



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Ventricular Arrhythmias and Atrial Fibrillation in 2022

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Disclosures:

Consultant: Biosense-Webster, St. Jude Medical, Medtronic, Boston Scientific

Research Grants: St Jude Medical, Biosense-Webster, Boston Scientific, MC10, Pfizer, Boehringer-Ingelheim

Equity: EPD , NewPace Ltd.

June 10, 2022

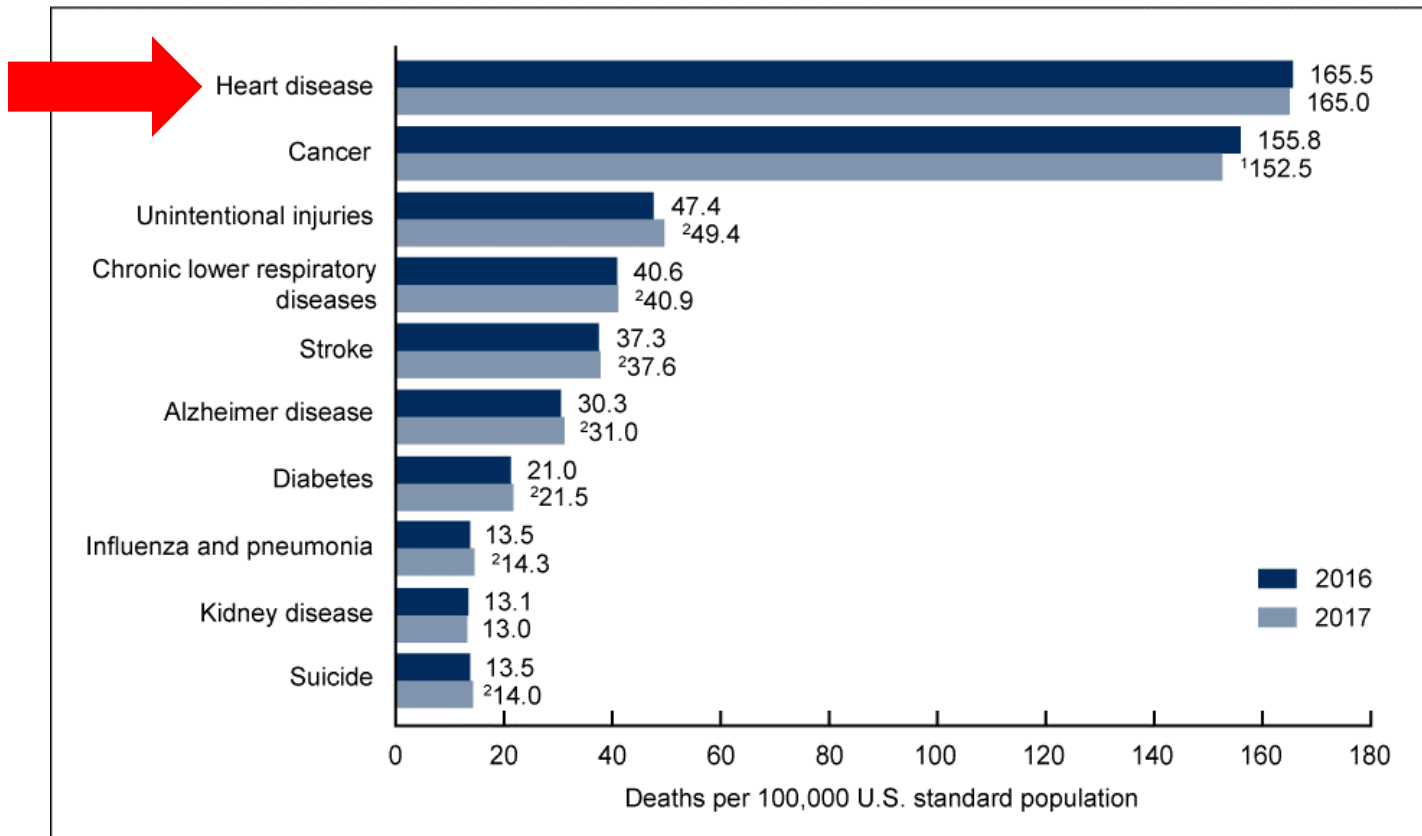


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Leading Causes of Death in the US in 2016-2017

Figure 4. Age-adjusted death rates for the 10 leading causes of death: United States, 2016 and 2017



¹Statistically significant decrease in age-adjusted death rate from 2016 to 2017 ($p < 0.05$).

²Statistically significant increase in age-adjusted death rate from 2016 to 2017 ($p < 0.05$).

NOTES: A total of 2,813,503 resident deaths were registered in the United States in 2017. The 10 leading causes accounted for 74.0% of all deaths in the United States in 2017. Causes of death are ranked according to number of deaths. Rankings for 2016 data are not shown. Data table for Figure 4 includes the number of deaths for leading causes. Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db328_tables-508.pdf#4.

SOURCE: NCHS, National Vital Statistics System, Mortality.

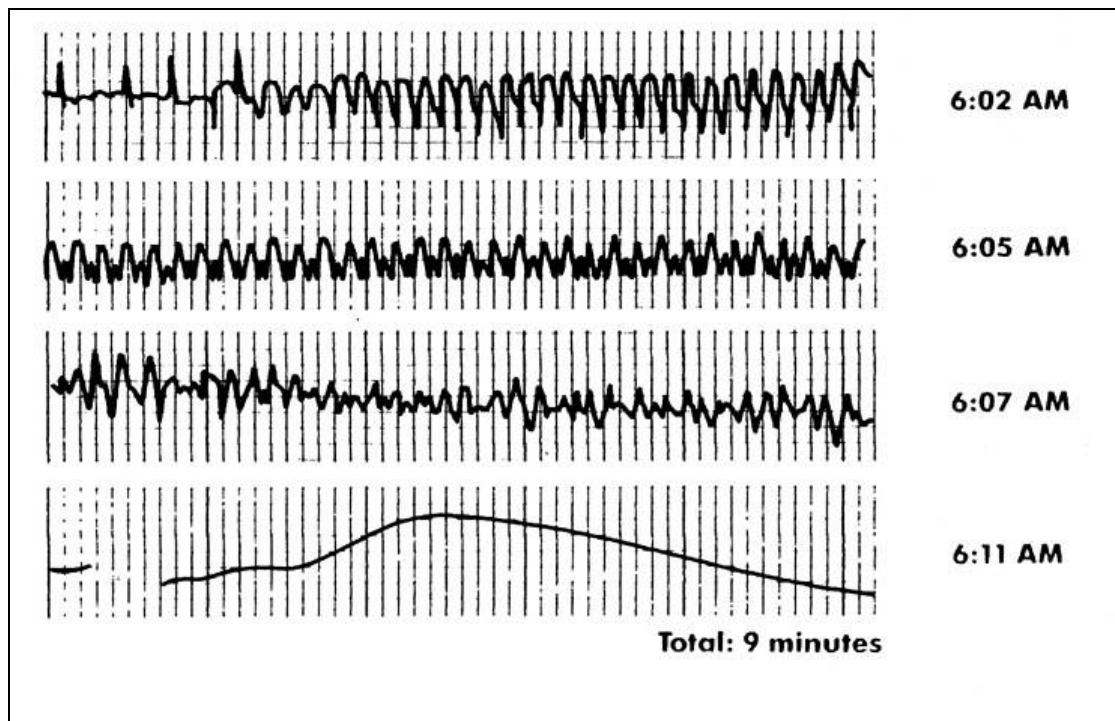
Sudden Cardiac Death

- 300,000-350,000/year in U.S.
- Majority occur outside a hospital
- 2-15% reach the hospital
- Half die before discharge
- High recurrence rate



Direct Cause of Sudden Cardiac Death

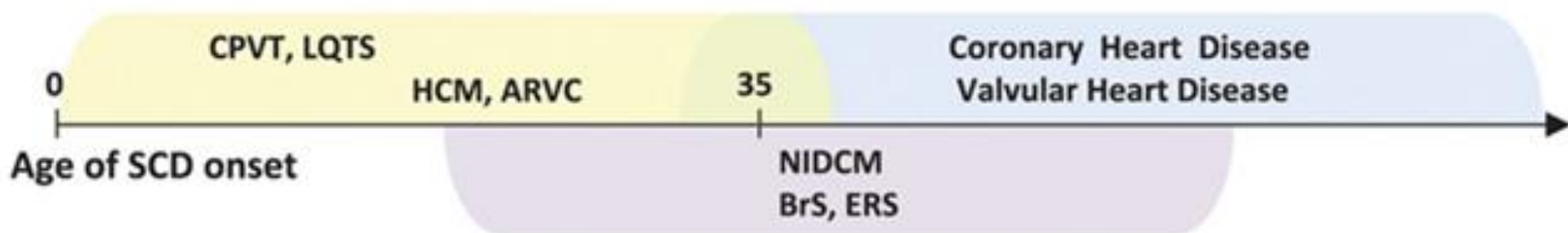
- Ventricular Arrhythmias (VT or VF) in 70-80%



Substrates for VT and VF

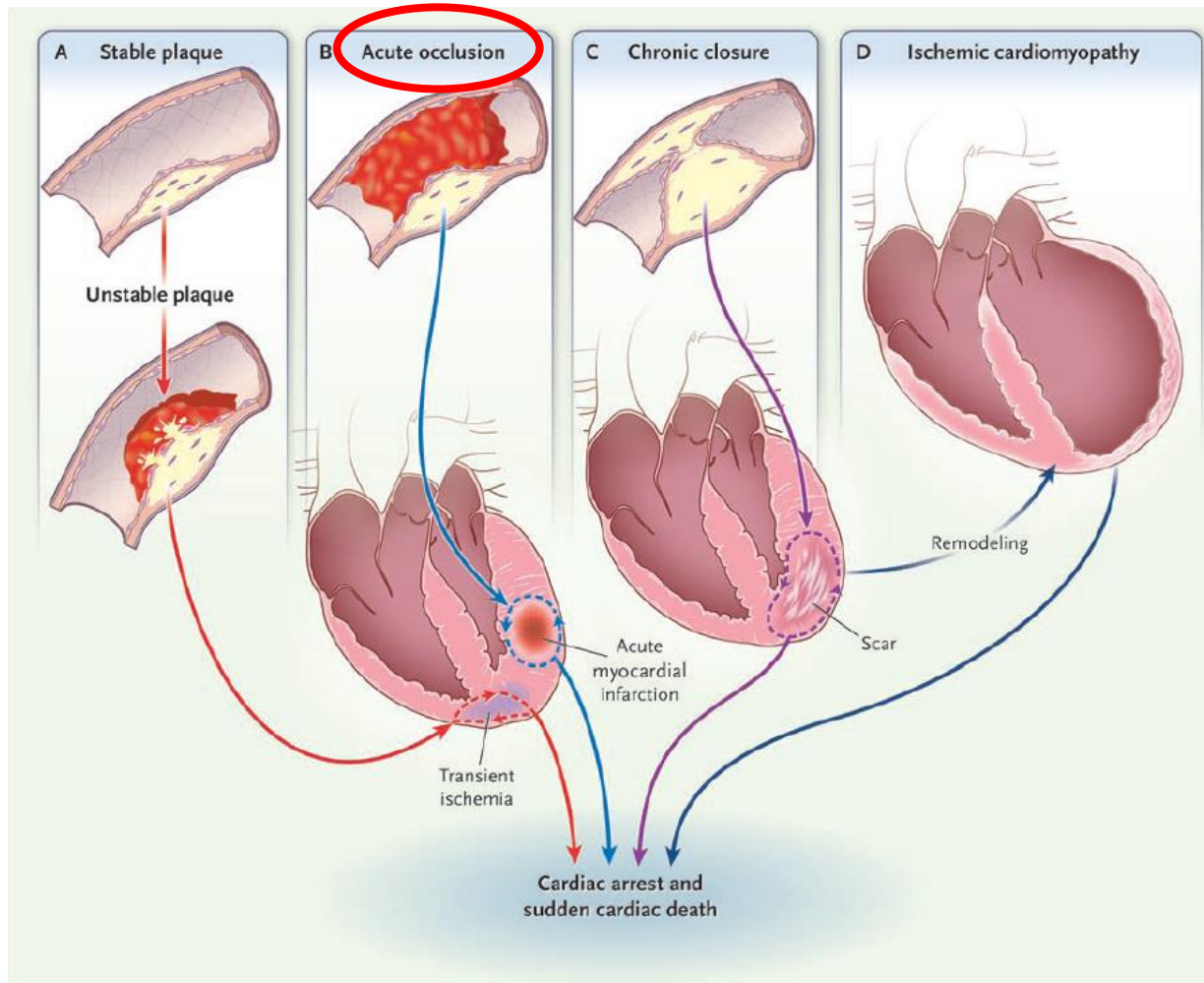
- Cardiomyopathy from CAD is the most common substrate
- Other cardiomyopathies (dilated,)
- Less common substrates:
 - HCM, long QT, Brugada

Age of SCD Onset in Each Disease



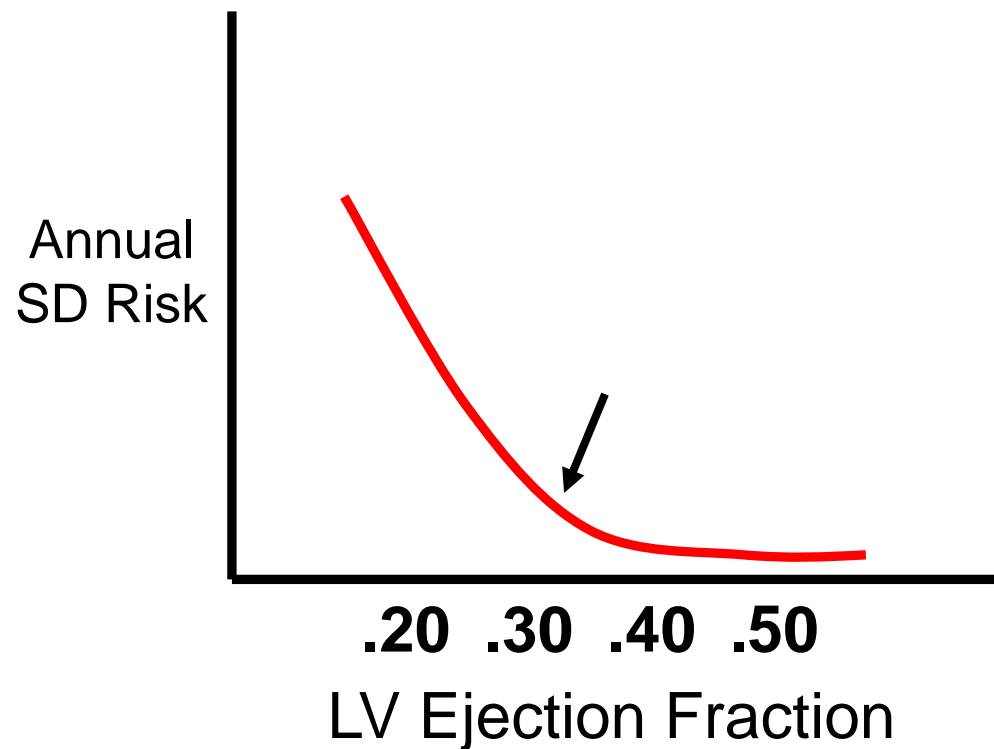
Meiso Hayashi et al. *Circ Res.* 2015;116:1887-1906

Pathophysiology of Life-Threatening Tachyarrhythmias in Coronary Heart Disease



Not all Patients with CAD are at Risk for Sudden Death

- There are risk factors for sudden death:
 - LV Dysfunction
 - CHF
 - Ischemia



Treatments for VT and VF

- Medications
- ICD
- Catheter ablation

Medications

Antiarrhythmic Drug Trials

Medications

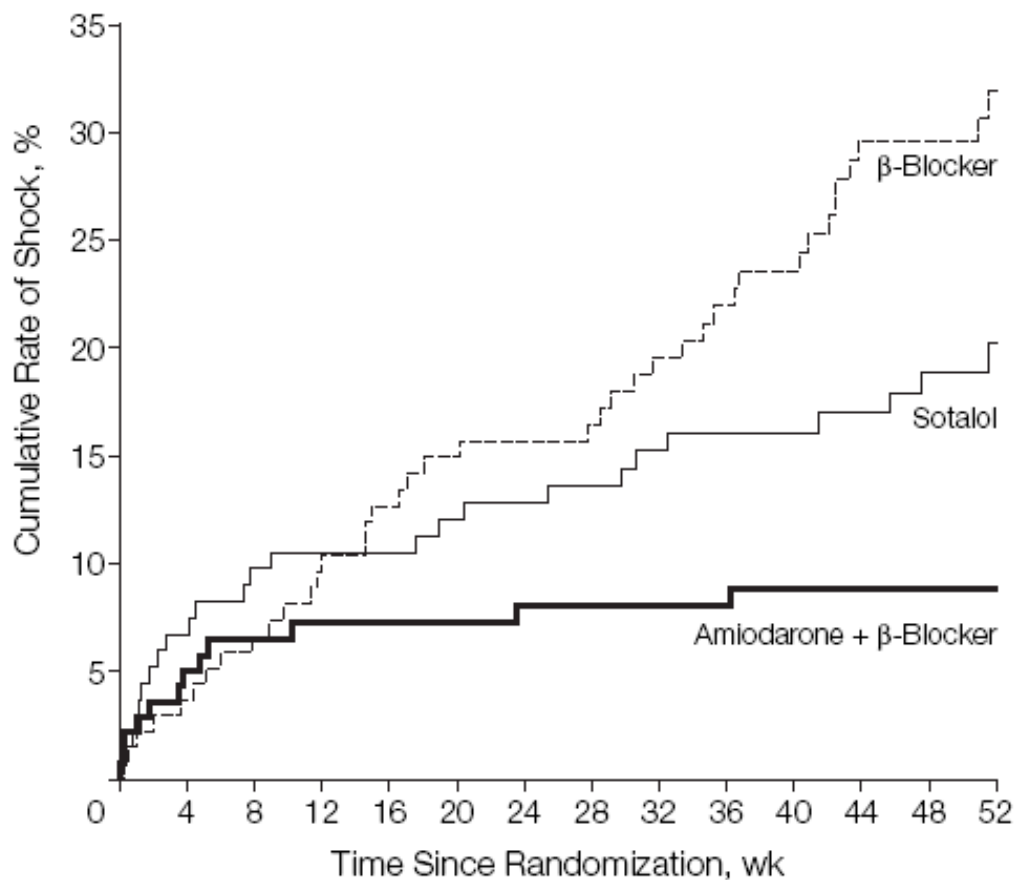
Antiarrhythmic Drug Trials

With respect to mortality



Either neutral (Amiodarone) or worsen mortality
(Class I such as Flecainide)

Reduction in ICD Shocks with Anti-arrhythmics



Daubert et al, JACC 2008;51:1357-65
Connolly et al, JAMA 2006;295:165.

ICD Therapy

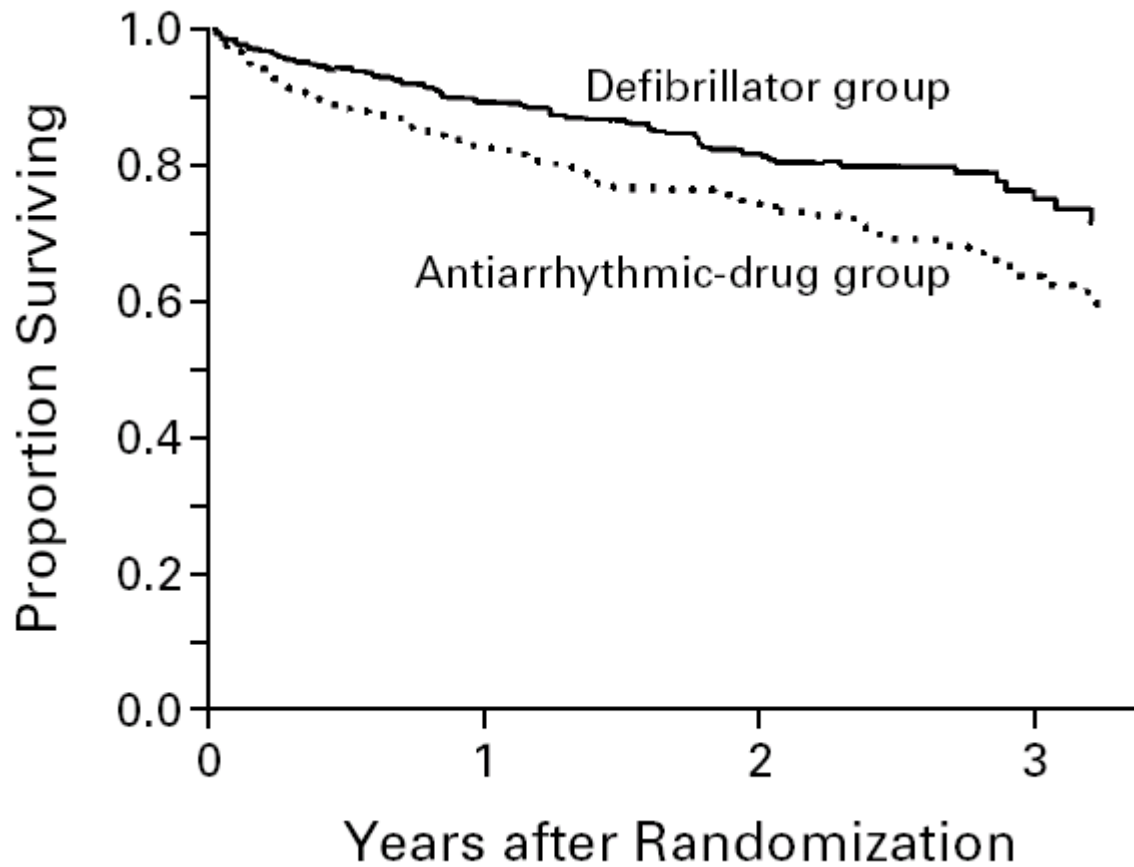
- ICD Trials

Secondary Prevention of SCD: AVID

Enrolled patients with:

- VF or
- Sustained VT with syncope or
- Sustained VT with symptoms and LVEF $\leq 40\%$ or
- Sustained VT with blood pressure < 80 and LVEF $\leq 40\%$

AVID



(Hazard ratio = 0.62, $P < 0.02$)

Sudden Cardiac Death

- 300,000-350,000/year in U.S.
- Majority occur outside a hospital
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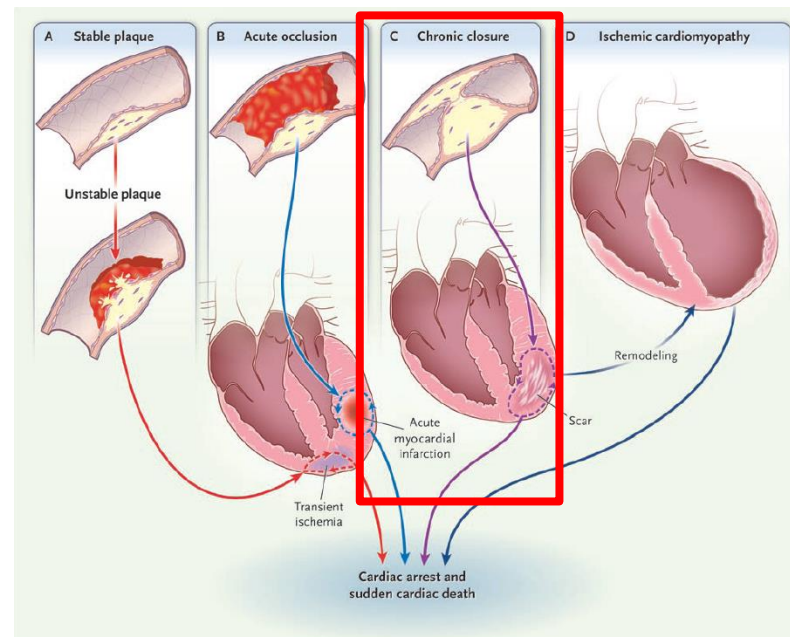
Importance of Primary Prevention

Primary Prevention ICD Trials

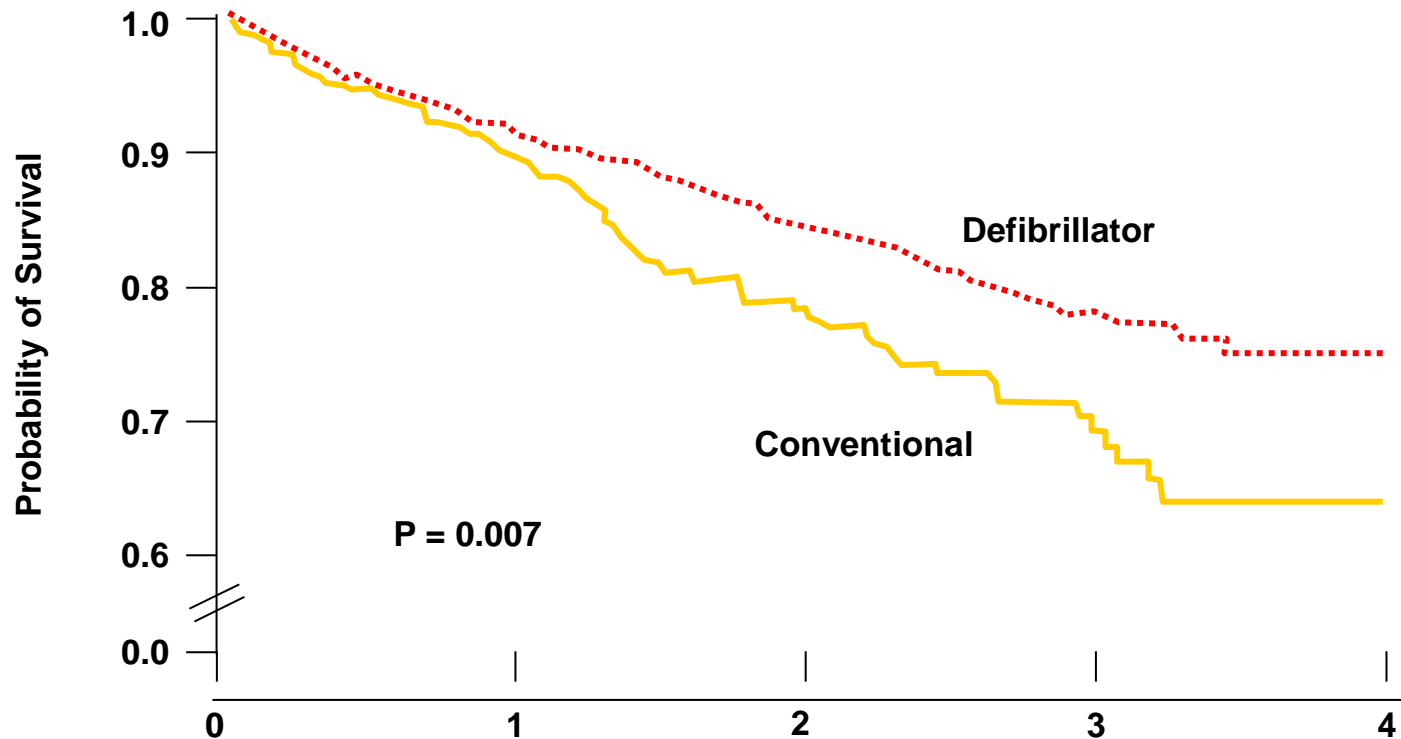
- MADIT II
- SCD-HeFT

MADIT-II

- Chronic CAD with prior MI
- $EF \leq 0.30$
- No arrhythmia requirement



MADIT-II Survival Results



No. At Risk

	Year 0	Year 1	Year 2	Year 3	Year 4
Defibrillator	742	502 (0.91)	274 (0.94)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3

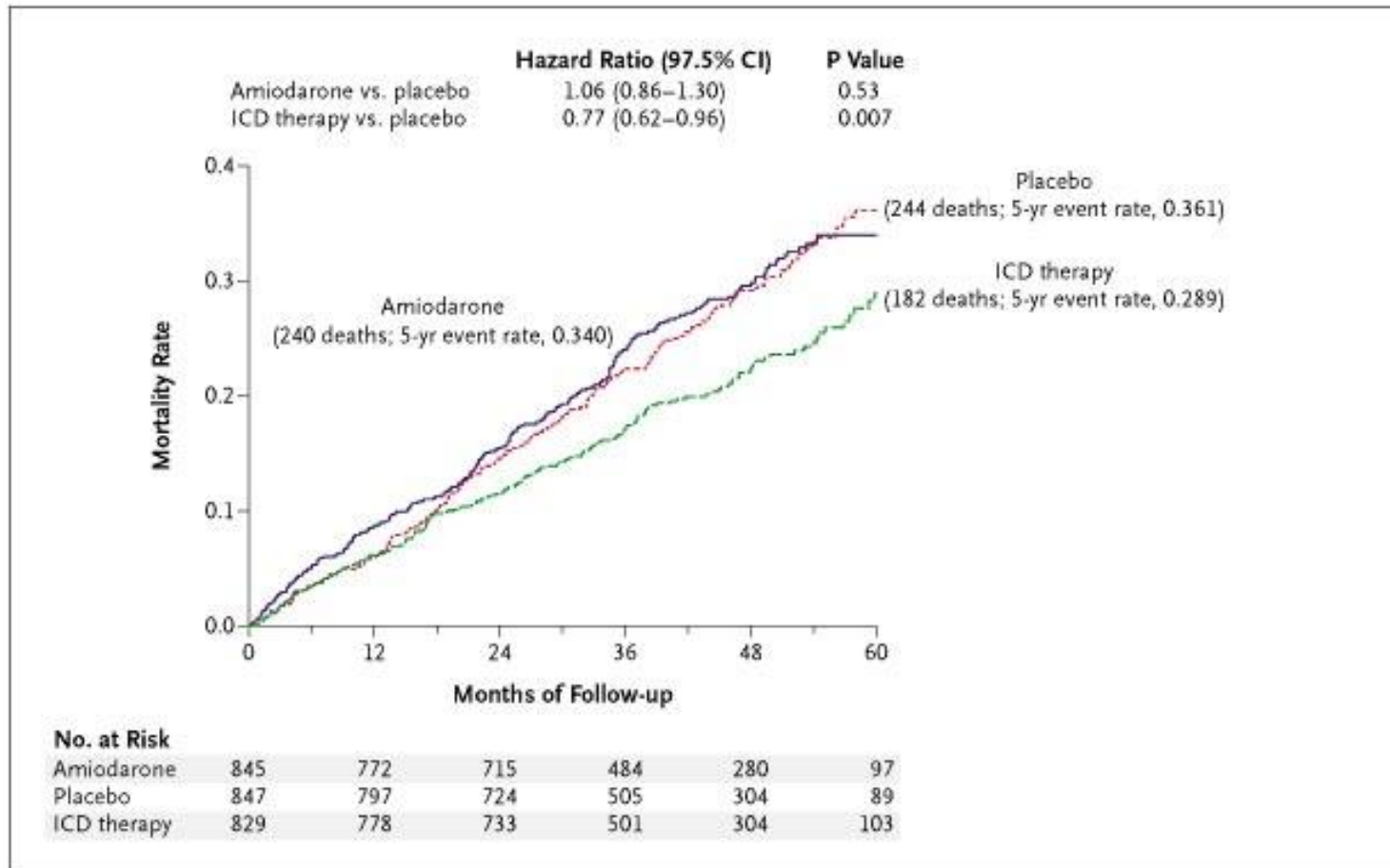
SCD-HeFT

Sudden Cardiac Death in Heart Failure Trial

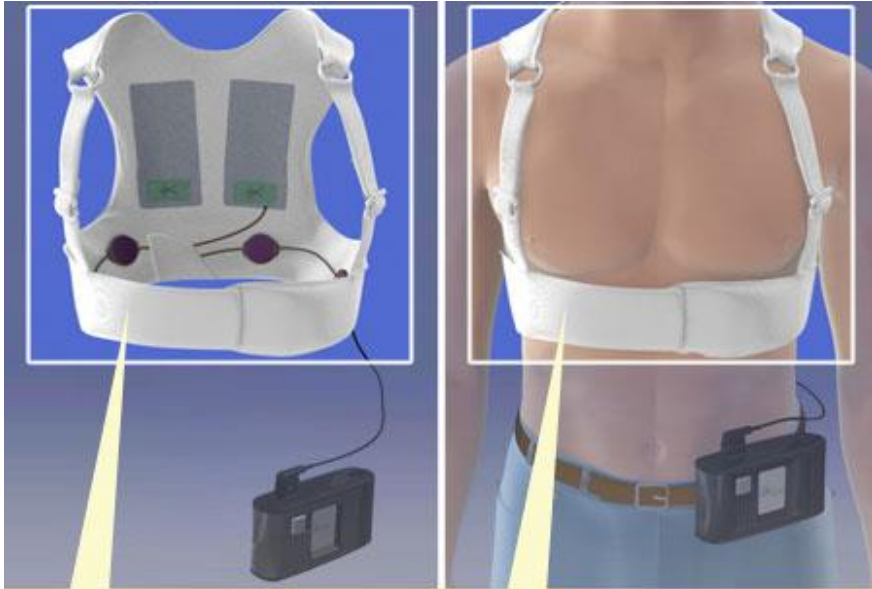
- 2521 patients with CHF NYHA II-III
- EF \leq 35%, of any cause (ischemic and not)
- Randomized to
 - Placebo
 - Amiodarone
 - ICD
- No arrhythmia requirement



SCD-HeFT



Wearable Defibrillator

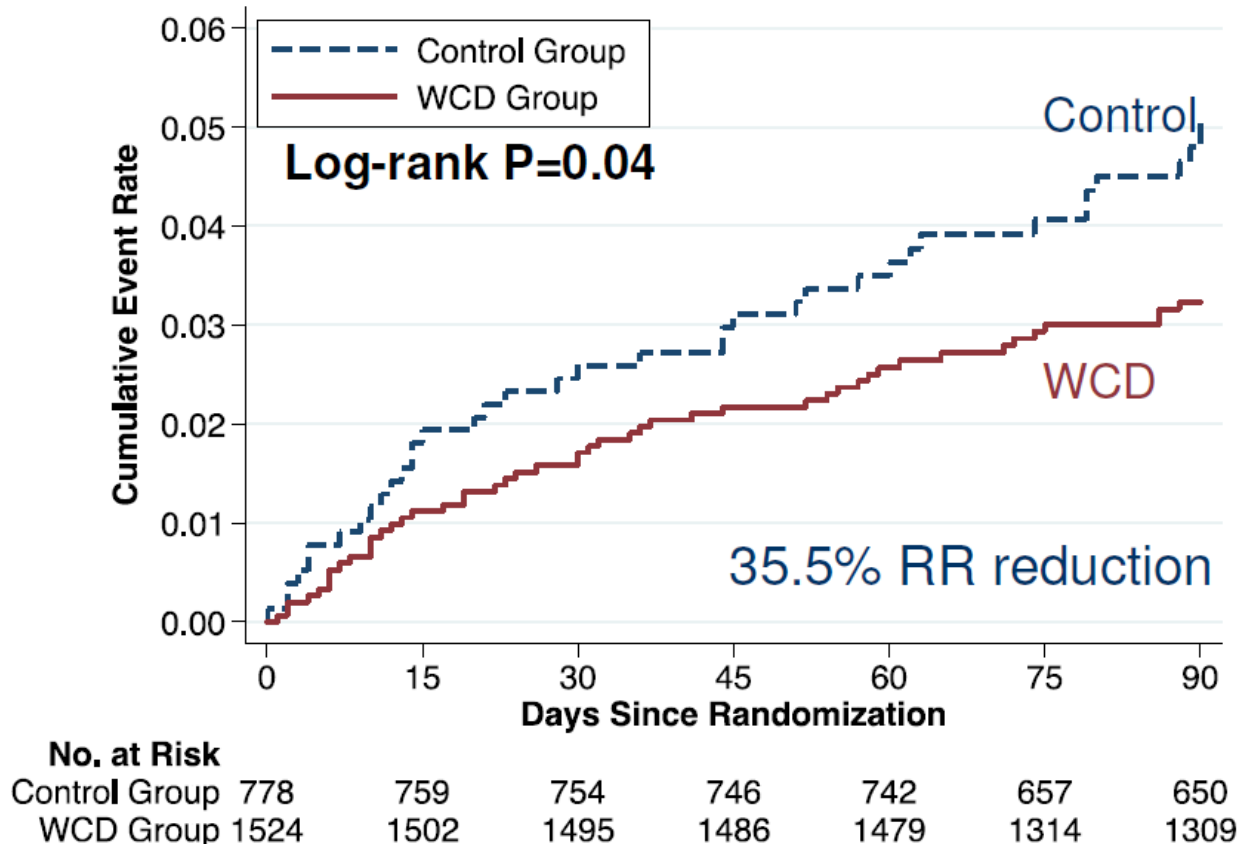


Vest Prevention of Early Sudden Death Trial (VEST)
In patients with recent MI and EF < 35%

VEST Trial Results

Secondary End point

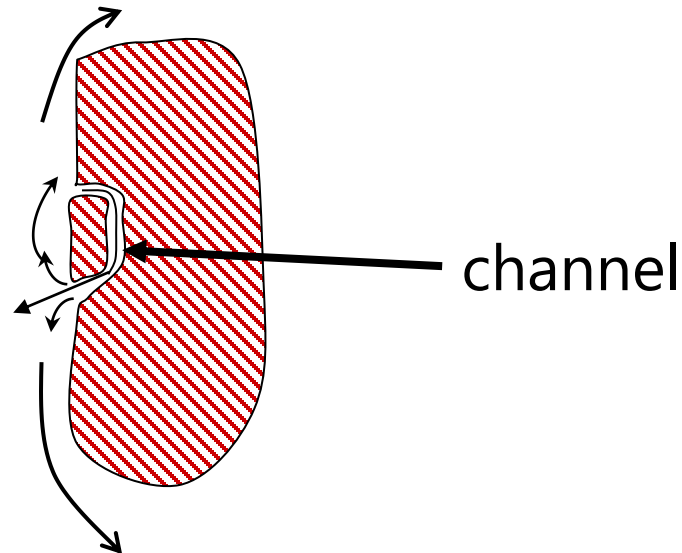
Death from Any Cause



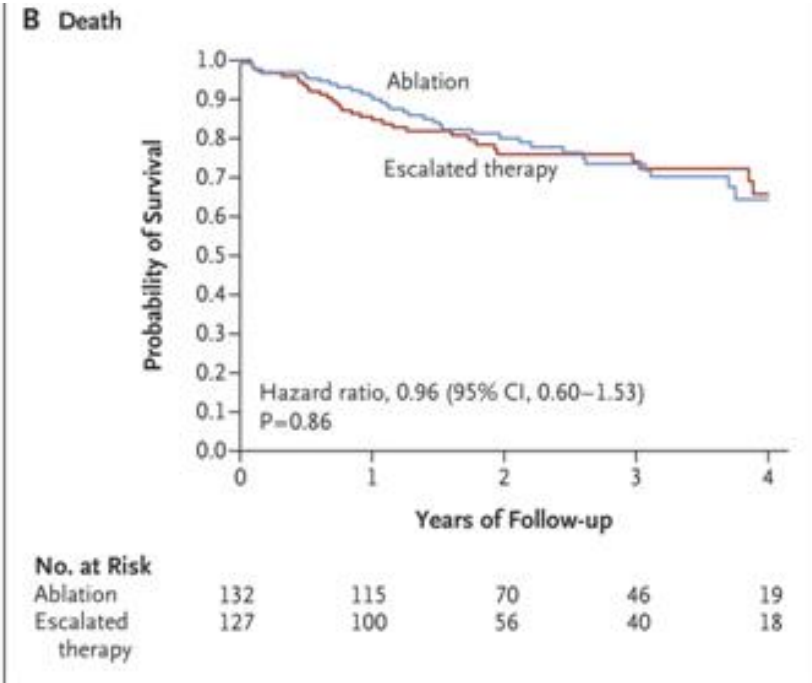
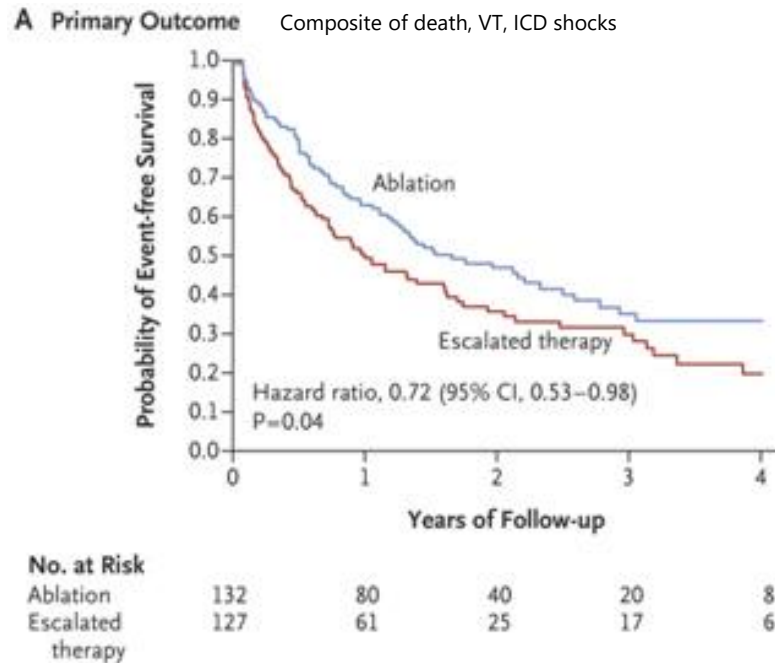
Catheter Ablation of Ventricular Tachycardia

How Does Catheter Ablation Work?

- Ablating the reentry the area of electrical reentry
- Usually involving a scar



Ablation vs. Escalated Medical Therapy



Sapp JL et al. N Engl J Med 2016. DOI: 10.1056/NEJMoa1513614

Summary for VT and VF

- Sudden cardiac death resulting from VT/VF is a leading cause of death in the US
- LV dysfunction is the most important cause for VT/VF
- ICD therapy is the only treatment modality proven to improve survival in patients at-risk

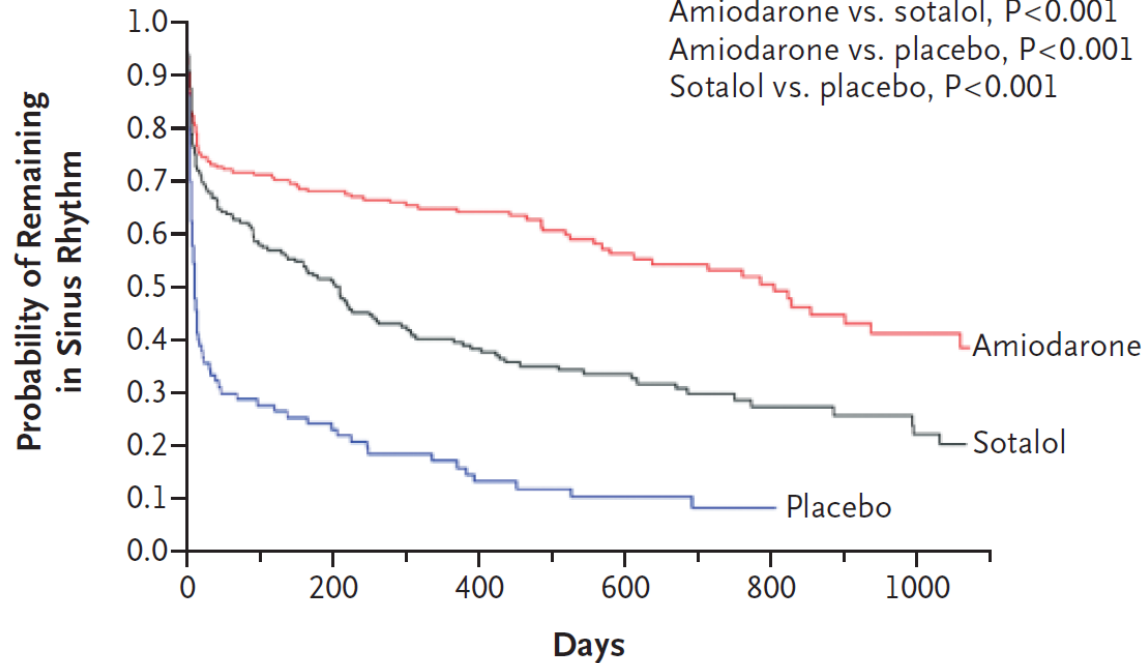
Atrial Fibrillation

- Rhythm control: medications vs. catheter ablation
- Stroke prevention

Rhythm Control with Medications

Amiodarone vs. Sotalol vs. Placebo

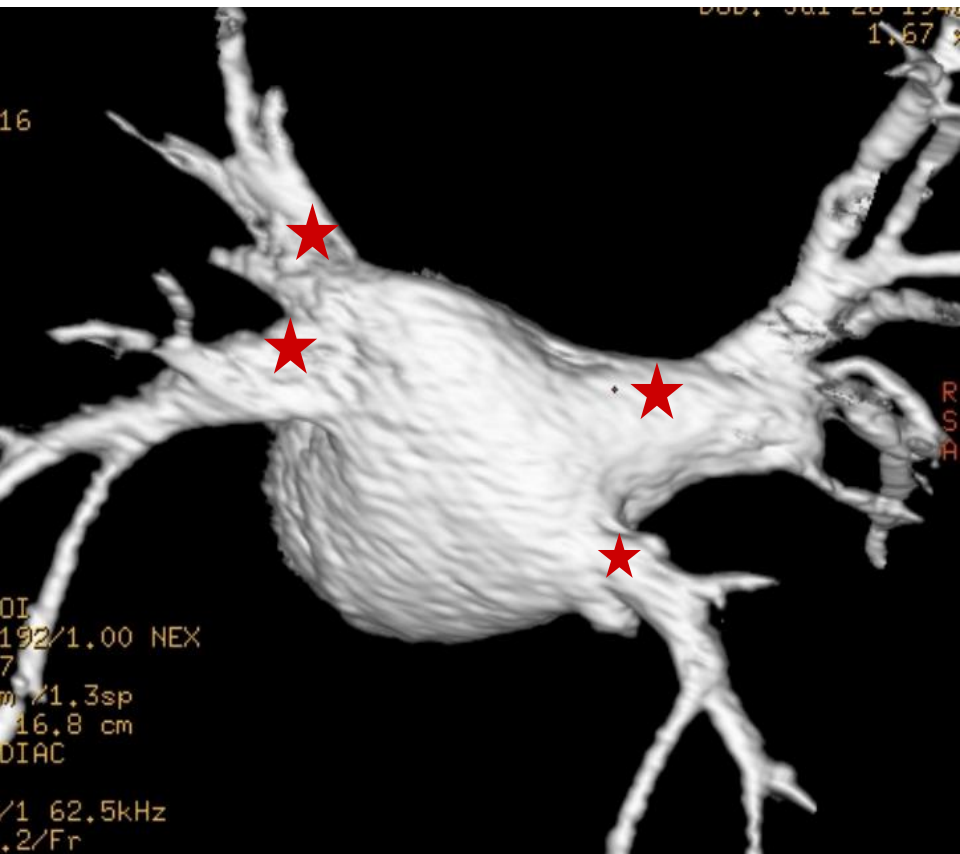
All Patients



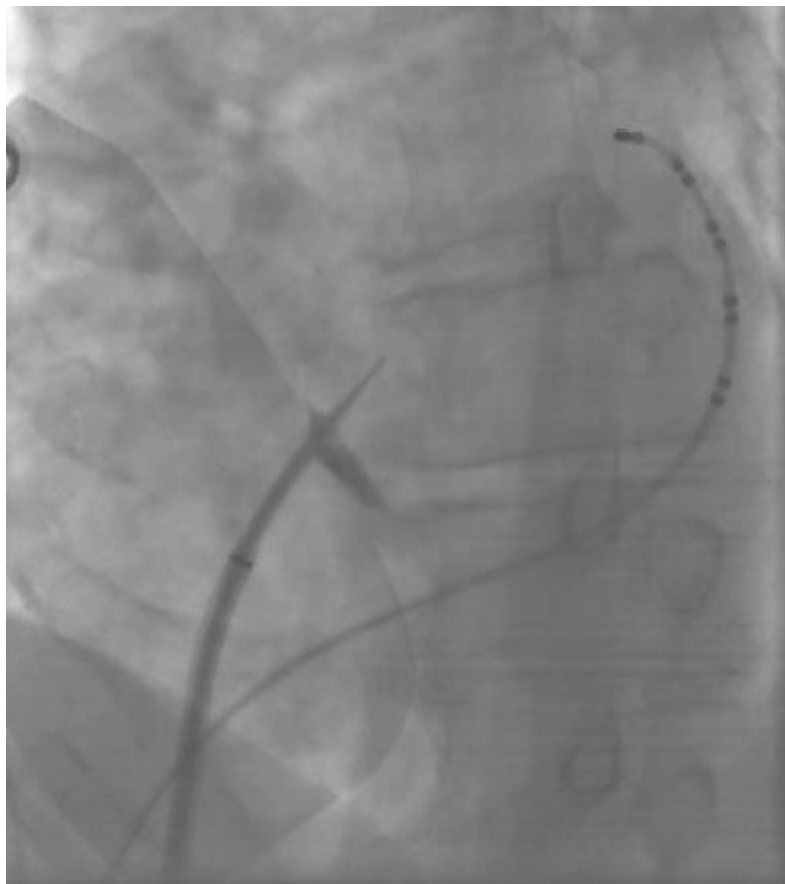
No. at Risk

Amiodarone	206	131	98	60	38	18
Sotalol	195	97	61	38	21	13
Placebo	90	21	11	8	5	2

Catheter Ablation for AF (aka Pulmonary Vein Isolation)



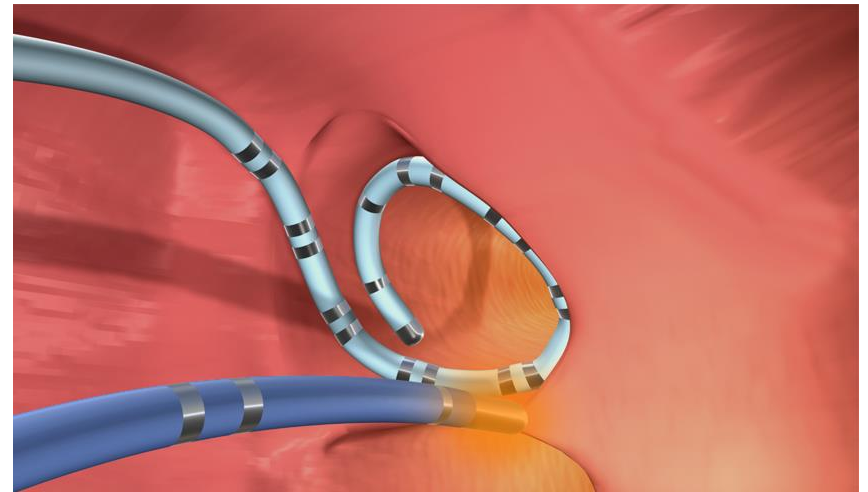
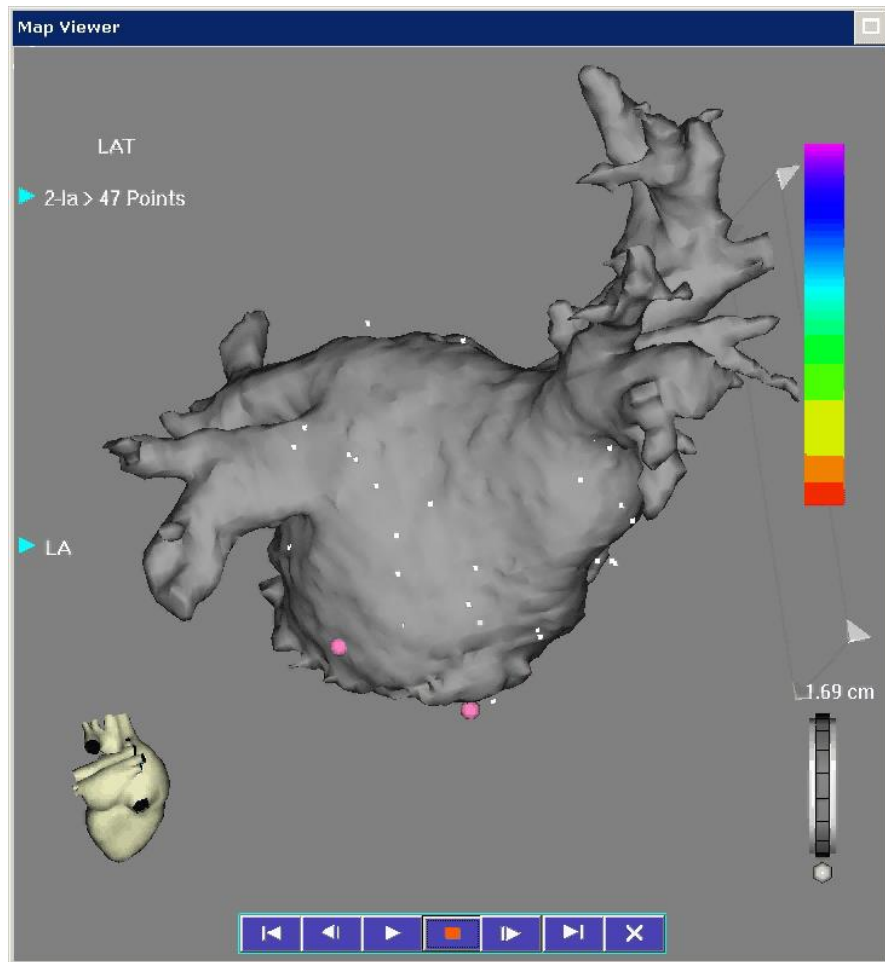
The Catheter is Introduced in the LA Using a Transseptal Puncture



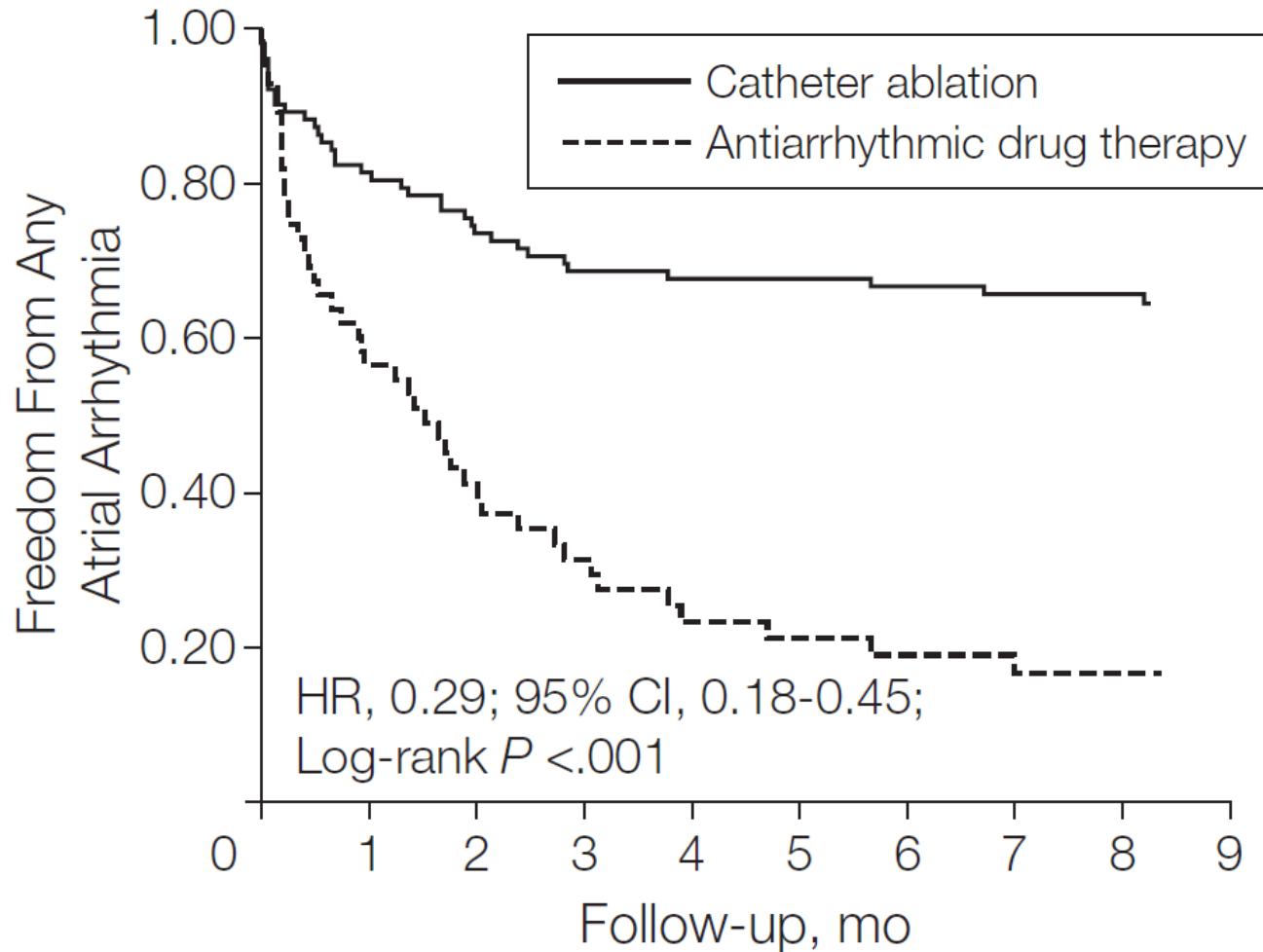
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Catheter Ablation



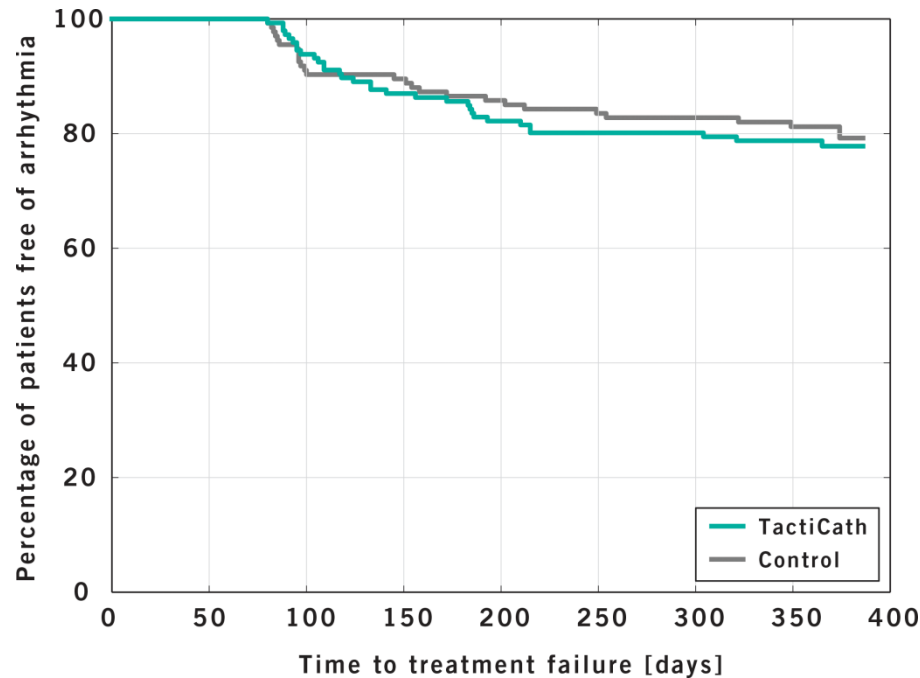
Medications vs. Catheter Ablation



Wilber et. al JAMA 2010

TOCCASTAR:

Catheter Ablation for PAF Using a Force Sensing Catheter



- Use of AAD in the absence of documented atrial arrhythmia or reablation is not a failure
- Up to 2 positive TTM/ECG with no intervention is not a failure

PRECEPT: Drug-refractory Symptomatic **Persistent AF** Can Be Successfully and Safely Treated by RF Catheter Ablation Using Contact-force-sensing Technologies

PROSPECTIVE MULTICENTER STUDY (PRECEPT)



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US & CANADIAN HOSPITALS

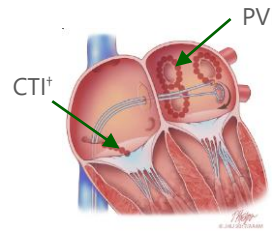


381
PATIENTS WITH DRUG REFRACTORY SYMPTOMATIC **PERSISTENT AF**†

71% MALE, 65 YRS
2.3 CHA2DS2-VASC SCORE
16 MOS IN SYMPTOMATIC PsAF
† Persistent AF = AF (>30s) for 7-365 days

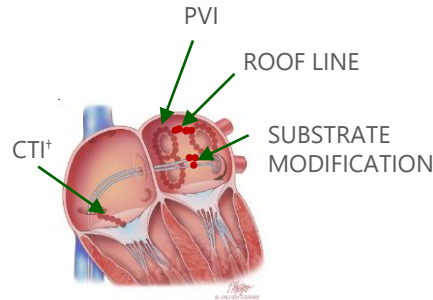
TAILORED ABLATION APPROACH

PVI



or

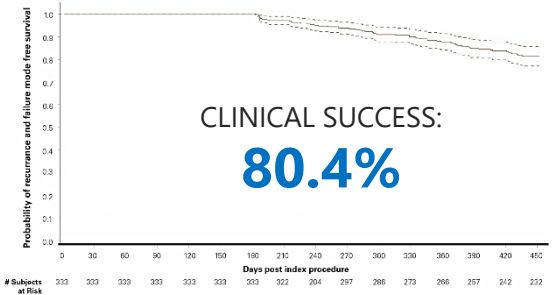
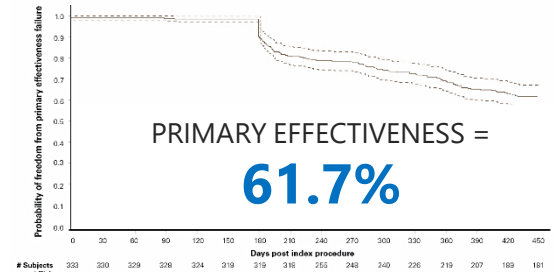
PVI+*



* Additional left atrial ablation per operator's discretion
† CTI ablation with documented atrial flutter
CTI = cavotricuspid isthmus; PVI = pulmonary vein isolation

KEY FINDINGS AT 15 MONTHS

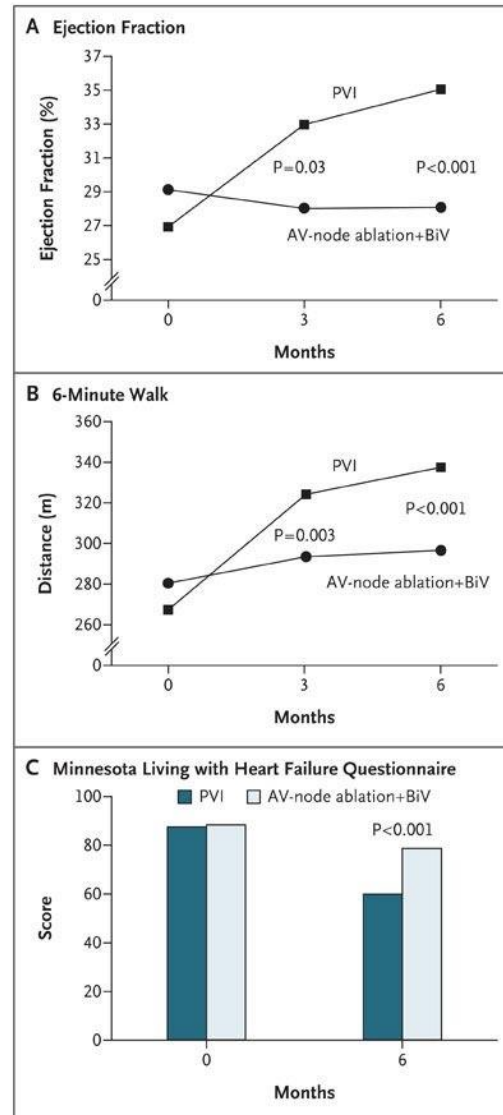
3.8%
PRIMARY AE RATE



Outcome of AF Ablation Beyond Symptoms Control

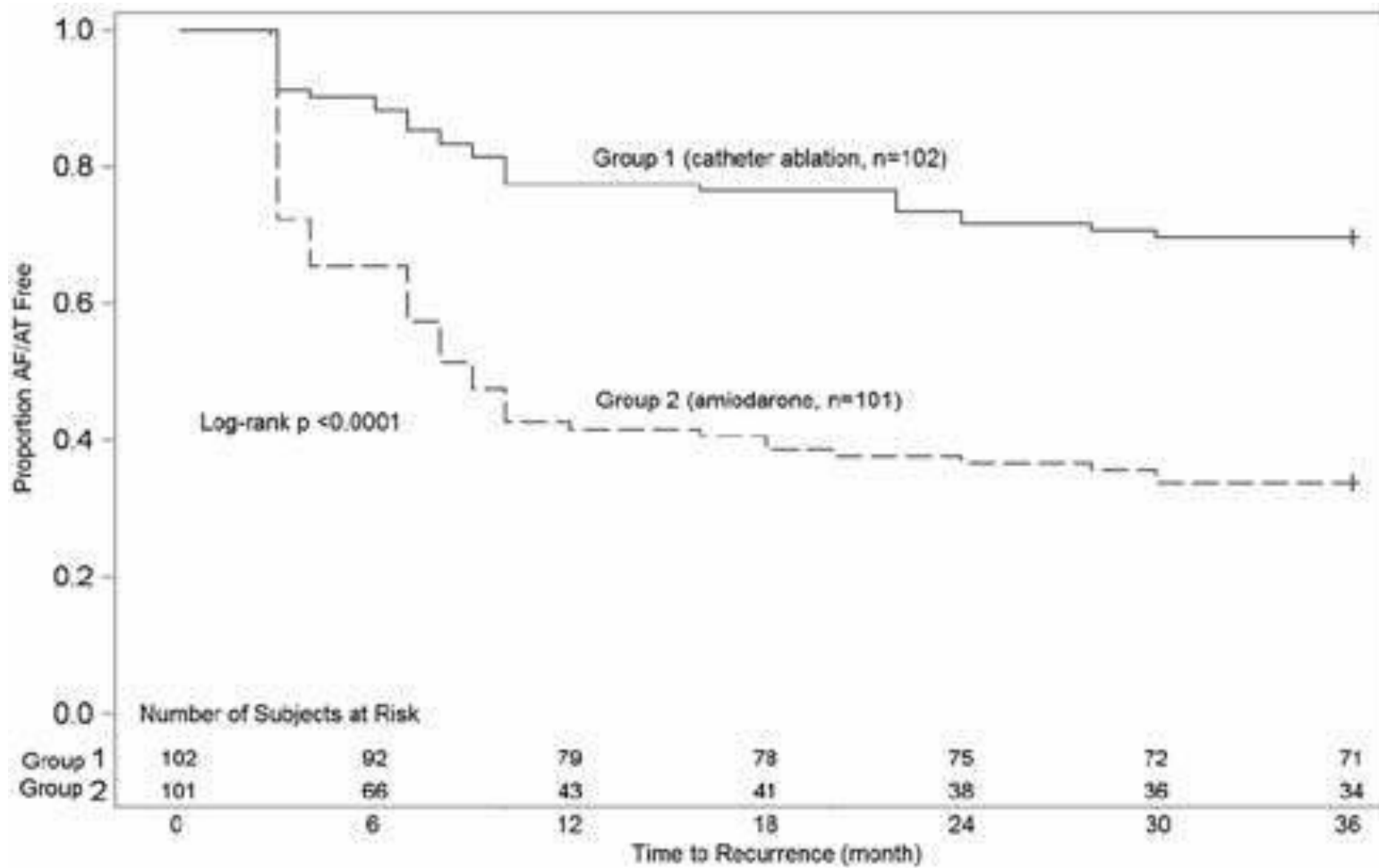
1. Effect of ablation on survival in patients with heart failure
2. Effect of early intervention in AF
3. Effect of ablation on the risk of stroke

AF Ablation in Patients with CHF: PVI vs. AV Node Ablation and Pacemaker (biventricular)



Khan et. al NEJM 2008

AF Ablation in Patients with CHF and Implantable PM/ICD/CRT: PVI vs. Amiodarone (AATAC Multicenter Randomized Trial)

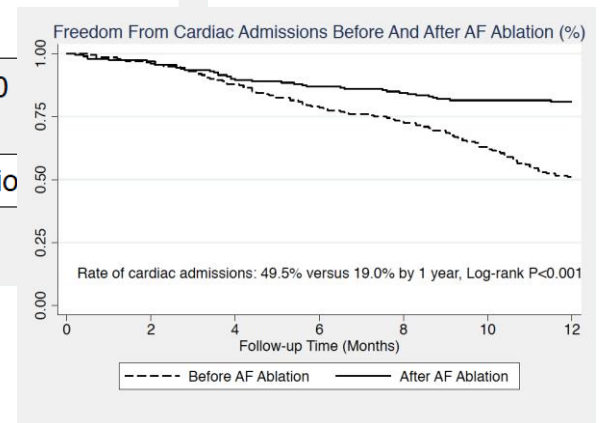
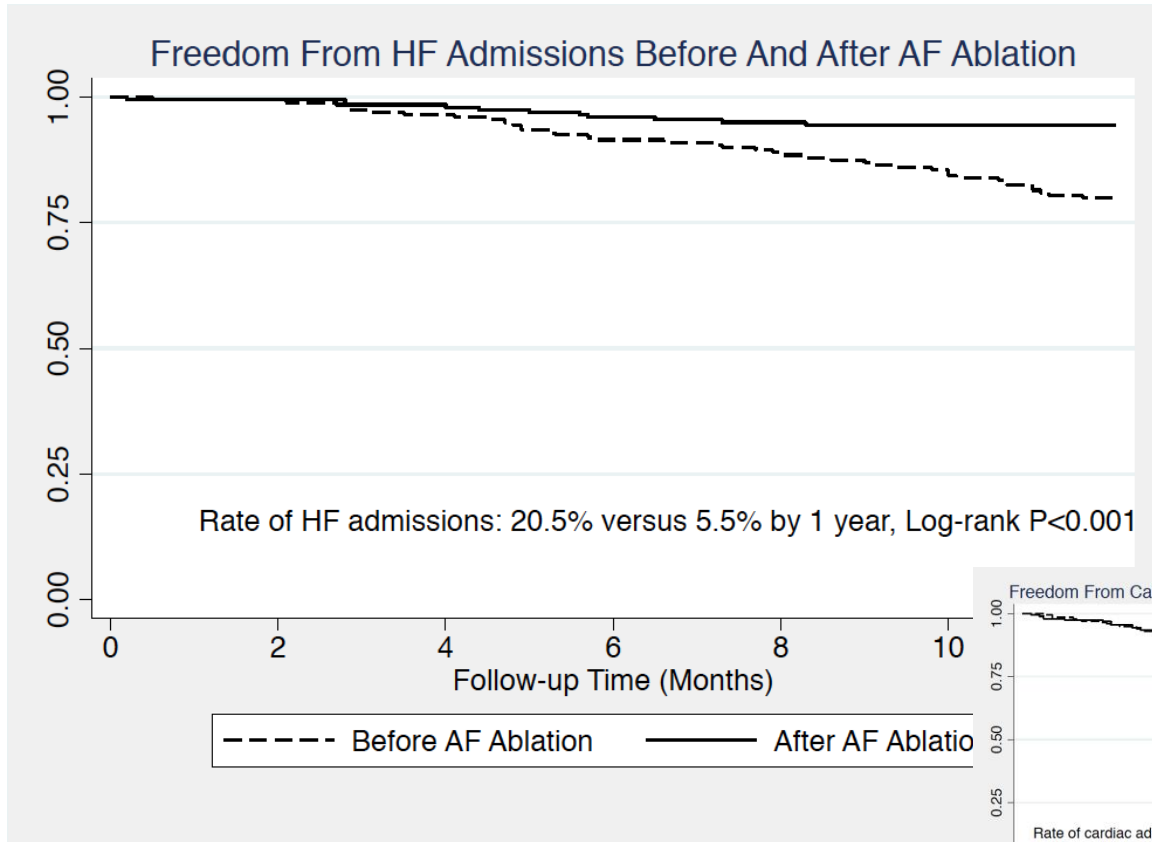


Di Biase et. al Circulation 2017

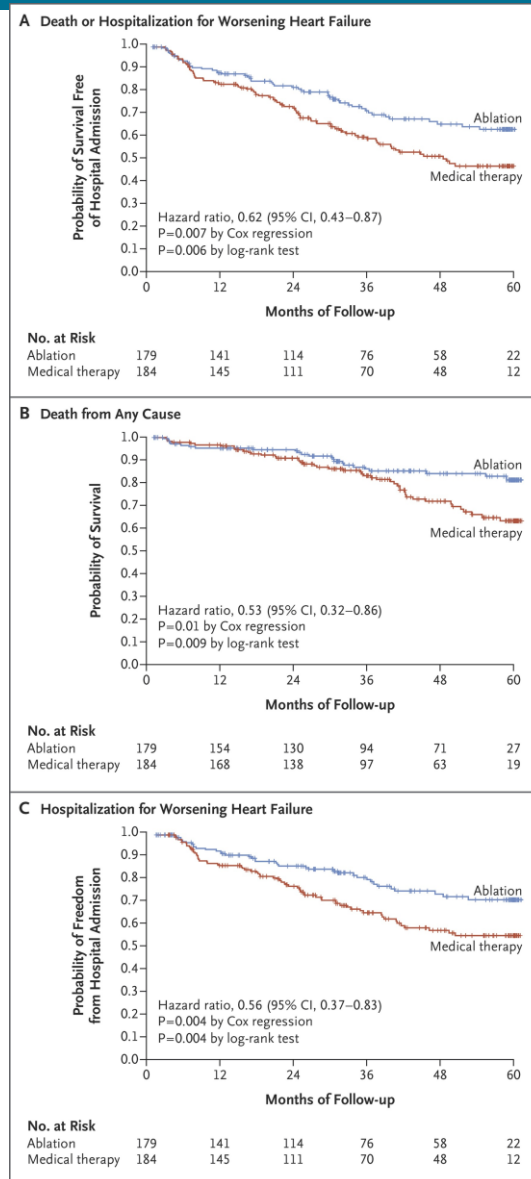
AF Ablation in Patients with CHF : PVI vs. Amiodarone (AATAC Multicenter Randomized Trial)

- Over the 2-year follow-up:
- Unplanned hospitalization rate:
 - 32 [31%] in group 1 and 58 [57%] in group 2; $P < 0.001$
 - 45% relative risk reduction (relative risk, 0.55; 95% confidence interval, 0.39–0.76).
- A significantly lower mortality was observed in CA (8 [8%] versus AMIO (18 [18%]; $P = 0.037$).

Effect of Ablation in Patients with HFpEF

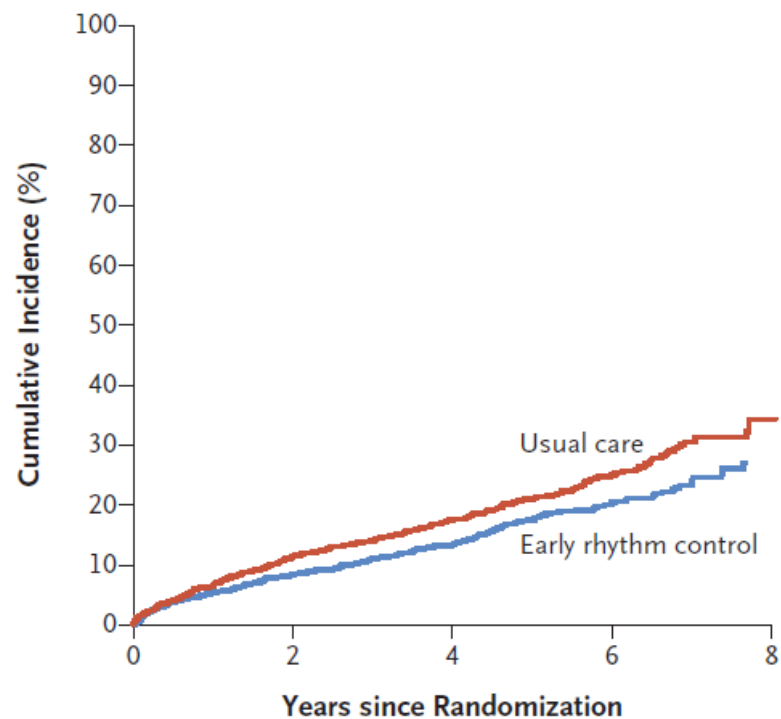


Catheter Ablation for Atrial Fibrillation with Heart Failure: CASTLE- AF



Marrouche et. al NEJM 2018

Early Rhythm-Control Therapy in Patients with Atrial Fibrillation (EAST-AFNET 4 Trial)



No. at Risk

Usual care	1394	1169	888	405	34
Early rhythm control	1395	1193	913	404	26

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.

Stroke Rate After AF Ablation in CHADS₂ ≥ 1 (5 Observational Studies - 2553 patients/7479yrs of f/u)

OACs stopped with no AF recurrence on ECG monitoring

*Gage BF, et al. *JAMA*. 2001;285(22):2864-2870

CHADS ₂ Score	Predicted Stroke Rate AF off OAC * Event Rate/Pt Yrs	Actual Stroke Rate off OAC - Post AF Ablation – No AF Event Rate/Pt Yrs
1	17/607 (2.8%/yr)	6/5376(0.112%/yr)
≥2	23/575 (4.0%/yr)	2/2103(0.095%/yr)

Modified from F Marchlinski AF Symposium 2018

Stroke in AF

- Patients with AF have 5 x the risk of stroke compared to patients without
- Stroke is more severe for patients with AF than those without
 - 70% chance of death or permanent disability
 - 30-day mortality is greater in AF strokes than in non-AF strokes
 - More recurrences of stroke during the first year of follow-up
- Generally occludes large intracranial arteries depriving a more extensive region of the brain of blood flow
- **Huge clinical and economical burden**

Stroke Prevention

- NOAC are generally safe and effective for stroke prevention
- Most society guidelines
 - CHA₂DS₂-VASc 0: no anticoagulation
 - CHA₂DS₂-VASc \geq 2: anticoagulation
 - CHA₂DS₂-VASc 1:
 - Class IIB, “For patients with AF and a CHA₂DS₂-VASc score of 1 in men and 2 in women, prescribing an oral anticoagulant to reduce thromboembolic stroke risk may be considered”

Major Bleeding Rates with NOACs

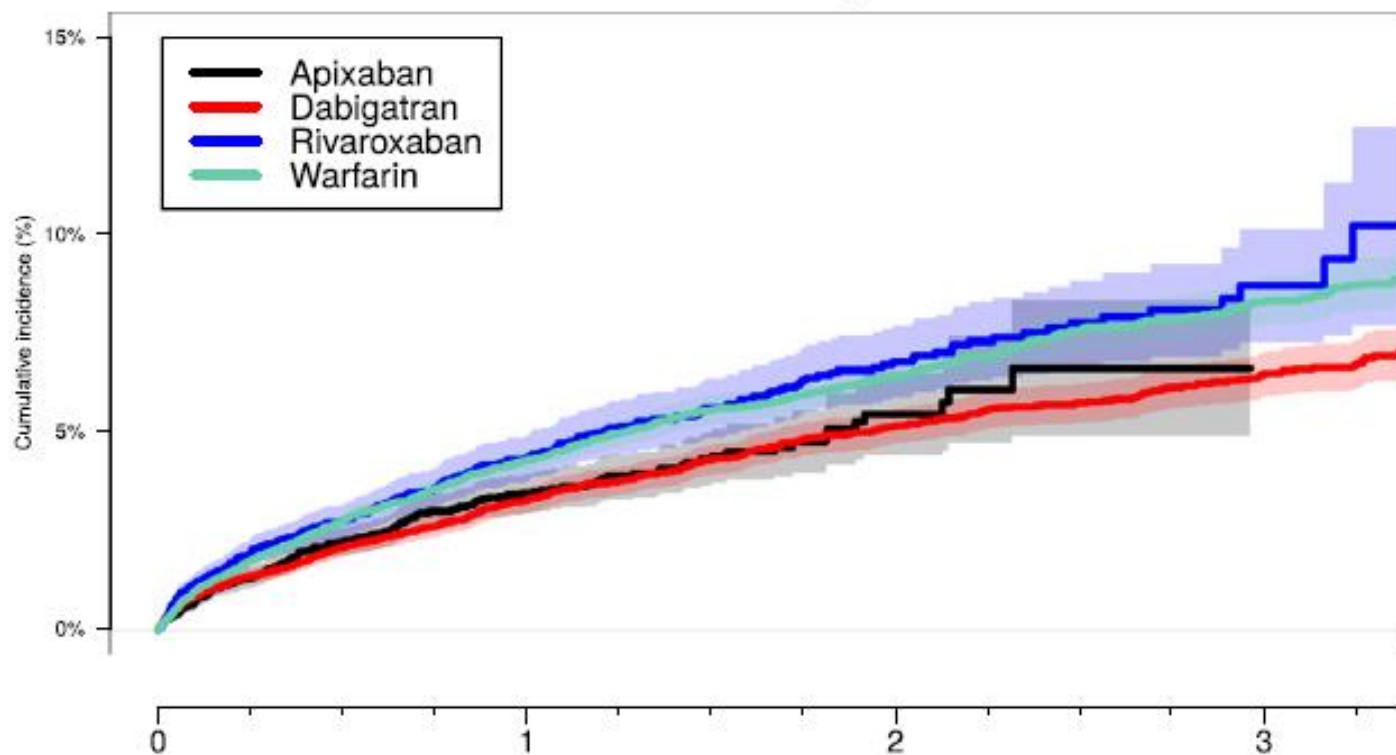
Study	Treatment	Major Bleeding	Hemorrhagic Stroke
RE-LY ¹	Dabigatran (110 mg)	2.71%	0.12%
	Dabigatran (150 mg)	3.11%	0.10%
	Warfarin	3.36%	0.38%
ROCKET-AF ²	Rivaroxaban	3.6%	0.5%
	Warfarin	3.4%	0.7%
ARISTOTLE ³	Apixaban	2.13%	0.24%
	Warfarin	3.09%	0.47%

1. Connelly SJ et al, *NEJM* 2009;361:1139-51
2. Patel MR et al, *NEJM* 2011;365:883-91
3. Granger J. et al, *NEJM* 2011;365:981-92

Real Experience with NOACs

54,321 Patients

Bleeding

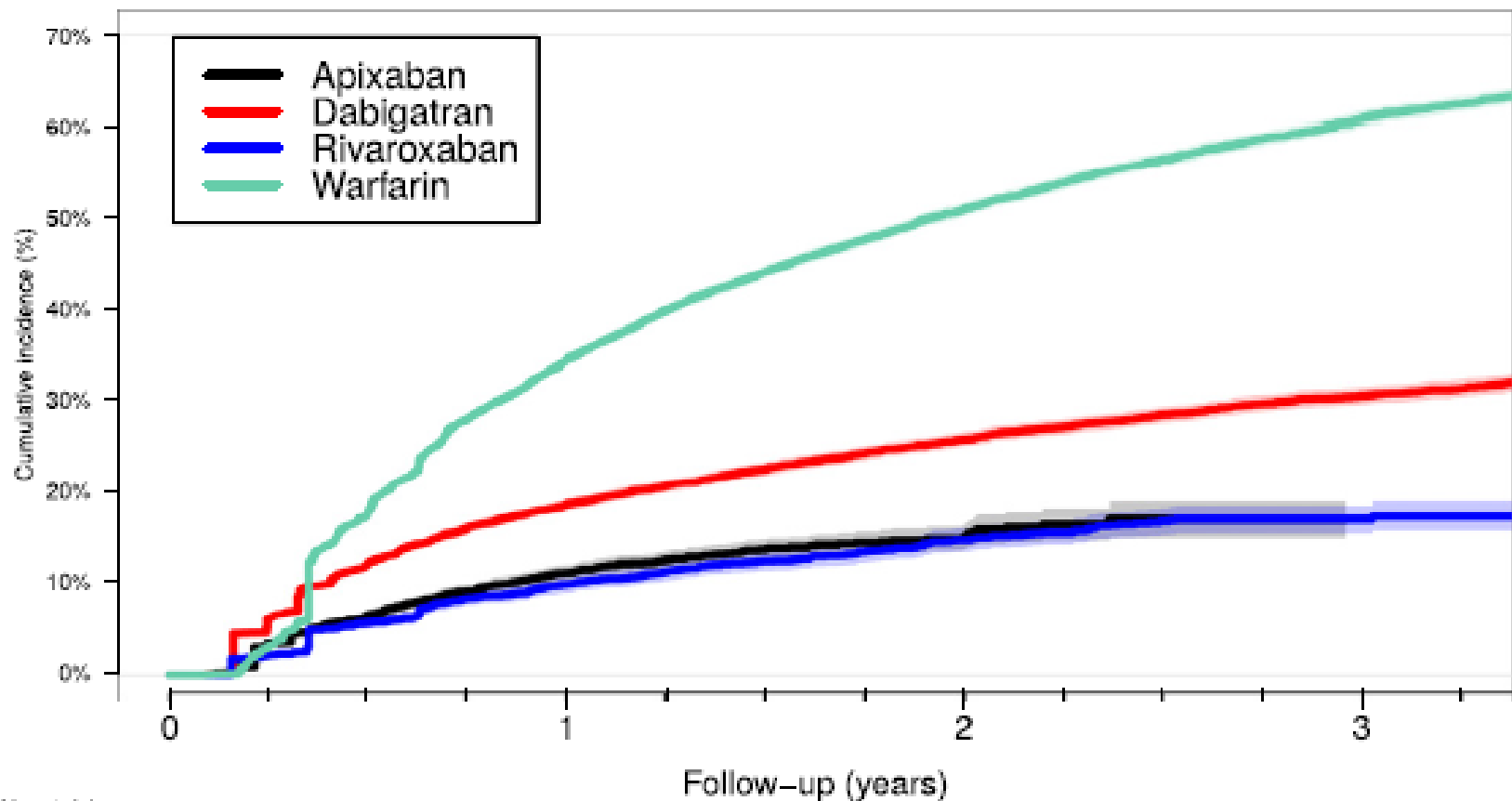


	0	1	2	3
No. at risk	7963	4349	2154	895
Apixaban	15413	10135	7884	6262
Dabigatran	6715	3683	2288	1592
Rivaroxaban	24230	14865	9119	6297
Warfarin				4448
				328
				4617
				3238
				82
				531
				3046
				0
				2127
				173
				1954

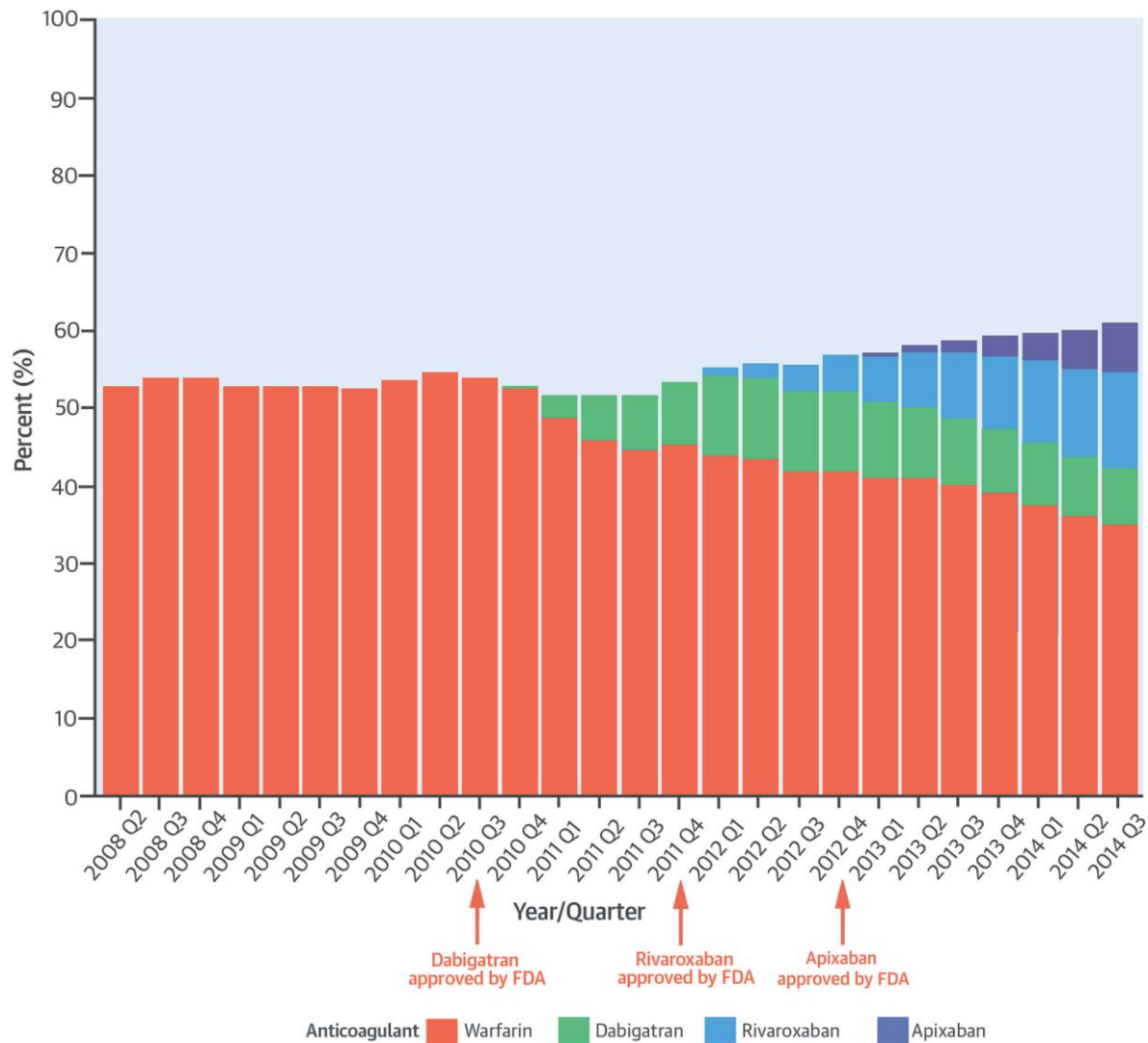
Real Experience with NOACs

54,321 Patients

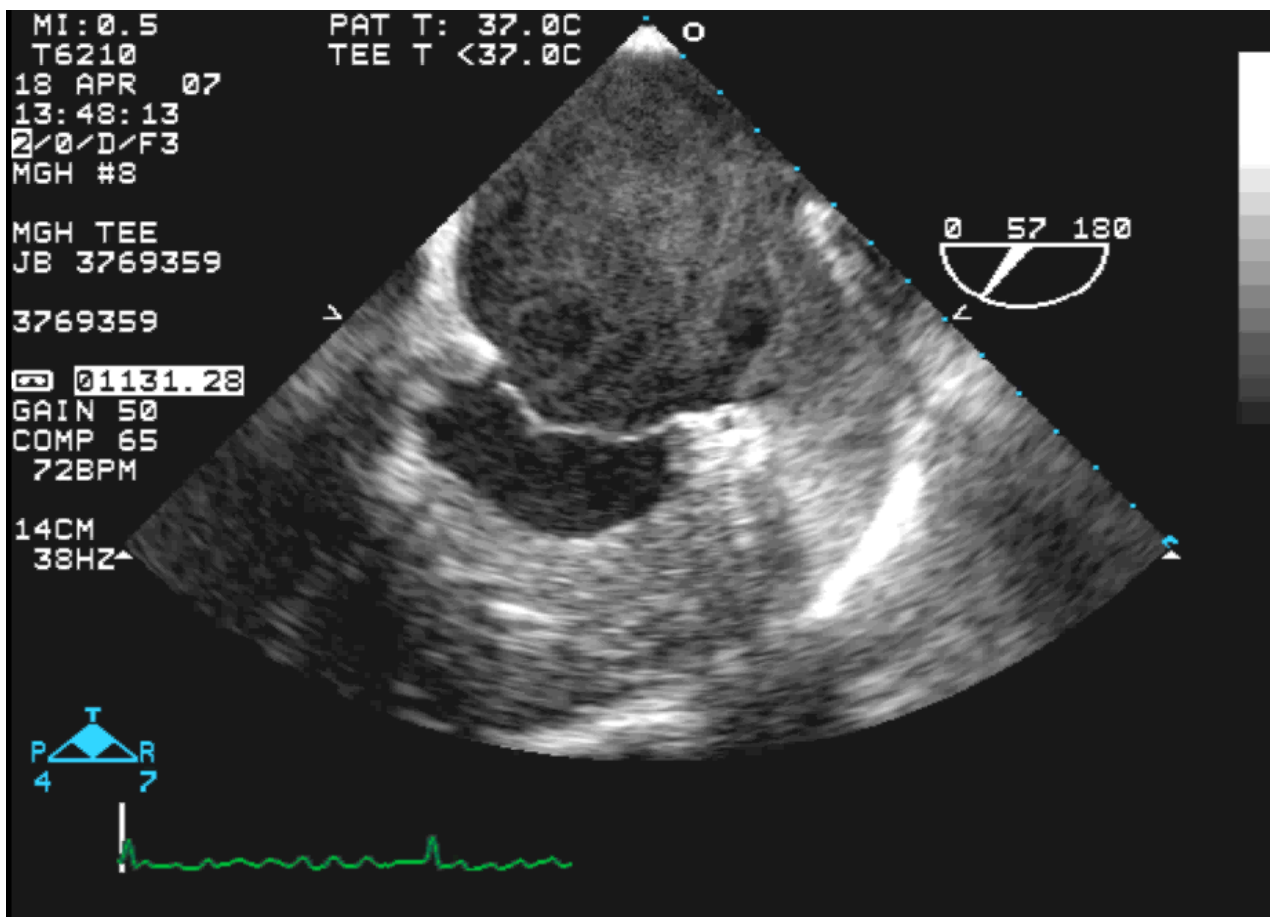
Non-persistence



Underutilization of Anticoagulation



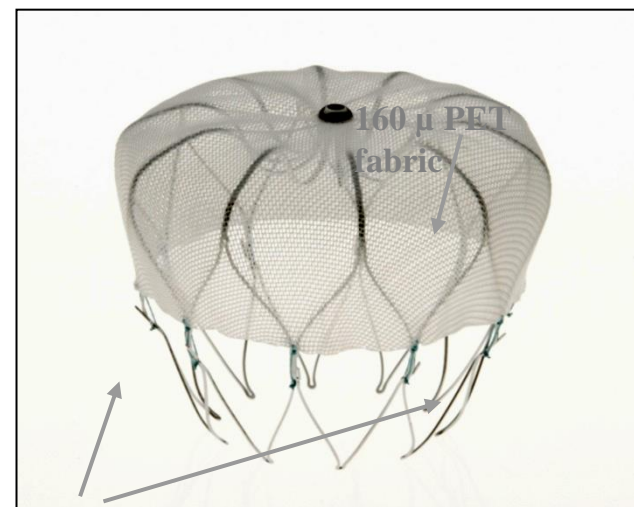
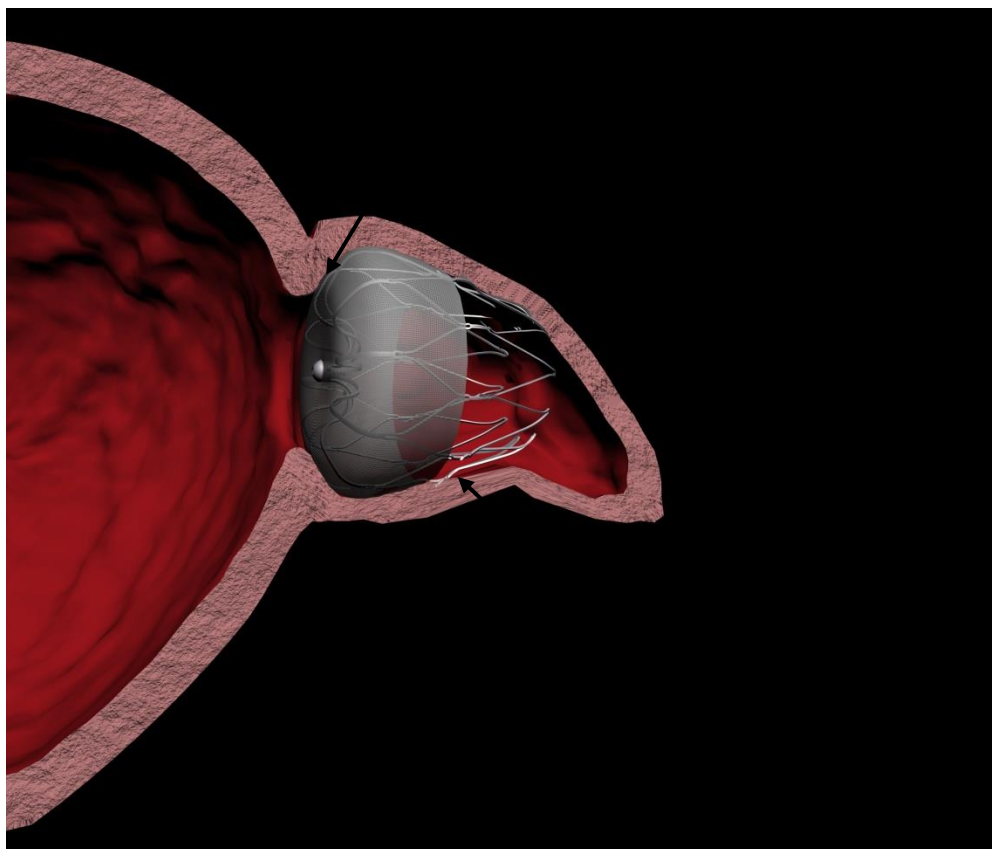
Clots are Located in the LAA in the Majority of the Patients



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Left Atrial Appendage Occlusion Watchman



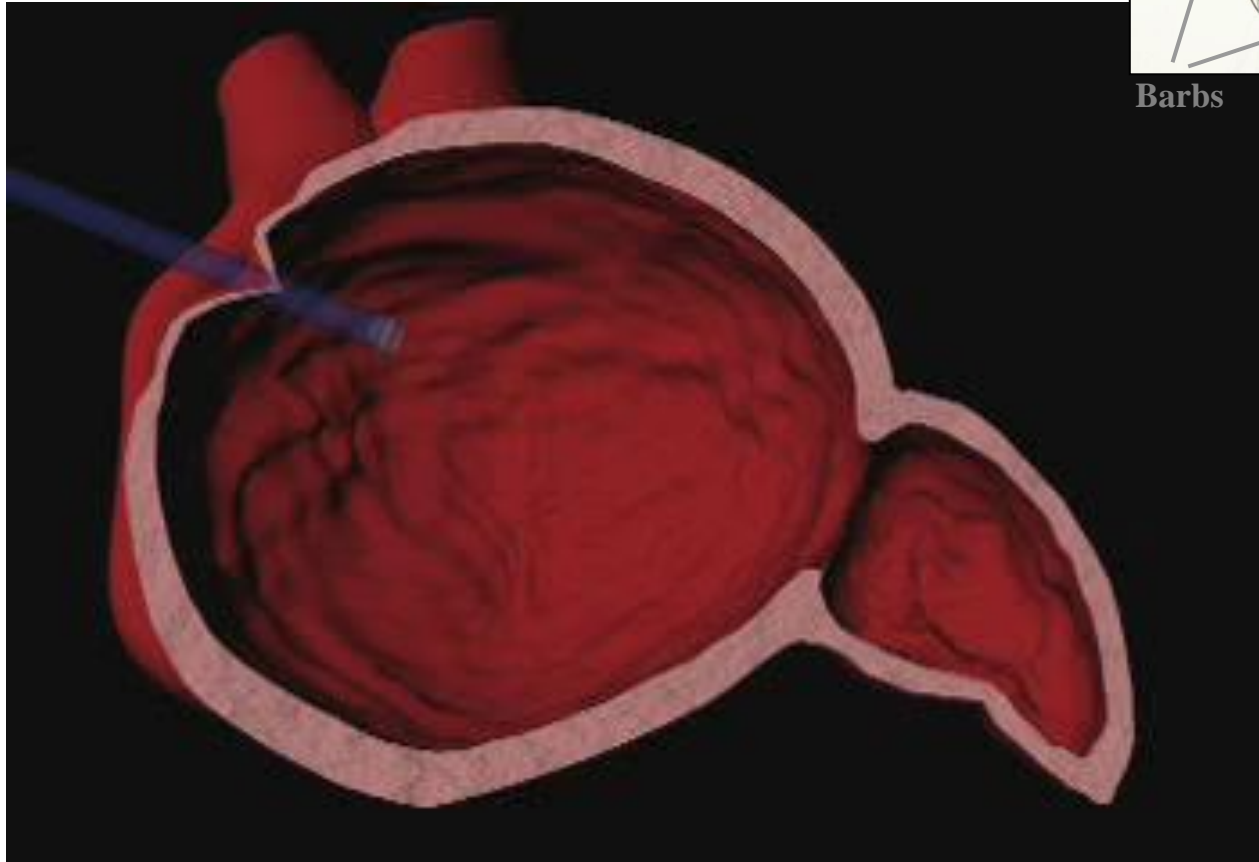
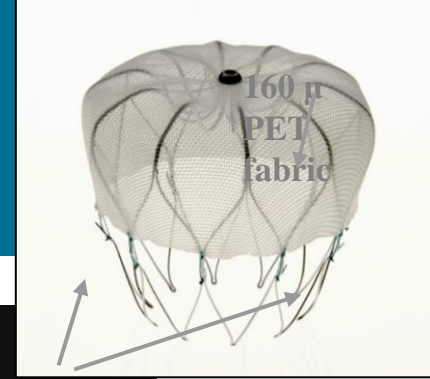
Barbs



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Watchman

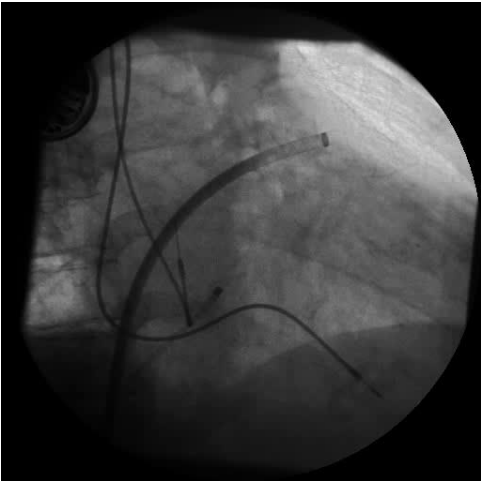


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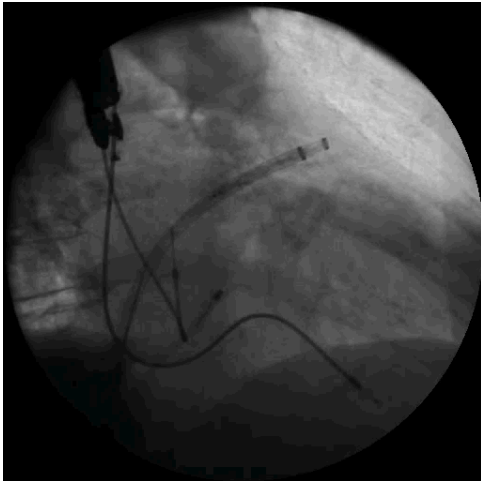
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Deployment of the Watchman Device

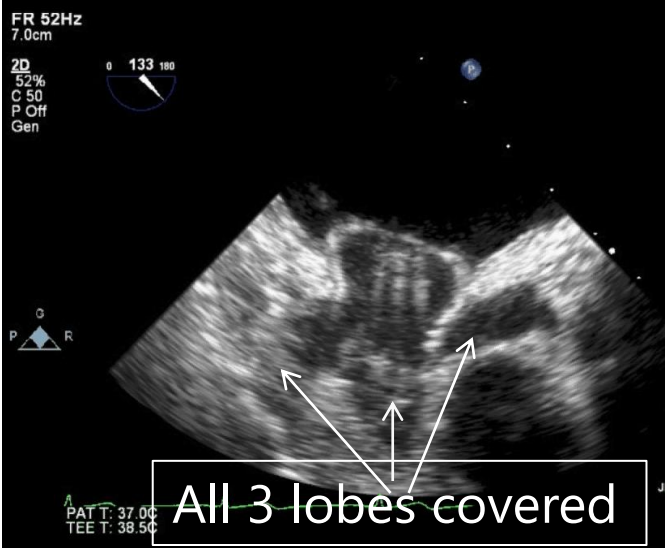
Contrast injection of the LAA



Device self-expansion (Watchman)



TEE



CT Angiogram at Follow up



Gross Pathology



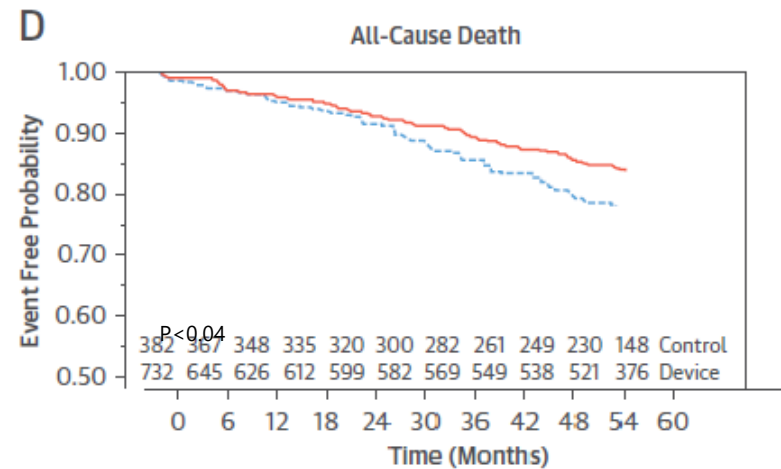
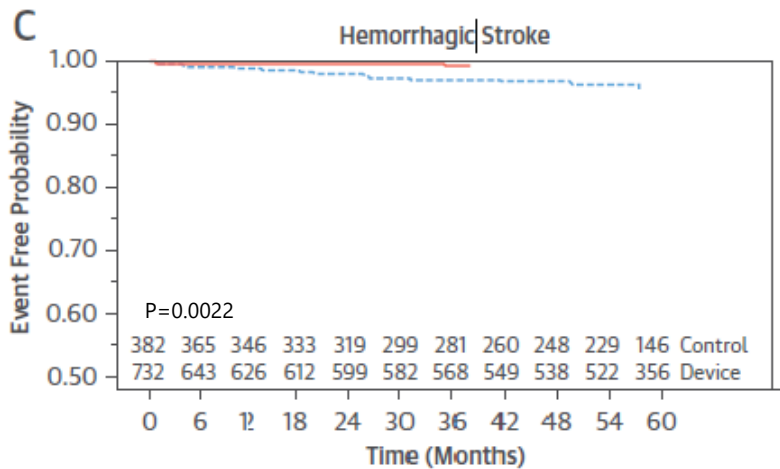
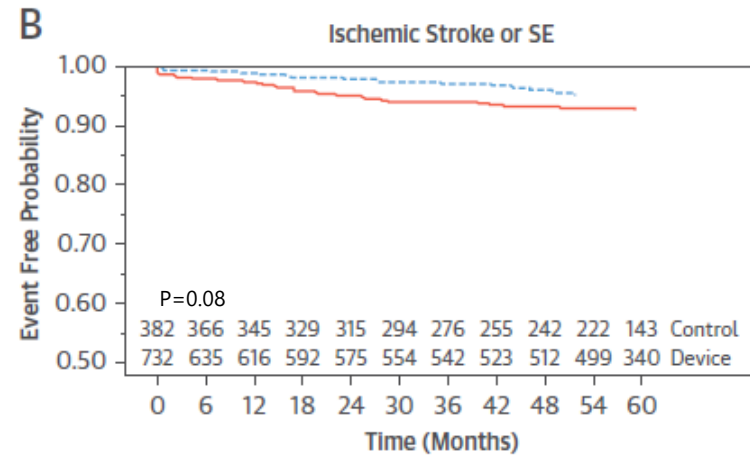
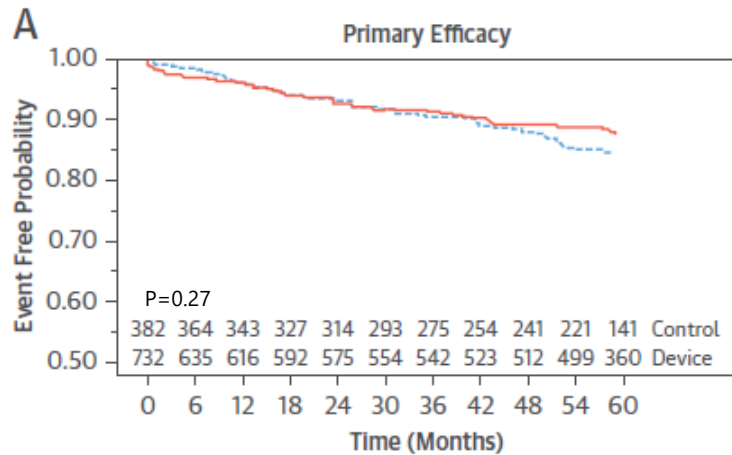
Canine-45 days



Human @ Autopsy – 9 months
(death 2^o abdominal aortic aneurysm)

Safety, Efficacy, and Cost Effectiveness Data

Left Atrial Appendage Closure vs. Warfarin 5-Year Results of PROTECT AF and PREVAIL



Treatment Arm --- Control — Device

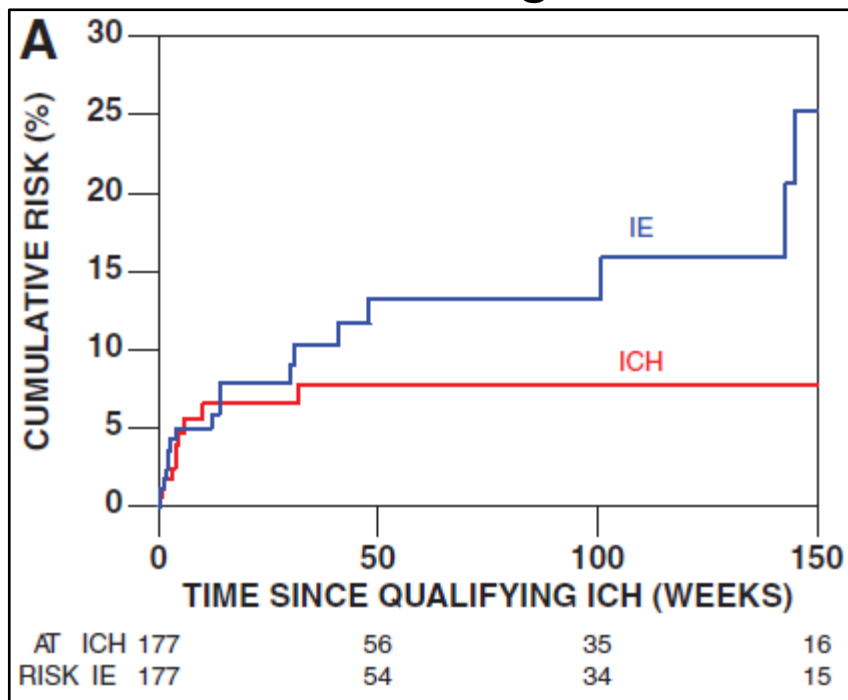
Major Complications Rates Across Watchman Clinical Studies

Procedural Parameters	Aggregate Clinical Data
Number of Procedures	6,720
Implantation Success, %	94.9%
Complication Rates	
Pericardial Tamponade	1.24%
Procedure-Related Stroke	0.18%
Device Embolization	0.25%
Procedure-Related Death	0.06%

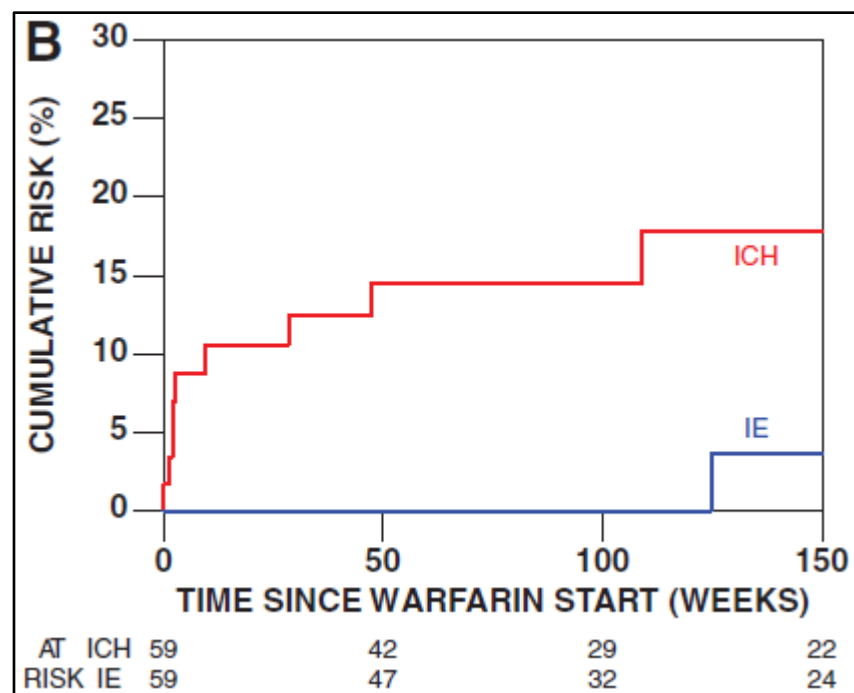
Patients with Intracranial Hemorrhage

Risk of Recurrent Intracranial Hemorrhage and Ischemic Event

Without Resuming Warfarin

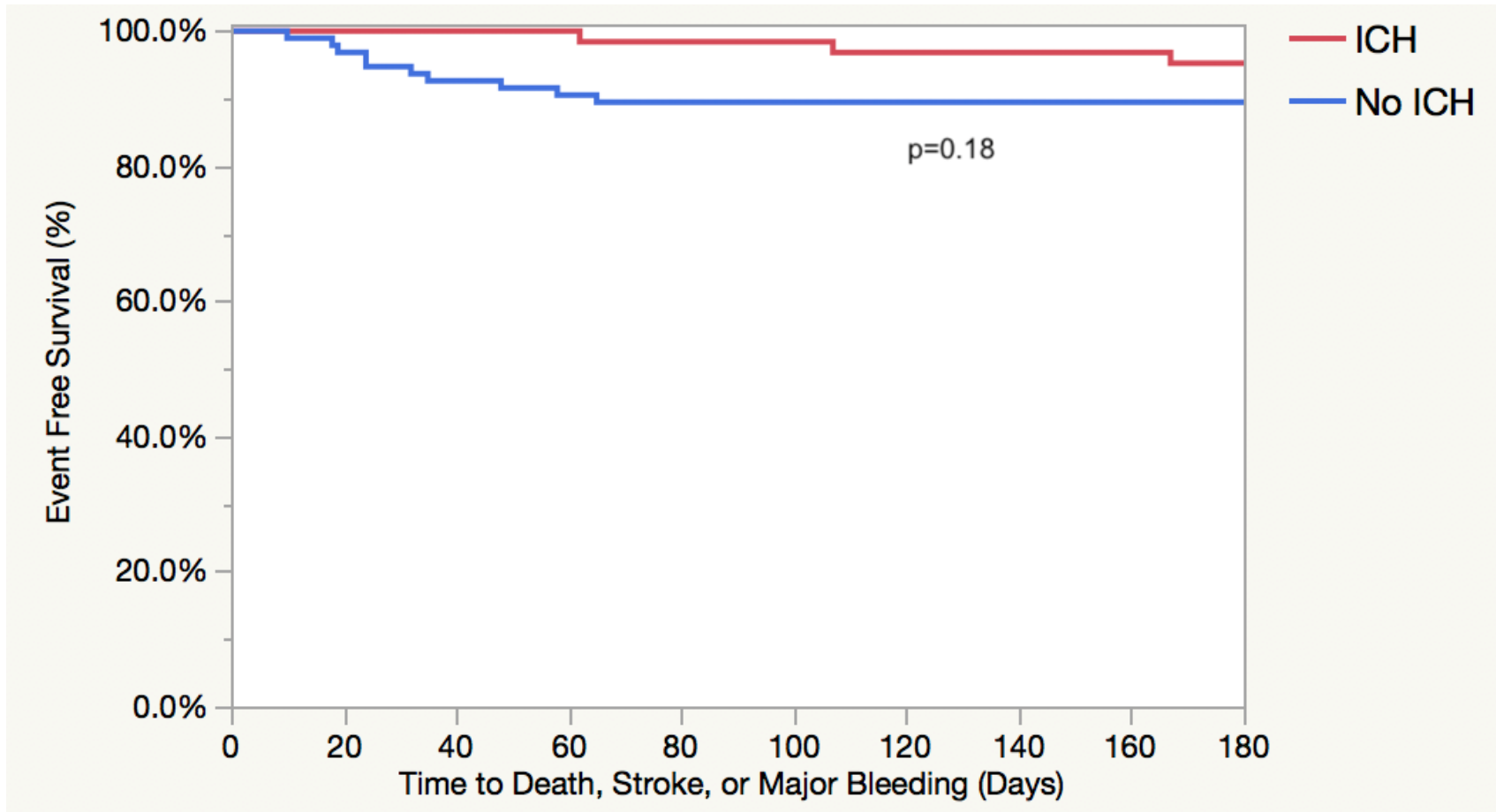


After Resuming Warfarin

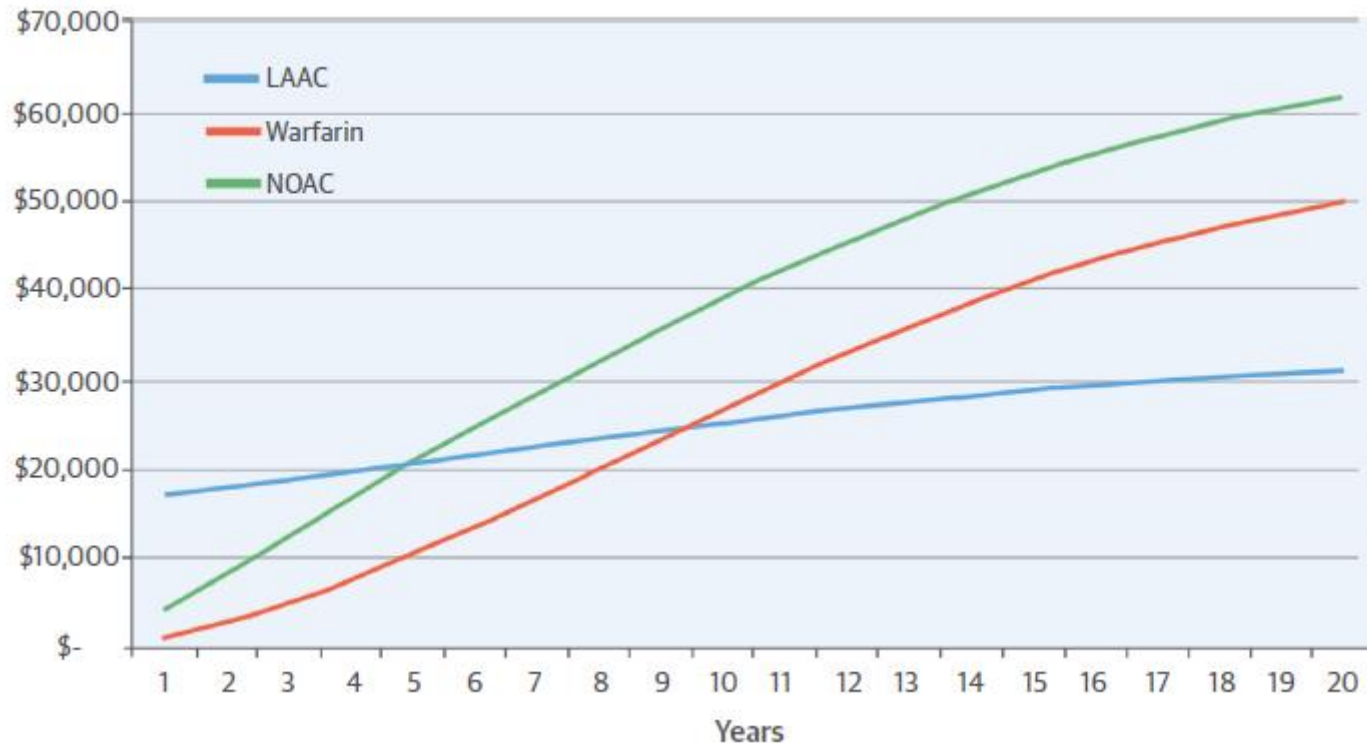


Majeed et al Stroke 2010

Composite Endpoint of Death, Stroke, or Major Bleeding After WATCHMAN



Time to Cost-Effectiveness Following Stroke Reduction Strategies in AF Warfarin Versus NOACs Versus LAA Closure



Reddy et al. JACC 2015

Summary

- Catheter ablation is more effective than medications for restoring normal sinus rhythm in patients with symptomatic AF
- Closure of the LAA provides an alternative strategy to chronic anticoagulation therapy for stroke prophylaxis in patients with AF