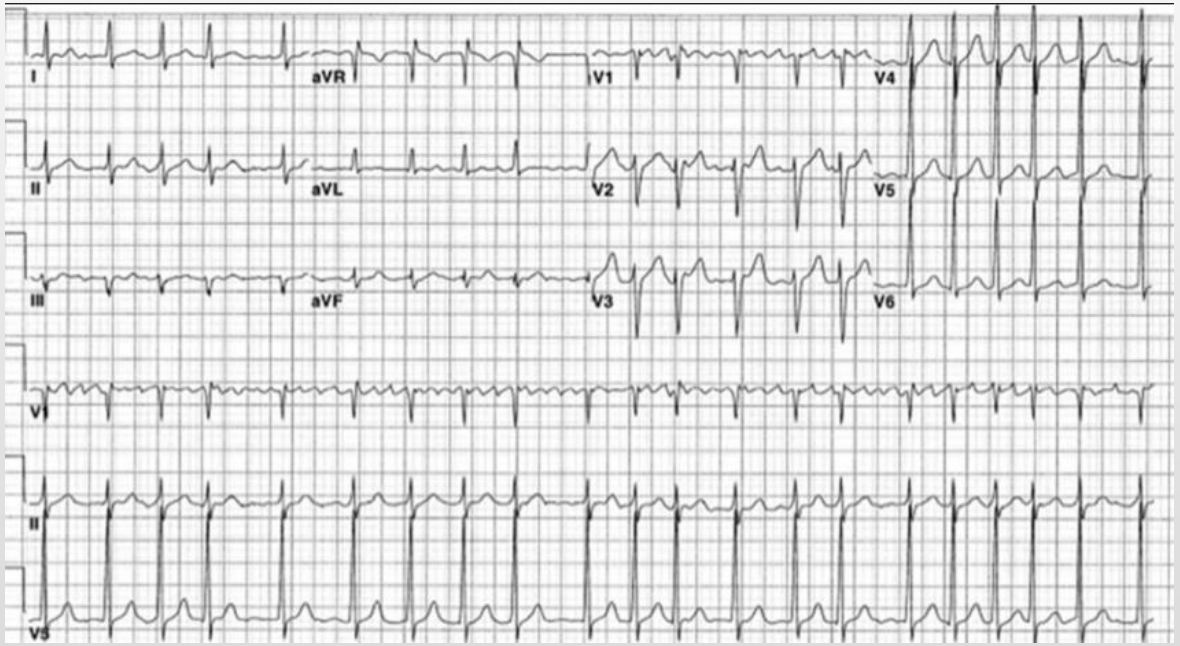
3. The decision for rhythm control over rate control in a patient with AF is based on the following:

- A. Age
- B. Symptoms
- C. AF burden
- D. Patient preference

4. The ideal antiarrhythmic drug for a 68yo woman with CAD, mild HFrEF and highly symptomatic AF who wishes to avoid invasive therapy:

- A. Flecainide
- B. Sotalol
- C. Amiodarone
- D. Dofetilide
- E. Ivabridine

5. 42yo man with HCM, DM2 presents to ER w/ palpitations, onset unclear but worsening over 24 hrs



- Cardiovert or ‘wait and see’?
- What about anticoagulation?
- Other plans?
- OAC
  - Short term and long term

6. You are caring for a 72yo lady w/HFpEF admitted for ADHF. She goes into rapid AF…

- Options?
- Other considerations?
- Acute v chronic, new v recurrent
- Long term options

Final question

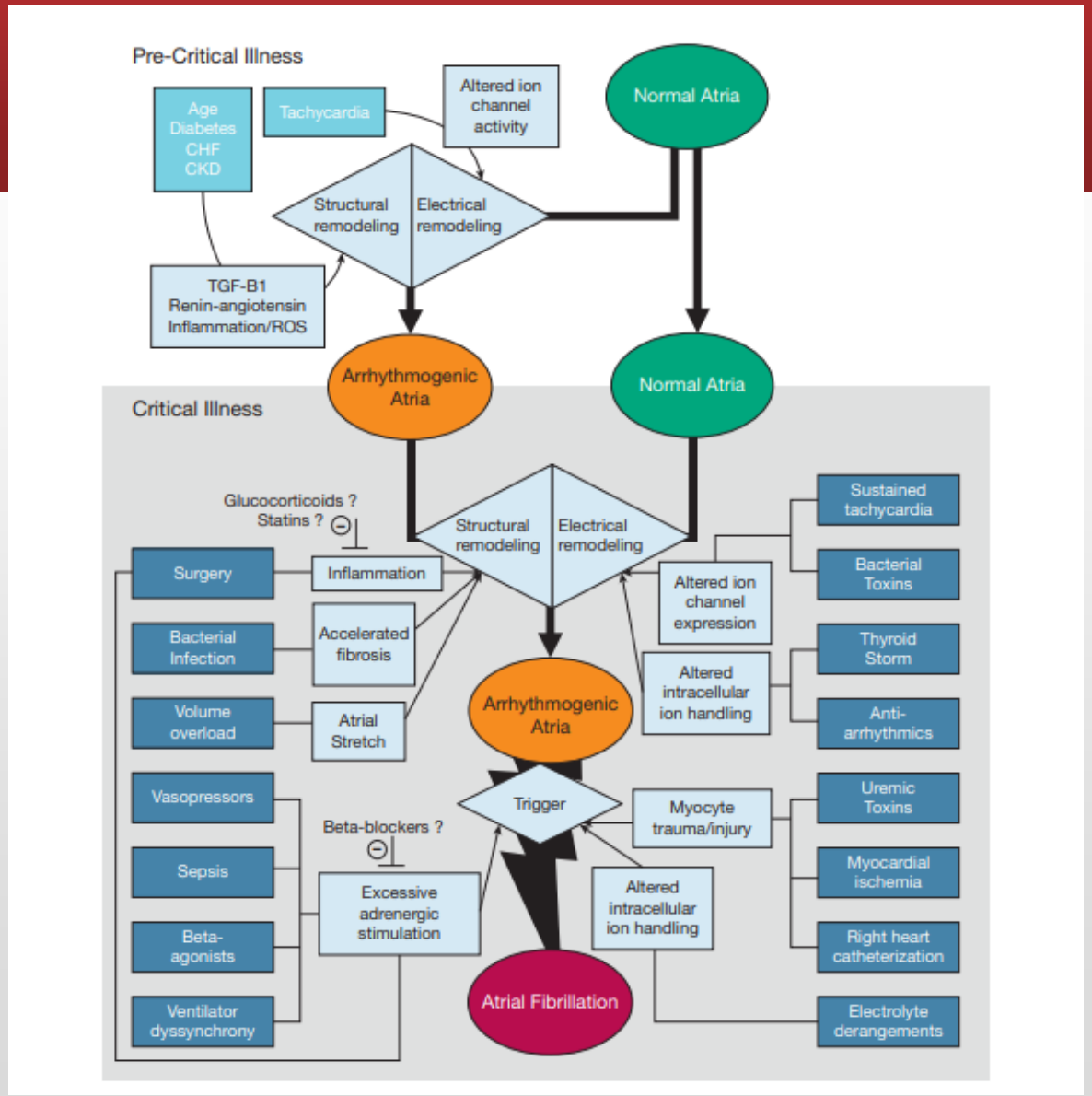
- Why is a Cardiologist better than a lie detector test?

Thank you!

- Questions?
- Apologies for cut-&-paste on some slide; having to work 1-handed on this prez was…challenging☺. References listed on some slides and again at end of the presentation
- Please reach out if questions arise or I can be of any help:
- Tracy.hagerty@uvmheath.org

Extra slides if time

AF in ICU



CHEST 2018; 154(6):1424-1434

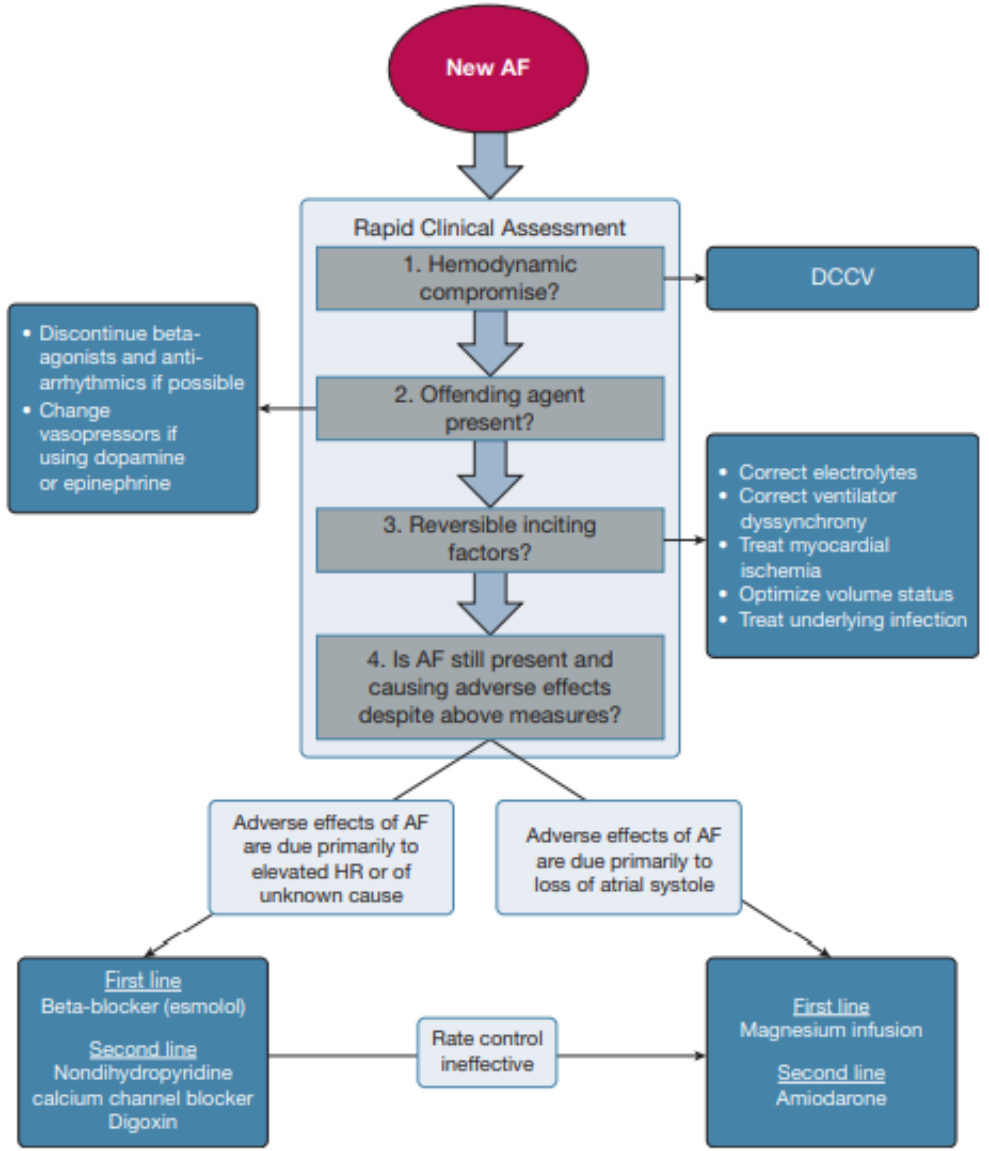


Figure 2 – *Acute management priorities in new-onset AF during critical illness. Identification of new-onset AF during critical illness should prompt a four-step rapid clinical assessment: (1) assessment for hemodynamic compromise requiring urgent DCCV, (2) removal of potential offending agents, (3) reversal of inciting acute factors, and (4) treatment to reduce rate or convert to sinus if AF persists and is associated with adverse effects. DCCV = direct current cardioversion; HR = heart rate. See Figure 1 legend for expansion of other abbreviation.*

Verapimil…best of both worlds?

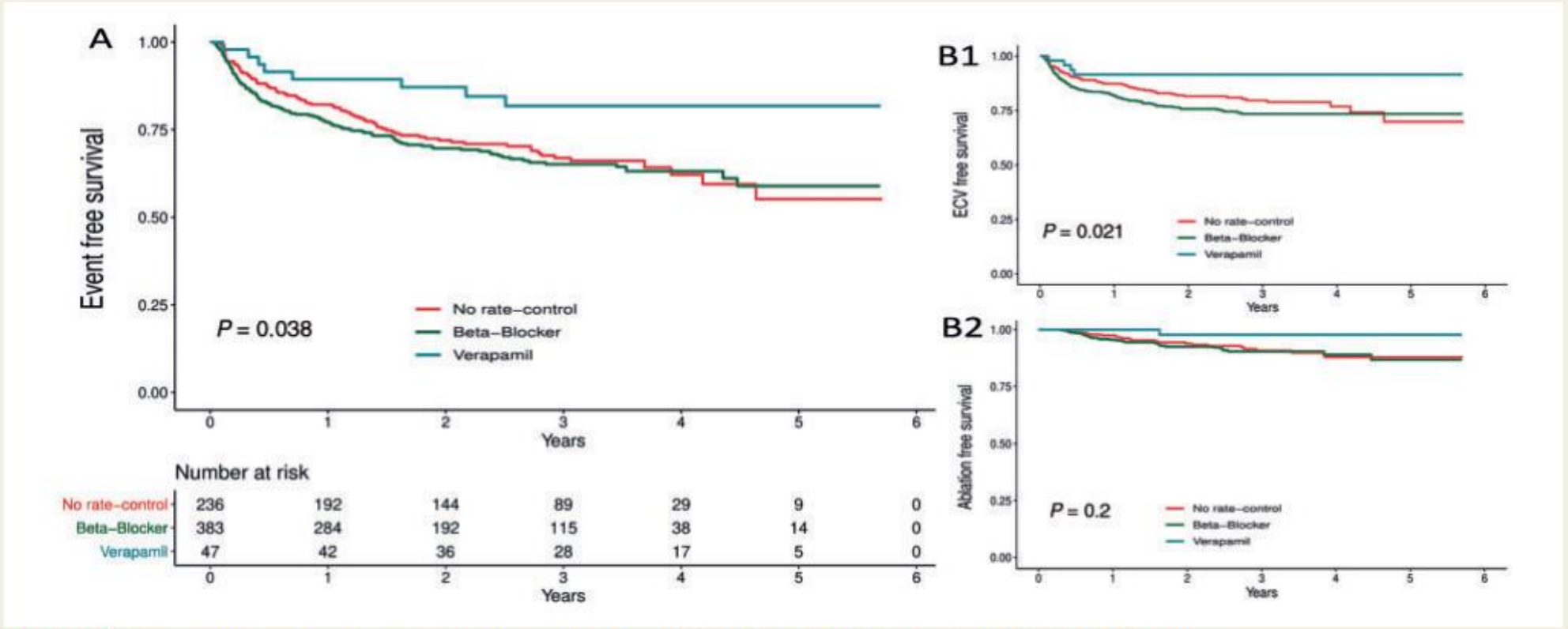
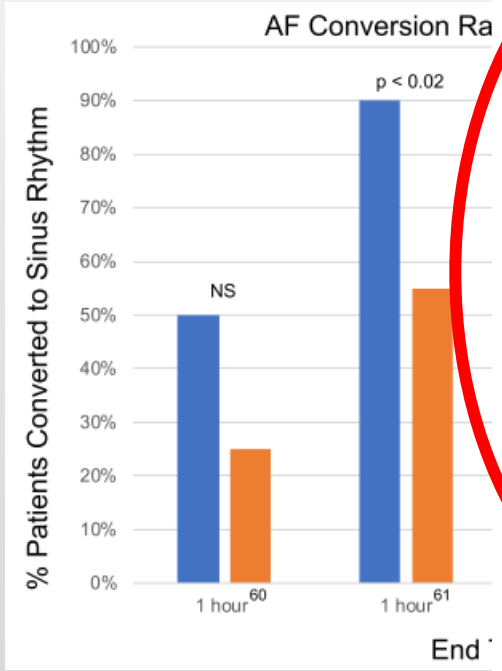


Figure 1 Rate control medication and event free survival from (A) ECV-CCV-Ablation, (B1) ECV and (B2) ablation.

Europace (2022) **24**, 384–389

Ic: Flecain

- Drugs-Ic



Chronic Suppression of AF With Flecainide Compared With Other AADs

Large retrospective studies and meta-analyses of AAD therapy that report 1-year AF recurrence rates range from 44% to 67%.[75–78] The efficacy of flecainide was found to be

Major Safety Issues With Flecainide

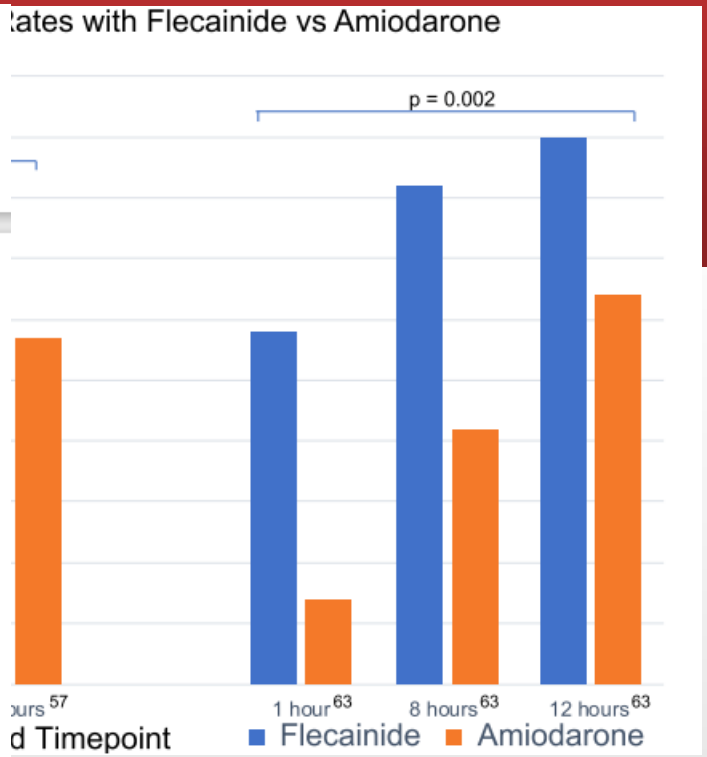
The 2.5-fold excess mortality due to proarrhythmic effects associated with the use of encainide and flecainide in the CAST occurred in a highly selected population of patients

with previous MI, frequent ventricular ectopy, and depressed LV ejection fraction.[71] Despite the fact that the CAST was carried out in a high-risk cohort of patients with advanced structural heart disease, potential safety concerns about the risk for ventricular proarrhythmia in other populations has persisted. Flecainide-induced proarrhythmia manifesting as ventricular tachycardia can be either monomorphic or polymorphic, but very rarely has the morphologic characteristics of torsade de pointes, as discussed in the section on flecainide electrophysiology. Despite these concerns, the safety of flecainide in patients without structural heart disease is now well established.

Three additional arrhythmia-related safety issues have been reported to be associated with the use of flecainide in patients with AF. First, there is the potential for AF to be converted to atrial flutter as a result of the conduction slowing effects of flecainide.[85] When this occurs, the atrial (flutter) rate may be slowed enough to permit one-to-one AV conduction, resulting in a rapid ventricular rate. In patients with healthy AV node function, the concomitant administration of a β blocker or nondihydropyridine calcium channel blocker markedly reduces the likelihood of this adverse event. Second, is the possibility of a prolonged sinus pause immediately following successful conversion of AF to SR.[86] These offset pauses occur primarily in patients with underlying sinus node dysfunction. Third, flecainide, like many other sodium channel blocking drugs, may unmask the ECG pattern of underlying Brugada syndrome, leading to ventricular tachycardia and, thereby, a risk for sudden cardiac death.

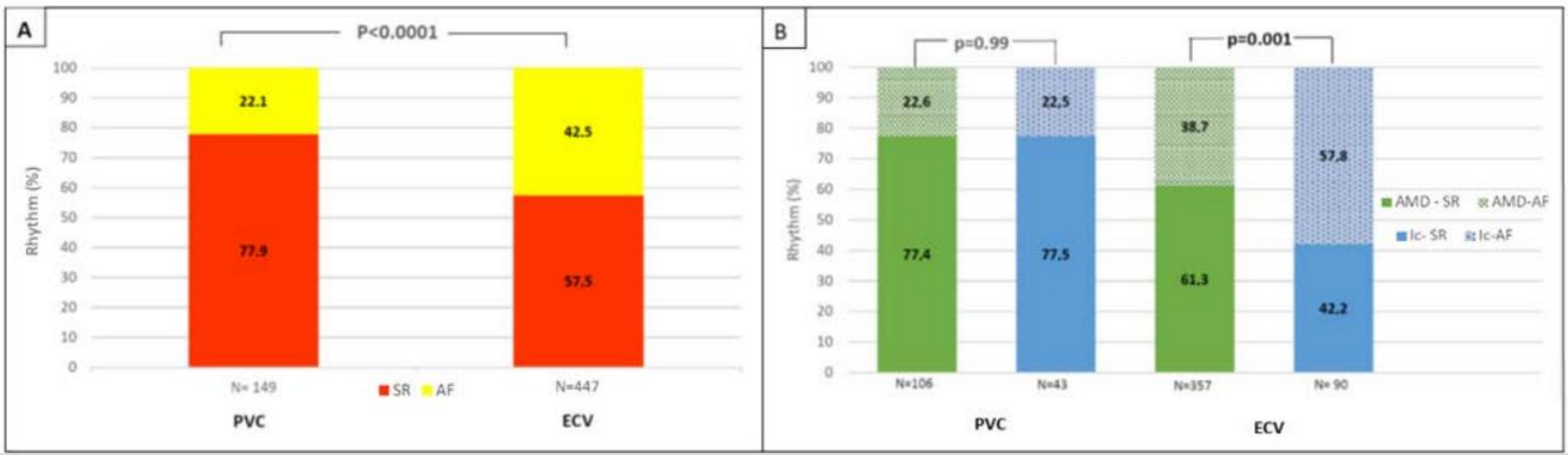
Another major safety issue associated with administration of flecainide is related to its potential for adverse hemodynamic effects resulting from the negative inotropic effect of the drug. Hypotension can be observed following IV administration regardless of underlying LV function. Worsening heart failure has been observed in patients with underlying LV dysfunction receiving chronic oral therapy, which is why the use of flecainide is contraindicated in patients with LV dysfunction or heart failure. Minor adverse effects associated with flecainide administration include dizziness, visual disturbances, paresthesias, headache, dyspnea, and nausea.

sotalol. A meta-analysis that compared 1-year mortality rates in 59 randomized controlled trials comprised of AADs for chronic AF suppression found that none resulted in a mortality benefit and that only Class IA agents and sotalol were associated with an increase in mortality compared with controls.[78] The AFFIRM trial randomized 4,060 patients to rate or rhythm control drug treatment strategies for AF using mortality as the primary end point.[89] Although no difference in mortality was observed between the rate versus rhythm control arms, a propensity score-matched subset analysis of mortality with individual AADs provided further insights.[90] There was no difference in mortality in the minority of patients randomized to rhythm control and receiving flecainide (8%) compared with the rate control arm. However, a majority of patients randomized to rhythm control received amiodarone (63%), resulting in a trend toward higher total mortality, and a significantly higher incidence of noncardiovascular mortality compared with the rate control arm. Furthermore, a separate AFFIRM analysis found that the (nonsignificant) excess mortality in the rhythm control arm was entirely noncardiovascular in etiology, and primarily pulmonary and cancer-related, which are disease states most closely associated with chronic amiodarone use.[91] Since the majority of patients in the rhythm control arm received amiodarone, it is plausible that the excess noncardiovascular mortality associated with amiodarone use was primarily responsible for the overall lack of difference in mortality between rate and rhythm strategies in the AFFIRM. Mortality was also compared in a propensity-matched cohort analysis of patients with LV hypertrophy treated for persistent AF with amiodarone and nonamiodarone AADs.[92] A trend toward higher mortality was found with amiodarone compared with nonamiodarone drugs, and a significantly higher mortality was found with amiodarone compared with the subset of patients receiving Class 1C agents. Overall, these analyses suggest that acute and chronic therapy with flecainide does not confer a mortality benefit or risk compared with controls in patients with AF, but that flecainide may confer a lower mortality risk compared with sotalol and amiodarone. Furthermore, there appears to be a higher risk of death with chronic amiodarone therapy compared with controls.



Am J Cardiol 2020;125:1123–1133

Effectiveness of Ic antiarrhythmics



J. Clin. Med. **2021**, *10*, 1029.

AF and HFrEF, HFpEF

death/HF hospitalization as compared with SR.[17] Higher prevalence has been shown in registry-based studies, likely due to the inclusion of more generalizable and contemporary populations, but with some variability that may be linked to different definitions of AF. Indeed, in the ADHERE Core registry, 48% of HFpEF patients had AF, which was associated with a 2.8% and 1.2% increased absolute risk of 30 day-mortality and HF hospitalization, respectively.[18] In a previous analysis of SwedeHF, AF was reported in 60% of patients with ejection fraction 40–49% and in 65% of those with ejection fraction ≥ 50%, with older age, male gender, longer HF duration, no history of myocardial infarction and prior stroke as important, common and independent associations with AF in both ejection fraction categories.[12] Additionally, AF vs. SR was associated with increased risk of mortality in both ejection fraction 40–49% and ≥ 50% (hazard ratio 1.11 and 1.22, respectively).[12]

Our current analysis confirms a very high prevalence of AF in HFpEF (≈ 50%), which is lower compared with a previous SwedeHF analysis, given that we excluded patients with history of paroxysmal AF, and reports an 8% and 15% absolute risk increase in 1- and 5-year mortality, respectively, in AF vs. SR. The high prevalence of AF in HFpEF reported in the present and previous studies can potentially be explained by shared risk factors and even pathogenesis (i.e. co-morbidity-driven global systemic inflammation[19]) in both AF and HFpEF, leading to parallel development of these two syndromes.[19–21] Instead, lower AF prevalence has been reported in HFrEF (ranging between 46–53% in registry-based studies) where neurohormonal activation and haemodynamic mechanisms may be determinant in a HFrEF–AF vicious cycle[12,18] and one might speculate that AF more commonly develops as a consequence of HF rather than in parallel. Nevertheless, AF vs. SR is associated with increased risk of clinical outcomes (i.e. not only stroke but also mortality and HF hospitalization) regardless of ejection fraction, an excess risk that may be even greater in HFpEF vs. HFrEF according to some but not all studies.[12,17,18]

AF and HFpEF

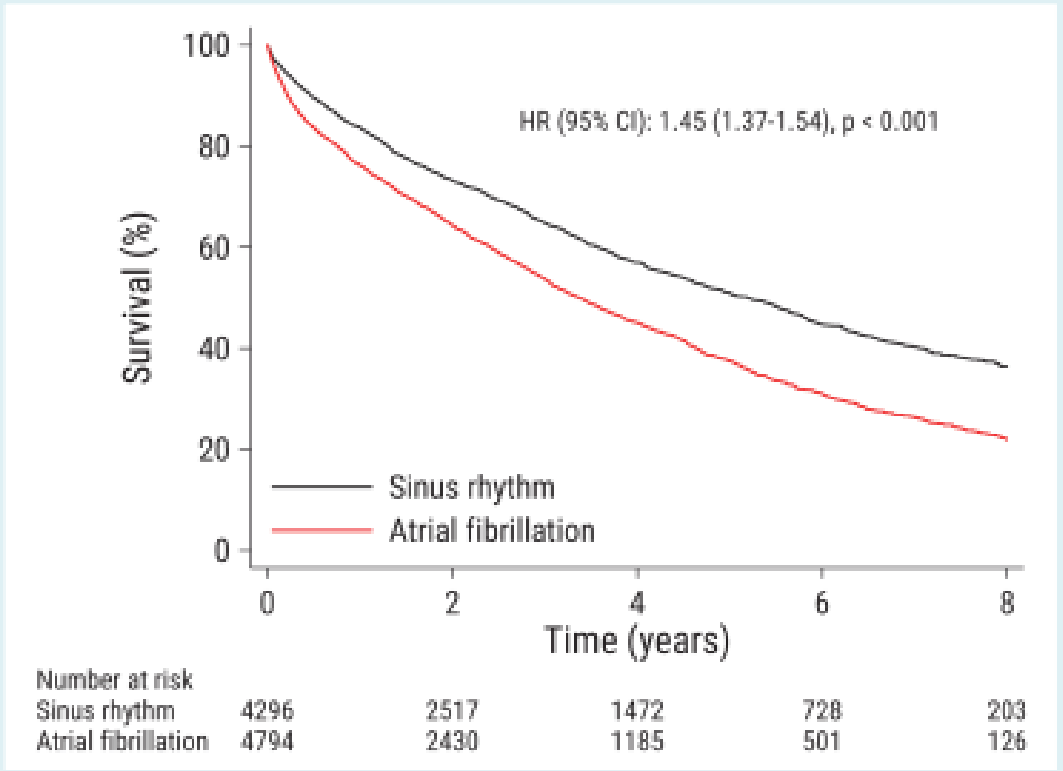


Figure 2 Overall survival according to heart rhythm in 9090 patients with heart failure with preserved ejection fraction. CI, confidence interval; HR, hazard ratio.

In this assessment of AF and HR in a HFpEF cohort from a nationwide registry, we show that: (i) half of the patients have AF; (ii) HR is higher in AF than in SR; (iii) AF is associated with an increased risk of death; and (iv) in HFpEF patients in SR, HR was observed to be linearly related to mortality, similar to HFrEF.[6,7] In those with HFpEF and AF at baseline, the relationship between HR and mortality was much weaker, with possible association of baseline HR in the short term, but unlike SR, convergence of mortality by baseline HR in longer-term follow-up.

European Journal of Heart Failure (2019) **21**, 471–479

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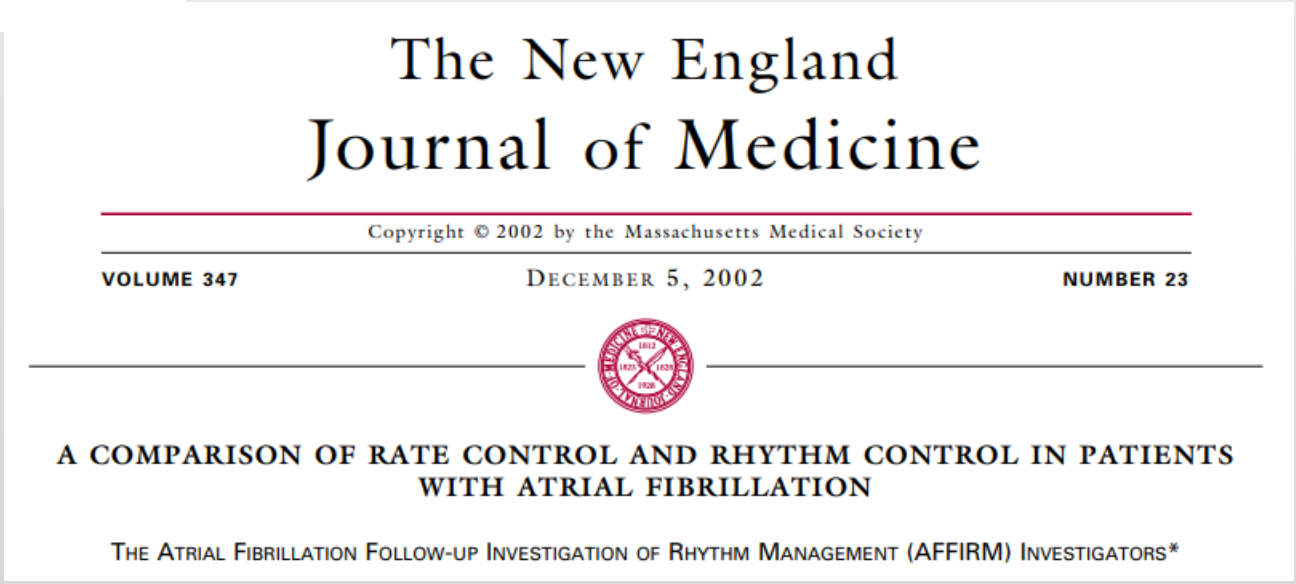
ESTABLISHED IN 1812 OCTOBER 1, 2020 VOL. 383 NO. 14

Early Rhythm-Control Therapy in Patients with Atrial Fibrillation

P. Kirchhof, A.J. Camm, A. Goette, A. Brandes, L. Eckardt, A. Elvan, T. Fetsch, I.C. van Gelder, D. Haase, L.M. Haegeli, F. Hamann, H. Heidbüchel, G. Hindricks, J. Kautzner, K.-H. Kuck, L. Mont, G.A. Ng, J. Rekosz, N. Schoen, U. Schotten, A. Suling, J. Taggeselle, S. Themistoclakis, E. Vettorazzi, P. Vardas, K. Wegscheider, S. Willems, H.J.G.M. Crijns, and G. Breithardt, for the EAST-AFNET 4 Trial Investigators*



The New England Journal of Medicine

VOLUME 347 DECEMBER 5, 2002 NUMBER 23

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

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

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Use of Flecainide for the Treatment of Atrial Fibrillation

Debra S. Echt, MD[a], and Jeremy N. Ruskin, MD[b,c,*]

Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with substantial morbidity and impairment of quality of life. Restoration and maintenance of normal sinus rhythm is a desirable goal for many patients with AF; however, this strategy is limited by the relatively small number of antiarrhythmic drugs (AADs) available for AF rhythm control. Although it is recommended in current medical guidelines as first-line therapy for patients without structural heart disease, the use of flecainide has been curtailed since the completion of the Cardiac Arrhythmia Suppression Trial. In clinical trials and real-world use, flecainide has proven to be more effective than other AADs for the acute termination of recent onset AF. Flecainide is also moderately effective and, with the exception of amiodarone, equivalent to other AADs for the chronic suppression of paroxysmal and persistent AF. In patients without structural heart disease, flecainide has been demonstrated to be safe and well tolerated relative to other AADs. Despite this favorable profile, flecainide is underutilized, likely due to a perceived risk of ventricular proarrhythmia, a concern that has not been borne out in patients without underlying structural heart disease. Guidelines for administration and use of flecainide are summarized in this review.
(Am J Cardiol 2020;125:1123–1133)

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 79, NO. 19, 2022

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

The Increasing Role of Rhythm Control in Patients With Atrial Fibrillation

JACC State-of-the-Art Review

A. John Camm, MD,[a] Gerald V. Naccarelli, MD,[b] Suneet Mittal, MD,[c] Harry J.G.M. Crijns, MD, PhD,[d] Stefan H. Hohnloser, MD,[e] Chang-Sheng Ma, MD,[f] Andrea Natale, MD,[g] Mintu P. Turakhia, MD, MAS,[h] Paulus Kirchhof, MD, DS[i,j,k,l]

ESC European Society of Cardiology
Europace (2020) **22**, 1149–1161
doi:10.1093/europace/euaa057

REVIEW

Cardioversion of atrial fibrillation and atrial flutter revisited: current evidence and practical guidance for a common procedure

Axel Brandes [1,2]*, Harry J.G.M. Crijns[3], Michiel Rienstra[4], Paulus Kirchhof[5], Erik L. Grove[6,7], Kenneth Bruun Pedersen[1], and Isabelle C. Van Gelder[1,2,4]

References

ESC European Society of Cardiology
Europace (2022) 24, 384–389 doi:10.1093/europace/euab191

CLINICAL RESEARCH
Atrial fibrillation

Rate control drugs differ in the prevention of progression of atrial fibrillation

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Ablation Versus Drug Therapy for Atrial Fibrillation in Racial and Ethnic Minorities

Journal of the American Heart Association

ORIGINAL RESEARCH

Generalizability of the EAST-AFNET 4 Trial: Assessing Outcomes of Early Rhythm-Control Therapy in Patients With Atrial Fibrillation

Jannis Dickow, MD; Paulus Kirchhof, MD; Holly K. Van Houten, BA; Lindsey R. Sangaralingham, MPH; Leon H. W. Dinshaw, MD; Paul A. Friedman, MD; Douglas L. Packer, MD; Peter A. Noseworthy, MD; Xiaoxi Yao, PhD, MPH

J. Clin. Med. **2021**, *10*, 1029. https://doi.org/10.3390/jcm10051029

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ORIGINAL INVESTIGATIONS

Presenting Pattern of Atrial Fibrillation and Outcomes of Early Rhythm Control Therapy

Andreas Goette, MD,[a,b] Katrin Borof, MS,[b,c] Günter Breithardt, MD,[b,d] A. John Camm, MD,[e] Harry J.G.M. Crijns, MD,[f] Karl-Heinz Kuck, MD,[g] Karl Wegscheider, PhD,[h] Paulus Kirchhof, MD,[c,i,j] on behalf of the EAST-AFNET 4 Investigators

Journal of *Clinical Medicine* MDPI

Review

How to Optimize Cardioversion of Atrial Fibrillation

K. E. Juhani Airaksinen

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ESC European Society of Cardiology

European Journal of Heart Failure (2019) 21, 471–479
doi:10.1002/ejhf.1389

RESEARCH ARTI

Association of heart rate with mortality in sinus rhythm and atrial fibrillation in heart failure with preserved ejection fraction

Ulrik Sartipy[1,2]*, Gianluigi Savarese[3], Ulf Dahlström[4], Michael Fu[5], and Lars H. Lund[1,3]

Journal of Thrombosis and Thrombolysis (2022) 54:1–6
https://doi.org/10.1007/s11239-022-02638-0

Relationship between temporal rhythm-based classification of atrial fibrillation and stroke: real-world vs. clinical trial

Wern Yew Ding[1] · José Miguel Rivera-Caravaca[1,2] · Francisco Marín[2] · Vanessa Roldán[3] · Gregory Y. H. Lip[1,4]

Monaldi Archives for Chest Disease 2018; volume 88:955

Rate-control *vs* rhythm-control of atrial fibrillation in elderly patients. From new, age-oriented outcomes to a more complex management strategy

Stefano Fumagalli, Serena Boni, Simone Pupo, Marta Migliorini, Irene Marozzi, Eleonora Barghini, Flavia Sacco, Niccolò Marchionni

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IJC Heart & Vasculature

journal homepage: www.journals.elsevier.com/ijc-heart-and-vasculature

Rhythm monitoring strategies for atrial fibrillation detection in patients with cryptogenic stroke: A systematic review and meta-analysis

Jean Jacques Noubiap [a,*], Thomas A. Agbaedeng [a], Joseph Kamtchum-Tatuene [b], John L. Fitzgerald [a,c], Melissa E. Middeldorp [a,c], Timothy Kleinig [d,e], Prashanthan Sanders [a,c]

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ESC European Society of Cardiology

European Journal of Heart Failure (2020) 22, 528–538
doi:10.1002/ejhf.1682

RESEARCH ARTICLE

Relationship between heart rate and outcomes in patients in sinus rhythm or atrial fibrillation with heart failure and reduced ejection fraction

Kieran F. Docherty[1], Li Shen[1], Davide Castagno[2], Mark C. Petrie[1], William T. Abraham[3], Michael Böhm[4], Akshay S. Desai[5], Kenneth Dickstein[6], Lars V. Køber[7], Milton Packer[8], Jean L. Rouleau[9], Scott D. Solomon[5], Karl Swedberg[10], Ali Vazir[11], Michael R. Zile[12], Pardeep S. Jhund[1], and John J.V. McMurray[1]*

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Original Article

Rhythm Control Vs Rate Control in a Contemporary Ambulatory Atrial Fibrillation Cohort: Post Hoc Analysis of the IMPACT-AF Trial

Arun Govindapillai, BHSc, MSc, PhD,[a] Jafna L. Cox, MD, FRCPC, FACC,[b] Lehana Thabane, PhD,[c,d] Steve Doucette, MSc,[e] Feng Xie, PhD,[f,g] James H. MacKillop, PhD,[h,i] Antonio Ciaccia,[j] Shurjeel H. Choudhri, MD,[k,l,m,n] Joanna M. Nemis-White, BSc, PMP,[o] Laura M. Hamilton,[b] and Ratika Parkash, MD, MS, FRCPC[b]

Li *et al. BMC Cardiovascular Disorders* (2019) 19:47
https://doi.org/10.1186/s12872-019-1024-4

BMC Cardiovascular Disorders

JAMA | Original Investigation

Effect of Long-term Continuous Cardiac Monitoring vs Usual Care on Detection of Atrial Fibrillation in Patients With Stroke Attributed to Large- or Small-Vessel Disease
The STROKE-AF Randomized Clinical Trial

Richard A. Bernstein, MD, PhD; Hooman Kamel, MD; Christopher B. Granger, MD; Jonathan P. Piccini, MD; Pramod P. Sethi, MD; Jeffrey M. Katz, MD; Carola Alfaro Vives, MS; Paul D. Ziegler, MS; Noreli C. Franco, PhD; Lee H. Schwamm, MD; for the STROKE-AF Investigators

JAMA | Original Investigation

Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation
The CABANA Randomized Clinical Trial

Douglas L. Packer, MD; Daniel B. Mark, MD, MPH; Richard A. Robb, PhD; Kristi H. Monahan, RN; Tristram D. Bahnson, MD; Jeanne E. Poole, MD; Peter A. Noseworthy, MD; Yves D. Rosenberg, MD, MPH; Neal Jeffries, PhD; L. Brent Mitchell, MD; Greg C. Flaker, MD; Evgeny Pokushalov, MD; Alexander Romanov, MD; T. Jared Bunch, MD; Georg Noelker, MD; Andrey Ardashev, MD; Amiran Revishvili, MD; David J. Wilber, MD; Riccardo Cappato, MD; Karl-Heinz Kuck, MD; Gerhard Hindricks, MD; D. Wyn Davies, MD; Peter R. Kowey, MD; Gerald V. Naccarelli, MD; James A. Reiffel, MD; Jonathan P. Piccini, MD, MHS; Adam P. Silverstein, MS; Hussein R. Al-Khalidi, PhD; Kerry L. Lee, PhD; for the CABANA Investigators

RESEARCH ARTICLE Open Access

A risk score for predicting atrial fibrillation in individuals with preclinical diastolic dysfunction: a retrospective study in a single large urban center in the United States

Dan L. Li[1†], Renato Quispe[1,2†], Nidhi Madan[1], Lili Zhang[3] and Cynthia C. Taub[3*]

Journal of the American Heart Association

ORIGINAL RESEARCH

Thirty-Year Trends in the Incidence of Atrial Fibrillation: The ARIC Study

Kunali P. Ghelani, MPH; Lin Yee Chen, MD, MS; Faye L. Norby, PhD, MPH; Elsayed Z. Soliman, MD MSc, MS; Silvia Koton, PhD, RN; Alvaro Alonso, MD, PhD

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Journal of the American Heart Association

ORIGINAL RESEARCH

Screening for Atrial Fibrillation in American Indian Adults in a Tribal Primary Care Clinic

Stavros Stavrakis, MD, PhD; Khaled Elkholey, MD; Marty M. Lofgren, MD; Zain U. A. Asad, MD; Lancer D. Stephens, PhD; Ben Freedman, MBBS, PhD

Journal of the American Heart Association

ORIGINAL RESEARCH

Incident Strokes Among American Indian Individuals With Atrial Fibrillation

José M. Sanchez, MD; Stacey E. Jolly, MD, MAS; Thomas A. Dewland, MD; Zian H. Tseng, MD, MAS; Gregory Nah, MA; Eric Vittinghoff, PhD, MPH; Gregory M. Marcus, MD, MAS

IJC Heart & Vasculature 28 (2020) 100538

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journal homepage: www.journals.elsevier.com/ijc-heart-and-vasculature

ELSEVIER

Impact of traditional risk factors for the outcomes of atrial fibrillation across race and ethnicity and sex groups

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Usefulness of the American Heart Association's Life Simple 7 to Predict the Risk of Atrial Fibrillation (From the REasons for Geographic And Racial Differences in Stroke [REGARDS] Study)

Parveen K Garg, MD, MPH[a], Wesley T O'Neal, MD, MPH[b], Adedotun Ogunsua, MD, MPH[c], Evan L Thacker, PhD[d], George Howard, DrPH[e], Elsayed Z Soliman, MD, MSc, MS[f], and Mary Cushman, MD, MSc[g]

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JCSM
Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Race, Sex, Age, and Regional Differences in the Association of Obstructive Sleep Apnea With Atrial Fibrillation: Reasons for Geographic and Racial Differences in Stroke Study

Lama Ghazi, MD[1]; Aleena Bennett, MS[2]; Megan E. Petrov, PhD[3]; Virginia J. Howard, PhD[4]; Monika M. Safford, MD[5]; Elsayed Z. Soliman, MD, MSC, MS[6]; Stephen P. Glasser, MD[7]

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Research article

Association between oral health and atrial fibrillation: A systematic review

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CARDIOVASCULAR MEDICINE AND SOCIETY

Sex and Race/Ethnicity Differences in Atrial Fibrillation

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Adherence to the 'Atrial Fibrillation Better Care' Pathway in Patients with Atrial Fibrillation: Impact on Clinical Outcomes—A Systematic

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Association of Multimorbidity with Cardiovascular Endpoints and Treatment Effectiveness in Patients 75 Years and Older with Atrial Fibrillation

CrossMark

J'Neka S. Claxton, MPH,[a] Alanna M. Chamberlain, PhD,[b] Pamela L. Lutsey, PhD,[c] Lin Y. Chen, MD, MS,[d] Richard F. MacLehose, PhD,[c] Lindsay G.S. Bengtson, PhD,[e] Alvaro Alonso, MD, PhD[a]

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References

MAYO CLINIC

The State of the Art: Atrial Fibrillation Epidemiology, Prevention, and Treatment

Daniel P. Morin, MD, MPH; Michael L. Bernard, MD, PhD; Christopher Madias, MD; Paul A. Rogers, MD, PhD; Sudarone Thihalolipavan, MD; and N.A. Mark Estes III, MD

Atrial Fibrillation Pathophysiology
Implications for Management

Yu-ki Iwasaki, MD, PhD*; Kunihiro Nishida, MD, PhD*; Takeshi Kato, MD, PhD; Stanley Nattel, MD

***Abstract*—**Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is an important contributor to population morbidity and mortality. An arrhythmia that is particularly common in the elderly, AF is growing in prevalence with the aging of the population. Our understanding of the basic mechanisms that govern AF occurrence and persistence has been increasing rapidly. This article reviews the basic pathophysiology of AF over a broad range of levels, touching on the tissue mechanisms that maintain the arrhythmia, the relationship between clinical presentation and basic mechanisms, ion channel and transporter abnormalities that lead to ectopic impulse formation, basic models and tissue determinants of reentry, ion channel determinants of reentry, the nature and roles of electric and structural remodeling, autonomic neural components, anatomic factors, interactions between atrial and ventricular functional consequences of AF, and the basic determinants of atrial thromboembolism. We then review the potential implications of the basic pathophysiology of the arrhythmia for its management. We first discuss consequences for improved rhythm control pharmacotherapy: targeting underlying conditions, new atrium-selective drug targets, new targets for focal ectopic source suppression, and upstream therapy aiming to prevent remodeling. We then review the implications of basic mechanistic considerations for rate control therapy, AF ablation, and the prevention of thromboembolic events. We conclude with some thoughts about the future of translational research related to AF mechanisms. **(*Circulation*. 2011; 124:2264-2274.)**

[Contemporary Reviews in Critical Care Medicine]

CHEST

Atrial Fibrillation in the ICU

Check for updates

Nicholas A. Bosch, MD; Jonathan Cimini, BS; and Allan J. Walkey, MD

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136 ***Current Cardiology Reviews*, 2019, *15*, 136-144**

REVIEW ARTICLE

Gender Differences in Atrial Fibrillation: A Review of Epidemiology, Management, and Outcomes

International Journal of *Molecular Sciences*

MDPI

Review

Atrial Fibrillation: Pathogenesis, Predisposing Factors, and Genetics

Marios Sagris [1,*], Emmanouil P. Vardas [1,2], Panagiotis Theofilis [1], Alexios S. Antonopoulos [1], Evangelos Oikonomou [1,3] and Dimitris Tousoulis [1]

Unfinished slides/backup data

Gender and AF: AAD drug mgt, qt interval

with it a real consequence. A meta-analysis of 22 multinational trials of patients treated with sotalol for both ventricular and atrial arrhythmias reviewed 3135 patients, 25% female. The authors found that women treated with sotalol were up to three times more likely than men to develop torsades de pointes [33].

Dofetilide is another potent class III agent. It can be an effective medication for controlling atrial fibrillation, and it has the benefit of relative safety in patients with heart failure. However, it can cause significant QT prolongation and has a 2-3% risk of torsades de pointes. The DIAMOND-CHF trial was a double-blind placebo-controlled study that examined the safety and efficacy of dofetilide for atrial fibrillation in patients with heart failure. Twenty-five percent of enrolled patients were female. Torsade de pointes occurred in 3.3% of patients. Female sex was significantly associated with the occurrence of torsade de pointes with an odds ratio of 3.2 [34].

The efficacy of dofetilide is directly related to its dosing. Steinberg *et al*. analyzed 308 patients, 24% female, admitted for dofetilide loading. There was no difference in pharmacologic conversion rates between men and women and no difference in excessive QT prolongation, though all episodes of torsades de pointes occurred in women. They found a dose-response that predicted pharmacologic conversion, where the rate of conversion based on the final dofetilide dosing was 75% for 500 mcg dosing, compared to 9% for 250 mcg dosing and 0% for 125 mcg dosing [35].

The recommended starting dose of dofetilide is 500 mcg twice daily due to the highest clinical efficacy of this dose, and dosing must be decreased for prolongation of the QT interval. Pokorney *et al*. studied a single center cohort of patients admitted between 2006 and 2012 for dofetilide initiation. 110 female and 100 male patients were matched and included in the study. Median age, creatinine clearance, and QTc interval were statistically similar between the two groups at baseline. Women were significantly more likely than men to have their dosing reduced or discontinued (55% vs 32%), primarily due to QT prolongation, but also due to bradycardia [36].

Many of the pharmacokinetic and pharmacodynamics studies performed on dofetilide enrolled only men. One pharmacokinetic study showed women have dofetilide clearance rates 12-18% lower than men, resulting in 14-22% higher plasma concentrations [36].

The fact that women may be less likely to tolerate the most effective dosing of dofetilide has clinical relevance for the efficacy of dofetilide to maintain sinus rhythm in women. Hassan Virk *et al*. evaluated the efficacy of dofetilide for cardioversion of atrial fibrillation. In a cohort of 160 patients, 26% female, female sex was associated with failure to convert to sinus rhythm and increased atrial fibrillation hospital readmissions at 1 year [37].

Gender and AF

Table 1. Risk factors related to the development of atrial fibrillation and odds ratio of developing atrial fibrillation in the presence of that risk factor.

Risk Factor	Women	Men
Valvular heart disease	3.4 (OR)	1.8 (OR)
Coronary artery disease	1.0 (OR)	2.4 (OR)
Congestive heart failure	5.9 (OR)	4.5 (OR)
Hypertension	1.4 (OR)	1.5 (OR)
Diabetes	1.6 (OR)	1.4 (OR)
Body Mass Index	1.18 (HR per standard deviation increase)	1.3 (HR per standard deviation increase)