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Atrial Fibrillation In Heart Failure

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Epidemiology

- HF and AF, despite recognition as being recognized and major causes of morbidity, mortality, and healthcare costs continue to rise in prevalence
  - Aging population
  - Obesity rates
  - Increased detection of AF thanks to new technologies
  - Improved survival rates in HF with optimal therapy

- By 2030 it is projected there will be 12 million people in the US with AF and 8 million with HF[1]

- The development of AF in HF patients is a negative prognostic factor[2]
  - Worse quality of life
  - Increased mortality
  - This is true regardless of ejection fraction

1 Circulation. 2015;131:e29–e322
2 Circ Res. 2013 Aug 30;113(6):646-59

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Epidemiology

- AF reduces cardiovascular performance in multiple ways[1]
  - Loss of AV synchrony
  - Reduced filling time in tachycardia
  - Reduced ejection time in tachycardia
  - Greater prevalence of right ventricular dysfunction[2]

- The prevalence of AF in patients with HF increases as the disease worsens[3]
  - In patients with NYHA I-II the prevalence is typically ~5%
  - NYHA III symptoms show around 26% prevalence
  - NYHA IV show up to 50% prevalence

1 J Clin Invest. 1968 Oct;47(10):2411-21.
2 Eur Heart J. 2014 Dec 21;35(48):3452-62.
3 Am J Cardiol.2003 Mar 20;91(6A):2D-8D

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Epidemiology

- The association of AF with age also means that it more common in HFpEF compared to HFrEF, as HFpEF patients are typically older than HFrEF patients and have more comorbidities[1]
  - It is twice as common in HFpEF compared to HFrEF
  - AF in HF patients results increased AF morbidity
  - It also worsens HF outcomes as well – All cause mortality, all cause readmission, HF mortality, HF readmissions

1 JACC Heart Fail. 2014 Feb;2(1):41-8

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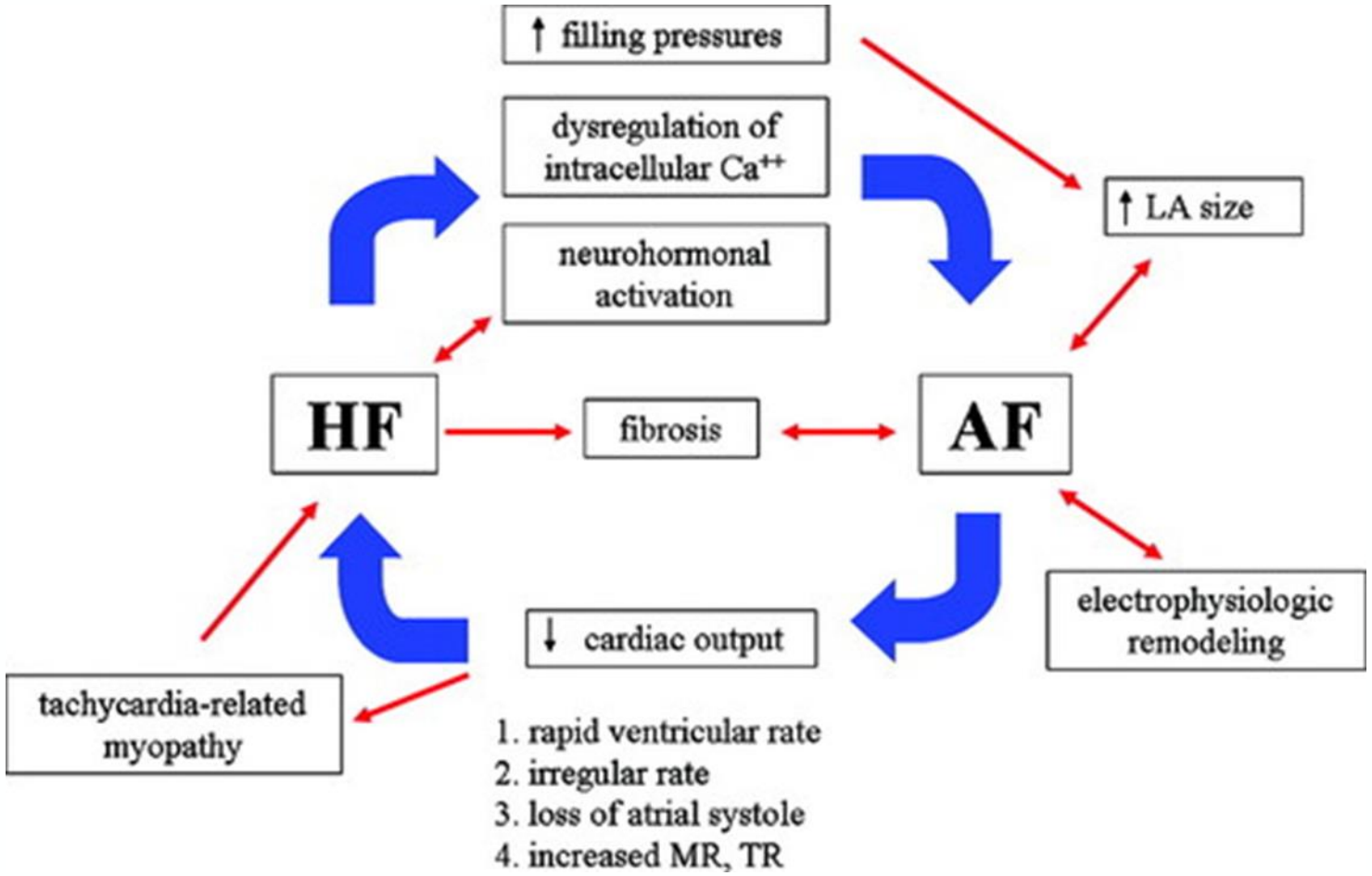
Cause or Consequence?



1 Circulation. 2009 May 12;119(18):2516-25.

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Cause or consequence?

- Atrial fibrosis[1]
  - Loss of reservoir, conduit, and booster functions with loss of atrial contraction
  - Increased wall stress, inflammatory cytokines, circulating neurohormonal factors
    - IL-6, TNF
  - This in turn increases atrial fibrosis resulting in a positive feedback loop

- Electrical abnormalities[2]
  - Increased atrial effective refractory period (esp. in the lateral RA and distal CS)
  - Slowing of impulse conductions in areas of fibrosis
  - Resting membrane potential (Vmax) more depolarized
  - Plateau phase amplitude is smaller in atrial cells in AF

1 Circulation. 2009 May 12;119(18):2516-25.
2 Circulation. 2003 Sep 23;108(12):1461-8.

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Mechanics

- Hemodynamic effects
  - Loss of atrial kick (reservoir, conduit, and booster functions)
  - Reduction of cardiac output – by as much as 25% with diastolic dysfunction[1]

- Effects of tachycardia[1]
  - Altered calcium handling
  - Increased sympathetic drive
  - Worsened ventricular function – can lead to tachycardia-mediated cardiomyopathy

1 J Am Coll Cardiol. 2015 Oct 13;66(15):1714-28

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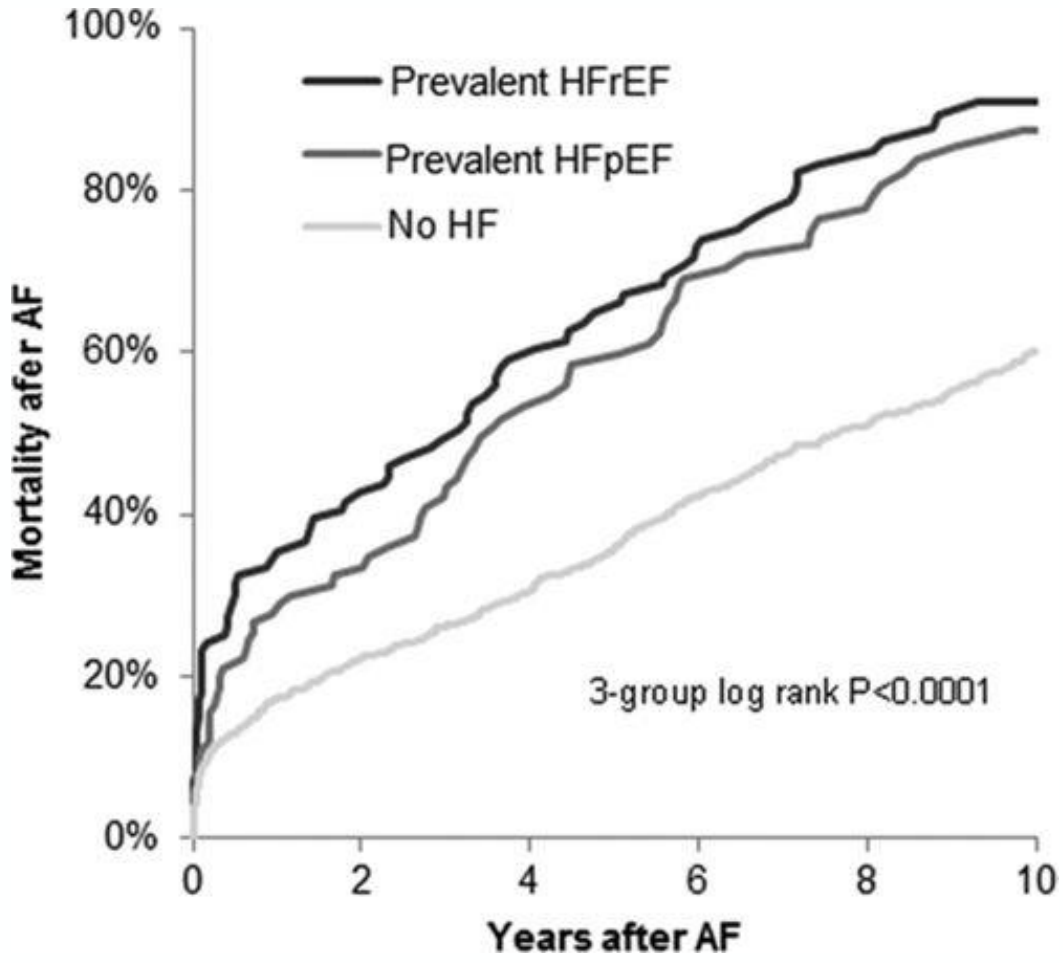
Cause or consequence?

- Realistically the answer is both
  - This creates a positive feedback loop
    - The appearance of both causes the progression of both
    - Treating AF when it appears in the HF population is something that should not only improves AF outcomes but HF outcomes as well
  - So how does this affect treatment?
    - We have to look at individual HF populations
      - HFrEF vs HFpEF



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HF_REF

- Guideline-directed medical therapy
  - Evidence-based beta-blockers
  - ACE inhibitors/Angiotensin receptor blockers/ARNI
  - Aldosterone blockers
  - Other therapies

- There no specific medical therapy guidelines that specifically target patients with both conditions
  - What does the data say?

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Guideline directed medical therapy

- Beta-blockers
  - Mixed data – what???
  - Beta-Blockers Heart Failure Collaborative Group[1] showed in a meta-analysis no improvement in al-cause mortality
  - ACF-HF sub-study data did show a mortality benefit (though no reduction in hospitalization)[2]
  - Other studies also suggest AF reduces the efficacy of evidence-based B-blockers[3]
  - Registry data from Sweden does show a mortality benefit[4]

1 Lancet. 2014 Dec 20;384(9961):2235-43
2 JACC Heart Fail. 2017 Feb;5(2):99-106
3 JACC Heart Fail. 2013 Feb;1(1):21-8
4 Circ Heart Fail. 2015 Sep;8(5):871-9

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Guideline directed medical therapy

- The studies all had major shortcomings
  - The Beta-Blockers Heart Failure Collaborative Group classified people based on a single EKG
  - The ACF-HF study was not designed to evaluate B-blockers – B-blockers were not randomized and the study was reliant on propensity matching – there may be an unmatched confounder

- No comparative outcome data with evidence-based beta-blockers
  - Pharmacodynamic data suggests metoprolol succinate may be more beneficial than carvedilol as it is better at suppressing adrenergic drive[1]

1 J Cardiovasc Pharmacol Ther. 2008 Mar;13(1):51-7

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ACE inhibitors and ARBs

- Affecting the incidence of AF
  - ACE inhibitors and ARBs do appear to reduce the incidence of new AF in HFrEF[1]
    - Mechanistically this makes sense – less neurohormonal activation -> less fibrosis
    - This affects overall atrial remodeling
      - Electrical
      - Structural
      - Reduction in inflammation

1 J Am Coll Cardiol. 2005 Jun 7;45(11):1832-9

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ACE inhibitors and ARBs

- Data has been primarily focused on incidence of AF in the HF
  - Primarily derived from post-hoc analysis of older RCTs
    - SOLVD (enalapril)
    - TRACE (tradolipril)
    - Val-HeFT (valsartan)
    - LIFE (losartan)
  - Some trials did not show this benefit
    - CHARM (candesartan)
    - GISSI-3 (lisinopril)

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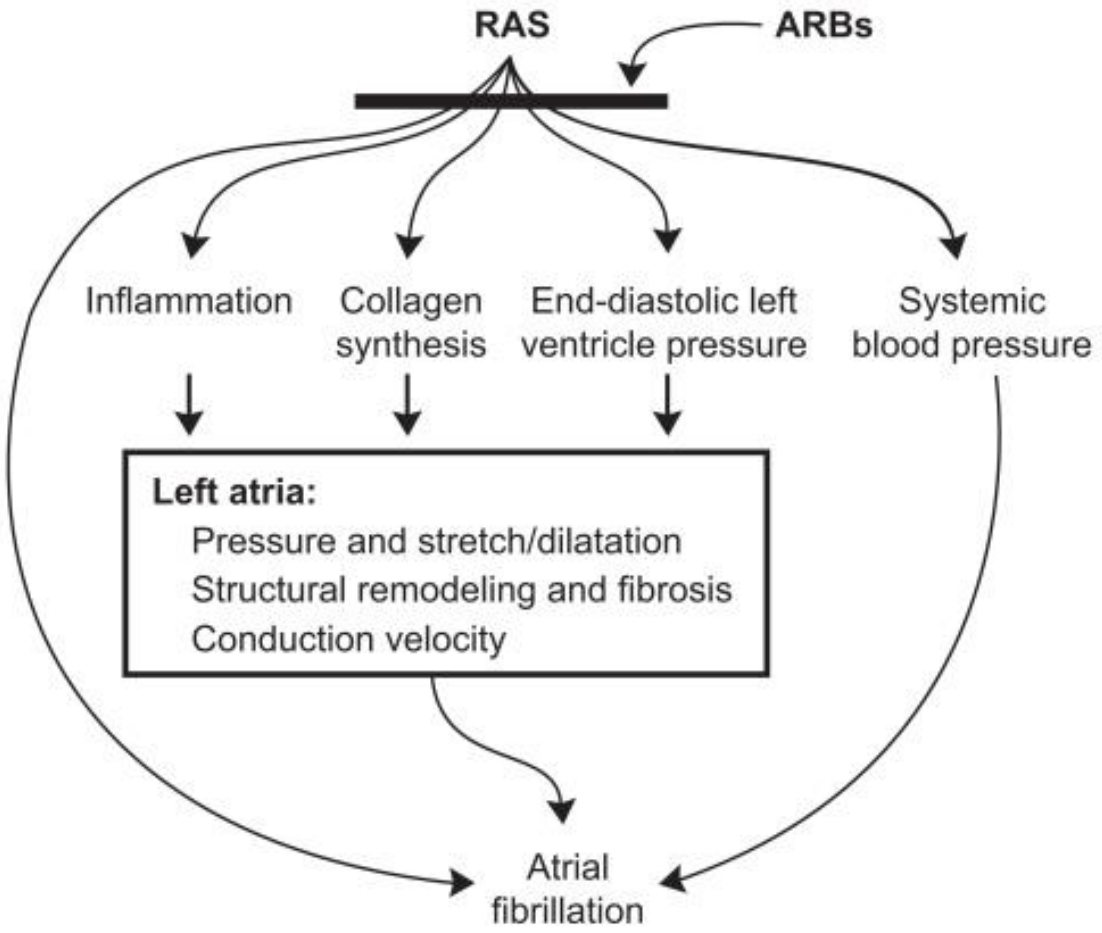
ACE inhibitors and ARBs



Possible preventive mechanisms of angiotensin II receptor blockers in atrial fibrillation

- The previous studies did not show significant mortality subgroup heterogeneity in their benefit for HF patients
- However, these analyses are not really powered to evaluate hard outcomes in patients with AF and HF

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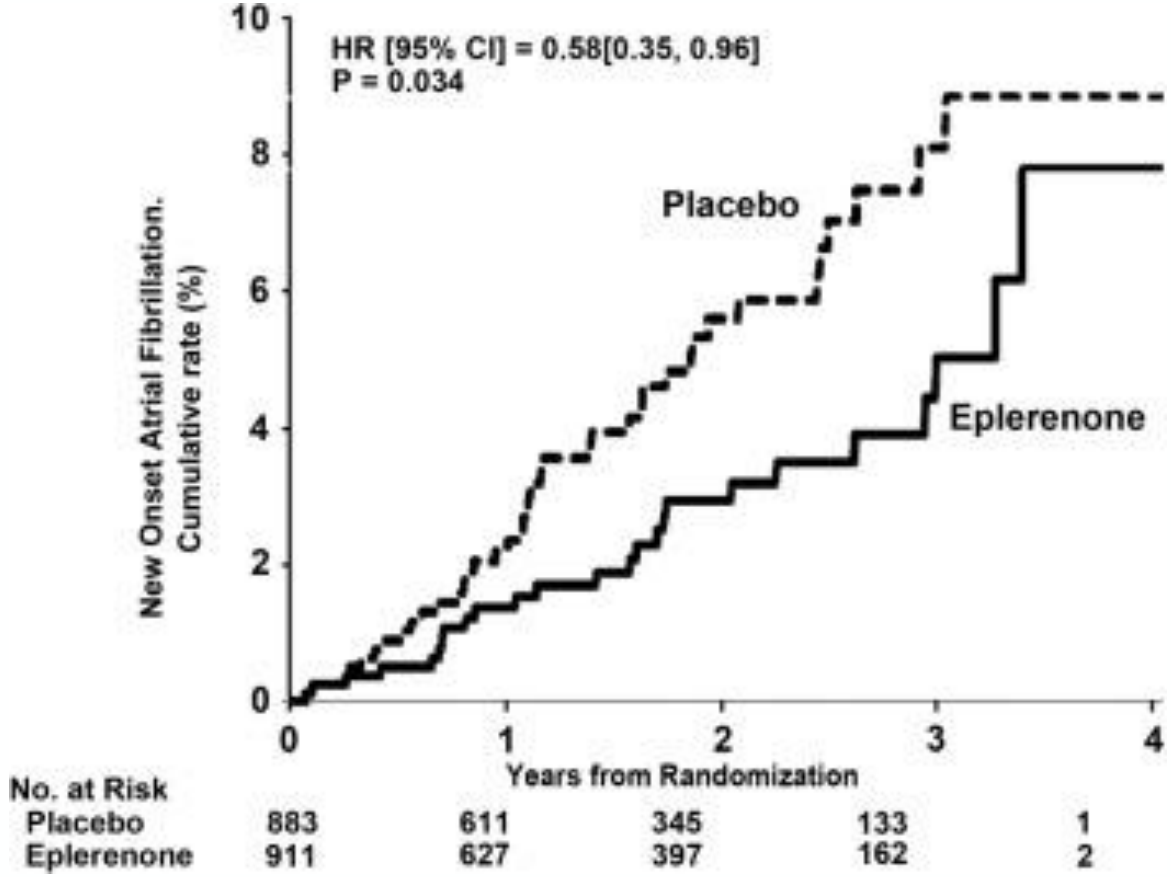
Aldosterone blockade

- May reduce the onset of AF as well
  - EMPHASIS-HF showed reduction in new onset AF with eplerenone[1]
    - The HF benefit was maintained regardless of baseline AF
  - SPIR-AF also showed a benefit for spironolactone[2]



1 J Am Coll Cardiol. 2012 May 1;59(18):1598-603.
2 Am J Cardiol. 2010 Dec 1;106(11):1609-14

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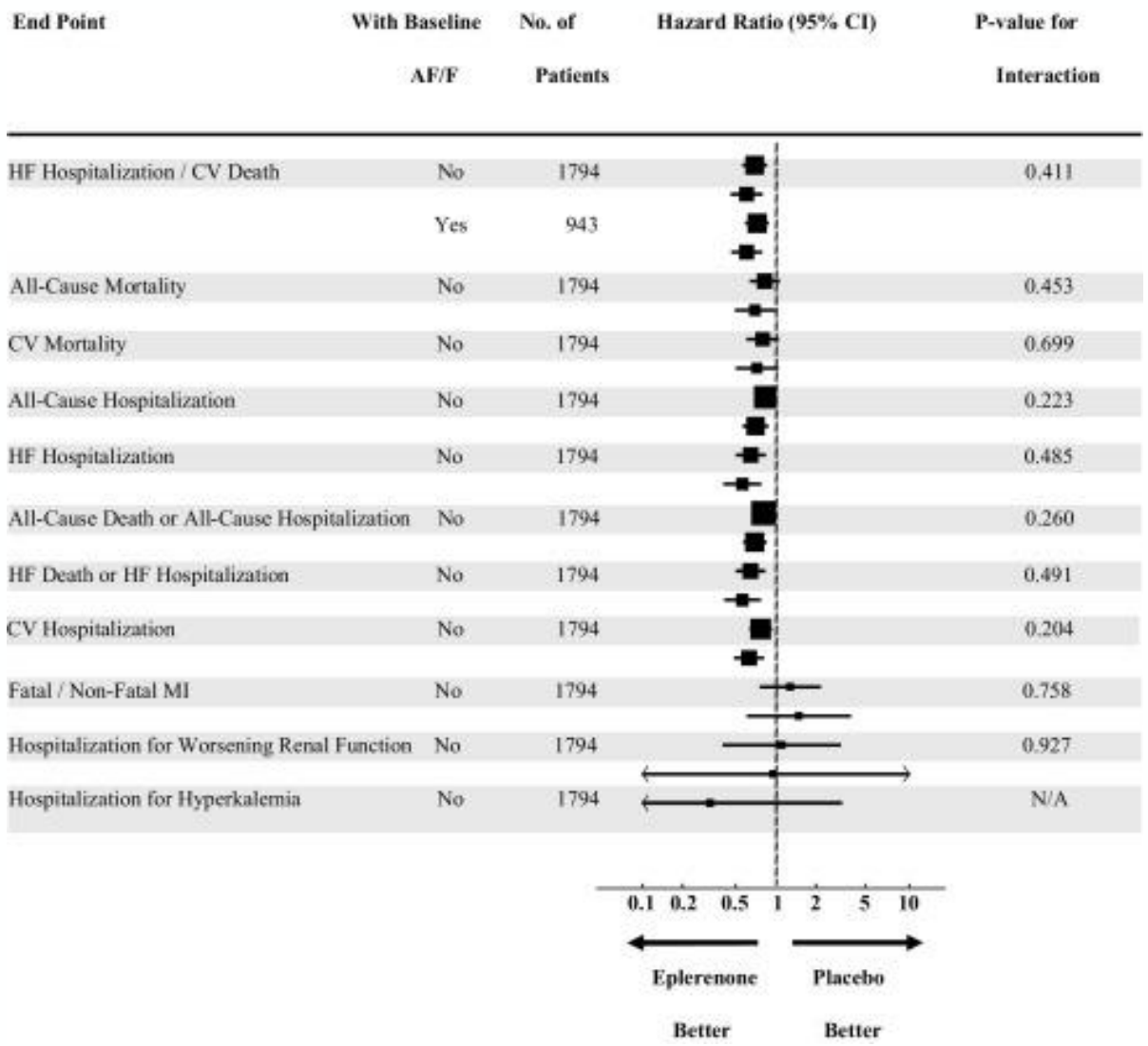
Aldosterone blockade



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HF_pEF

- Guideline directed medical therapy has not proven to be effective in affecting outcomes
- Treatment is geared toward volume and BP control

- TOPCAT trial – no reduction in composite of CV death , cardiac arrest, or HF hospitalization
  - Reduction in HF hospitalizations?

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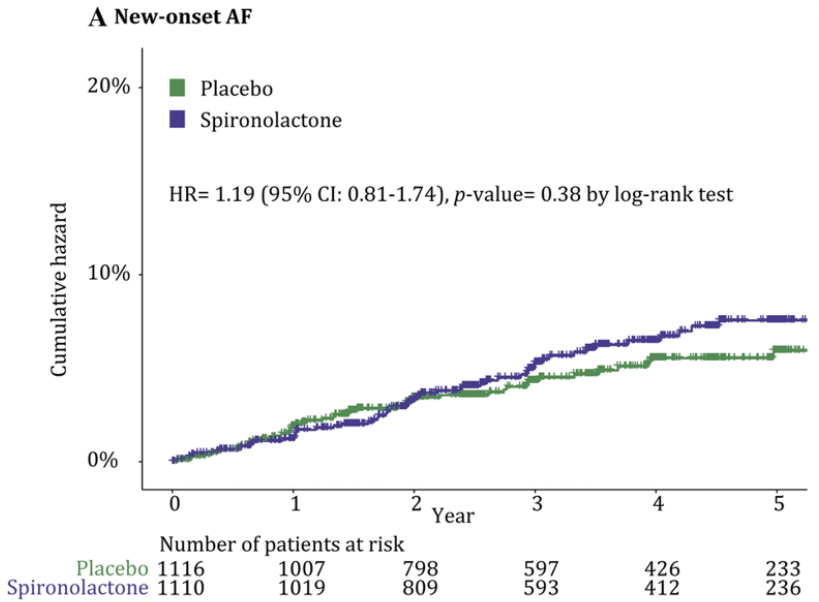
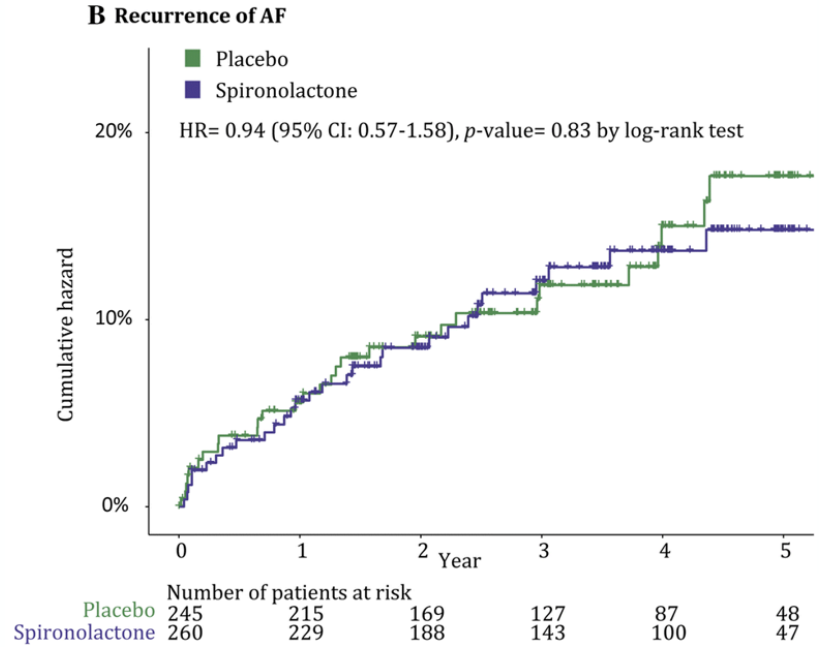
Preventing AF in HF_pEF

- ACE inhibitors may reduce new onset AF in HFpEF patients
  - Data from TOPCAT[1]
- Aldosterone blockade does not
  - Also data from TOPCAT[2,3]
  - Median follow-up was 3.1 years





1 J Am Coll Cardiol. 2019 Mar, 73 (9 Supplement 1) 519.
2 Am J Cardiovasc Drugs. 2019 Jun 19
3 JACC Heart Fail. 2018 Aug;6(8):689-697

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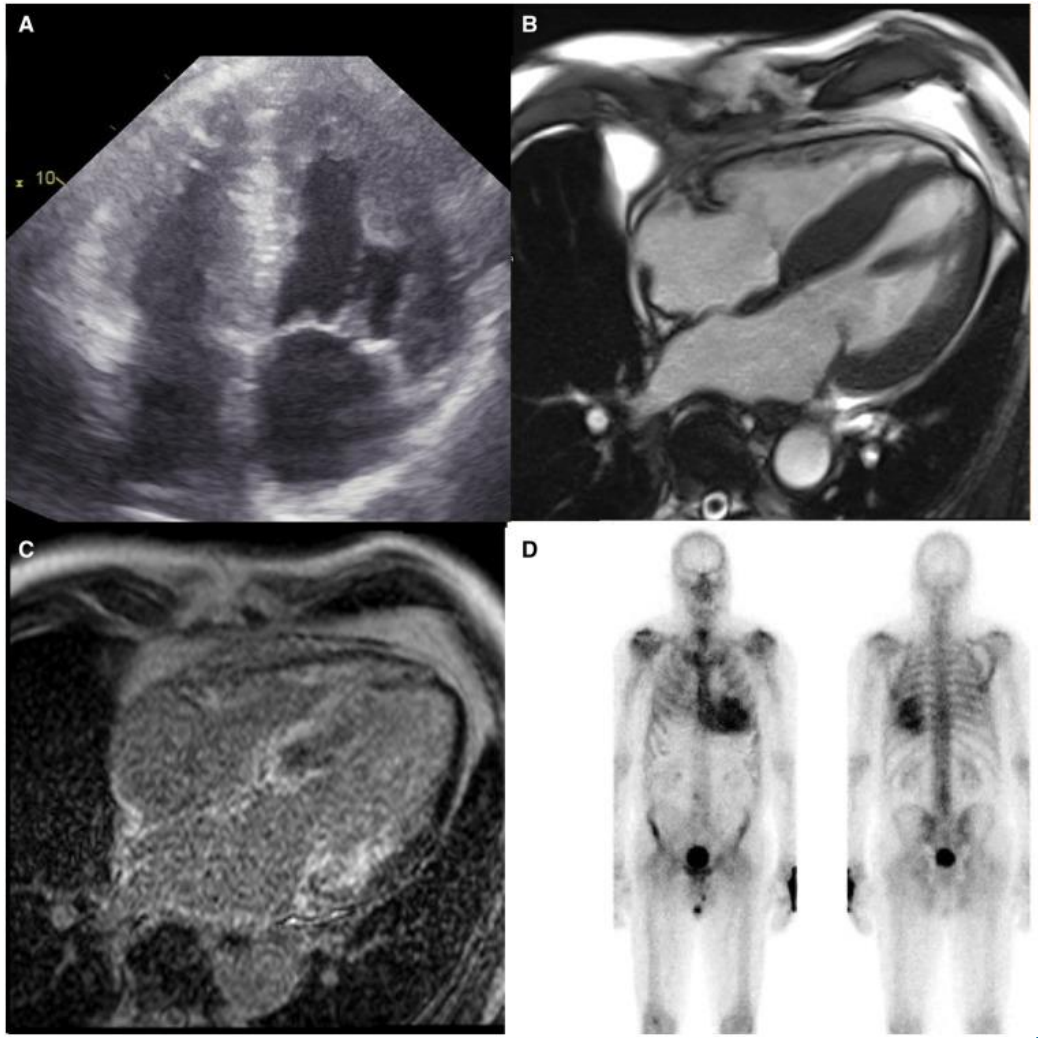
Amyloidosis, HFpEF, and AF?

- Increasing recognition of amyloidosis as a cause of HFpEF
- Amyloidosis is associated with AF as well
  - Isolated atrial amyloidosis is a well established cause of AF[1]
- New diagnostic modalities and treatments may help



1 Eur Heart J. 2019 Apr 21;40(16):1287-1293

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Treating the atrial fibrillation

- 2014 AHA/ACC/HRS
  - Rhythm and rate control are considered equally effective
  - Aggressive rhythm control is recommended only in highly symptomatic patients despite rate control
    - As a IIa
      - " For patients with AF and rapid ventricular response causing or suspected of causing tachycardia-induced cardiomyopathy, it is reasonable to achieve rate control by either AV nodal blockade or a rhythm-control strategy"
      - " For patients with chronic HF who remain symptomatic from AF despite a rate-control strategy, it is reasonable to use a rhythm-control strategy."
    - As a IIb
      - "Oral amiodarone may be considered when resting and exercise heart rate cannot be adequately controlled using a beta blocker (or a nondihydropyridine CCB in patients with HF*p*EF) or digoxin, alone or in combination."
      - "AV node ablation may be considered when the rate cannot be controlled and tachycardia-mediated cardiomyopathy is suspected."
  - PVI/AF ablation?
    - Not mentioned

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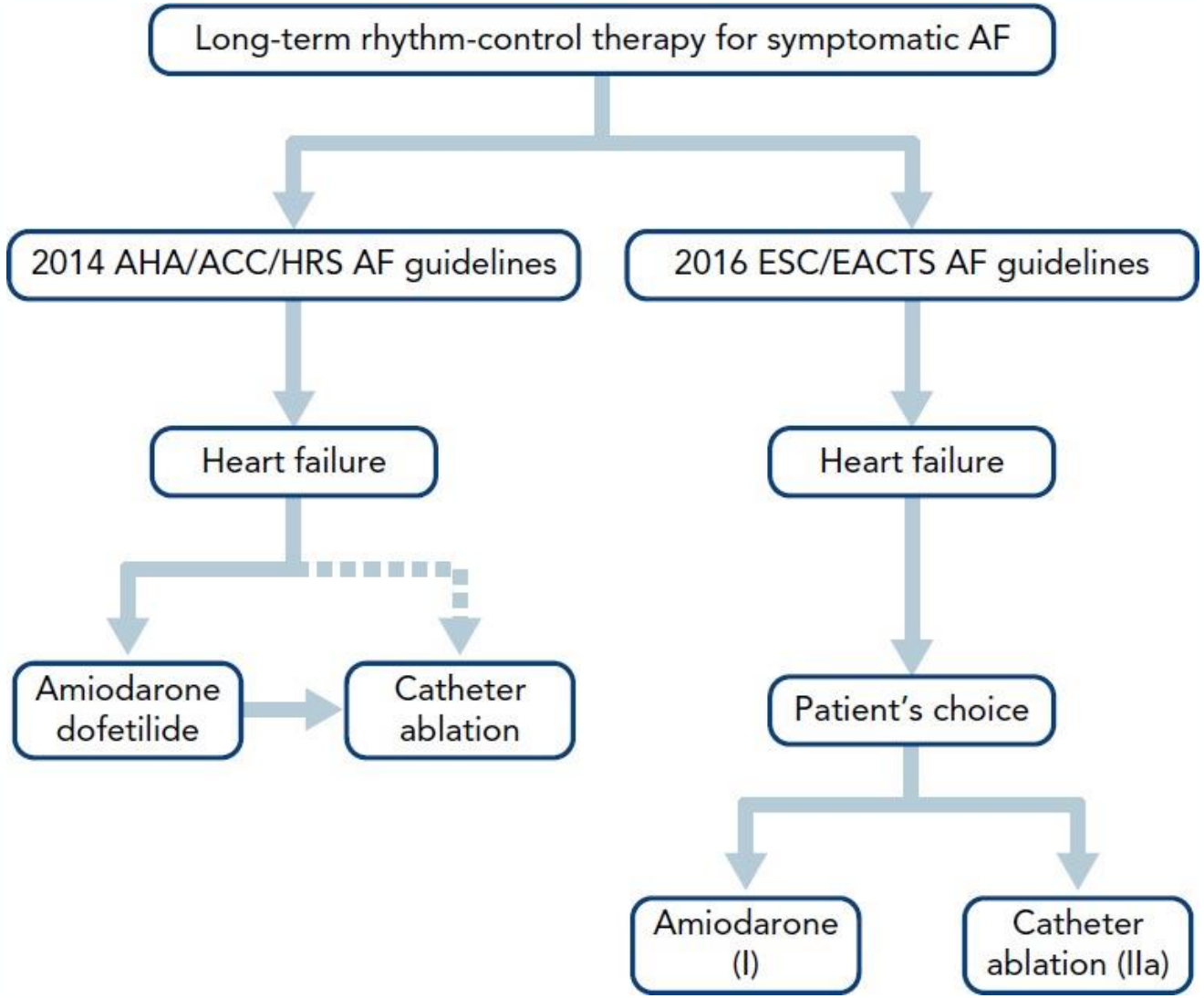
Treating the atrial fibrillation



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Treating the atrial fibrillation

- 2017 HRS/EHRA/ECAS/APHRS/SOLAECE (expert consensus statement on catheter and surgical ablation of atrial fibrillation)
  - As a IIa
    - "It is reasonable to use similar indications for AF ablation in selected patients with heart failure as in patients without heart failure."
    - This refers to a PVI ablation rather than an AV nodal ablation
  - On the basis of several smaller trials
    - PABA-HF[1]
    - Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomized controlled trial[2]
    - A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure[3]
    - CAMTAF[4]
  - No hard outcomes

1 N Engl J Med. 2008 Oct 23;359(17):1778-85
2 Heart. 2011 May;97(9):740-7
3 J Am Coll Cardiol. 2013 May 7;61(18):1894-903
4 Circ Arrhythm Electrophysiol. 2014 Feb;7(1):31-8

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Treating the atrial fibrillation

- Outcomes
  - PABA-HF Composite EF, 6 min walk, MLWHF score; freedom from AF (secondary) – at 6 months
  - Trial 2
    - Change in LVEF, sinus rhythm at 6 months (secondary) – at 6 months
  - Trial 3
    - Change in peak O_2 consumption
  - CAMTAF
    - Change in LVEF at 6 months, freedom from multiple AF procedures

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Treating the atrial fibrillation

- 2019 AHA/ACC/HRS focused update on the 2014 guideline
  - As a IIb
    - AF catheter ablation may be reasonable in selected patients with symptomatic AF and HF with reduced left ventricular (LV) ejection fraction (HFrEF) to potentially lower mortality rate and reduce hospitalization for HF
      - "New evidence, including data on improved mortality rate, have been published for AF catheter ablation compared with medical therapy in patients with HF"

- Associated trials
  - CASTLE-AF[1]
  - CAMERA-MRI[2]
  - CABANA[3]

N Engl J Med 2018; 378:417-427
J Am Coll Cardiol. 2017 Oct, 70 (16) 1949-1961
JAMA. 2019;321(13):1261-1274

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Ablation trials

CASTLE-AF

- Patients with HFrEF with paroxysmal or persistent AF
  - All had AICD or CRT-D
  - Patients did not respond to or could not take antiarrhythmic drugs
  - Randomized to receive ablation versus medical therapy (rate or rhythm control) in addition to GDMT

- Outcomes:
  - Reduced overall mortality
  - Reduced HF hospitalization
  - Improved LVEF
  - More time in NSR (per device interrogation)

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Ablation trials

CABANA

- Symptomatic AF patients (not pure HF population)
- Randomized to receive ablation vs medical therapy (rate or rhythm control)

- Outcomes:
  - No difference in primary outcomes: composite end point of death, disabling stroke, serious bleeding, or cardiac arrest
  - Low event rate, high cross-over rate – benefit noted with as treated analysis
  - Small benefit in secondary outcomes: better symptomatology, fewer hospitalizations
  - HF subgroup analysis did show mortality benefit
    - HF patients included HFrEF and HFpEF

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Conclusions

- Heart failure and atrial fibrillation are increasing in frequency and the development of atrial fibrillation worsens the HF prognosis

  - Treating AF aggressively can help improve HF outcomes in this population
    - Will likely improve the efficacy of guideline directed medical therapy
    - This can also help with HFpEF patients

  - This may potentiate the effects of GDMT

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Conclusions

- Ablation should be considered
- Amyloidosis identification and treatment may offer a new avenue for treatment
- More research is needed geared toward evaluating hard outcomes in patients with both of these conditions

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History of atrial fibrillation

- Described as far back as 1187 by Joseph Maimoinides – a Sephardic Jewish philosopher and physician (and personal doctor to Saladin)
  - Described differences in regularly irregular and irregularly irregular pulses
  - Described it as a problem with the constitution of the heart

- Jean Baptiste de Sénac noticed a relationship between a “rebellious rhythm” rheumatic heart disease in the 1749

- Described again by Stokes, Wenckebach, and MacKenzie in the late 1800’s
  - James MacKenzie famously published a monograph of jugular pulsations, which showed the lack a-waves in atrial fibrillation patients

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History of atrial fibrillation

- Einthoven produced the first EKG of atrial fibrillation in 1906
- Phillips and Levine in 1949 saw that many patients in atrial fibrillation had heart failure that improved when the rhythm regularized
- Lown performed the first cardioversion in 1962
  - The relationship between AF and stroke was noted by Hinton in 1977 and Wolf in 1978
  - Trials with warfarin began in 1989
  - First guidelines (that I found) mentioning warfarin and atrial fibrillation was in Stroke and Circulation– in 1994 for management of TIAs and CVAs

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