Half Moon Bay 2018

Treatment of Atrial Fibrillation

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Disclosures: Investor Farapulse

Things a Primary Care Doctor Should be Able to do for Atrial Fibrillaiton

- Make the diagnosis
- Start a NOAC
- Start a rate control drug
- Call an electrophysiologist
- Do not panic! The ER is rarely necessary

Points to Cover

- Anticoagulation: who and with what drug
- Drug therapy
  - Rate control
  - Antiarrhythmic drugs
- Ablation

Who to anticoagulate?

- Everyone with atrial fibrillation has a greater risk of a stroke than a similar person without atrial fibrillation
- It has been considered that the risk of stroke was the same for paroxysmal AF and persistent AF
- The real concern with oral anticoagulation is intracranial bleeding (about 1% for warfarin and 0.5% for NOACs)

Flies in the Ointment?

- The $CHADS_2$ score was derived in the 1990s
- The risk of a stroke is now lower for all $CHADS_2$ scores than it was in the 1990s
- CHA_2DS_2-VASc may predict strokes better but it…..
  - May include some atherosclerotic stokes
  - Was derived and/or validated largely in Scandinavian hospitalized patients with AF
  - Markedly increase the number of patients needing anticoagulation
- The only trials of anticoagulation ***randomized to placebo or ASA*** were done largely before either score was developed
- Low atrial fibrillation "burden" may carry lower risk of stroke
- What about diastolic heart failure?
- What about controlled hypertension?

$CHADS_2$ Risk Criteria

Score	$CHADS_2$ Risk Criteria
1 point	Congestive heart failure
1 point	Hypertension
1 point	Age ⩾75 years
1 point	Diabetes mellitus
2 points	Stroke/transient ischemic attack

$CHADS_2$ Score and Corresponding Annual Stroke Risk

CHADS2 Score	Adjusted Stroke Risk (%)
0	1.9
1	2.8
2	4
3	5.9
4	8.5
5	12.5
6	18.2

CHA_2DS_2-VASc Risk Criteria

Score	CHA_2DS_2-VASc Risk Criteria
1 point	Congestive heart failure
1 point	Hypertension
2 points	Age ⩾75 years
1 point	Diabetes mellitus
2 points	Stroke/Transient Ischemic Attack/Thromboembolic event
1 point	Vascular disease (prior MI, PAD, or aortic plaque)
1 point	Age 65 to 74 years
1 point	Sex category (ie, female sex)

CHA_2DS_2-VASc Score and Corresponding Annual Stroke Risk

CHA_2DS_2-VASc Score	Adjusted Stroke Risk, (%per year)
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

Treatment Recommendations Based on CHA_2DS_2-VASc Score

CHA_2DS_2-VASc Score	Recommendation
0	None
1	None or aspirin or OAC
2 or more	OAC

Europace
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CLINICAL RESEARCH

Comparison of $CHADS_2$ and CHA_2DS_2-VAS_C anticoagulation recommendations: evaluation in a cohort of atrial fibrillation ablation patients

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Aims Atrial fibrillation (AF) is associated with a high incidence of strokes/thromboembolism. The $CHADS_2$ score assigns points for several clinical variables to identify stroke risk. The CHA_2DS_2-VAS_C score uses the same variables but also incorporates age 65 to 74, female gender, and vascular disease in an effort to provide a more refined risk of stroke/thromboembolism. We aimed to examine oral anticoagulation (OAC) recommendations for a cohort of patients undergoing AF ablation depending upon whether thrombo-embolic risk was determined by the $CHADS_2$ or CHA_2DS_2-VAS_C score.

Methods and results For 1411 patients we compared OAC recommendations for each of these risk stratification schemes to one of the three OAC strategies: (i) NO-OAC, (ii) CONSIDER-OAC, and (iii) DEFINITE-OAC. Compared with the $CHADS_2$ score, the CHA_2DS_2-VAS_C score reduced NO-OAC from 40.3 to 21.8% and CONSIDER-OAC from 36.6 to 27.9% while increasing DEFINITE-OAC from 23.0 to 50.2% of patients. Age 65 to 74 and female gender accounted for 95.2% and vascular disease for only 4.8% of recommendations for more aggressive OAC using CHA_2DS_2-VAS_C. Most vascular disease occurred in patients with higher $CHADS_2$ scores already recommended for DEFINITE-OAC ($P < 0.0001$). Reclassifying 30 females of age <65 with a CHA_2DS_2-VAS_C score of 1 to the NO-OAC group had minimal effect on the overall recommendations.

Conclusion Compared with the $CHADS_2$ score, in our AF ablation population, the CHA_2DS_2-VAS_C score markedly increases the number of AF patients for whom OAC is recommended. It will be important to determine by randomized trials if this major paradigm shift to greater use of OAC using the CHA_2DS_2-VAS_C scoring improves patient outcomes.

Keywords Atrial fibrillation • Anticoagulation • CHA_2DS_2-VAS_C score • $CHADS_2$ score

Prior Randomized Trials of OAC vs. Placebo or ASA

Table 3 Summary of randomized trials of OAC vs. aspirin in patients with non-valvular AF with outcomes evaluated by stroke risk (not specified, low risk or high risk)

Study	Number of patients	Patient population	Stroke risk		
			Not specified	Low risk	High risk
AFASAK[6]	1007	Ambulatory, no CVA within 1 month	Warfarin superior		
SPAF[9]	1100	Age >60, no CVA within 2 years	Warfarin = Aspirin		
PATAF[5]	729	Ambulatory patients, average age = 75	Warfarin = Aspirin		
BFTA[4]	973	Ambulatory, age >75		Warfarin superior[a]	Warfarin = aspirin[b]
Meta-analysis[29]	4052	Six randomized trials warfarin vs. aspirin		Warfarin = aspirin[c]	Warfarin superior[d]
AVERROES[13]	5599	High risk for CVA and unsuitable for warfarin		Apixaban = aspirin[e]	Apixaban superior[f]
EAFT[3]	455	All patients with recent CVA/TIA			Warfarin superior[g]

[a]$CHADS_2$ scores 1 and 2.
[b]$CHADS_2$ scores 3–6 (small number of patients).
[c]No hypertension, diabetes, or prior CVA/TIA.
[d]Hypertension, diabetes, or prior CVA/TIA.
[e]$CHADS_2 = 0$ or 1.
[f]$CHADS_2 \geq 2$.
[g]Prior CVA/TIA.

Influence of Vascular Disease as Defined by CHA_2DS_2-VASc on Recommendation for OAC

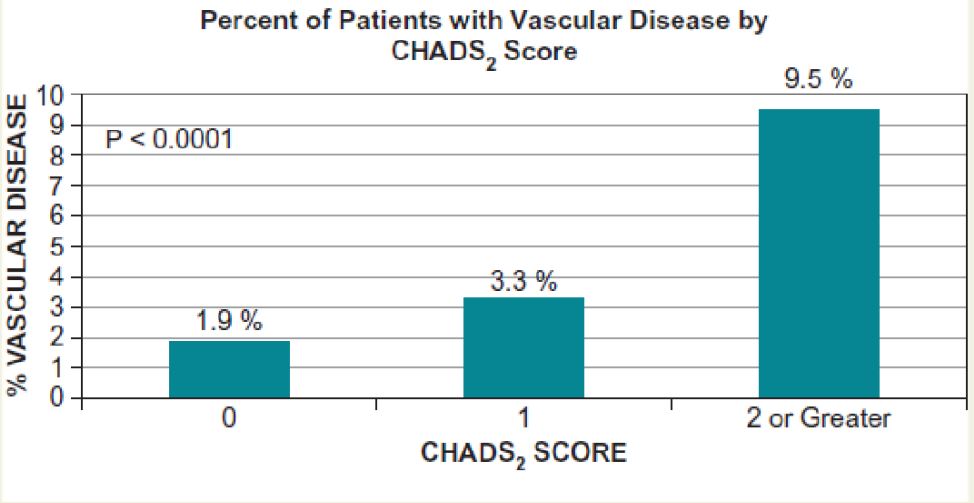


Figure 1 The percent of patients in each $CHADS_2$ score range with vascular disease. Most vascular disease occurs in patients with a $CHADS_2$ score of ≥ 2 and therefore rarely changes the anti-coagulant recommendation when patients are evaluated using the $CHA_2DS_2VAS_C$ scoring system.

Compared to the $CHADS_2$ score, the CHA_2DS_2-VAS_C score

- Reduced NO-OAC from 40.3% to 21.8%
- Reduced CONSIDER-OAC from 36.6 to 27.9%
- Increased DEFINITE-OAC from 23.0% to 50.2% of patients.
- Age 65 to <75 and female gender accounted for 95.2% and vascular disease for only 4.8% of recommendations for more aggressive OAC using CHA_2DS_2-VAS_C.
- Most vascular disease occurred in patients with higher $CHADS_2$ scores already recommended for DEFINITE-OAC ($P<0.0001$).
- Reclassifying 30 females < age 65 with a CHA_2DS_2-VAS_C score of 1 to the NO-OAC group had mimimal impact on overall recommendations
- We need randomized trial data to justify the adopting recommendations for widespread use of OAC in moderately low and intermediate risk AF patients.

Current Anticoagulant Drugs for AFib

Drug	Mchanism of Action	Usual Dose Comments	Common Side Effects (Other than bleeding)	Reversal agent
Warfarin	Vitamin K antagonist	Depends on prothrombin time Lots of interactions Must be used for mechanical heart valves	Very few	PCC (prothrombin complex concentrate) Fresh frozen plasma Vitamin K
Dabigatran	Direct thrombin inhibitor	75 or 150 mg bid Lower dose with impaired renal function(CrCl 15-30)	GI	Idarucizumab (Praxbind) Fab binds to drug
Rivaroxaban	Factor Xa inibitor	15 or 20 mg a day with largest meal Lower dose CrCl 15-50	Very few	Andexxa Recombinent Factor Xa
Apixaban	Factor Xa inibitor	2.5 or 5 mg bid Least renal excretion (30%) Lower dose if 2 of 3 Age $\geq$ 80 Weight $\leq$ 60 Cr $\geq$ 1.5	Very few	Andexxa Recombinent Factor Xa
Edoxaban	Factor Xa inibitor	30 or 60 mg daily 50% Renal Lower dose if CrCl 15-50	Very few	PCC, ? Andexxa Recombinent Factor Xa

Generalizations
Warfarin vs NOACS for non-valvular AF

- Faster onset of anticoagulation with NOACs (? pill in pocket)
- Higher drug cost with NOACs
- Similar thromboembolic stroke prevention
- Fewer drug interactions with NOACs
- Slightly lower rates of non ICH bleeding with NOACs
- Lower rate of ICH with NOACs
- Slight mortality benefit for NOACs due to reduced ICH
- NOACs should be drug of choice for almost all patients

Oral Rate Control Drugs

- Diltiazem
  - My drug of choice for rate control
  - Works as well as beta blockers
  - Less fatigue, depression and bradycardia
  - For pill in pocket use short acting drug
  - For higher doses divide 24 hour capsules into AM and PM dosing
- Beta blockers
  - Probably most widely used
  - Side effects are a problem, especially at higher doses
  - Drug of choice if CAD or CHF present
- Digoxin
  - Not in vogue due to concerns for safety
  - Remember renal excretion and interactions with verapamil and amiodarone
  - Rate control largely seen at rest, easily overcome with exercise
  - Useful if low blood pressure is a problem

Antiarrhythmic Drugs

- Cause a lot of side effects including death
- Most do not work very well for patients with atrial fibrillation
- Many cannot be given to patients with poor LV function, CAD, sick sinus etc.
- All have “black box” warnings from the FDA which are scary to patients

Current Antiarrhythmic Drugs for AFib

Drug	Vaughn Williams Class	Usual Dose	Common Side Effects	Contraindicated
Amiodarone	III,I,II	100-400 mg a day (long loading period needed)	Skin (discoloration, sunburn) Eyes Thyroid Lung Bradycardia	Reasonable life expectancy or long duration of Rx needed
Sotalol	II,III	40-160 mg bid Renal excretion	Bradycardia Fatigue Torsade	Bradycardia Renal disease Long QT
Dronederone	III	400 mg bid	Very few	Persistent AF CHF
Propafenone	IC,II	150-300 mg tid 225-425 bid for CR	Constipation Wheezing Rapid flutter conduction	Bradycardia Conduction disease CAD with scar or ischemia LV dysfunction
Flecainide	IC	50-200 mg bid	Blurred vision Rapid flutter conduction	Bradycardia Conduction disease CAD with scar or ischemia LV dysfunction
Dofetilide	III	125-500 mcg bid	Torsade	Renal disease

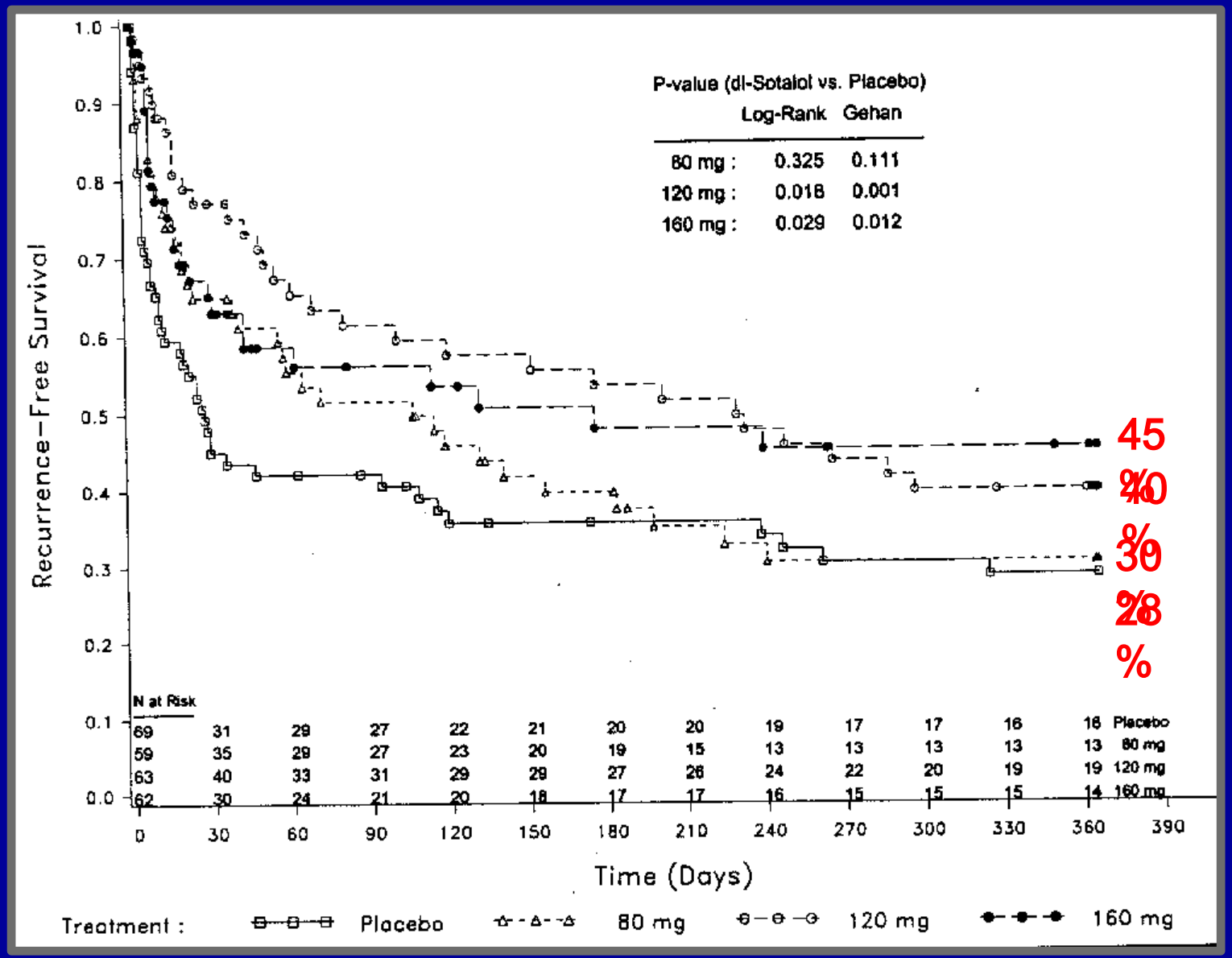
Maintenance of Sinus Rhythm with Oral Sotalol in Patients with Symptomatic Atrial Fib / Flutter

(Benditt et al AJC 1999;84:270-277)

- 253 patients with atrial fibrillation / flutter
- Multicenter, randomized, double-blind study
- Evaluated safety and efficacy of 3 fixed doses of d,l-sololol (80, 120 or 160 mg bid)
- Primary endpoint: time to recurrence of AF
- Treatment continued 1 year or until AF recurred
- Transtelephonic monitoring used

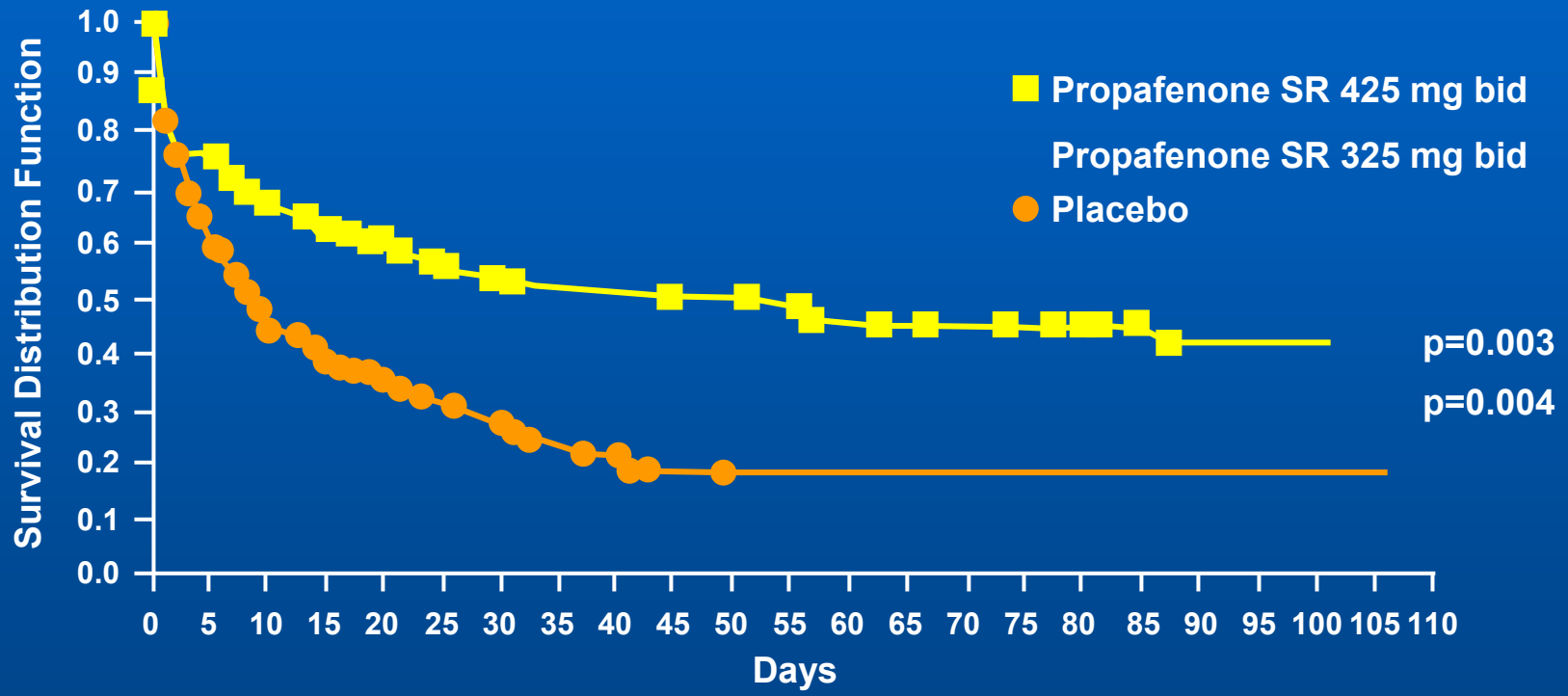
Time to documented AF on Sotalol (80, 120, 160 mg bid) or placeb0
Intention to Treat

PATIENT Axis



FDA

Tachycardia-Free Period (absence of symptomatic AF or flutter) from Day 5 of Randomization in ERAFT



Patients at risk	276	102	79	63

Meinertz T, et al. *Am J Cardiol*. 2002; 90: 1300 - 1306

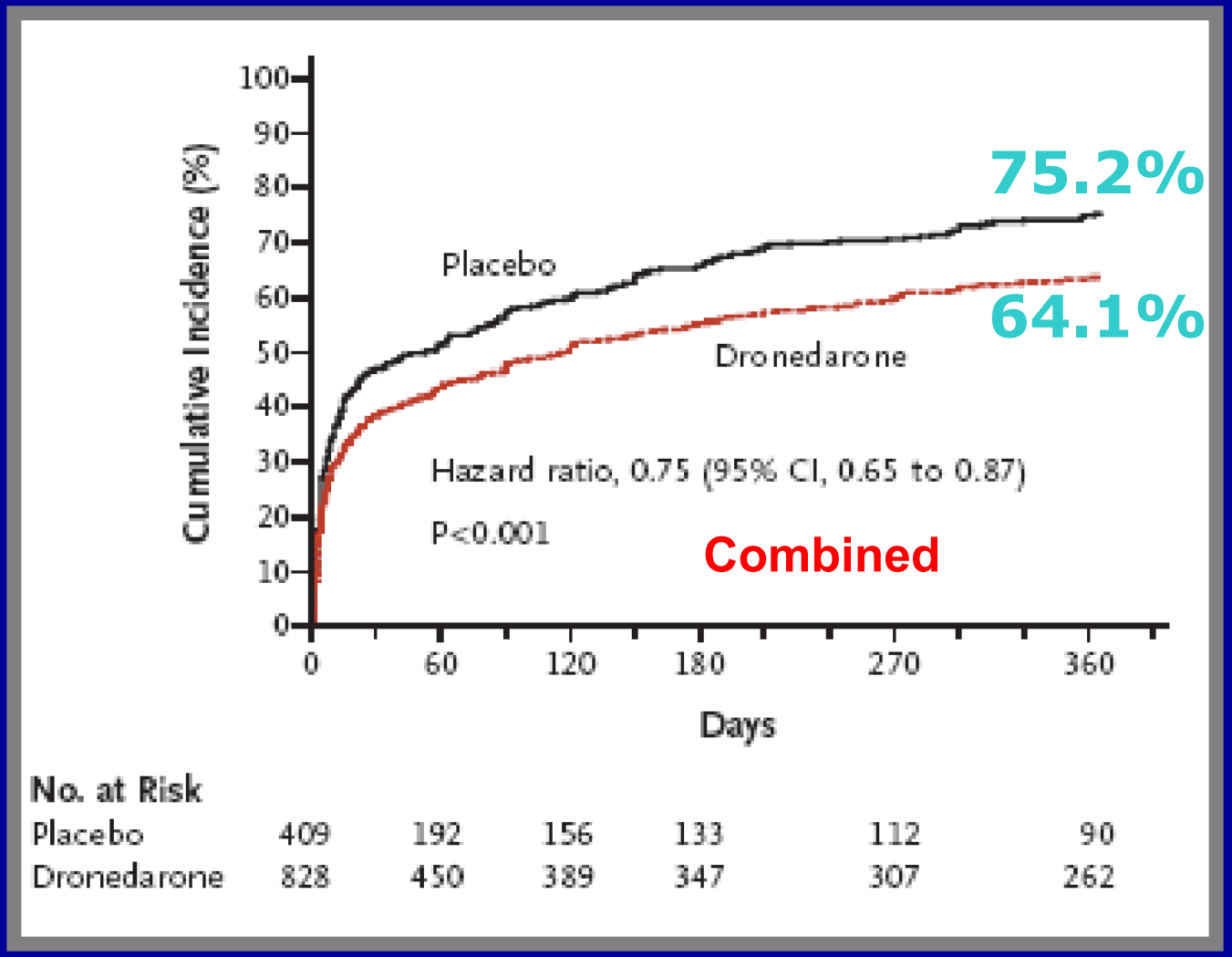
EURIDIS AND ADONIS

(Singh B et al. N Engl J Med 2007;357:987-999)

- Age >21 years
- One episode of Afib in prior 3 months
- In NSR for one hour before randomization
- Randomized 2:1 Dronedarone 400mg bid or placebo
- Endpoint: ***Time to first documented AF lasting 10 minutes***
- Secondary endpoints
  - Symptoms related to AF
  - Mean Ventricular Rate during first AF recurrence

Kaplan-Meier Incidence of First Recurrence of A Fib or Flutter

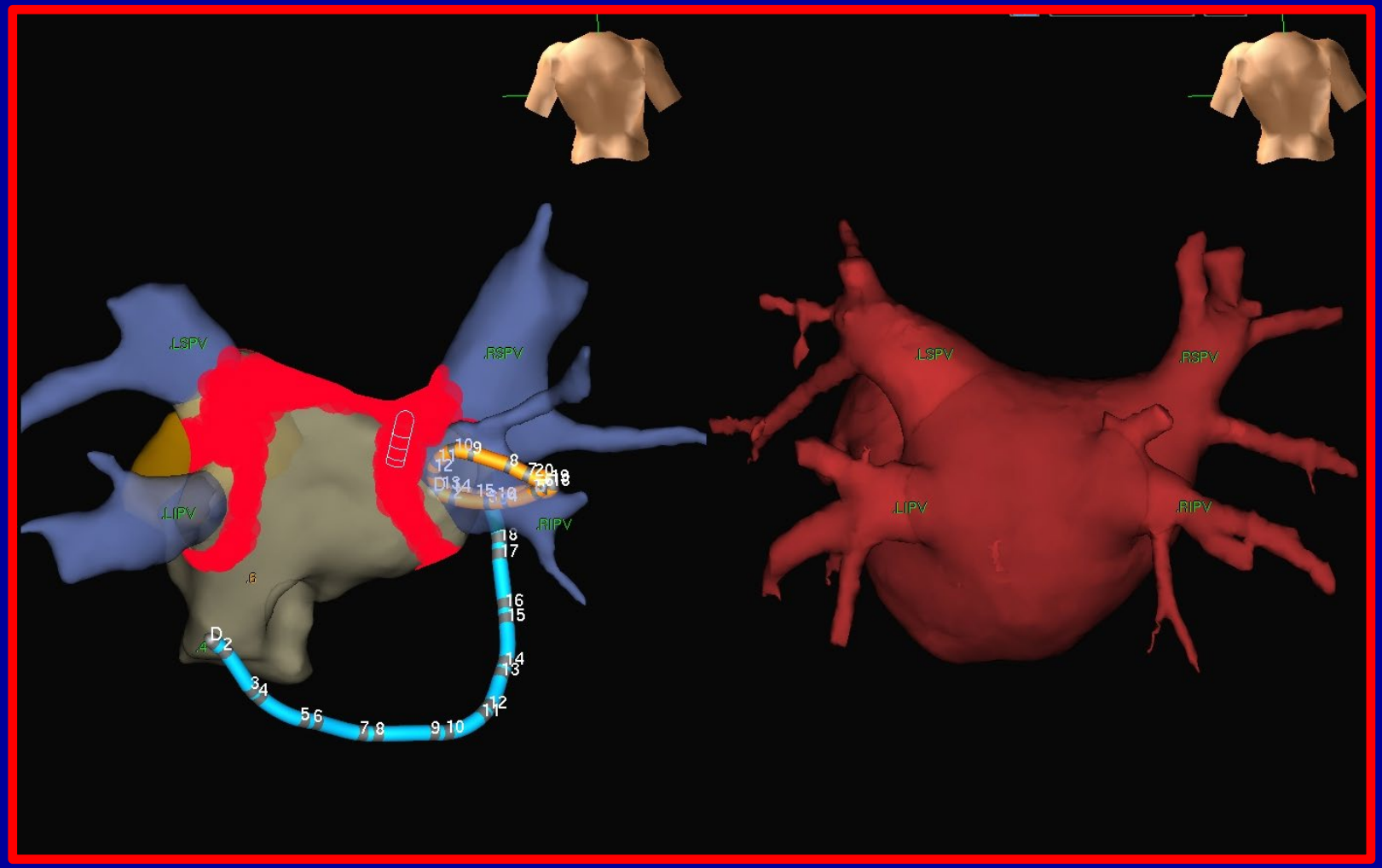
(Singh et al NEJM 2007;357:987-99)



Who Should Have an AF Ablation?

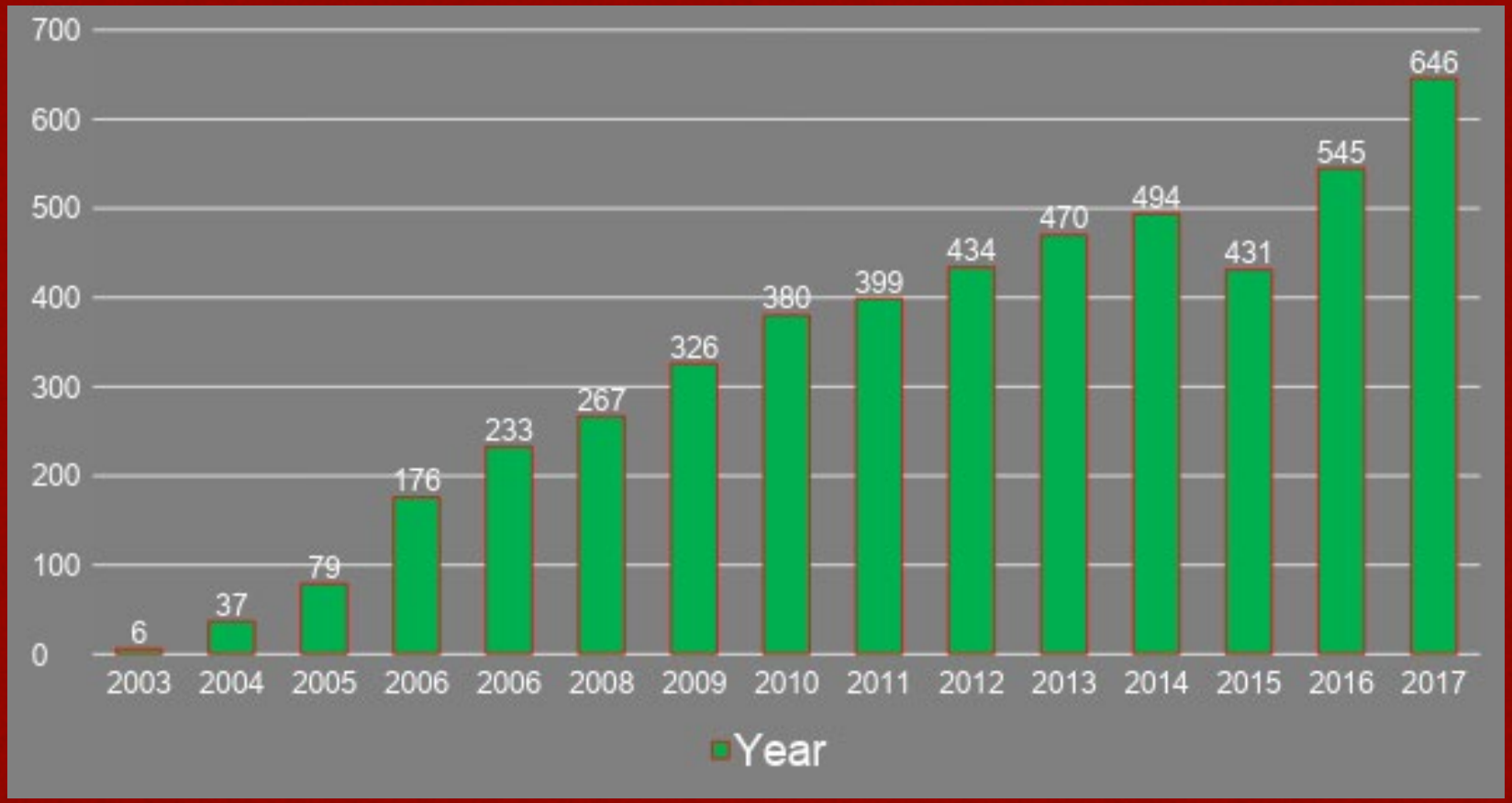
- The primary benefit of AF ablation is elimination of the symptoms of AF and improvement in quality of life.
- Recent CABANA Trial suggests there is also be a benefit it terms of reduced long term mortality and disabling stroke. Approximately 30 % immediate crossover rate
- Asymptomatic patients who may be good candidates for AF ablation include
  - Younger patients in order to avoid a lifetime of drugs
  - Patients with reduced EF or ejection fraction and/or congestive heart failure) and AF. These patients feel better and live longer after ablation
  - Patients who might need a pacemaker to be able to take drugs for AF

What is done at an AF ablation

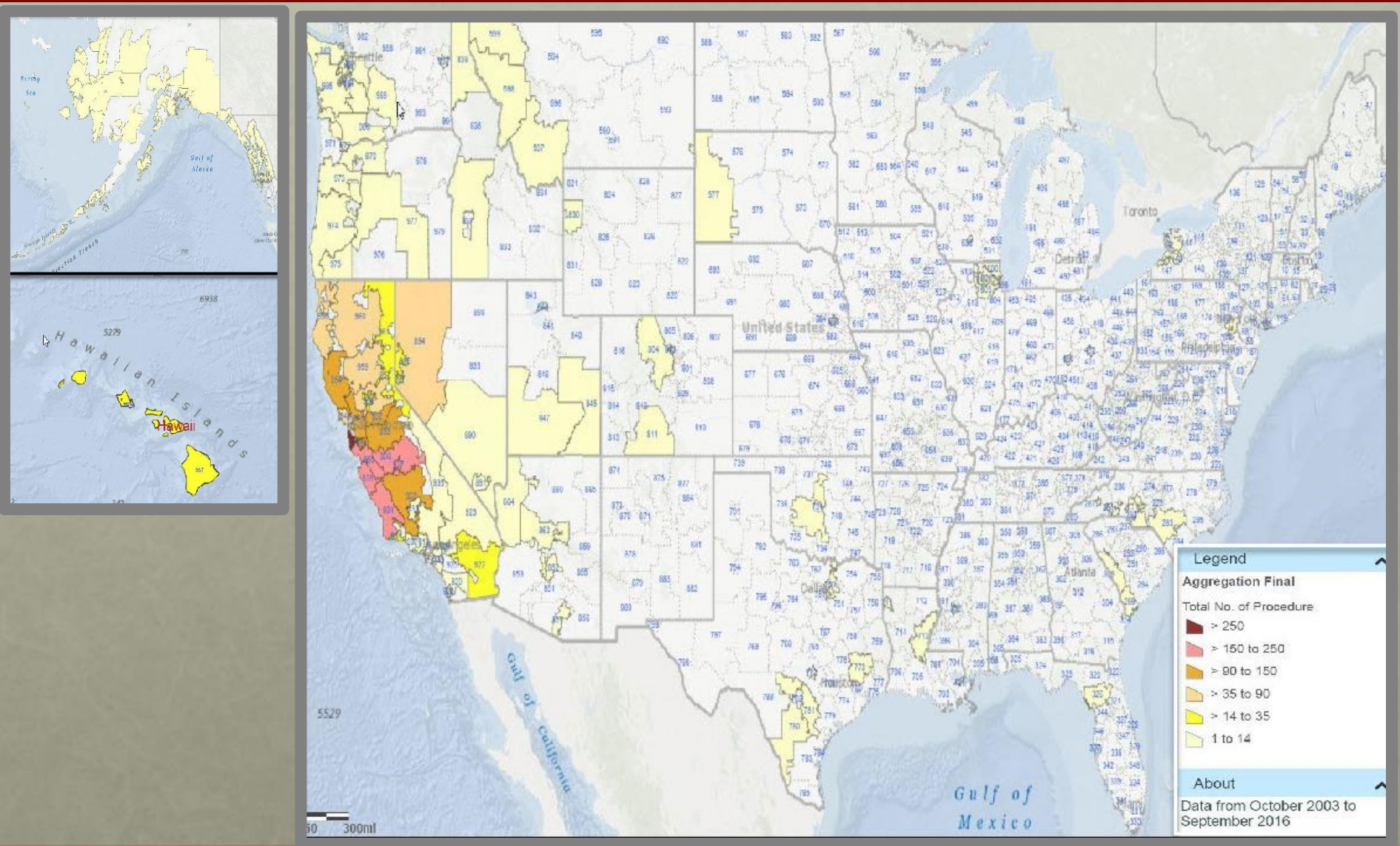


Silicon Valley Cardiology Afib Ablations

(4923 ablations through Dec 31, 2017)



Sequoia AFIB Ablation Patients:
Distribution by Zip Code



Sequoia Hospital AF Ablation: Impact of number of AADs failed pre-ablation

(Winkle et al. Europace 2012;14:646-652)

Europace
doi:10.1093/europace/eur370

CLINICAL RESEARCH

Prior antiarrhythmic drug use and the outcome of atrial fibrillation ablation

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Aims Atrial fibrillation (AF) ablation is generally performed after patients fail antiarrhythmic drug (AAD) therapy. Some patients have drug contraindications or choose to avoid a lifetime of drug therapy. Little is known about the impact of previous drug therapy on ablation outcomes. We evaluated AAD use before AF ablation and its impact on ablation outcomes.

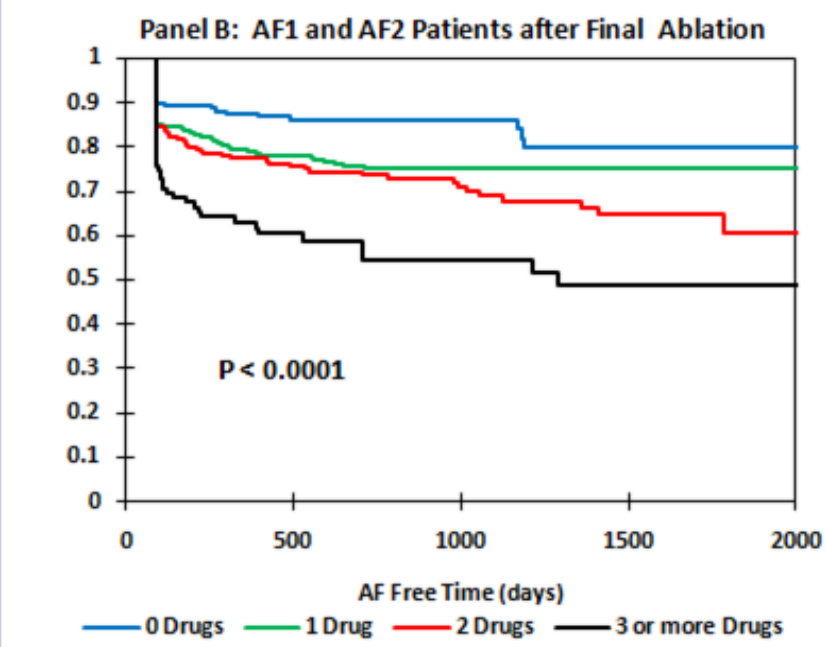
Methods and results We evaluated freedom from AF after ablation and patients' clinical characteristics by number of AADs failed in 1125 patients undergoing 1504 ablations. We also evaluated reasons why some patients did not receive prior drug therapy. Cox multivariate analysis examined factors predicting ablation failure. Patients failing more drugs before ablation were older ($P = 0.001$), had a longer duration of AF ($P = 0.0001$), were more likely female ($P = 0.037$), had more repeat ablations ($P = 0.045$), and less paroxysmal AF ($P = 0.003$). For patients with either paroxysmal or persistent AF, the number of drugs failed predicted AF recurrence ($P = 0.0001$). Other factors predicting AF recurrence following final ablation included age ($P = 0.004$), left atrial size ($P = 0.002$), female gender ($P = 0.0001$), and persistent AF ($P = 0.0001$). The reason for not receiving prior drug therapy was medical in 21.5% and patient choice in 78.5%. Number of drugs failed did not influence ablation outcome for patients with long-standing persistent AF ($P = 0.352$).

Conclusions For paroxysmal and persistent AF patients undergoing ablation, those failing fewer AADs have different clinical characteristics than those who fail more drugs. Our study also suggests that the more drugs failed pre-ablation, the lower the freedom from AF post-procedure, possibly due to AF progression during drug trials.

Keywords Atrial fibrillation • Ablation • Antiarrhythmic drugs • AF ablation outcomes

Sequoia Hospital: AF Ablation Outcome after Initial and Final Ablation by Number of AADs failed Pre-Ablation

(Winkle et al. Europace 2012;14:646-652)

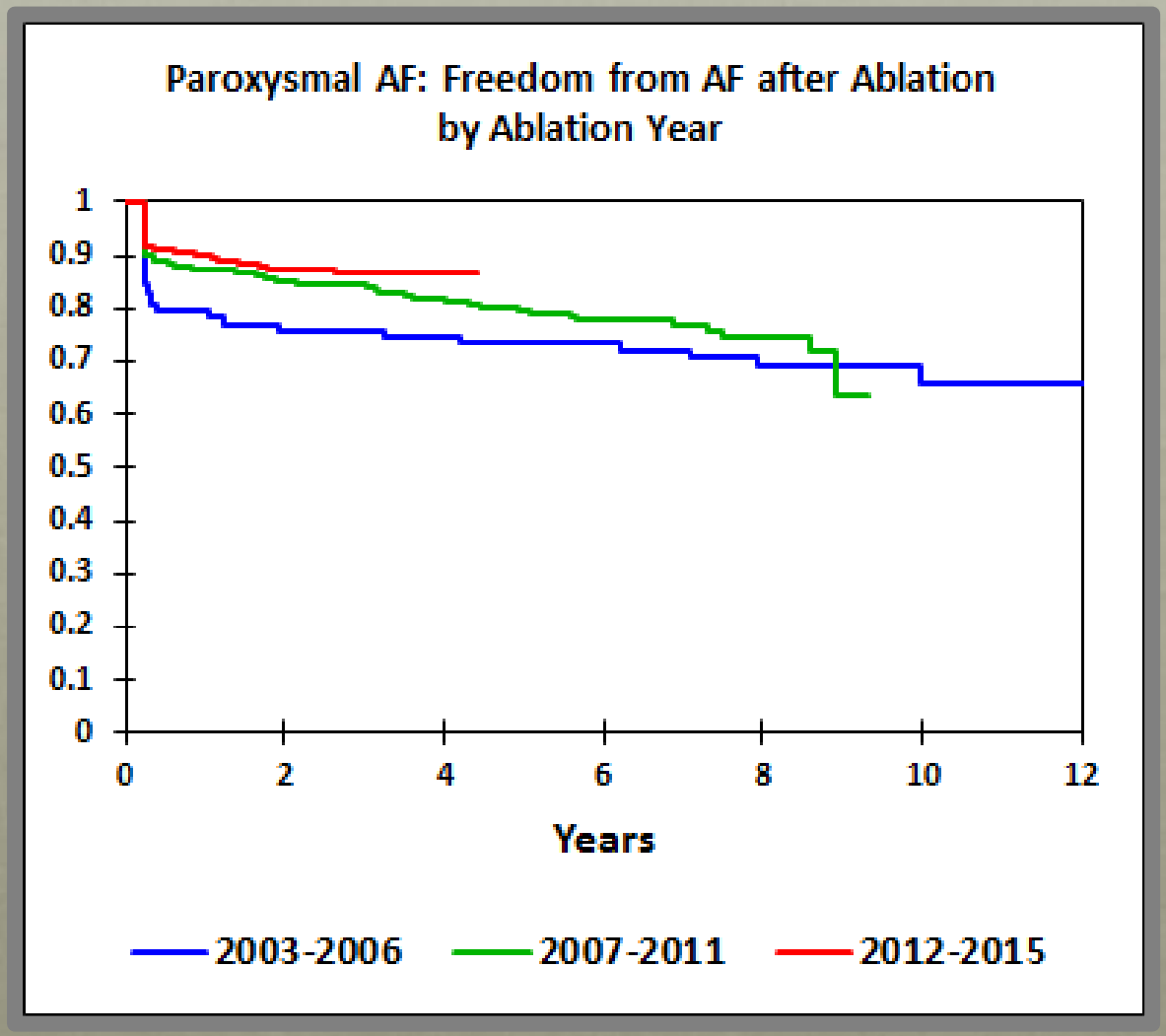


# Drugs	number	1 year	2 year	3 year	4 year
none	195	87.5%(134)	86.0%(81)	86.0%(50)	79.8%(21)
1	400	79.1%(239)	75.0%(156)	75.0%(99)	75.0%(50)
2	232	77.4%(147)	73.7%(101)	69.0%(64)	64.7%(38)
≥3	115	63.0%(50)	54.7%(27)	54.7%(22)	48.6%(14)

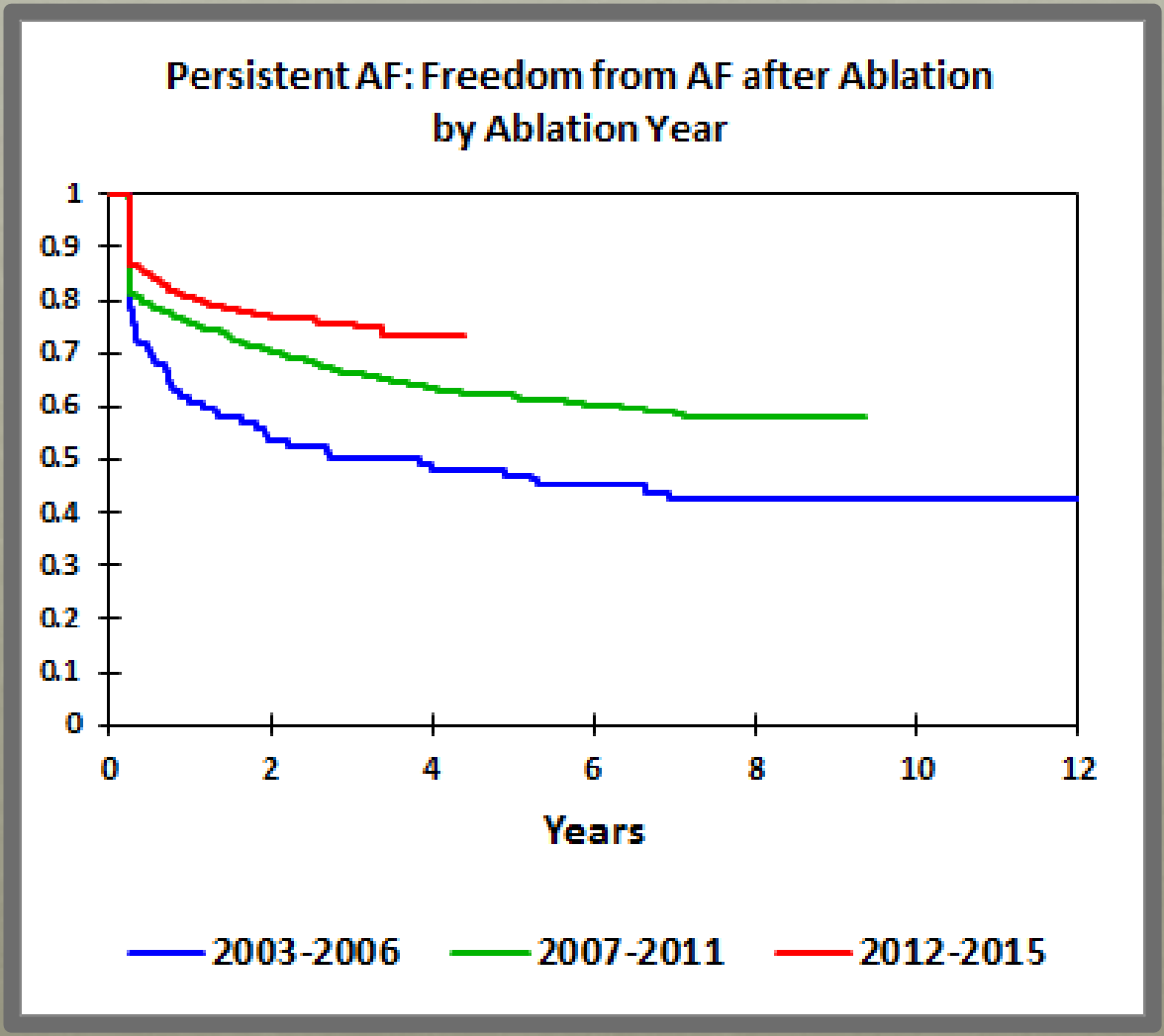
Redo ablations are getting much less frequent as ablations improve

	2003-06 Redo Rate	2007-11 Redo Rate	2012-15 Redo Rate
Paroxysmal	42.2%	30.5%	15.3%
Persistent	58.3%	41.7%	24.1%
Long-standing	55.8%	57.7%	26.4%

Paroxysmal AF

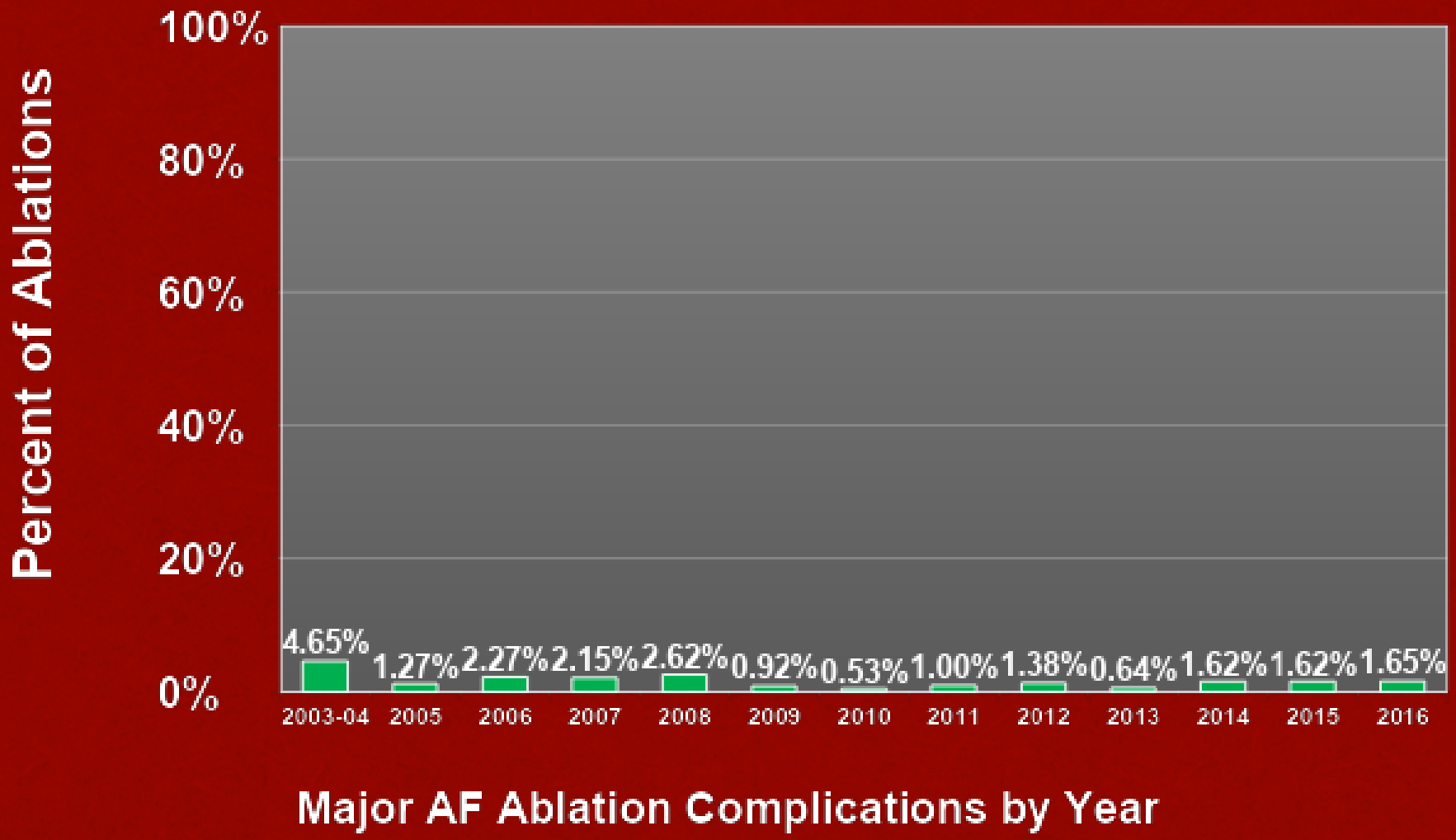


persistent AF

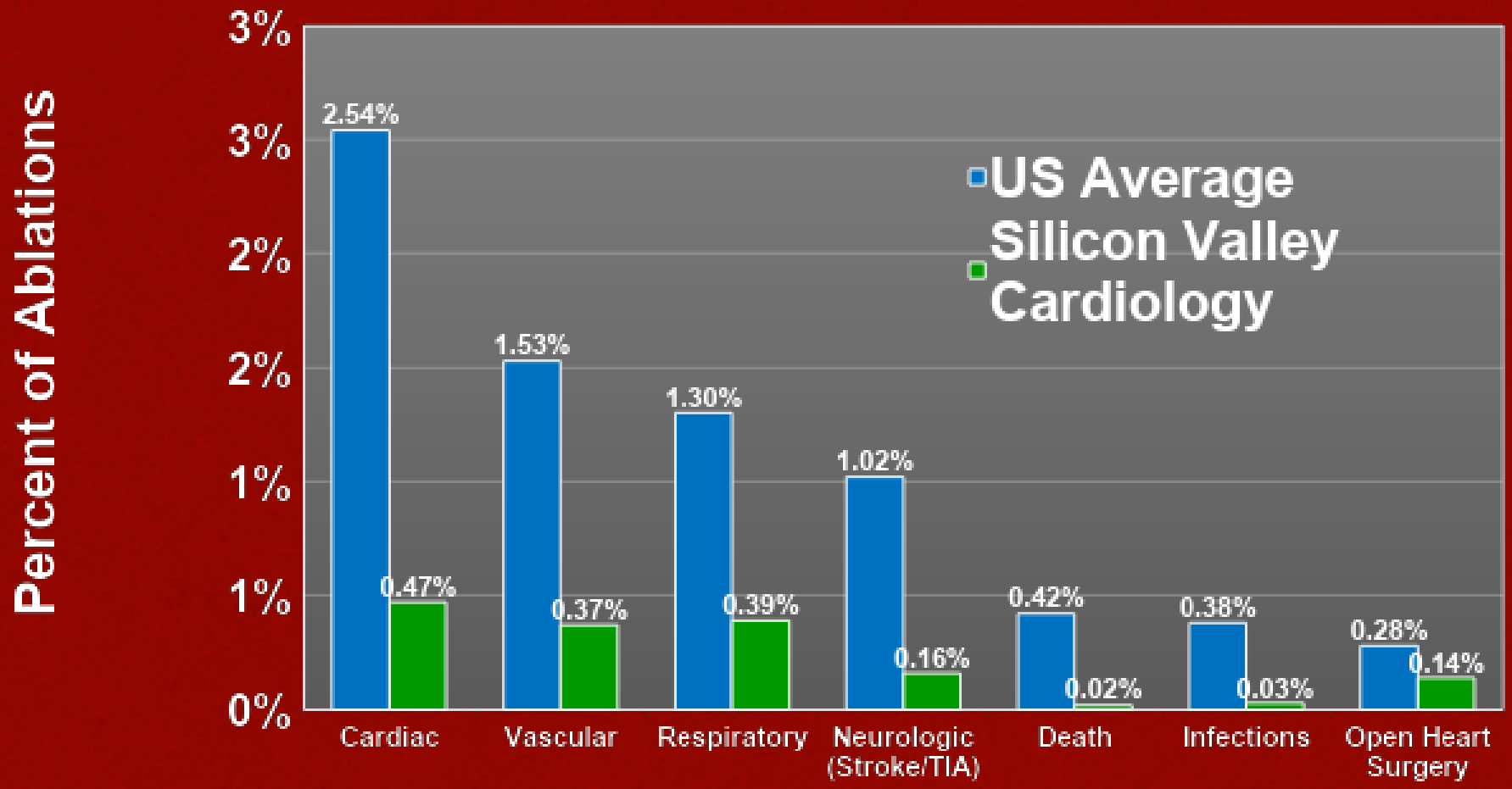


Sequoia Hospital Major AF Ablation Complications by Year

(4277 ablations through 2016)

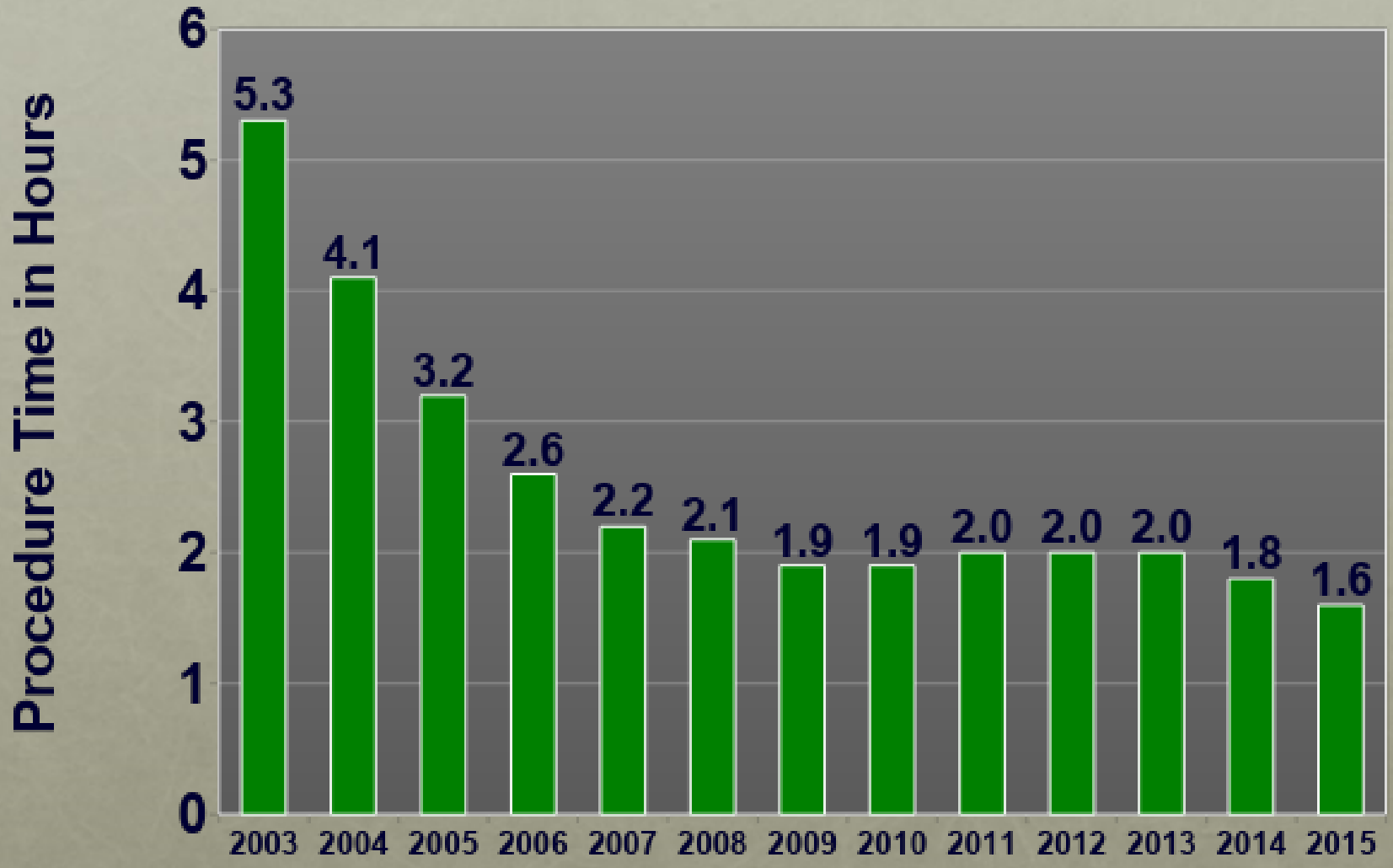


Silicon Valley Cardiology AF Ablation Complications Compared to US Average



AF Ablation Complications: US Average vs. Silicon Valley Cardiology

Sequoia Hospital Afib Ablation Procedure Times by Year



Conclusions

- Antiarrhythmic drugs do not work very well over the long term
- Ablation therapy is superior to AADs
  - More pts free of afib
  - Reduced stroke risk
  - Frequently improves or normalizes LV function
  - May avoid pacer in some patients
- Patients should be referred earlier for ablation
  - Before their LA increases too much
  - Before they become persistent or long=standing
  - Before they fail lots of AADs