# Atrial Fibrillation Updates

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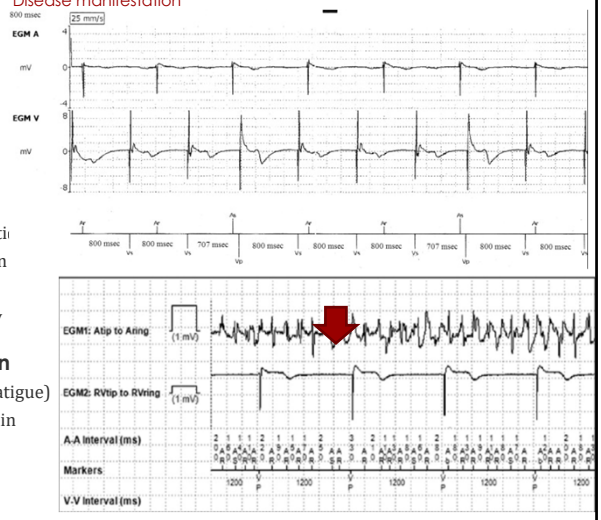
## Atrial Fibrillation Updates

- Introduction
- Management of atrial fibrillation updates and recent evidences
- Three pillars of management of atrial fibrillation
- **Focused Update of the AHA/ACC/HRS Atrial Fibrillation Guideline Jan 2019**

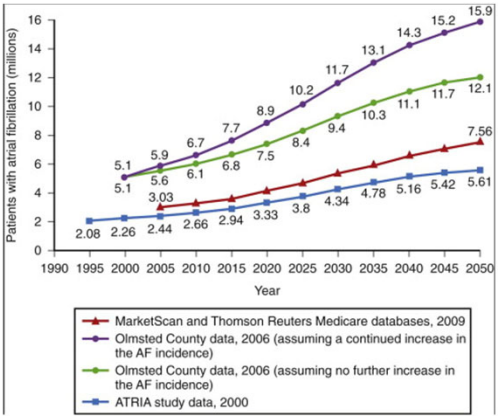
# A FIB

Electrical problem
Mechanical problem
Disease manifestation

- **Electrical Problem**
  - Atrial rate 300-400bpm
  - Vent rate 100-150bpm
- **Mechanical Problem**
  - High Heart rate
    - 4-6 wks –LV dysfuncti
  - Loss of atrial contraction
    - Stroke
    - Loss of AV synchrony
- **Disease Manifestation**
  - Heart failure Sx( SOB, Fatigue)
  - Palpitation and chest pain
  - Stroke
  - Fatigue and SOB




# Incidence of Atrial fibrillation

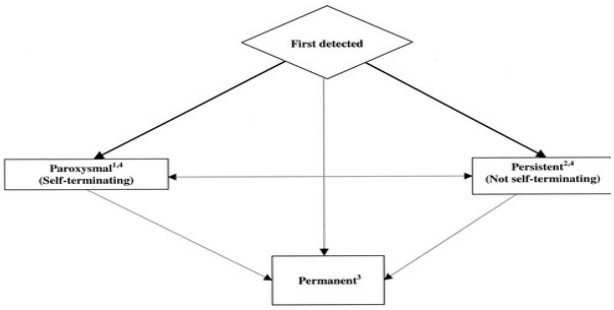



Electrophysiological Disorders of the Heart
Camm, A. John; Savelieva, Irina… Show all.; Ho, Siew Yen; Lindsay, Bruce D.; Nattel, Stanley; Shinagawa, Kaori. Published December 31, 2011. Pages 559-624.

# Significance of Afib

- In the United States alone, it is estimated that between 3 and 5 million people have AF, and that by 2050 this number will exceed 8 million.
- AF **increases risk of stroke by an average of 5-fold**. AF-related strokes are more severe than those not related to AF.
- AF increases mortality, and has **been linked to an increased risk of sudden death**.
- AF increases **the risk of HF**.
- Recent studies have linked AF with **the development of dementia**.
- AF causes a wide variety of symptoms, including fatigue and reduced exercise tolerance, and significantly impairs quality of life (QOL).
- AF is also important when considered in terms of use of health care resources and cost. In the United States, AF accounts for more than **450,000 hospitalizations** yearly and has contributed to more than 99,000 deaths.
- AF has been reported to increase annual health care costs by $8700 per patient, resulting in a $26 billion annual increase in U.S. health care costs.

Valentin Fuster. Circulation. 2001 ACC/AHA/ESC 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 and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation) Developed in Collaboration With the North American Society of Pacing and Electrophysiology, **Volume: 104, Issue: 17, Pages: 2118-2150, DOI: (10.1161/circ.104.17.2118)**



Circulation
Volume 140, Issue 2, 9 July 2019; Pages e125-e151
https://doi.org/10.1161/CIR.0000000000000665

ACC/AHA/HRS GUIDELINE

# 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons

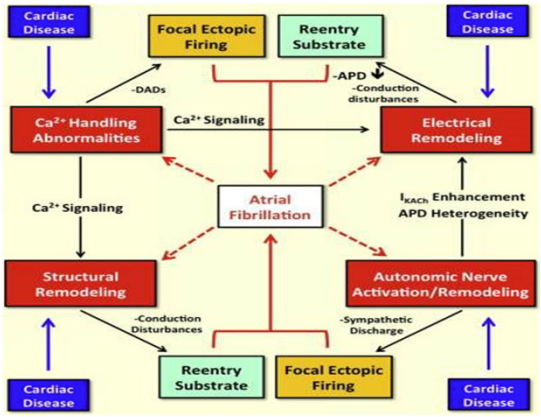
**Craig T. January, MD, PhD, FACC, Chair, L. Samuel Wann, MD, MACC, FAHA, Vice Chair, Hugh Calkins, MD, FACC, FAHA, FHRS, Lin Y. Chen, MD, MS, FACC, FAHA, FHRS, Joaquin E. Cigarroa, MD, FACC, Joseph C. Cleveland Jr, MD, FACC, Patrick T. Ellinor, MD, PhD, Michael D. Ezekowitz, MBChB, DPhil, FACC, FAHA, Michael E. Field, MD, FACC, FAHA, FHRS, Karen L. Furie, MD, MPH, FAHA, Paul A. Heidenreich, MD, FACC, FAHA, Katherine T. Murray, MD, FACC, FAHA, FHRS, Julie B. Shea, MS, RNCS, FHRS, Cynthia M. Tracy, MD, FAHA, and Clyde W. Yancy, MD, MACC, FAHA**

| | |
|---|---|
| Paroxysmal atrial fibrillation | Paroxysmal AF is defined as AF that terminates spontaneously or with intervention within 7 days of onset. |
| Early Persistent atrial fibrillation | Early persistent AF is defined as AF that is sustained beyond 7 days but is less than 3 months in duration. |
| Long standing Persistent atrial fibrillation | Long-standing persistent AF is defined as continuous AF of greater than 12 months' duration. |
| Silent atrial fibrillation | Silent AF is defined as asymptomatic AF diagnosed with an opportune ECG |
| Permanent atrial fibrillation | Permanent AF is defined as the presence of AF that is accepted by the patient and physician, and for which no further attempts to restore or maintain sinus rhythm will be undertaken. The term permanent AF represents a therapeutic attitude on |

# Symptoms

- Palpitation
- Chest Pain
- Syncope
- Lightheadedness
- SOB
- Fatigue
- Nonspecific aches
- Asymptomatic

# Mechanism of Atrial Fibrillation




Nattel et al JAAC 2014

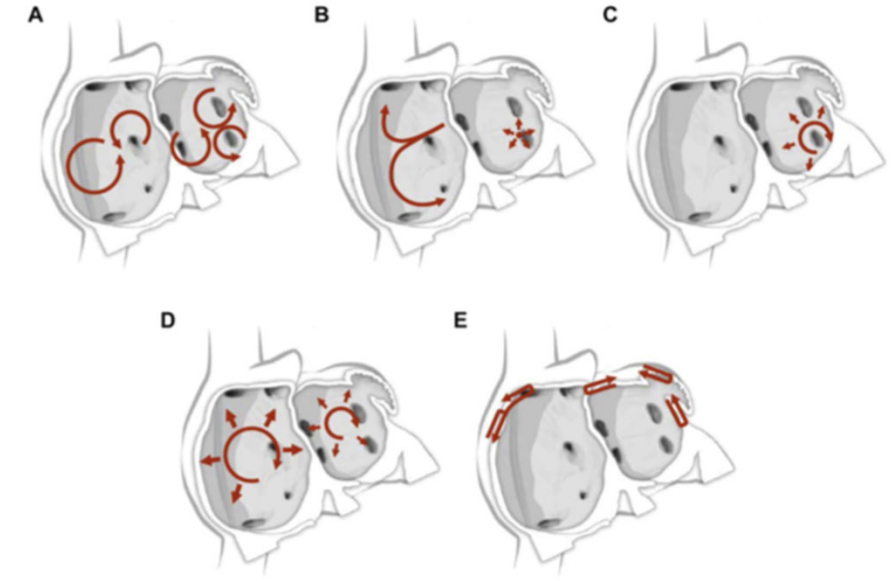
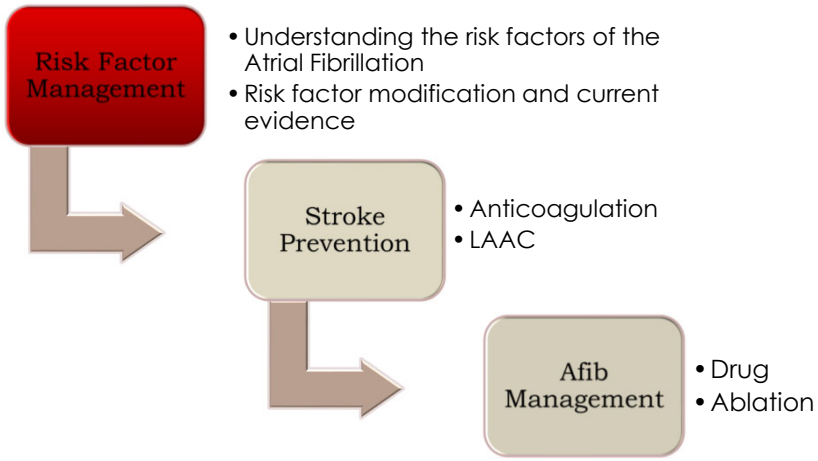



**Figure 3** Schematic drawing showing various hypotheses and proposals concerning the mechanisms of atrial fibrillation. **A:** Multiple wavelets hypothesis. **B:** Rapidly discharging automatic foci. **C:** Single reentrant circuit with fibrillatory conduction. **D:** Functional reentry resulting from rotors or spiral waves. **E:** AF maintenance resulting from dissociation between epicardial and endocardial layers, with mutual interaction producing multiplying activity that maintains the arrhythmia.

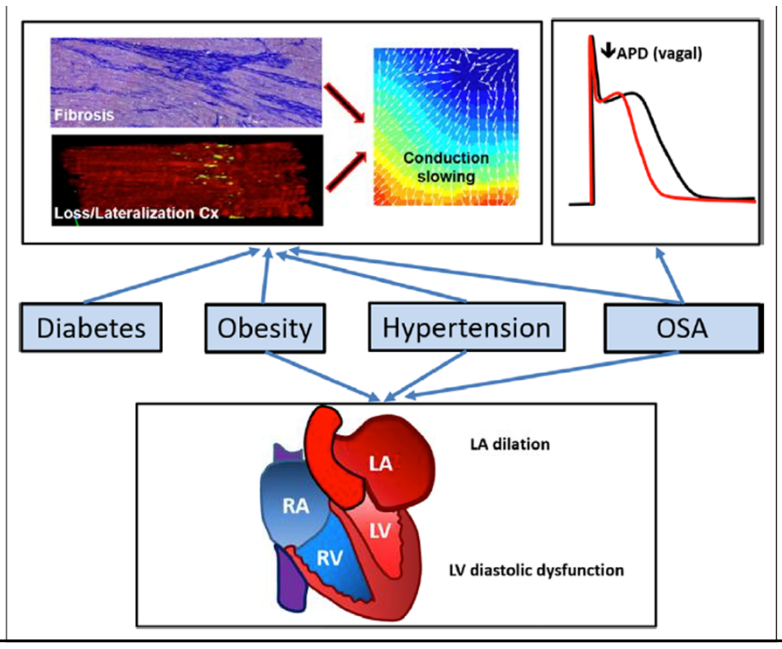
# Management of Atrial Fibrillation Updates

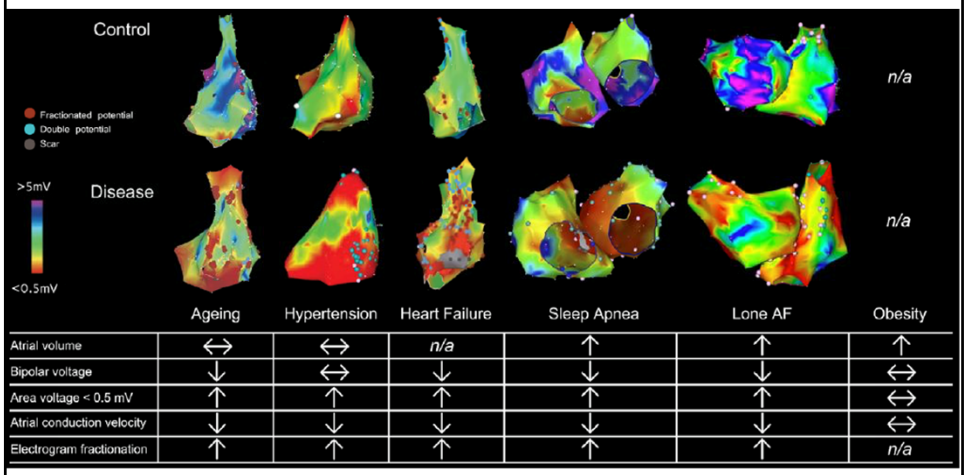
Integrated approach




| Modifiable Risk Factor | Non Modifiable Risk Factor |
|---|---|
| Hypertension | Age |
| Obesity | Sex |
| Obstructive sleep apnea (OSA) | Family History |
| Endurance exercise | Race |
| Alcohol consumption | Tall stature |
| Thyroid disease | |
| | |

Among people of European descent, the lifetime risk of developing AF after age 40 is 26% for men and 23% for women age is perhaps the most powerful.

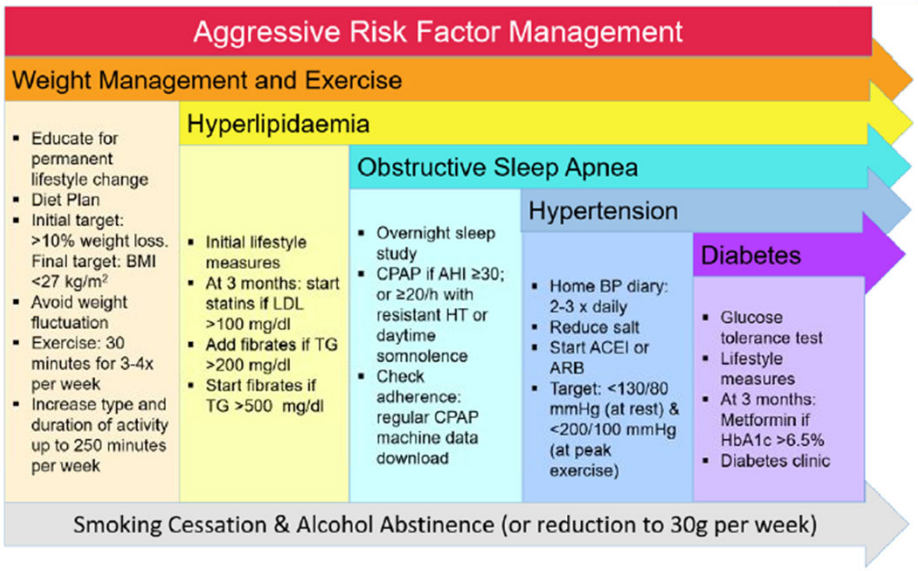



| | Ageing | Hypertension | Heart Failure | Sleep Apnea | Lone AF | Obesity |
|---|---|---|---|---|---|---|
| Atrial volume | ↔ | ↔ | *n/a* | ↑ | ↑ | ↑ |
| Bipolar voltage | ↓ | ↔ | ↓ | ↓ | ↓ | ↔ |
| Area voltage < 0.5 mV | ↑ | ↑ | ↑ | ↑ | ↑ | ↔ |
| Atrial conduction velocity | ↓ | ↓ | ↓ | ↓ | ↓ | ↔ |
| Electrogram fractionation | ↑ | ↑ | ↑ | ↑ | ↑ | *n/a* |

Circulation. 2017.Modifiable Risk Factors and Atrial Fibrillation.

Lau DH(1), Nattel S(1), Kalman JM(1), Sanders P(2)



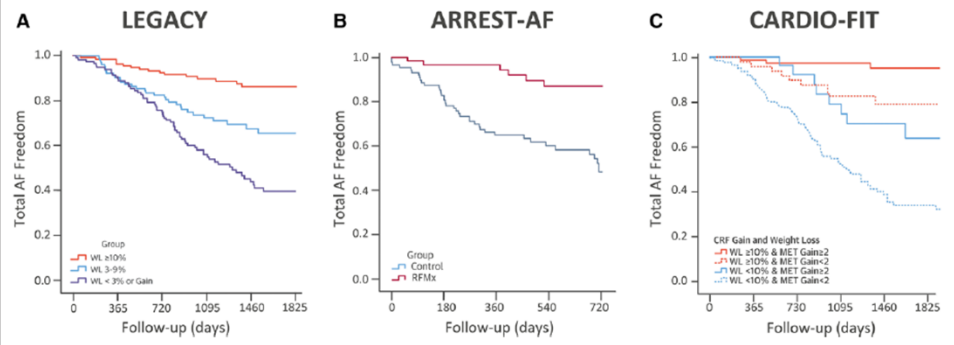
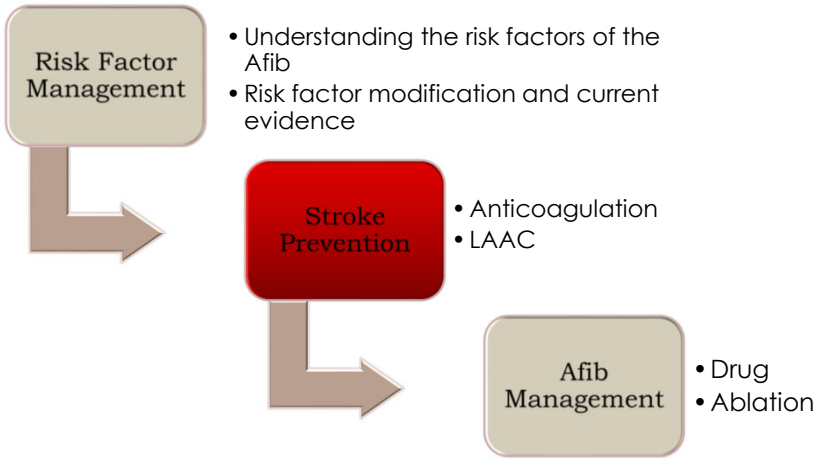



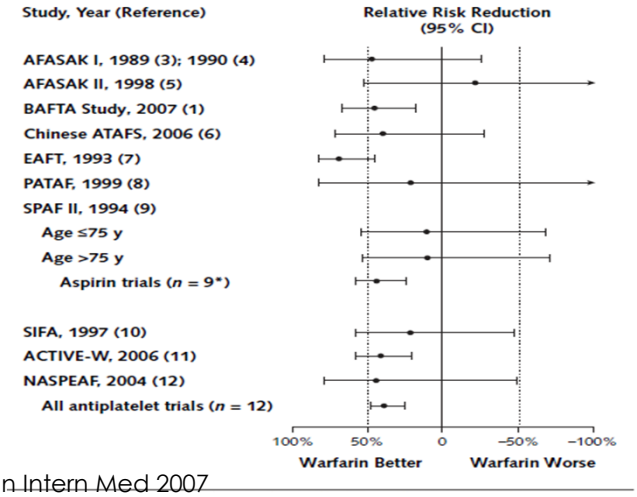

**Figure 6. Kaplan-Meier curves of various lifestyle modifications.**
The benefits of lifestyle and risk factor modifications on AF-free survival are evident from these Kaplan-Meier survival graphs adapted with permission from Pathak et al.[11–13] **A,** In the LEGACY study, greater freedom from AF was seen with greater degree of weight loss (WL) as a marker of overall management of risk factors. **B,** In the ARREST-AF Cohort Study, risk factor management (RFM) confers greater AF-free survival following catheter ablation procedure versus usual care. **C,** In the CARDIO-FIT study (Cardiorespiratory Fitness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation), gain in cardiorespiratory fitness (MET, metabolic equivalent) confers independent and incremental AF-free survival to changes in weight. AF indicates atrial fibrillation.




## Stroke Prevention

- No bleeding risk
  - Warfarin
  - Dabigatran
  - Apixaban
  - Edoxaban
  - Rivaroxabon
- Major bleeding history
  - Left atrial appendage closure device
  - Surgical ligation
  - Larriat

# Warfarin in stroke prevention




All cause mortality reduced to 26%

Hart et al Ann Intern Med 2007

# NOAC vs Warfarin Trial

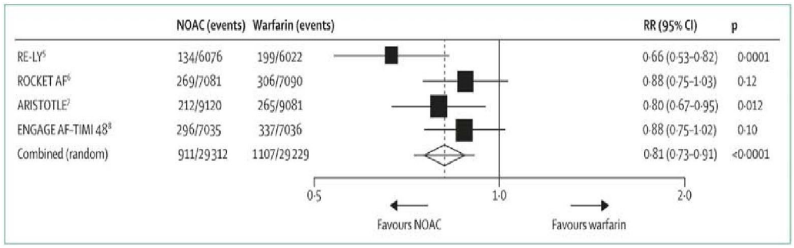
Major phase III trials for NOAC versus Warfarin in non-valvular atrial fibrillation.

| | RE-LY Dabigatran[5, 7] | ARISTOTLE Apixaban[5, 6] | ROCKET AF Rivaroxaban[5, 8] | ENGAGE AF TIMI 48 Edoxaban[5, 9] |
|---|---|---|---|---|
| Drug mechanism | IIa inhibitor | Factor Xa inhibitor | Factor Xa inhibitor | Factor Xa inhibitor |
| Onset of action | 2 h | 1–2 h | 2–4 h | 1–2 h |
| Half-life | 12–17 h | Approx. 12 h | 6–13 h | 10–14 h |
| Study population | N = 18,113 | N = 18,201 | N = 14,264 | N = 21,105 |
| Dosing | 150 mg twice daily<br>110 mg twice daily | 5 mg twice daily<br>2.5 mg twice daily if age > 80, weight < 60 kg, Creatinine >1.5 mg/dl | 20 mg daily<br>15 mg daily if CrCl <50 ml / min | 60 mg daily<br>30 mg daily if CrCl 30–50 ml / min, w use of P-glycoprotein inhibitors |
| Average $CHADS_2$ | 2.1 | 2.1 | 3.5 | 2.8 |
| Stroke/SE reduction vs. VKAs | 110 mg: Non-Inferior*<br>150 mg: Superior** | Superior** | Non-inferior* | 30 mg: Non-inferior*<br>60 mg: Superior** |

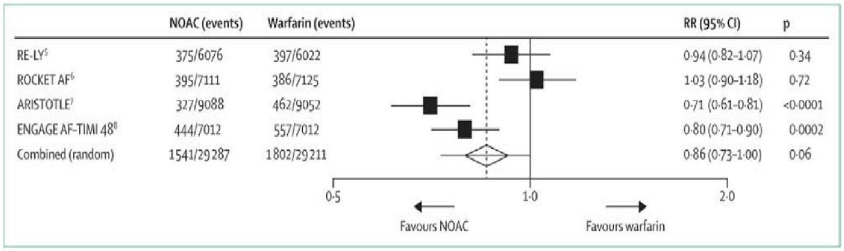
* **Non-inferiority** All comparisons p < .001 except Edoxaban 30 mg (p = .005).
** **Superiority** p < .001 for Dabigatran (150 mg); p = .01 for Apixaban; p = .02 for Edoxaban (60 mg).

- S.T. Chen, M.R.Patel / Progressin CardiovascularDiseases60 (2018) 514–523

Stroke or Systemic embolism




Major Bleeding



# Choice of NOACs in high risk population

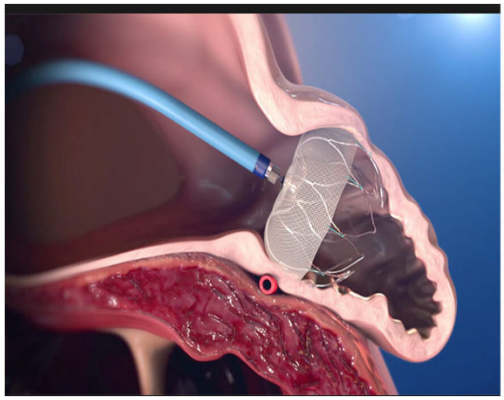
| | Choice of NOACs | Considerations |
|---|---|---|
| Gastrointestinal Bleeding[6] | Apixaban | Only NOAC with smaller number of GI bleeds in the original studies. |
| Elderly[17–19] | Rivaroxaban<br>Apixaban<br>Edoxaban<br>110 mg dabigatran | 150 mg dabigatran showed trend toward higher bleeding in the elderly. |
| Impaired Renal Function[26–29] | Apixaban<br>Rivaroxaban<br>Edoxaban | Caution for edoxaban in patients with CrCl >95 ml/min; Dabigatran should be avoided due to high renal clearance |
| Coronary Artery Disease[33, 97] | Rivaroxaban | Only NOAC with a proven benefit after ACS. |
| Diabetes Mellitus[55] | Apixaban<br>Dabigatran<br>Edoxaban<br>Rivaroxaban | No interaction between DM and efficacy and safety of NOACs |
| Cardioversion[86, 87] | Edoxaban<br>Rivaroxaban | Both prospectively found to be viable alternatives to warfarin for cardioversion. |
| Mechanical Heart Valve[95] | None | NOACs have been associated with higher rates of thromboembolic and bleeding events |
| Bioprosthetic Valve[96] | More data needed | Comparable treatment effects between apixaban and VKAs in a small number of patients with bioprosthetic valves in ARISTOTLE. |
| Non-mechanical, Non-rheumatic valvular disease[93, 98] | Apixaban<br>Edoxaban<br>Dabigatran | Rivaroxaban was associated with higher rates of bleeding in those with native valvular disease. |

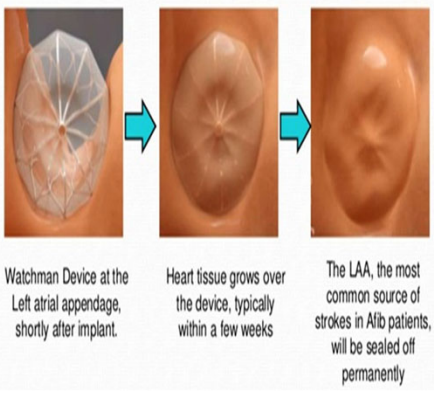
- Stroke prevention in Afib patient after major or minor bleeding

# LAAC Device

- WATCHMAN is a self-expanding nitinol frame with fixation anchors and a permeable fabric cover
- It is designed to be permanently implanted at or slightly distal to the opening of the LAA to trap potential emboli before they exit the LAA

- Five sizes of device (21, 24, 27, 30 and 33 mm) allow for precise fit within ostium
- It is implanted via a transseptal approach by use of a catheter-based delivery system
- The delivery catheter is capable of recapturing the device if necessary





# LAAC Device

- Safety
- Efficacy
  - PROTECT-AF Trial Results
  - PREVAIL Trial Results

**TABLE 2** WATCHMAN Studies and Key Results

| Study (Ref. #) | Design | CHADS2, Mean ± SD | Procedural Success, % | Follow-Up Duration | Efficacy Events | Important Safety Issues With WM |
|---|---|---|---|---|---|---|
| PROTECT-AF (29,31) | RCT, N = 707: 2 WM; 1 warfarin | 2.2 ± 1.2 | 90.9 | 1,065 pt-yrs (mean 1.8 yrs) | Primary endpoint: stroke, systemic embolism, CV death: 3.0% WM, 4.9% warfarin per 100 pt-yrs; RR: 0.62. Met noninferiority criteria. | Serious pericardial effusion 4.8%, procedural stroke 1.3%, device embolization 0.6%, major bleeding 3.5% (4.1% warfarin), hemorrhagic stroke 0.2% (2.5% warfarin). |
| | | | | 1,588 pt-yrs (mean 2.3 yrs) | Primary endpoint: 3.0% WM, 4.3% warfarin per 100 pt-yrs; RR: 0.71. Met noninferiority criteria. | |
| | | | | 2,621 pt-yrs (45 months) | Primary endpoint: 2.3% WM, 3.8% warfarin per 100 pt-yrs; RR: 0.6. Met noninferiority and superiority criteria. | Major bleeding 4.8% (7.4% warfarin), hemorrhagic stroke 0.6% (3.7% warfarin). |
| PREVAIL (32) | RCT, N = 407: 2 WM; 1 warfarin | 2.6 ± 1.0 | 95.1 | 18 months | Stroke, systemic embolism, CV, and unexplained death at 18 months: 0.064 both groups, RR: 1.07. Did not meet noninferiority criteria (<90 pts at 18-month follow-up). Ischemic stroke or systemic embolism >7 days met noninferiority criteria: 0.0253 WM; 0.0201 warfarin. | 7-day death, ischemic stroke, systemic embolism, and procedure complications met noninferiority criteria (2.2% WM). Pericardial effusion needing pericardiocentesis, window, or surgery 1.9%. Procedure stroke 0.4%. Device embolization 0.8%. |
| CAP (30) | Registry, N = 460 | 2.4 ± 1.2 | 95.0 | Median 0.4 yr | | Procedural stroke 0%, serious pericardial effusion 2.2%. |
| ASAP (33) | Registry, N = 150 | 2.8 ± 1.2 | 94.7 | 14 months | All-cause stroke and systemic embolism 2.3%/yr. Observed ischemic stroke rate was 77% lower than expected. | Serious procedure- or device-related events 8.7%. Pericardial effusion with tamponade 1.3%, device embolism 1.3%, device thrombus 4.0% (with 0.7% causing stroke). |

ASAP = ASA Plavix Feasibility Study With WATCHMAN Left Atrial Appendage Closure Technology; CAP = Continued Access Protocol; CHADS2 = congestive heart failure history, hypertension history, age ≥75 years, diabetes mellitus history, stroke or transient ischemic attack symptoms previously; CV = cardiovascular; PREVAIL = Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation vs. Long-Term Warfarin Therapy; PROTECT-AF = WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation; pt-yrs = patient-years; RCT = randomized controlled trial; RR = risk ratio; WM = WATCHMAN.

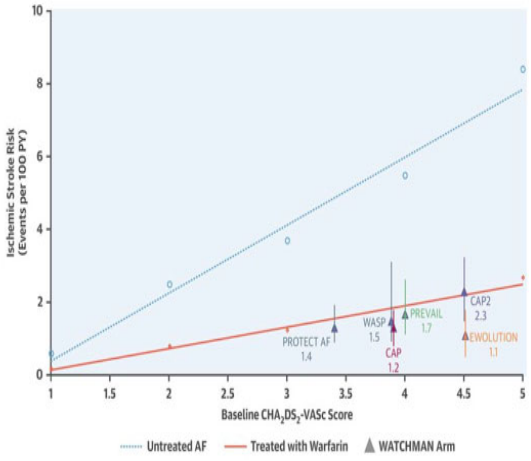
Saw J JACC Intv 2014

# Meta-analysis

- **5-Year Outcomes After Left Atrial Appendage Closure From the PREVAIL and PROTECT AF Trials**

Vivek Y. Reddy, Shephal K. Doshi, Saibal Kar, Douglas N. Gibson, Matthew J. Price, Kenneth Huber, Rodney P. Horton, Maurice Buchbinder, Petr Neuzil, Nicole T. Gordon, David R. Holmes Jr. and on behalf of the PREVAIL and PROTECT AF Investigators

Stroke Prevention in Nonvalvular Atrial Fibrillation With LAA Closure



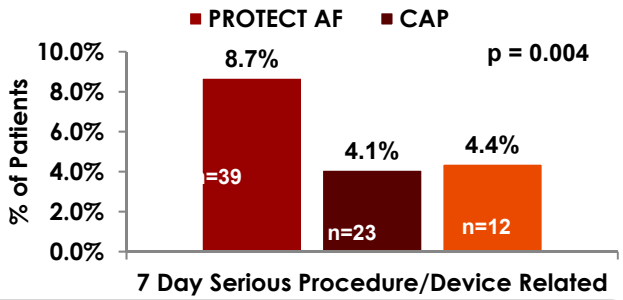
# 5-Year Patient-Level Meta-Analysis of PROTECT AF and PREVAIL (2:1 Randomization)

| | Device Group (n = 732) | | Control Group (n = 382) | | Hazard Ratio (95% Confidence Interval) | p Value |
|---|---|---|---|---|---|---|
| | No. of Events | Rate (per 100 PY) | No. of Events | Rate (per 100 PY) | | |
| Efficacy: stroke/SE/CV death | 79/2,856.0 | 2.8% | 50/1,472.8 | 3.4% | 0.82 (0.58–1.17) | 0.27 |
| All stroke or SE | 49/2,849.4 | 1.7% | 27/1,472.9 | 1.8% | 0.96 (0.60–1.54) | 0.87 |
| Ischemic stroke or SE | 45/2,850.2 | 1.6% | 14/1,479.1 | 0.95% | 1.71 (0.94–3.11) | 0.08 |
| Hemorrhagic stroke | 5/2,954.8 | 0.17% | 13/1,499.0 | 0.87% | 0.20 (0.07–0.56) | 0.0022 |
| Ischemic stroke or SE >7 days | 37/2,862.1 | 1.3% | 14/1,479.1 | 0.95% | 1.40 (0.76–2.59) | 0.28 |
| Disabling stroke | 13/2,943.0 | 0.44% | 15/1,493.8 | 1.0% | 0.45 (0.21–0.94) | 0.03 |
| Nondisabling stroke | 31/2,879.1 | 1.1% | 12/1,484.3 | 0.81% | 1.38 (0.71–2.68) | 0.35 |
| CV/unexplained death | 39/2,960.5 | 1.3% | 33/1,505.2 | 2.2% | 0.59 (0.37–0.94) | 0.027 |
| All-cause death | 106/2,961.6 | 3.6% | 73/1,505.2 | 4.9% | 0.73 (0.54–0.98) | 0.035 |
| Major bleeding, all | 85/2,748.4 | 3.1% | 50/1,414.7 | 3.5% | 0.91 (0.64–1.29) | 0.60 |
| Major bleeding, non-procedure-related | 48/2,853.6 | 1.7% | 51/1,411.3 | 3.6% | 0.48 (0.32–0.71) | 0.0003 |

Two strokes in PREVAIL are excluded because the baseline MRS score was unavailable.

# Vascular Complications

- **Composite of vascular complications includes cardiac perforation, pericardial effusion with tamponade, ischemic stroke, device embolization, and other vascular complications[1]**

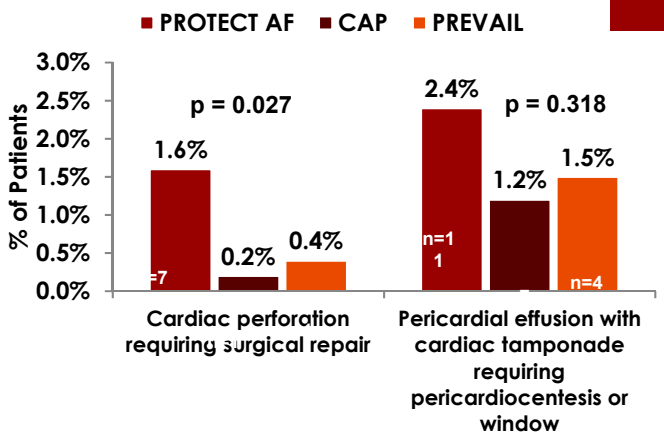



**No procedure-related deaths reported in any of the trials**

PROTECT-AF and CAP data from Reddy, VY et al. *Circulation*. 2011;123:417-424.

[1]Includes observed PE not necessitating intervention, AV fistula, major bleeding requiring transfusion, pseudoaneurysm, hematoma

# Pericardial Effusions Requiri Intervention

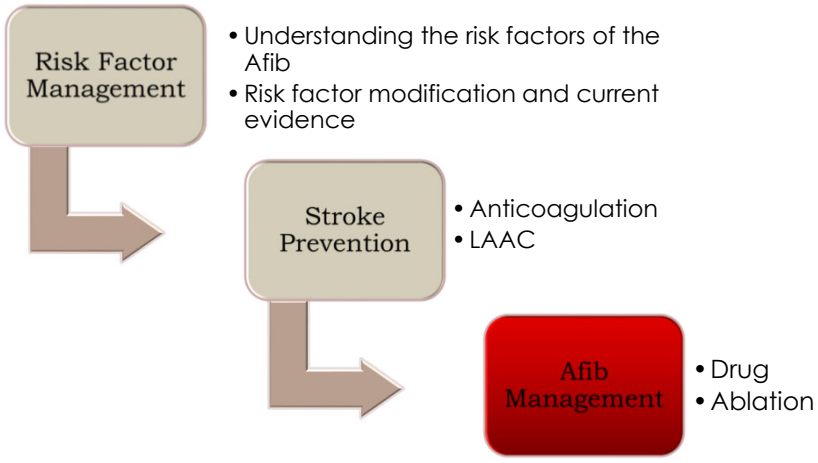



PROTECT AF and CAP data
from Reddy, VY et al. *Circulation*. 2011;123:417-424.

**5-year meta-analysis: Mortality outcomes**

- Statistically significant 41% decrease in cardiovascular mortality and a 27% decrease in all-cause mortality
  - mechanism of mortality benefit is driven in part by the 80% decrease in hemorrhagic stroke with LAAC
  - In addition, it is possible that some of the mortality benefit may also be driven by reduced noncranial bleeding.
  - That is, the primary benefit of LAAC is the ability to avoid OAC and its associated bleeding risk.

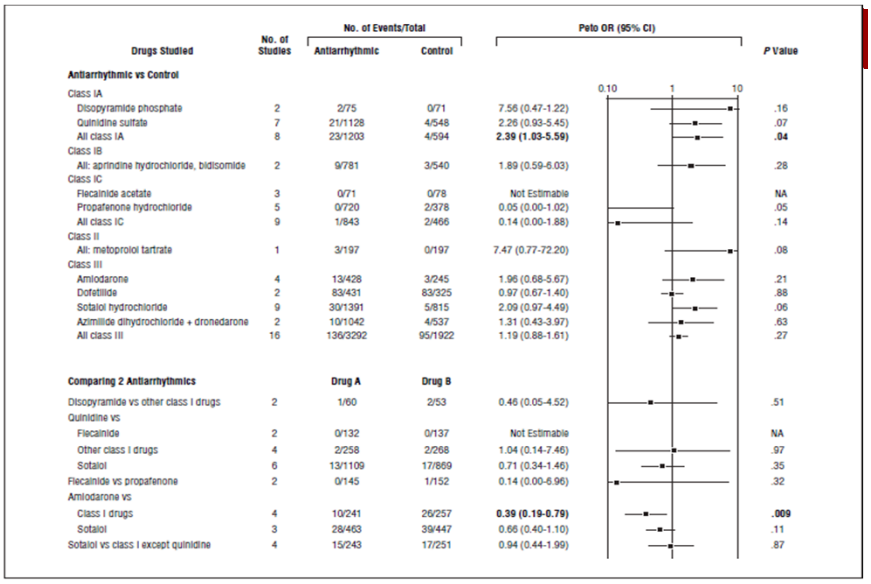
- The long-term 5-year outcomes of the PREVAIL trial, combined with the 5-year outcomes of the PROTECT AF trial, demonstrate that LAAC with the Watchman device provides stroke prevention in nonvalvular AF patients to a similar degree as OAC with warfarin.
- Furthermore, by virtue of its ability to minimize major bleeding, particularly hemorrhagic stroke, LAAC results in less disability or death than warfarin.



# Atrial Fibrillation Managment

Rhythm Control
Rate Control

## Rhythm Control Strategy

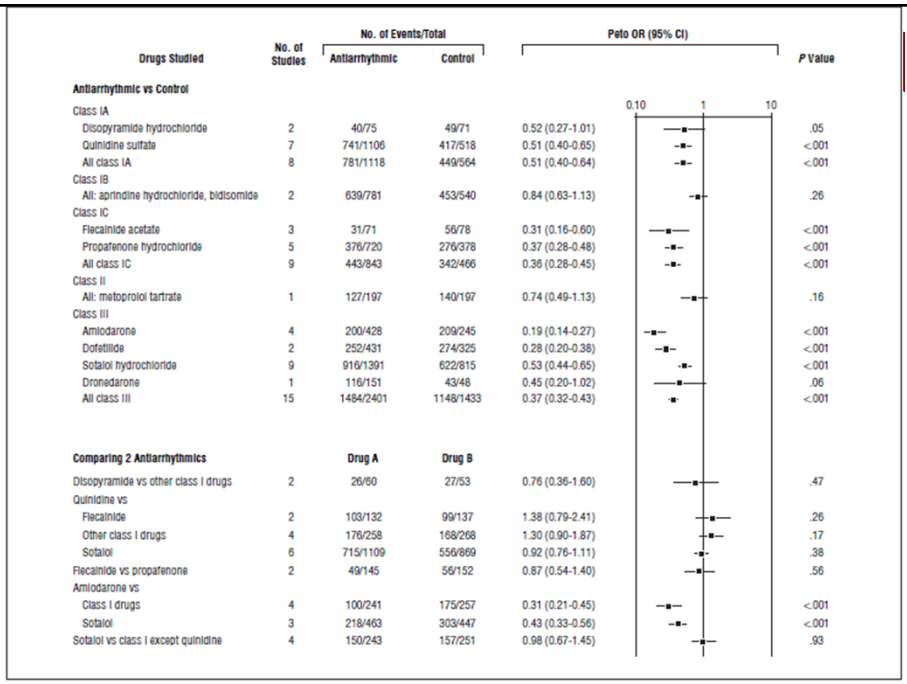


| Drugs Studied | No. of Studies | No. of Events/Total: Antiarrhythmic | No. of Events/Total: Control | Peto OR (95% CI) | *P* Value |
|---|---|---|---|---|---|
| **Antiarrhythmic vs Control** | | | | | |
| Class IA | | | | | |
| Disopyramide phosphate | 2 | 2/75 | 0/71 | 7.56 (0.47-1.22) | .16 |
| Quinidine sulfate | 7 | 21/1128 | 4/548 | 2.26 (0.93-5.45) | .07 |
| All class IA | 8 | 23/1203 | 4/594 | **2.39 (1.03-5.59)** | **.04** |
| Class IB | | | | | |
| All: aprindine hydrochloride, bidisomide | 2 | 9/781 | 3/540 | 1.89 (0.59-6.03) | .28 |
| Class IC | | | | | |
| Flecainide acetate | 3 | 0/71 | 0/78 | Not Estimable | NA |
| Propafenone hydrochloride | 5 | 0/720 | 2/378 | 0.05 (0.00-1.02) | .05 |
| All class IC | 9 | 1/843 | 2/466 | 0.14 (0.00-1.88) | .14 |
| Class II | | | | | |
| All: metoprolol tartrate | 1 | 3/197 | 0/197 | 7.47 (0.77-72.20) | .08 |
| Class III | | | | | |
| Amiodarone | 4 | 13/428 | 3/245 | 1.96 (0.68-5.67) | .21 |
| Dofetilide | 2 | 83/431 | 83/325 | 0.97 (0.67-1.40) | .88 |
| Sotalol hydrochloride | 9 | 30/1391 | 5/815 | 2.09 (0.97-4.49) | .06 |
| Azimilide dihydrochloride + dronedarone | 2 | 10/1042 | 4/537 | 1.31 (0.43-3.97) | .63 |
| All class III | 16 | 136/3292 | 95/1922 | 1.19 (0.88-1.61) | .27 |
| **Comparing 2 Antiarrhythmics** | | **Drug A** | **Drug B** | | |
| Disopyramide vs other class I drugs | 2 | 1/60 | 2/53 | 0.46 (0.05-4.52) | .51 |
| Quinidine vs | | | | | |
| Flecainide | 2 | 0/132 | 0/137 | Not Estimable | NA |
| Other class I drugs | 4 | 2/258 | 2/268 | 1.04 (0.14-7.46) | .97 |
| Sotalol | 6 | 13/1109 | 17/869 | 0.71 (0.34-1.46) | .35 |
| Flecainide vs propafenone | 2 | 0/145 | 1/152 | 0.14 (0.00-6.96) | .32 |
| Amiodarone vs | | | | | |
| Class I drugs | 4 | 10/241 | 26/257 | **0.39 (0.19-0.79)** | **.009** |
| Sotalol | 3 | 28/463 | 39/447 | 0.66 (0.40-1.10) | .11 |
| Sotalol vs class I except quinidine | 4 | 15/243 | 17/251 | 0.94 (0.44-1.99) | .87 |



**Figure 3.** Overall mortality. Some studies compared more than 2 drugs, so the total numbers of studies and patients in the figure are greater than the absolute numbers of studies and patients included. CI indicates confidence interval; NA, not applicable; and OR, odds ratio. Boldface values are significant.

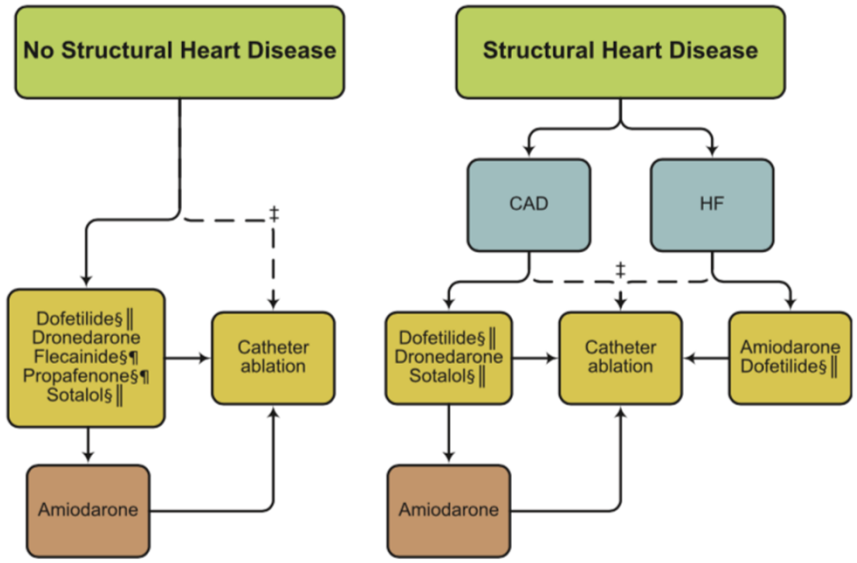
**Antiarrhythmic Drugs for Maintaining Sinus Rhythm After Cardioversion of Atrial Fibrillation**
***A Systematic Review of Randomized Controlled Trials***
*Carmelo Lafuente-Lafuente, MD; Ste´phane Mouly, MD, PhD; Miguel Angel Longa´ s-Tejero, MD, PhD; Isabelle Mahe´, MD, PhD; Jean-Francois Bergmann, MD*



| Drugs Studied | No. of Studies | No. of Events/Total: Antiarrhythmic | No. of Events/Total: Control | Peto OR (95% CI) | *P* Value |
|---|---|---|---|---|---|
| **Antiarrhythmic vs Control** | | | | | |
| Class IA | | | | | |
| Disopyramide hydrochloride | 2 | 40/75 | 49/71 | 0.52 (0.27-1.01) | .05 |
| Quinidine sulfate | 7 | 741/1106 | 417/518 | 0.51 (0.40-0.65) | <.001 |
| All class IA | 8 | 781/1118 | 449/564 | 0.51 (0.40-0.64) | <.001 |
| Class IB | | | | | |
| All: aprindine hydrochloride, bidisomide | 2 | 639/781 | 453/540 | 0.84 (0.63-1.13) | .26 |
| Class IC | | | | | |
| Flecainide acetate | 3 | 31/71 | 56/78 | 0.31 (0.16-0.60) | <.001 |
| Propafenone hydrochloride | 5 | 376/720 | 276/378 | 0.37 (0.28-0.48) | <.001 |
| All class IC | 9 | 443/843 | 342/466 | 0.36 (0.28-0.45) | <.001 |
| Class II | | | | | |
| All: metoprolol tartrate | 1 | 127/197 | 140/197 | 0.74 (0.49-1.13) | .16 |
| Class III | | | | | |
| Amiodarone | 4 | 200/428 | 209/245 | 0.19 (0.14-0.27) | <.001 |
| Dofetilide | 2 | 252/431 | 274/325 | 0.28 (0.20-0.38) | <.001 |
| Sotalol hydrochloride | 9 | 916/1391 | 622/815 | 0.53 (0.44-0.65) | <.001 |
| Dronedarone | 1 | 116/151 | 43/48 | 0.45 (0.20-1.02) | .06 |
| All class III | 15 | 1484/2401 | 1148/1433 | 0.37 (0.32-0.43) | <.001 |
| **Comparing 2 Antiarrhythmics** | | **Drug A** | **Drug B** | | |
| Disopyramide vs other class I drugs | 2 | 26/60 | 27/53 | 0.76 (0.36-1.60) | .47 |
| Quinidine vs | | | | | |
| Flecainide | 2 | 103/132 | 99/137 | 1.38 (0.79-2.41) | .26 |
| Other class I drugs | 4 | 176/258 | 168/268 | 1.30 (0.90-1.87) | .17 |
| Sotalol | 6 | 715/1109 | 556/869 | 0.92 (0.76-1.11) | .38 |
| Flecainide vs propafenone | 2 | 49/145 | 56/152 | 0.87 (0.54-1.40) | .56 |
| Amiodarone vs | | | | | |
| Class I drugs | 4 | 100/241 | 175/257 | 0.31 (0.21-0.45) | <.001 |
| Sotalol | 3 | 218/463 | 303/447 | 0.43 (0.33-0.56) | <.001 |
| Sotalol vs class I except quinidine | 4 | 150/243 | 157/251 | 0.98 (0.67-1.45) | .93 |



**Figure 5.** Atrial fibrillation recurrence. Some studies compared more than 2 drugs, so the total numbers of studies and patients in the figure are greater than the absolute numbers of studies and patients included. CI indicates confidence interval; OR, odds ratio.




## Rhythm Control and Ablation

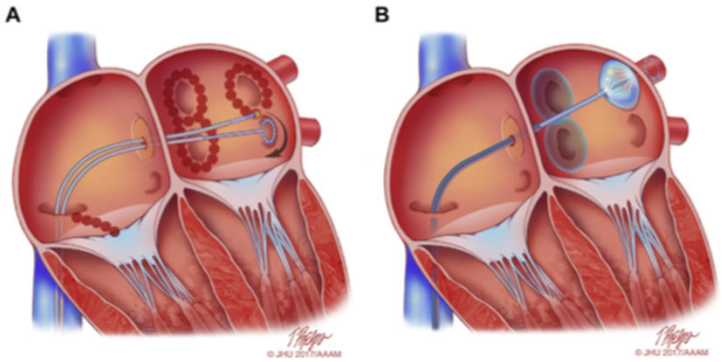



**Figure 9** Schematic drawing showing catheter ablation of atrial fibrillation using either RF energy or cryoballoon AF ablation. **A:** Shows a typical wide area lesion set created using RF energy. Ablation lesions are delivered in a figure of eight pattern around the left and right PV veins. Also shown is a linear cavotricuspid isthmus lesion created for ablation of typical atrial flutter in a patient with a prior history of typical atrial flutter or inducible isthmus-dependent typical atrial flutter at the time of ablation. A multielectrode circular mapping catheter is positioned in the left inferior PV. **B:** Shows an ablation procedure using the cryoballoon system. Ablation lesions have been created surrounding the right PVs, and the cryoballoon ablation catheter is positioned in the left superior PV. A through the lumen multielectrode circular mapping catheter is positioned in the left superior PV. *Illustration: Tim Phelps © 2017 Johns Hopkins University, AAM.*

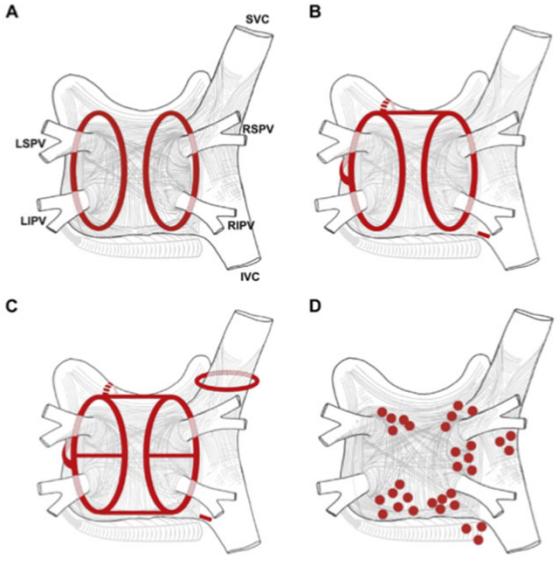



**Figure 6** Schematic of common lesion sets employed in AF ablation. **A:** The circumferential ablation lesions that are created in a circumferential fashion around the right and the left PVs. The primary endpoint of this ablation strategy is the electrical isolation of the PV musculature. **B:** Some of the most common sites of linear ablation lesions. These include a "roof line" connecting the lesions encircling the left and/or right PVs, a "mitral isthmus" line connecting the mitral valve and the lesion encircling the left PVs at the end of the left inferior PV, and an anterior linear lesion connecting either the "roof line" or the left or right circumferential lesion to the mitral annulus anteriorly. A linear lesion created at the cavotricuspid isthmus is also shown. This lesion is generally placed in patients who have experienced cavotricuspid isthmus-dependent atrial flutter clinically or have it induced during EP testing. **C:** Similar to 6B, but also shows additional linear ablation lesions between the superior and inferior PVs resulting in a figure of eight lesion sets as well as a posterior inferior line allowing for electrical isolation of the posterior left atrial wall. An encircling lesion of the superior vena cava (SVC) directed at electrical isolation of the SVC is also shown. SVC isolation is performed if focal firing from the SVC can be demonstrated. A subset of operators empirically isolates the SVC. **D:** Representative sites for ablation when targeting rotational activity or CFAEs are targeted. Modified with permission from Calkins et al. Heart Rhythm 2012; 9:632–696.e21.[2]

## 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation

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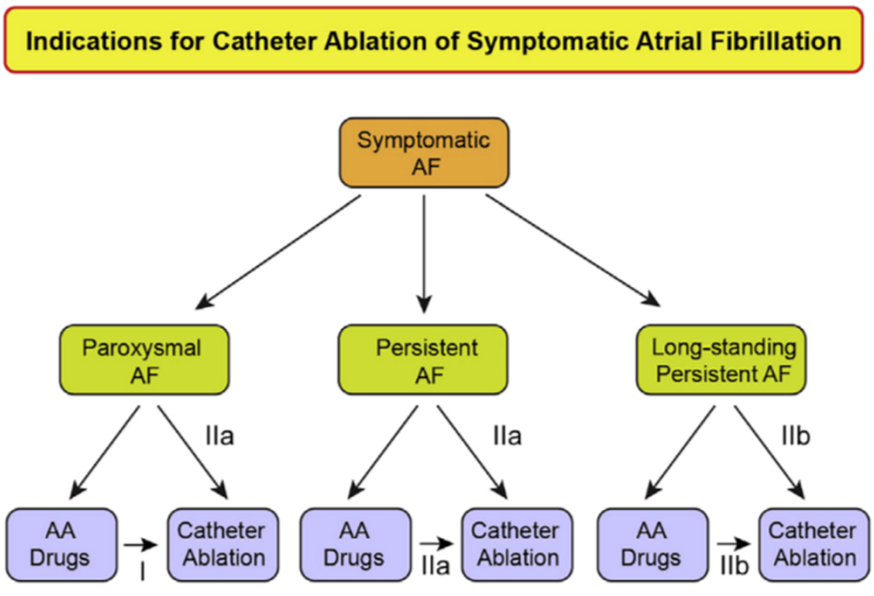
## Paroxysmal AF and ablation

| Trial | Year | Type | N | AF type | Ablation strategy | Initial time frame | Effectiveness endpoint | Ablation success | Drug/ Control success | P value for success | Ablation complications | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| First-Line Therapy Trials | | | | | | | | | | | | |
| JAMA 2005; 293: 2634-2640 (RAAFT)[177] | 2005 | Randomized to drug, multicenter | 70 | Paroxysmal (N=67), persistent (N= 3) | PVI | 12 months | Freedom from detectable AF | 84% | 37% | <0.01 | 9% | 11% |
| NEJM 2012; 367:1587-1595 (MANTRA-PAF)[178] | 2012 | Randomized to drug, multicenter | 294 | Paroxysmal AF | PVI, roof line, optional mitral and tricuspid line | 24 months | Cumulative AF burden | 13% AF burden | 19% AF burden | NS | 17% | 15% |
| JAMA 2014; 311: 692-700 (RAAFT-2)[179] | 2014 | Randomized to drug multicenter | 127 | Paroxysmal AF | PVI plus optional non-PVI targets | 24 months | Freedom from detectable AF, flutter, tachycardia | 45% | 28% | 0.02 | 9% | 4.9% |
| Other Paroxysmal AF Ablation Trials | | | | | | | | | | | | |
| JACC 2006; 48: 2340-2347 (APAF)[1027] | 2006 | Randomized to drug single center | 198 | Paroxysmal AF | PVI, mitral line and tricuspid line | 12 months | Freedom from detectable AF, flutter, tachycardia | 86% | 22% | <0.001 | 1% | 23% |
| Circulation 2008; 118: 2498-2505 (A4)[181] | 2008 | Randomized to drug | 112 | Paroxysmal | PVI (optional LA lines, CTI, focal) | 12 months | Freedom from AF | 89% | 23% | <0.0001 | 5.7% | 1.7% |
| NEJM 2016; 374: 2235-2245 (FIRE AND ICE)[489] | 2016 | Randomized RF vs Cryo, multicenter | 762 | Paroxysmal AF | PVI | 12 months | Freedom from detectable AF, flutter, tachycardia | 64.1% (RF) | 65.4% (cryo) | NS | 12.8% | 10.2% |

# Persistent AF and ablation

| Trial | Year | Type | N | AF type | Ablation strategy | Initial time frame | Effectiveness endpoint | Ablation success | Drug/ Control success | *P* value for success | Ablation complications |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Other Persistent AF Ablation Trials | | | | | | | | | | | |
| NEJM 2006; 354: 934-941[1026] | 2006 | Randomized to RF ablation or to CV and short term amio | 146 | Persistent | PVI, roof, mitral line | 12 months | No AF or flutter month 12 | 74% | 58% | 0.05 | 1.3% |
| EHJ 2014; 35: 501-507 (SARA)[1030] | 2014 | Randomized to drug (2:1 ablation to drug), multicenter | 146 | Persistent | PVI (optional LA lines, CFAEs) | 12 months | Freedom from AF/flutter lasting >24h | 70% | 44% | 0.002 | 6.1% |
| NEJM 2015; 372: 1812-1822[245] | 2015 | Randomized ablation strategies, multicenter | 589 | Persistent | PVI alone versus PVI & CFAEs or PVI & lines | 18 months | Freedom from afib with or without drugs | 59% (PVI alone) | 49% & 46% | NS | 6% |
| Other Mixed Paroxysmal and Persistent AF Ablation Trials | | | | | | | | | | | |
| J Med Assoc Thai 2003; 86 (Suppl 1): S8-S16[1025] | 2003 | Randomized to RF ablation or amiodarone | 30 | Paroxysmal (70%), Persistent (30%) | PVI, mitral line, CTI, SVC to IVC | 12 months | Freedom from AF | 79% | 40% | 0.018 | 6.70% |
| EHJ 2006; 27: 216-221[1028] | 2006 | Randomized to RF ablation or drug, multicenter | 137 | Paroxysmal (67%), Persistent (33%) | PVI, mitral line, CTI | 12 months | Freedom from AF, flutter, tachycardia | 66% | 9% | <0.001 | 4.40% |
| JCVEP 2009, 20: 22-28[1029] | 2009 | Randomized to RF ablation or drug, multicenter | 70 | Paroxysmal (41%), Persistent (59%) & type 2 DM | PVI, CTI, optional mitral line and roof line | 12 months | Freedom from AF and atypical atrial flutter | 80% | 43% | 0.001 | 2.90% |



**Indications for catheter ablation of atrial fibrillation**

| | | | |
|---|---|---|---|
| **A. Indications for catheter ablation of atrial fibrillation** | | | |
| Symptomatic AF refractory or intolerant to at least one Class I or III antiarrhythmic medication | Paroxysmal: Catheter ablation is recommended. | I | A |
| | Persistent: Catheter ablation is reasonable. | IIa | B-NR |
| | Long-standing persistent: Catheter ablation may be considered. | IIb | C-LD |
| Symptomatic AF prior to initiation of antiarrhythmic therapy with a Class I or III antiarrhythmic medication | Paroxysmal: Catheter ablation is reasonable. | IIa | B-R |
| | Persistent: Catheter ablation is reasonable. | IIa | C-EO |
| | Long-standing persistent: Catheter ablation may be considered. | IIb | C-EO |

# Rate Control Strategy

## RACE II: Lenient versus Strict Rate Control in Patients with Atrial Fibrillation

Multicenter, open-label, parallel-group, randomized controlled noninferiority trial

Objective: To compare rate control of HR <110 bpm versus strict rate control of HR <80 bpm in preventing cardiovascular events in patients with permanent AF

**614** patients Age ≤80 years with permanent AF for up to 12 months were randomized to


### Primary Outcomes

| 12.9% | Composite of CV mortality, CHF, stroke and major CV and arrhythmia events (HR 0.84; 95% CI 0.58-1.21; P<0.001 for non-inferiority) | 14.9% |
|---|---|---|

### Secondary Outcomes

| | | |
|---|---|---|
| 2.9% | CV mortality (HR 0.79; 0.38-1.65) | 3.9% |
| 5.6% | All-cause mortality (HR 0.91; 90% CI 0.52-1.59) | 6.6% |

**TABLE 10** Common Medication Dosage for Rate Control of AF

| | Intravenous Administration | Usual Oral Maintenance Dose |
|---|---|---|
| **Beta blockers** | | |
| Metoprolol tartrate | 2.5-5.0 mg IV bolus over 2 min; up to 3 doses | 25-100 mg BID |
| Metoprolol XL (succinate) | N/A | 50-400 mg QD |
| Atenolol | N/A | 25-100 mg QD |
| Esmolol | 500 mcg/kg IV bolus over 1 min, then 50-300 mcg/kg/min IV | N/A |
| Propranolol | 1 mg IV over 1 min, up to 3 doses at 2-min intervals | 10-40 mg TID or QID |
| Nadolol | N/A | 10-240 mg QD |
| Carvedilol | N/A | 3.125-25 mg BID |
| Bisoprolol | N/A | 2.5-10 mg QD |
| **Nondihydropyridine calcium channel antagonists** | | |
| Verapamil | 0.075–0.15 mg/kg IV bolus over 2 min; may give an additional 10.0 mg after 30 min if no response, then 0.005 mg/kg/min infusion | 180-480 mg QD (ER) |
| Diltiazem | 0.25 mg/kg IV bolus over 2 min, then 5–15 mg/h | 120-360 mg QD (ER) |
| **Digitalis glycosides** | | |
| Digoxin | 0.25 mg IV with repeat dosing to a maximum of 1.5 mg over 24 h | 0.125-0.25 mg QD |
| **Others** | | |
| Amiodarone* | 300 mg IV over 1 h, then 10-50 mg/h over 24 h | 100-200 mg QD |

*Multiple dosing schemes exist for the use of amiodarone.

AF indicates atrial fibrillation; BID, twice daily; ER, extended release; IV, intravenous; N/A, not applicable; QD, once daily; QID, 4 times a day; and TID, 3 times a day.

**B. Indications for catheter atrial fibrillation ablation in populations of patients not well represented in clinical trials**

| | | | | |
|---|---|---|---|---|
| Congestive heart failure | It is reasonable to use similar indications for AF ablation in selected patients with heart failure as in patients without heart failure. | IIa | B-R | 233–237,384,386–395,1042 |
| Older patients (>75 years of age) | It is reasonable to use similar indications for AF ablation in selected older patients with AF as in younger patients. | IIa | B-NR | 396–398,401–404 |
| Hypertrophic cardiomyopathy | It is reasonable to use similar indications for AF ablation in selected patients with HCM as in patients without HCM. | IIa | B-NR | 385,1043,1044 |
| Young patients (<45 years of age) | It is reasonable to use similar indications for AF ablation in young patients with AF (<45 years of age) as in older patients. | IIa | B-NR | 405,1045 |
| Tachy-brady syndrome | It is reasonable to offer AF ablation as an alternative to pacemaker implantation in patients with tachy-brady syndrome. | IIa | B-NR | 381–383 |
| Athletes with AF | It is reasonable to offer high-level athletes AF as first-line therapy due to the negative effects of medications on athletic performance. | IIa | C-LD | 370–372 |
| Asymptomatic AF** | Paroxysmal: Catheter ablation may be considered in select patients.** | IIb | C-EO | 416,418 |
| | Persistent: Catheter ablation may be considered in select patients. | IIb | C-EO | 417 |

# Background
# Incidence of CHF in atrial fibrillation population

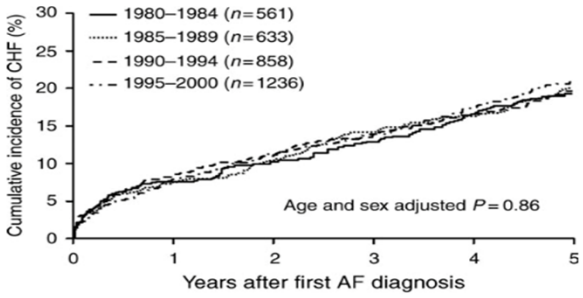



**Figure 2** Time trends for cumulative incidence of first CHF following first AF.

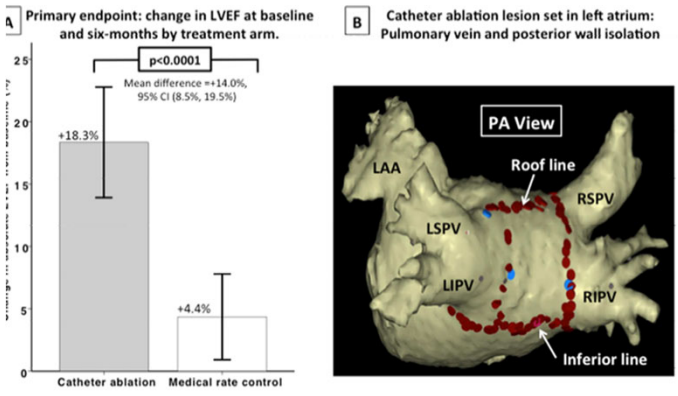
One in four of the AF patients in this study developed CHF during follow-up and that the lifetime risk of AF in the Framingham Heart cohort was also one in four

# Article

**Catheter Ablation Versus Medical Rate control in Atrial Fibrillation and Systolic Dysfunction (CAMERA-MRI)**

TheBakerHeart&DiabetesInstitute,Melbourne,Australia; TheAlfredHospital, Melbourne, Australia; Monash Heart, Melbourne, Australia; Royal Melbourne Hospital, Melbourne, Australia; University of Melbourne, Melbourne, Australia; Monash University, Melbourne, Australia.

# Outcome

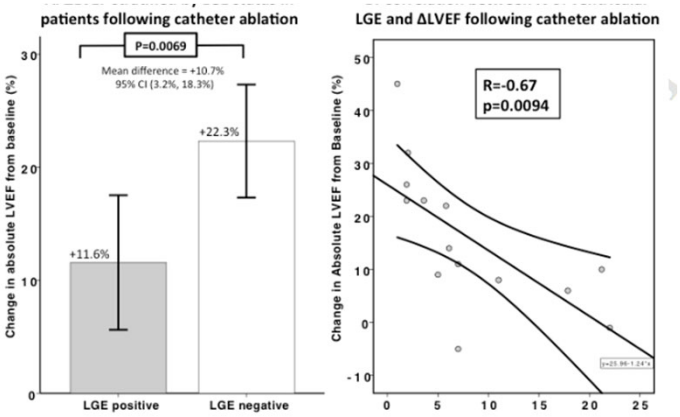


| Primary and secondary endpoints | Catheter ablation (n=33) | | Medical rate control (n=33) | | Comparison between treatment arms | |
|---|---|---|---|---|---|---|
| | Baseline | 6 months | Baseline | 6 months | Mean Difference | P value* |
| ***Primary endpoint*** | | | | | | |
| LVEF (MRI) (%) | 31.8 ± 9.4 | 50.1 ± 11[§] | 34.1 ± 7.8 | 38.5 ± 8.7[‡] | +14.0 (8.5, 19.5) | **<0.0001** |
| ***Secondary endpoints*** | | | | | | |
| LVEF (echocardiography) (%) | 35.0 ± 9.8 | 52.7 ± 11.9[§] | 34.8 ± 43.7 | 43.7 ± 12.7[‡] | +7.5 (+1.6, +13.5) | **0.0137** |
| LV end systolic volume (ml/m$^2$) | 79.5 ± 33.3 | 55.3 ± 30.5[§] | 76.3 ± 27.2 | 68.2 ± 26.3[†] | -16.1 (-27.7, -4.5) | **0.0075** |
| LV end diastolic volume (ml/m$^2$) | 114 ± 40 | 106 ± 33[†] | 113 ± 32 | 109 ± 39 | -2.1 (-14.5, +10.4) | 0.74 |
| LA volume (ml/m$^2$) | 54.4 ± 16.1 | 43.4 ± 13.3[§] | 53.9 ± 18.9 | 55.6 ± 14.6 | -13.4 (-20.4, -6.5) | **0.0003** |
| LV stroke volume (ml/m$^2$) | 34.9 ± 12.7 | 50.5 ± 10.1[§] | 38.6 ± 12.5 | 40.5 ± 14.8 | -16.1 (-27.7, -4.45) | **<0.0001** |
| Average NYHA Class | 2.55 ± 0.62 | 1.33 ± 0.48[§] | 2.45 ± 0.56 | 2.06 ± 0.50[‡] | -0.82 (-1.13, -0.51) | **<0.0001** |
| BNP (log[ng/L]) | 2.34 ± 0.38 | 1.84 ± 0.37[§] | 2.27± 0.43 | 2.14 ± 0.56 | -0.38 (-0.65, -0.11) | **0.0063** |
| BNP (ng/L)[ll] | 266 ± 210 | 98 ± 77 | 256 ± 208 | 247 ± 197 | | **0.0131** |
| 6 minute walk test distance (m) | 491 ± 147 | 546 ± 82[†] | 489 ± 132 | 518 ± 119[†] | +27 (-28, +79) | 0.34 |
| SF-36 Physical component scores | 41.6 ± 11.6 | 48.5 ± 8.2[§] | 38.8 ± 10.4 | 44.6 ± 11.2[‡] | 1.3 (-3.9, +6.5) | 0.62 |
| SF-36 Mental component scores | 49.1 ± 10.6 | 53.3 ± 7.7[‡] | 50.3 ± 11.2 | 52.9 ± 8.9 | 1.6 (-3.1, +6.3) | 0.49 |

# Results

| Comparison within each group (LGE positive vs LGE negative) | | | | |
|---|---|---|---|---|
| **Patients undergoing catheter ablation (n=36)** | **LGE positive (n=14)** | **LGE negative (n=22)** | **Mean difference** | **P value** |
| Baseline LVEF | 32.1 ± 8.7% | 31.7 ± 9.4% | 0.4% (-5.9,%, 6.8%) | 0.89 |
| 6 month LVEF | 43.7 ± 11.2% | 54.0 ± 8.5% | +10.3% (3.3%, 17.0%) | **0.0036** |
| Change in LVEF from baseline | +11.6 ± 10.3% | +22.3 ± 11.3% | +10.7% (3.2%, 18.3%) | **0.0069** |
| LVEF ≥50% at 6 months (%) | 29% (4) | 73% (16) | 44.2% (10.7%, 66.1%) | **0.0093** |
| Improvement in LVEF by ≥15% | 29% (4) | 82% (18) | 53.2% (20.2%, 73.3%) | **0.0014** |
| **Patients undergoing medical rate control (n=30)** | **LGE positive (n=10)** | **LGE negative (n=20)** | **Mean difference** | **P value** |
| Baseline LVEF | 29.0 ± 7.8% | 36.8 ± 7.0 % | 7.7% (2.1%, 13.3%) | **0.0089** |
| 6 month LVEF | 33.8 ± 7.3% | 39.3 ± 9.8% | 5.5% (-1.0%, 12.0%) | 0.09 |
| Change in LVEF from baseline | +4.8 ± 8.5% | +2.9 ± 9.8% | 2.3% (-5.1%, 9.7%) | 0.54 |
| LVEF ≥50% at 6 months (%) | 0% (0) | 10% (2) | 10% (-25%, 33%) | 0.30 |
| Improvement in LVEF by ≥15% | 0% (0) | 10% (2) | 10% (-25%, 33%) | 0.30 |
| **Comparison between treatment arms (catheter ablation and medical rate control)** | | | | |
| **LGE positive** | **Mean difference** | **95% CI** | **P value** | |
| Change in LVEF from baseline | +6.8% | -1.5%, 15.0% | 0.10 | |
| LVEF ≥50% at 6 months (%) | 29% | -3.9%, 54.7% | 0.06 | |
| **LGE negative** | **Mean difference** | **95% CI** | **P value** | |
| Change in LVEF from baseline | +19.8% | 13.1%, 26.4% | **<0.0001** | |
| LVEF ≥50% at 6 months (%) | 63% | 30.0%, 80.4% | **<0.0001** | |

# Results




# Focused Update of the AHA/ACC/HRS Atrial Fibrillatio Guideline Jan 2019

- **NOAC recommended** over warfarin except in moderate mitral stenosis and prosthetic valve patient( Class I, LOE A)
- **Renal and hepatic function** need to be tested before initiating NOAC treatment and yearly thereafter ( Class I, LOE B)
- In AF patients with a $CHA_2DS_2$-VASc score ≥2 in men or ≥3 in women and a creatinine clearance <15 ml/min or who are on dialysis, it is reasonable to use warfarin or apixaban for oral anticoagulation (COR IIa, LOE B-NR).
- **Percutaneous left atrial appendage** occlusion may be considered for at-risk AF patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation (COR IIb, LOE B-NR).

# Focused Update of the AHA/ACC/HRS Atrial Fibrillatio Guideline Jan 2019

- AF catheter **ablation may be reasonable in symptomatic patients with heart failure** and a reduced ejection fraction to reduce mortality and heart failure hospitalizations (COR IIb, B-R).
- In at-risk AF patients who have undergone coronary artery stenting, **double therapy with clopidogrel and low-dose rivaroxaban (15 mg daily) or dabigatran (150 twice daily) is reasonable** to reduce the risk of bleeding as compared to triple therapy (COR IIa, B-R).
- **Weight loss** combined with risk factor modification is recommended for overweight and obese patients with AF (COR I, LOE B-R).

Thank you