EP Today and Tomorrow: Where Are We and Where Are We Going

Gerald V. Naccarelli, MD
Bernard Trabin Chair in Cardiology
Professor of Medicine; Chief, Division of Cardiology
Vice Chair Operations and Research
Penn State HVI
Penn State University College of Medicine Hershey, PA

Consultant: Sanofi, Acesion, Milestone, Glaxo Smith Kline, InCardia Therapeutics

Clinical Cardiac Electrophysiology: Then and Now

- 1970's: His Bundle recordings; Conduction studies; Site of Block; Early days of SVT and VT initiation by programmed stimulation; VVI and early days of dual chamber pacing
- 1980's: Serial Drug Testing for VT; Mapping and Surgery for VT and WPW; DC shock AVJ ablation; VVIR and DDD pacing; OR implant of ICDs with epicardial patches for secondary prevention of SCD; RF catheter ablation of PSVT; Internal catheter DC Cardioversion
- 1990's: Growth of PSVT ablations; Biphasic shock transvenous ICDs implanted; Limited growth of MAZE procedures; First observation of pulmonary vein triggers for AF
- 2000-2023: Primary prevention ICDs; CRT-ICDs; Marked decrease in sustained VT in CAD due to lytics and PCI; Growth of AF and VT ablations; Lead Extractions, ILRs

Antiarrhythmic Drugs Approved over Last 40 Years

- Verapamil (IV, oral)
- Diltiazem (IV, oral)
- Mexiletine
- Tocainide
- Encainide
- Flecainide
- Propafenone
- Ethmozine
- Sotalol (IV, oral)
- Amiodarone (IV, oral)
- Dofetilide
- Dronedarone

All but dofetilide and dronedarone initially developed for the treatment of ventricular arrhythmias

IV and Oral amiodarone used frequently but with only a VT/VF indication

USA FDA Approved Antiarrhythmic Drugs for Rx of AF

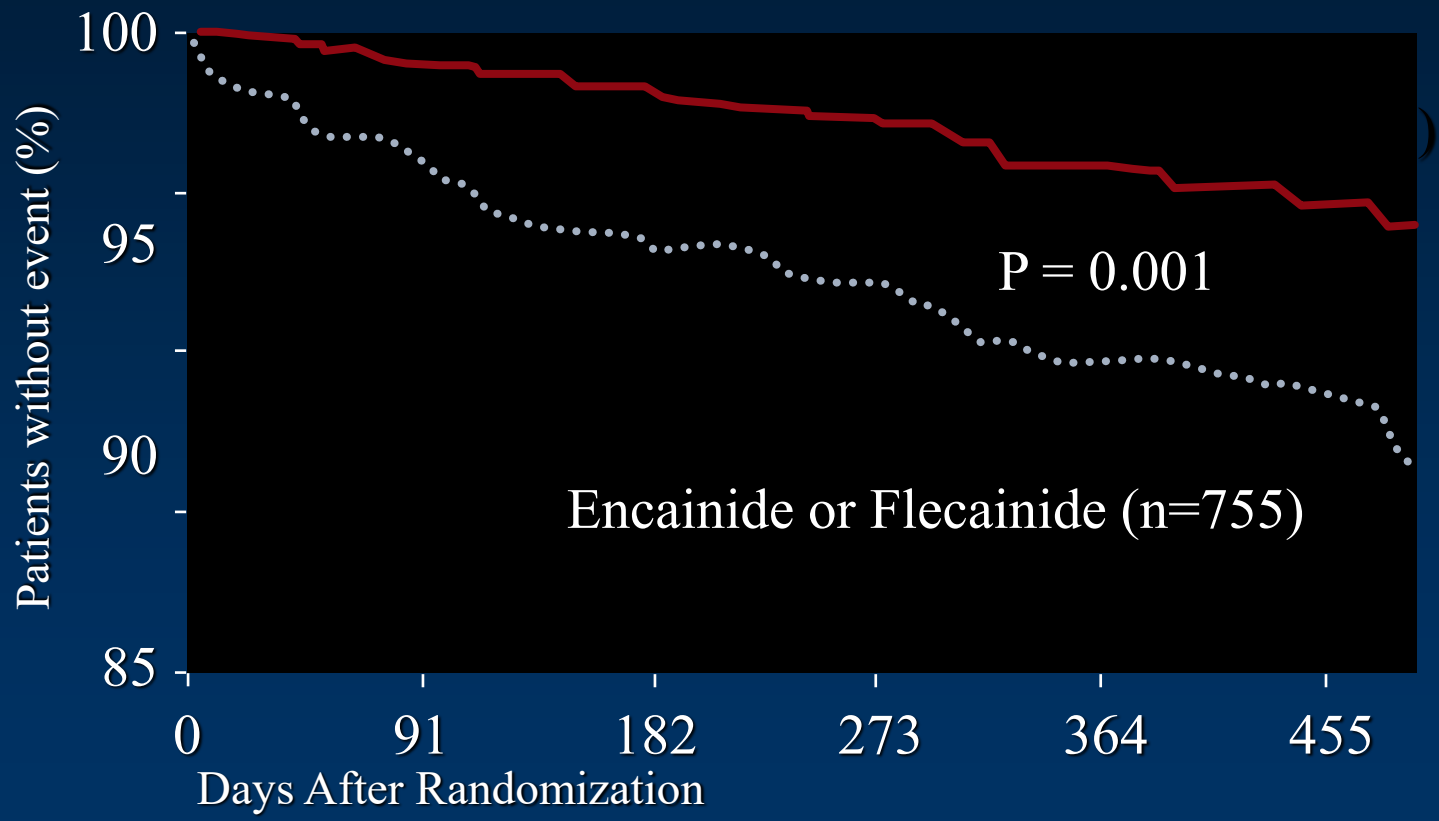
- Quinidine – pre-1970
- Flecainide (Tambocor) -1987
- Propafenone (Rythmol; Rythmol-SR) - 1988
- Sotalol (Betapace-AF) - 1996
- Ibutilide (Corvert) - 1997
- Dofetilide (Tikosyn) - 2001
- Dronedarone (Multaq) - 2009

Antiarrhythmic Drug Trials That Altered Clinical Landscape over Last 40 Years

- CAST
- AFFIRM
- ATHENA
- PALLAS
- EAST AF-NET

CAST-1

Prognosis of Post-MI Patients Treated with Placebo vs. Encainide/Flecainide



Echt DS. N. Engl J Med. 1991; 324:781-788

Trials of Rhythm and Rate Control in AF
AFFIRM, RACE, AF-CHF, PIAF, STAF, HOT CAFÉ

- Major overall findings
  - Rhythm control was not superior to rate control in terms of morbidity/mortality
  - Rate control is an acceptable primary therapeutic option
  - Patients with AF and risk factors for stroke should receive anticoagulation indefinitely, even when sinus rhythm appears to be restored and maintained
- Both strategies are acceptable but…
- Rate control does not apply to all patients with AF
  - Particularly to very symptomatic patients (symptomatic despite rate control)
  - Young patients
  - Patients in whom exercise tolerance is important
  - Patients in whom rate control failed
  - Some patients with depressed LV function
- Clinician's should adapt the therapeutic strategy to the individual

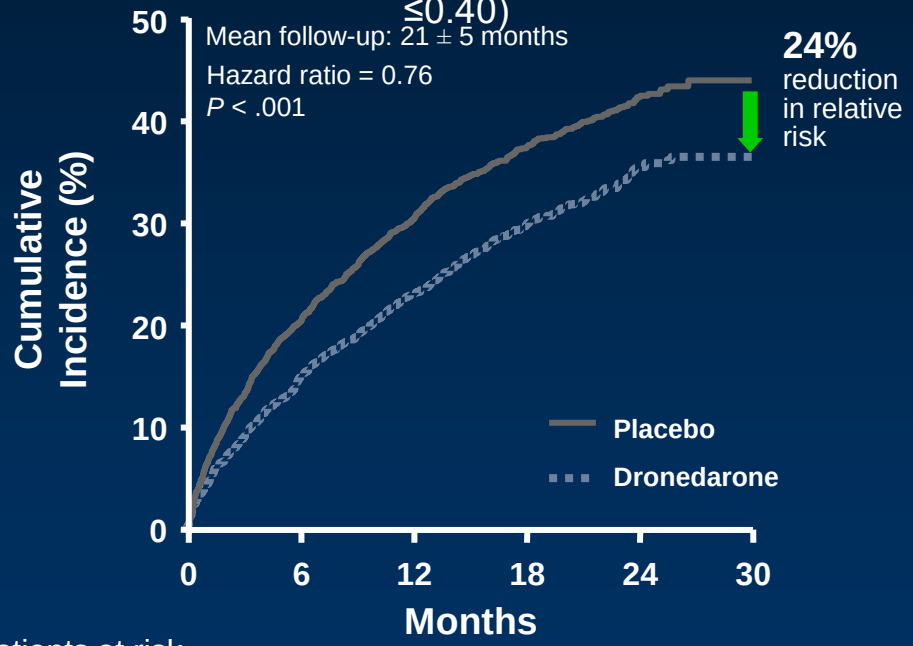
Hohnloser SH, et al. Lancet. 2000;356:1789-1794. Wyse DG, et al. N Engl J Med. 2002;347(23):1825-1833. Van Gelder IC, et al. N Engl J Med. 2002;347(23):1834-1840. Opolski G, et al. Chest. 2004;126: 476-486. Vora A, et al. J Cardiovasc Pharmacol Ther. 2004;9(2):65-73. Ogawa S, et al. Circ J. 2009; 73(2):242-248. Carlsson J, et al. J Am Coll Cardiol. 2003;41(10):1690-1696. Roy D, et al. N Engl J Med. 2008;358(25):2667-2677. Reiffel JA. J Atr Fibrillation 2008; 1:31-47.

Dronedarone: ATHENA and PALLAS

ATHENA: PAF or Persistent AF

Primary outcome: time to first CV hospitalization or death

N = 4628 (PAF or persistent AF) randomized
≥75 y with or w/o additional RF *or* ≥70 y and ≥1 RF (HTN, DM, prior stroke/TIA, LA diameter ≥50 mm, LVEF ≤0.40)



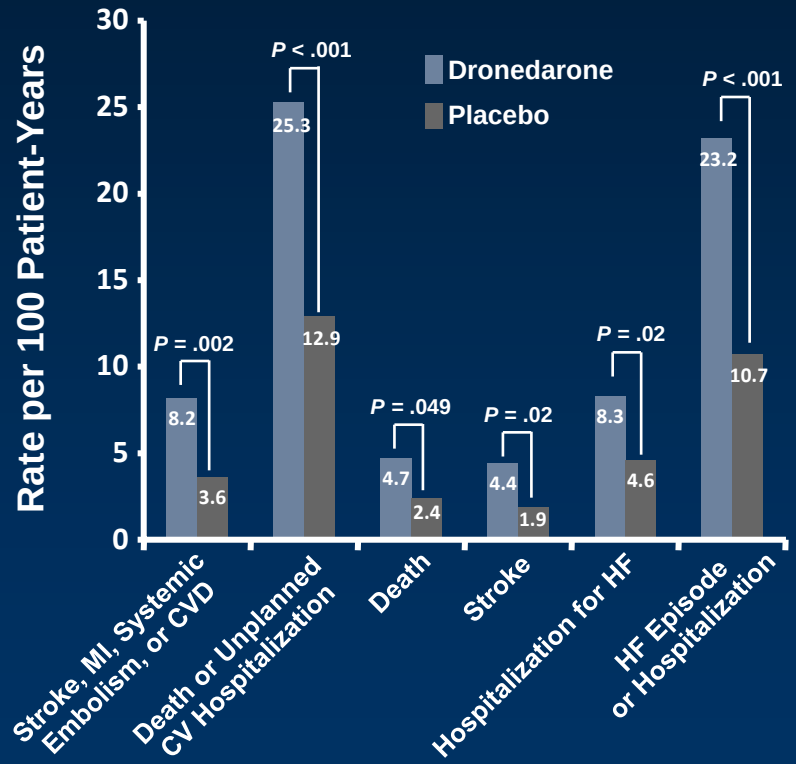
Patients at risk

Placebo	2327	1858	1625	1072	385	3
Dronedarone	2301	1963	1776	1177	403	2

PALLAS: Permanent AF

N = 3236; ≥ 65 y with > 6 mo h/o permanent AF and risk factors for major vascular event

Study stopped for safety reasons



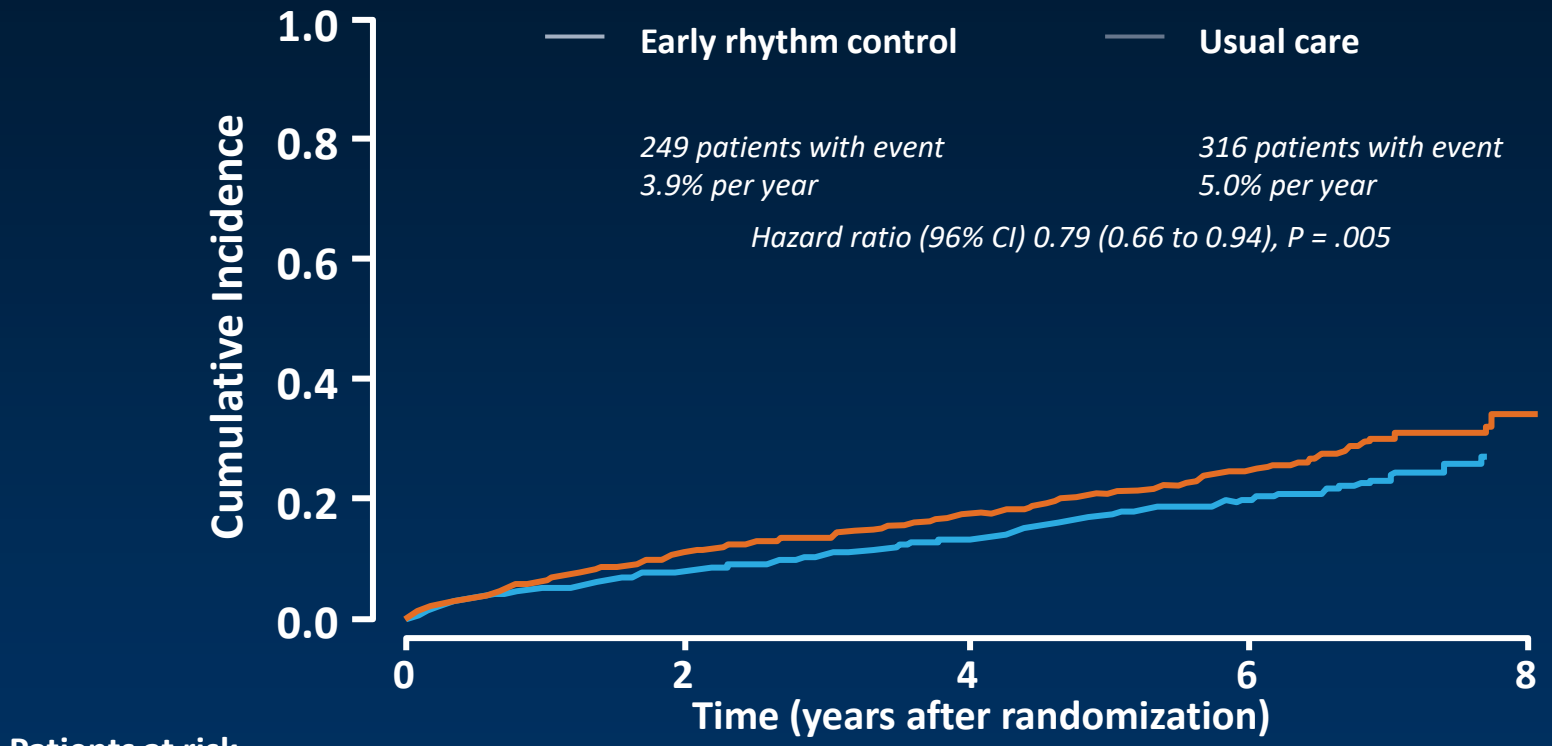
RF = risk factor; HTN = hypertension; DM = diabetes mellitus; TIA = transient ischemic attack; h/o = history of.

Hohnloser S, et al. N Engl J Med. 2009;360:668-678. Connolly S, et al. N Engl J Med. 2011:365:2268-2676.

Singh D, et al. J Am Coll Cardiol. 2010;55:1569-1576.

EAST-AFNET: Primary Outcome

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



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

Sinus rhythm at 2 years: **82.1% in early rhythm control** vs 60.5% in usual care study arm

Kirchoff P, et al. N Engl J Med. 2020;383:1305-1316

Post-MI Secondary Prevention Drug Trials

- ACE inhibitors
  - CONSENSUS II
  - SMILE
  - AIRE
  - TRACE
- Aldosterone antagonists
  - EPHESUS
- β-blockers
  - BHAT
  - BMIS
  - Goteborg
  - APSI
  - CAPRICORN
- ARBs
  - VALIANT
- Amiodarone
  - EMIAT
  - CAMIAT
- Other AAD
  - DIAMOND-MI
  - CAST
  - IMPACT
  - Julian
  - SWORD

Class I – worsened survival
Class III – neutral survival

CHF: Primary Prevention Drug Trials

- ACE Inhibitors
  - CONSENSUS
  - SOLVD etc
- Aldosterone antagonists
  - RALES
  - EPHESUS
- Digoxin
  - DIG Trial
- Beta-blockers
  - COPERNICUS
  - CIBIS-II
  - MERIT
  - BEST
- ARB
  - ELITE-I, II
  - VAL-HeFT
  - CHARM
- Amiodarone
  - GESICA
  - CHF-STAT
  - SCD-HeFT
- Dofetilide
  - DIAMOND-CHF

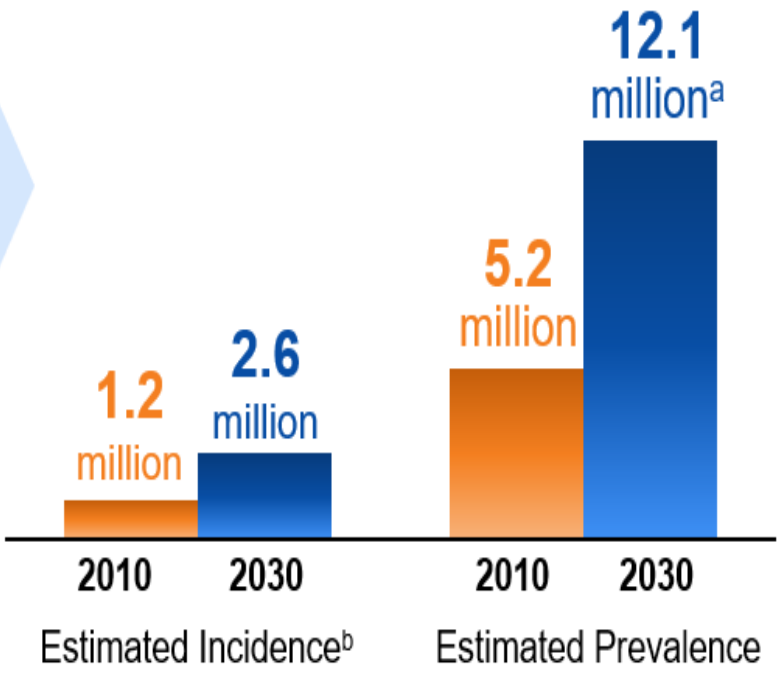
AF: A Rising Epidemic

Aging population & improved survival rates from co-morbidities are contributing to rising AF prevalence[1]

Technological innovations are improving AF detection and can facilitate early diagnosis and treatment[2,3]

Burden on cardiologists is considerable, with AF rated the 2nd most difficult disease to manage[4]

The number of individuals with AF in the US is projected to more than double by 2030[5,6]



[a]Projections of 12.1 million assumes logarithmic growth in incidence of AF from 2007–2030.
[b]Incidence was defined as the rate of acquiring a new AF diagnosis in the health claims data within a 1-year time period.
CV, cardiovascular; US, United States.

1. Morillo CA, et al. *J Geriatr Cardiol*. 2017;14(3):195-203. 2. Reiffel JA, et al. *JAMA Cardiol*. 2017;2(10):1120-1127. 3. Perez MV, et al. *N Engl J Med*. 2019;381(20):1909-1917. 4. Aliot E, et al. *Europace*. 2010;12(5):626-633. 5. Virani SS, et al. *Circulation*. 2020;141(9):e139-e596. 6. Colilla S, et al. *Am J Cardiol*. 2013;112(8):1142-1147.

Screening for AF Comes with Many Snags

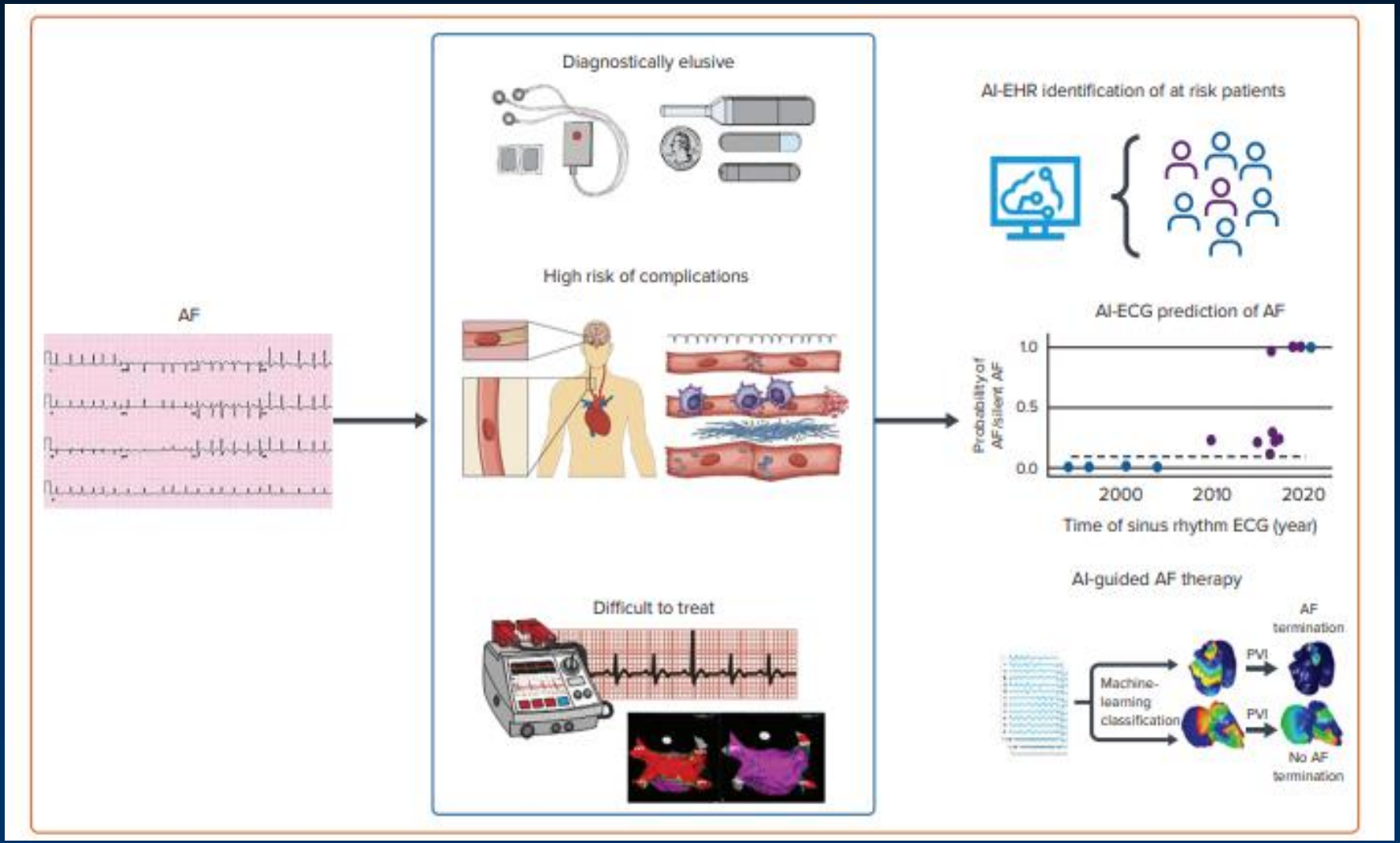
Manufacturer	Apple	Samsung	Withings	Fitbit	AliveCor
Version	Watch 6	Galaxy Watch3	ScanWatch	Sense	Kardia Mobile
Sensitivity (95% CI)	85% (72%-94%)	85% (72%-94%)	58% (42%-72%)	66% (51%-79%)	79% (64%-89%)
Specificity (95% CI)	75% (67%-83%)	75% (66%-82%)	75% (67%-83%)	79% (70%-86%)	69% (60%-77%)
Inconclusive tracings	18%	17%	24%	21%	26%
Preferred Choice*a	39%	12%	24%	15%	5%
Limit of HR interpretation*b	50-150 beats/min	50-120 beats/min	No information	50-120 beats/min	50-100 beats/min
Battery capacity*c	18 h*d	45 h*d	720 h*d	144 h*d	90 h / 2 y*e
Price*d	449	265	303	244	147

A systematic review for the US Preventive Services Task Force (USPSTF) Recommendation Statement found the current evidence insufficient to assess the balance of benefits and harms of screening for AF…. Screening may deliver more harm than benefit; risk of stroke/benefit of OACs not studied in this population

These methods may help ECG confirmation of AF diagnosis

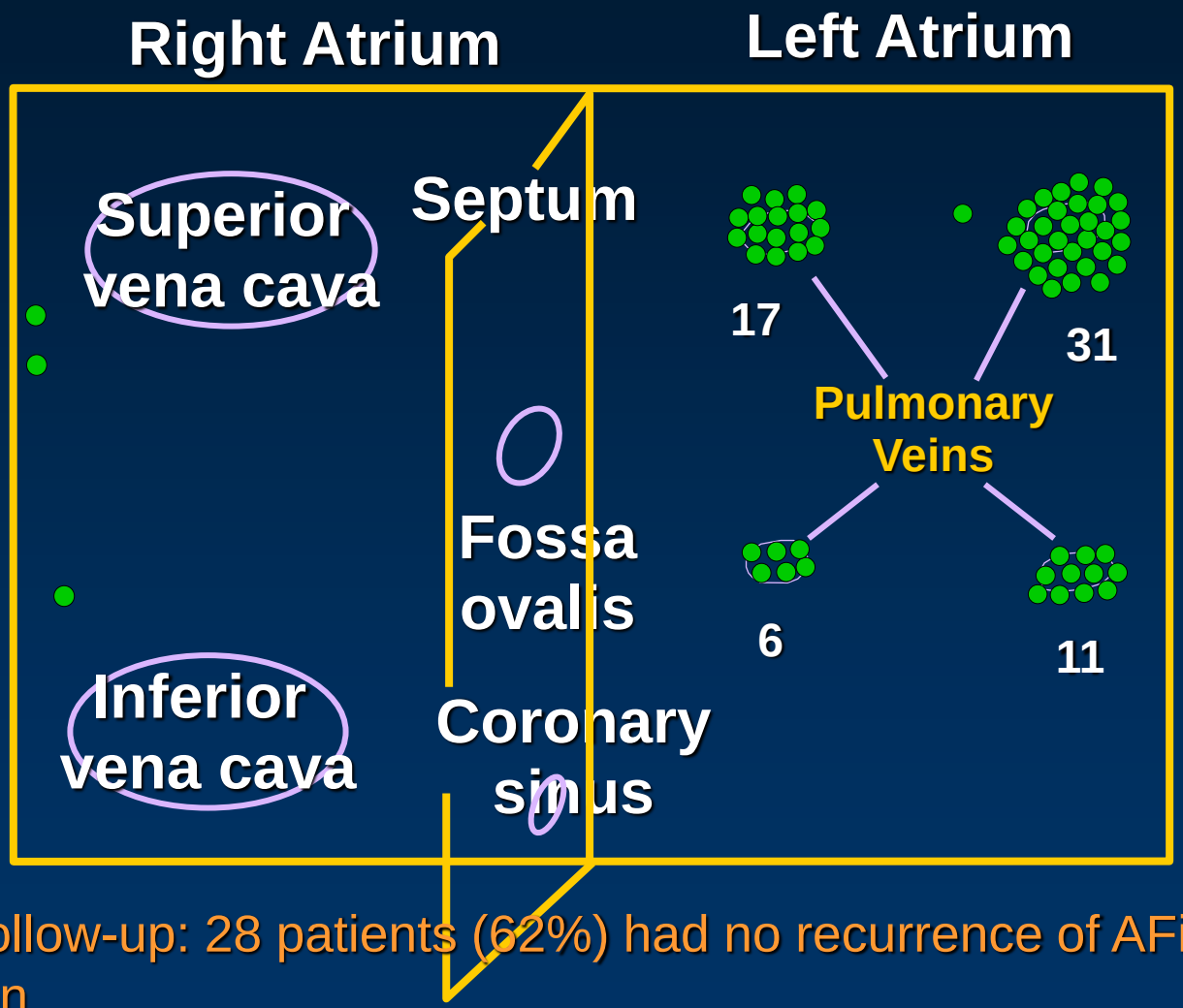
Mannhart D, et al. JACCEP 2023;9:232-242.

AI Identification of High Risk AF Patients



Harmon DM, et al. AER 2023;12 e12

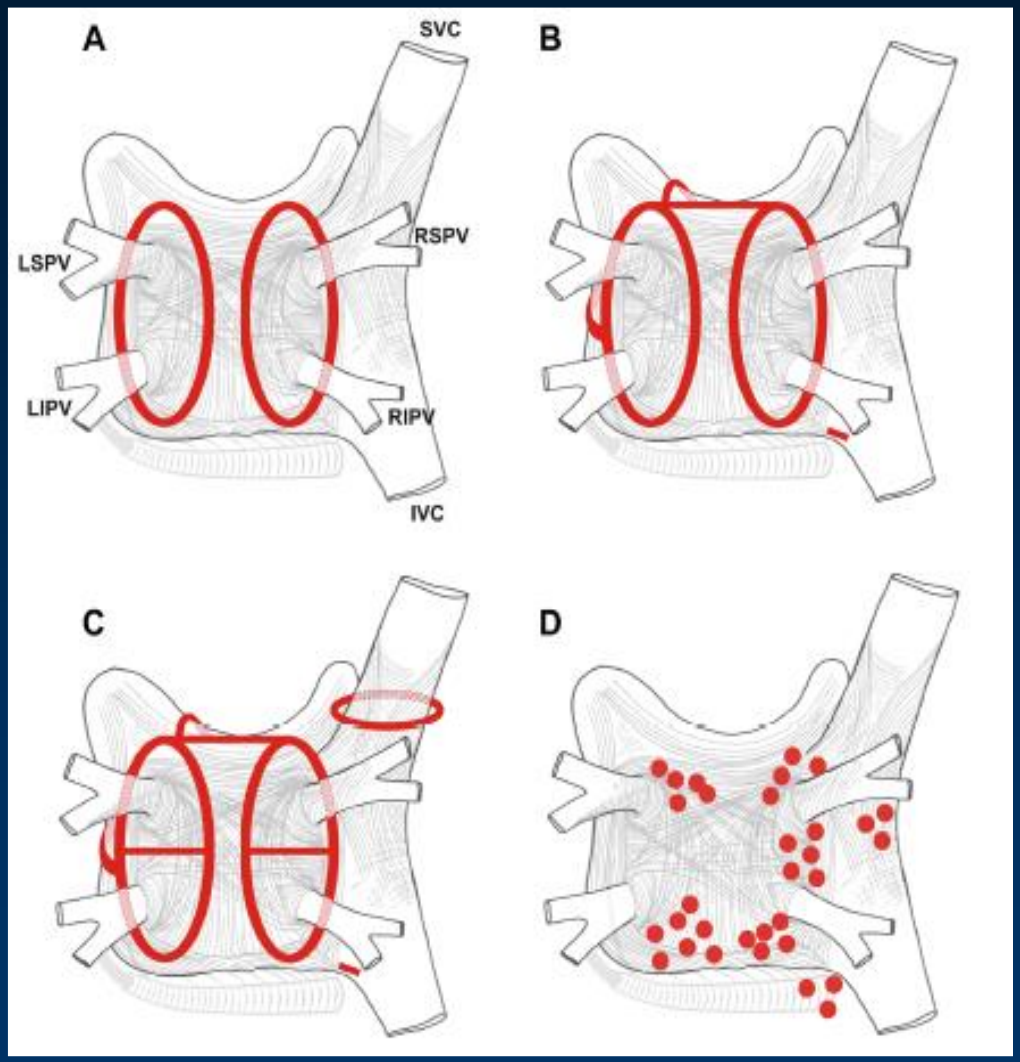
Sites of 69 Foci Triggering AF in 45 Patients



8±6 month follow-up: 28 patients (62%) had no recurrence of AFib after RF focus ablation

Haïssaguerre et al. N Engl J Med. 1998;339:659-666.

AF Catheter Ablation: Approaches



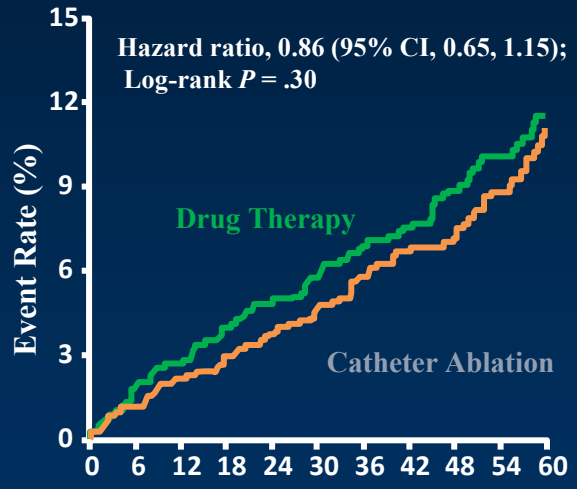
- Isolation of the triggers and perpetuating re-entrant circuits located in the PVs
- Disruption of the substrate for perpetuating rotors in the antra of the PVs
- Disruption of the putative dominant rotors in the left and right atria, recognized by high frequency complex fractionated electrograms
- Targeted ablation of ganglionated autonomic plexi in the epicardial fat pads

Calkins H, et al. HRS/EHRA/ECAS Consensus. Heart Rhythm 2007

Aliot E, Ruskin JN. Eur Heart J 2008;10:H32-52

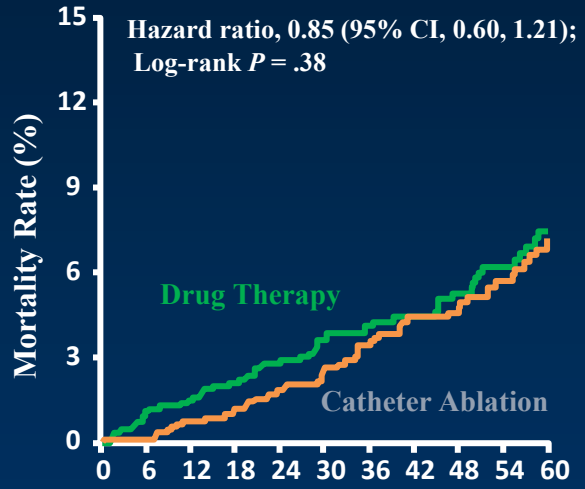
CABANA: Catheter Ablation vs Drug Therapy (ITT)

Primary endpoint (death, disabling stroke, serious bleeding, cardiac arrest)



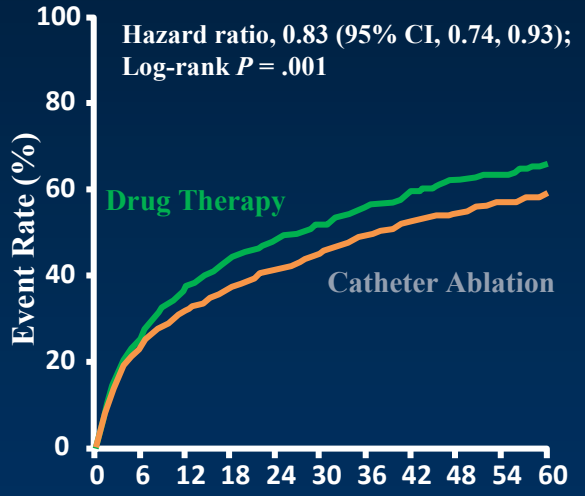
No. at risk											
Drug therapy	1096	1036	1006	970	880	763	652	578	499	418	312
Catheter ablation	1108	1045	1006	996	915	793	700	614	535	432	309

All-cause mortality



No. at risk											
Drug therapy	1096	1046	1023	992	903	783	679	606	527	445	334
Catheter ablation	1108	1058	1035	1013	933	814	724	632	555	455	332

Mortality or CV hospitalization



No. at risk											
Drug therapy	1096	778	643	563	474	387	302	244	197	165	112
Catheter ablation	1108	807	708	643	558	450	372	307	261	207	137

CABANA = The Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation trial.

Packer D, et al. JAMA. 2019;321(13):1261-1274.

Future of AF Ablation

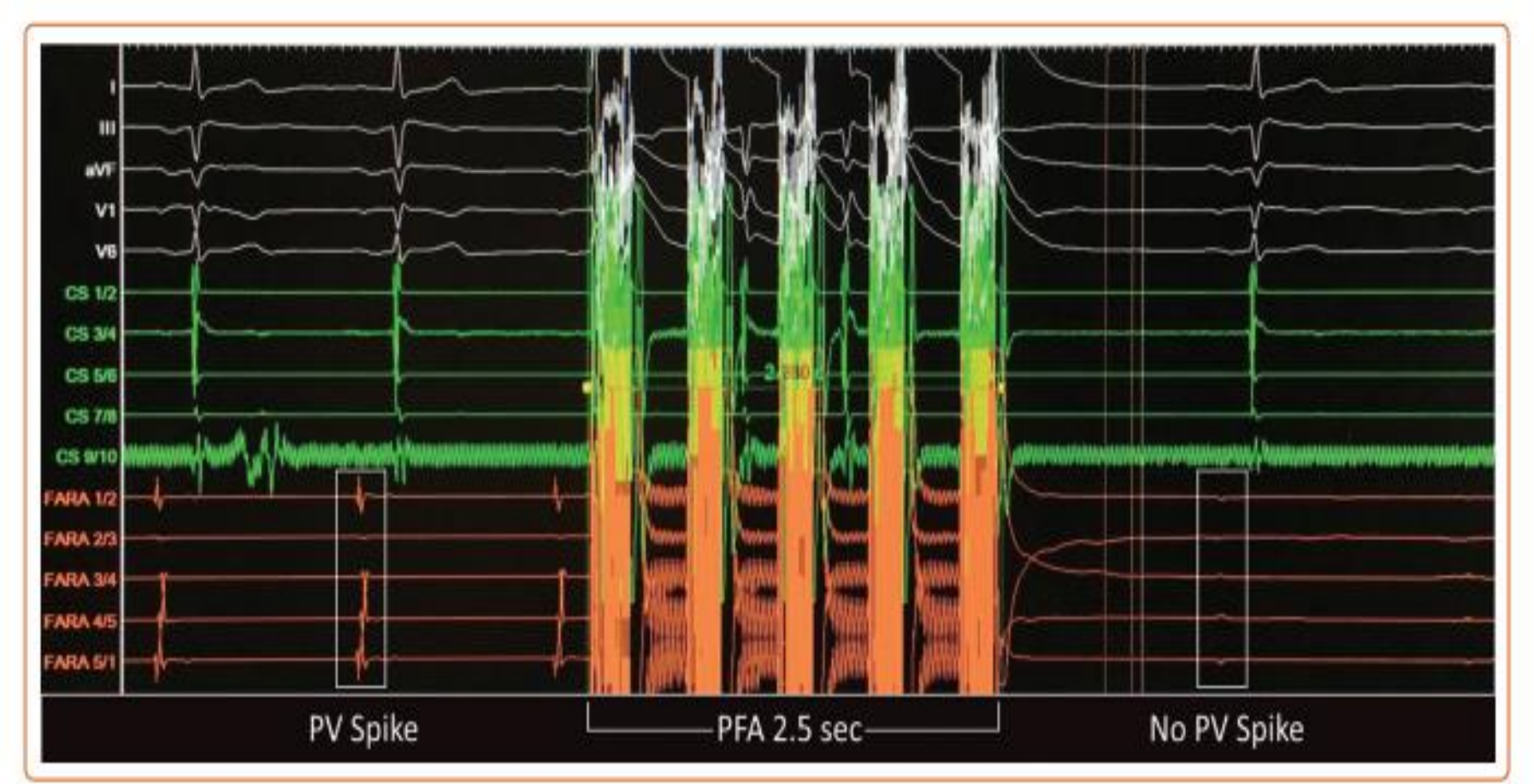
- Improved Image Integration
- High Resolution Electro-anatomical mapping systems
- Delayed-Enhancement MRI for patient selection
- Contact Force
- Injectable Electrodes
- AI
- Alternative Energy Sources to RF
  - (Cryoablation; Laser)
  - Pulsed Field Ablation

Clinical Mapping Approaches for AF

Mapping Technique	AF Type Mapped	Number of Ablation Targets	Atrial Location	Source Characterisation	Acute Termination Percentage	Freedom from AF at 12 Months, with/ without PVI
Panoramic Contact Mapping						
FIRM (RhythmView)[10,62,63]	Paroxysmal, persistent and long standing persistent	3–5	LA 70% RA 30% PV 24%	Stable rotations 76%, focal sources 24%[10]	56% (60% to sinus)[10] RA in 22%[62] In meta-analyses 27–53% (sinus or AT)	Meta-analysis: 72.5%[7] Persistent AF RCT: 77.7% (FIRM + PVI subgroup)[25]
Electrographic flow mapping (Ablacon)[35,36]	Persistent AF	4–6	LA 70% RA 30% PV 40%	Rotational 51%, focal 49%	100% RA in 10%	Pending
Sequential Contact Mapping						
CARTOFINDER (Biosense Webster)[37,38,42]	Persistent and long standing persistent	1–3	LA 63% RA 27% Non-PV 79%[64]	Rotational activity 70%, focal activations 30–100%[38,42]	63% (58% to AT)[42] 15% (all sinus)[64]	71%[38] 70%[64]
Spatiotemporal dispersion (Volta Medical)[43]	Persistent AF	4–6	LA 80% RA 20% PV/LAA 80%	Regions of micro-re-entry	95% (85% to AT)	85% without PVI (1.4 procedures, at 18 months)
STAR[45]	Persistent AF	2–3 (post PVI)	LA 95% RA 5%	Early sites of activation	29% (75% to AT)	80% (AT/AF at 18 months)
RADAR (CardioNXT)[46]	Persistent AF Longstanding AF	3.9 ± 1.3 (LA) 2.5 ± 1.4 (RA)	Inconsistent RA mapping	Rotational (73%) and focal sites	55%	74% AF freedom at 13 months (on/off drugs)
Non-contact Mapping						
Charge/dipole density (Acutus)[48,65]	Persistent AF	2–3	RA not mapped LA anterior 70%	Localised irregular activity Localised rotational activity Focal activity	50–60%	73%[65]
Body surface, ECGI (CardioInsight, EP Solutions)[13,51,66]	Persistent and long standing persistent	3–6	LA 70% RA 30% LPV/LAA 82%[13] LA 53% RA 27% Septum 20%[51]	Re-entries 80% Focal breakthrough 20%[13]	80% (66% to AT)[13] 64% (79% to AT) (PVs 37%, LA 35%, RA in 28%)[51]	85%[13] 78%[51]

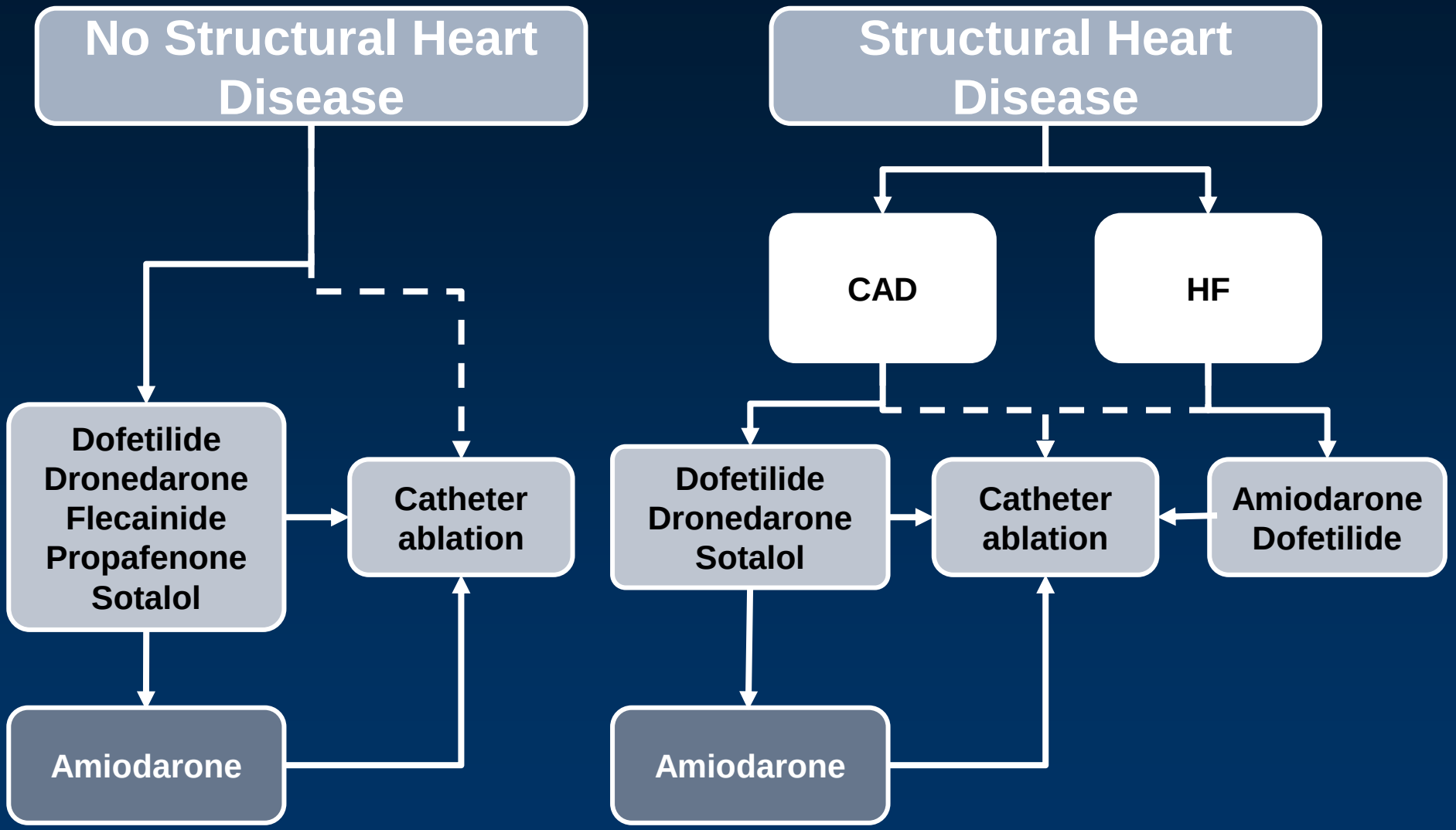
Zaman JAB, et al. Arrhythmia Electrophysiol Rev 2022

PVI with Pulsed Field Ablation



Schaack D, et al. Arrhythm Electrophysiol Rev 2023

AHA/ACC/HRS: AF Rhythm Control



American College of Cardiology (ACC). 2014 ACC Guidelines. (http://eguideline.guidelinecentral.com/i/387793-atrial-fibrillation/17?m4=). Accessed October 5, 2020. January C, et al. J Am Coll Cardiol. 2014;64(21):e1-e76.

AAD Development Graveyard for Most

Modification of existing drug

Amiodarone analogs

Dronedarone (IKr IKs b1 ICa Ito INa)
Celivarone (IKr IKs b1 ICa Ito INa)
Budiodarone
ATI-2042 (IKr IKs b1 ICa Ito INa)
ATI-2001 (IKr IKs b1 ICa Ito INa)
GYKI-16638 (IKr IKI INa)
KB 130015 (IKAch INa ICa IKATP)

Conventional class III agents

Azimilide (IKr IKs)
Tedisamil (IKr Ito IKATP IKur INa)
Bertosamil (IKr Ito IKATP IKur INa)
SB-237376 (IKr)
NIP-142 (IKur IKAch)
L-768673 (IKs)
HMR-1556 (IKs)
HMR-1402(IKs. IATP)

Miscellaneous compounds

Ersentilide (IKr b)
Trecetilide (IKr b)
CP060S (INa ICa)
KB-R7943 (INa ICa)
Cariporide (INa IH)
JTV-519 (INa IKr ICa)

Novel Mechanism of Action

Serotonin type 4 antagonists

Piboserod
RS100302
SB203186

Atrial selective repolarization delaying agents

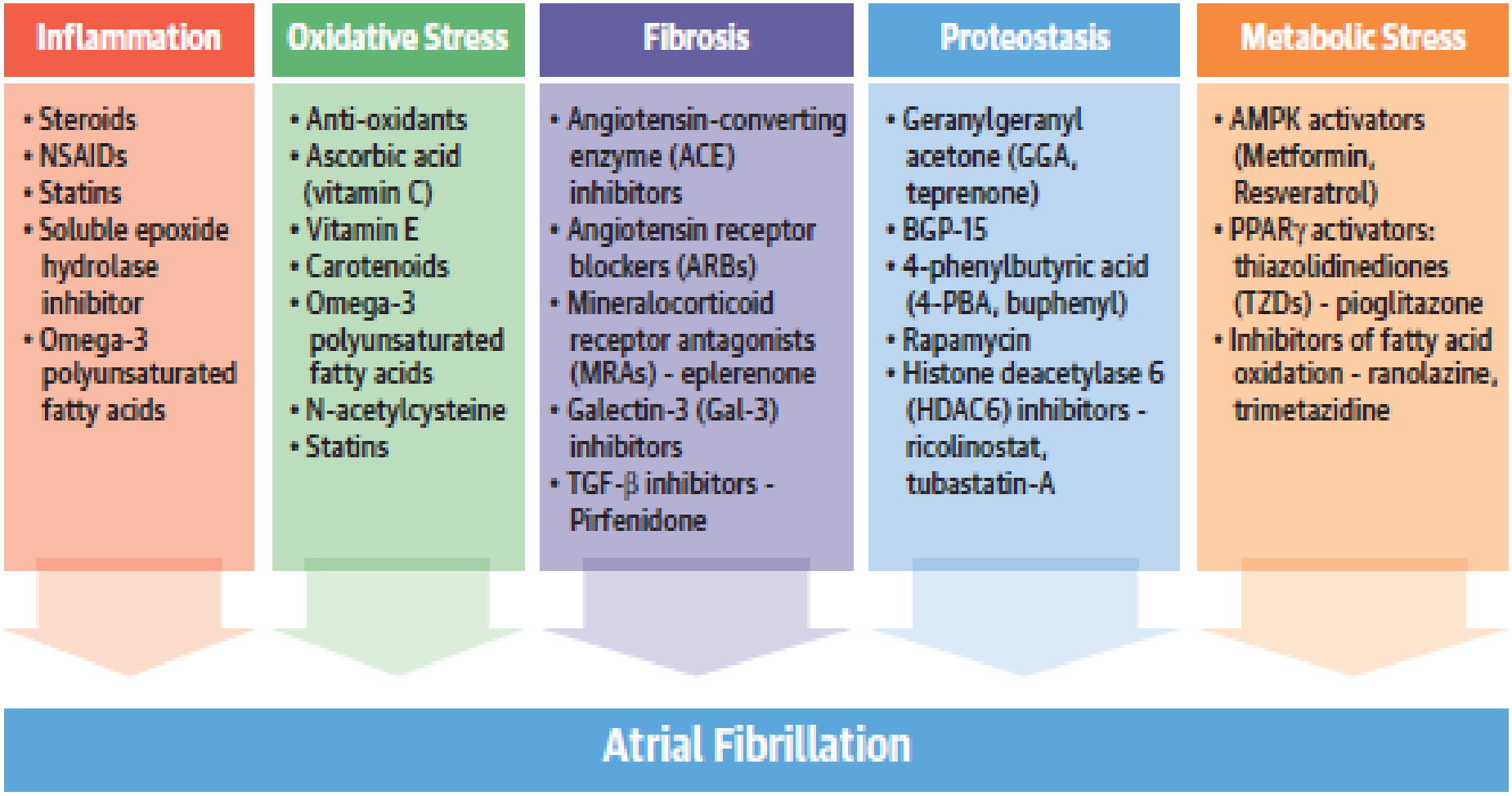
AZD 7009 (IKr INa IKur)
AVE 0118 (IKur Ito)
AVE 1231 (IKur Ito)
Vernakalant (IKur Ito INa IAch)
Almokalant (IKur Ito INa IAch)
Terikalant (IKur Ito INa IAch)
Nifekalant (IKur Ito INa IAch)
S-9947 (IKur)
S-20951 (IKur)

Miscellaneous compounds

ZP-123 (GAP 486)
AAP 10 (connexin modulator)
GsMtx4 (stretch receptor)
Ranolazine
AP303363 (SK ion channel inhibitor)
OMT-28

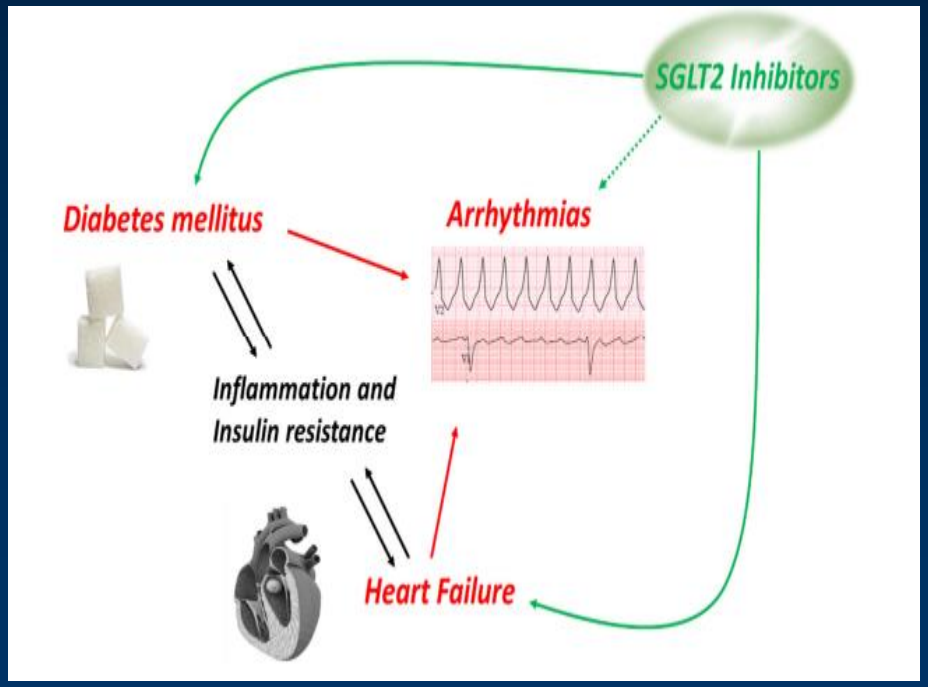
Musco S. Med Clin N Am 92:121–141, 2008

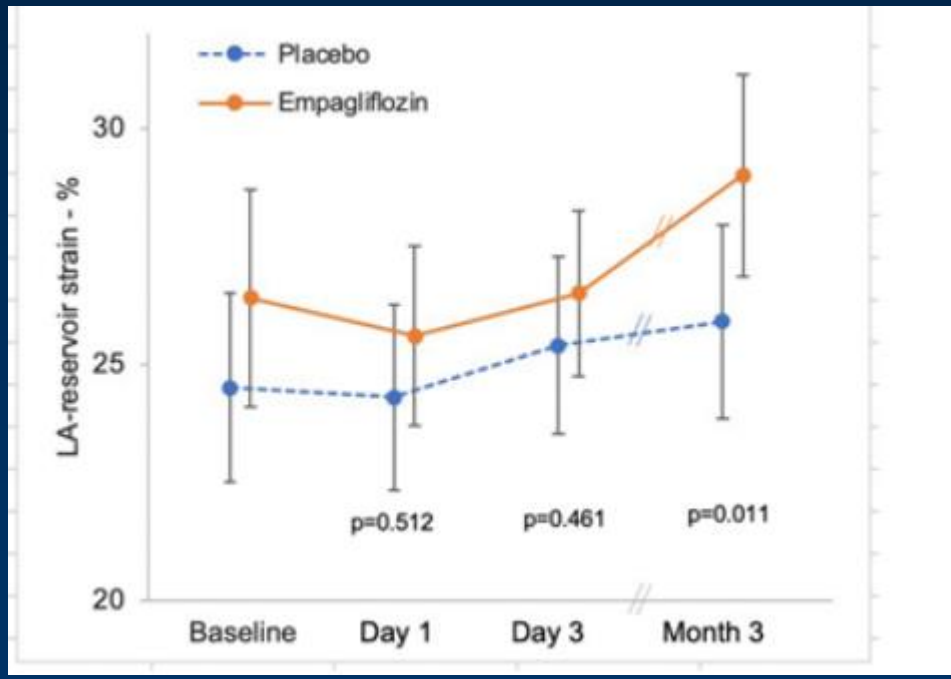
Targetable Upstream Pathways Predisposing to AF



Future Antiarrhythmic Drugs for AF

- New effective and safe AF rhythm control drugs for acute termination of AF and prevention of AF
- Non-arrhythmic drugs (SGLT2 inhibitors) that improve arrhythmic outcomes





Lifestyle Modification to Reduce AF

- Quitting smoking decreased AF by 36%
- Controlling Hypertension may reduce AF
- Alcohol – 10% increased risk of AF with only 1 drink a day
- Stimulants – caffeine, adrenergic drugs
- Sleep deprivation – Rx OSA reduces AF
- DM – increased risk of AF
- Mediterranean diet may reduce AF
- Obesity – weight loss reduces AF
- Healthy Mindset and Stress Mx – Yoga reduced AF by 24%
- Physical Activity – reduces AF

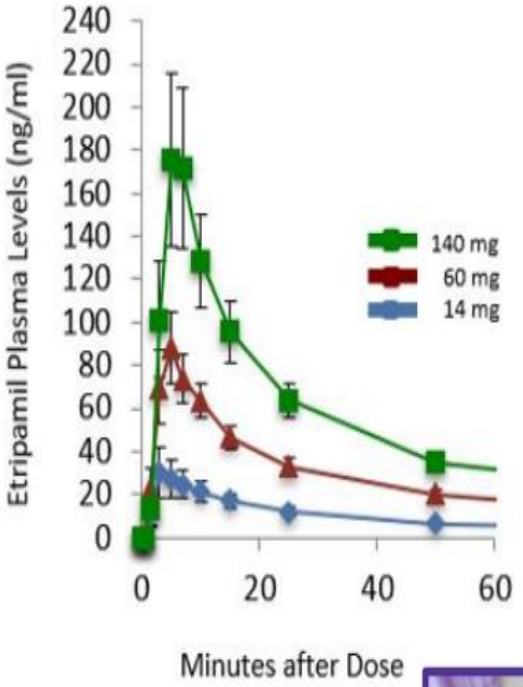
Subzwari SRA, et al. Cureus 2018

AADs: Novel Methods of Administration

- Nasally administered L-type calcium channel blocker for acute SVT termination (Milestone)
- Inhaled flecainide for acute AF termination (InCarda)
- Intravenous AA drug release from implanted reservoir following arrhythmia detection
- Self-absorbing epicardial patch containing an antiarrhythmic drug for post-op AF (EDGE)

Etripamil Nasal Spray: A Novel CCB Designed to be Fast, Convenient, and Patient-Empowering

- Clinically-validated mechanism
  - CCBs prolong refractoriness and slow conduction over the AV node, terminating most PSVTs
- Formulated for intranasal self-administration with rapid onset of action
- Designed to be rapidly inactivated by ubiquitous human blood esterase enzymes
- Patent protection until 2036



Stroke Trials

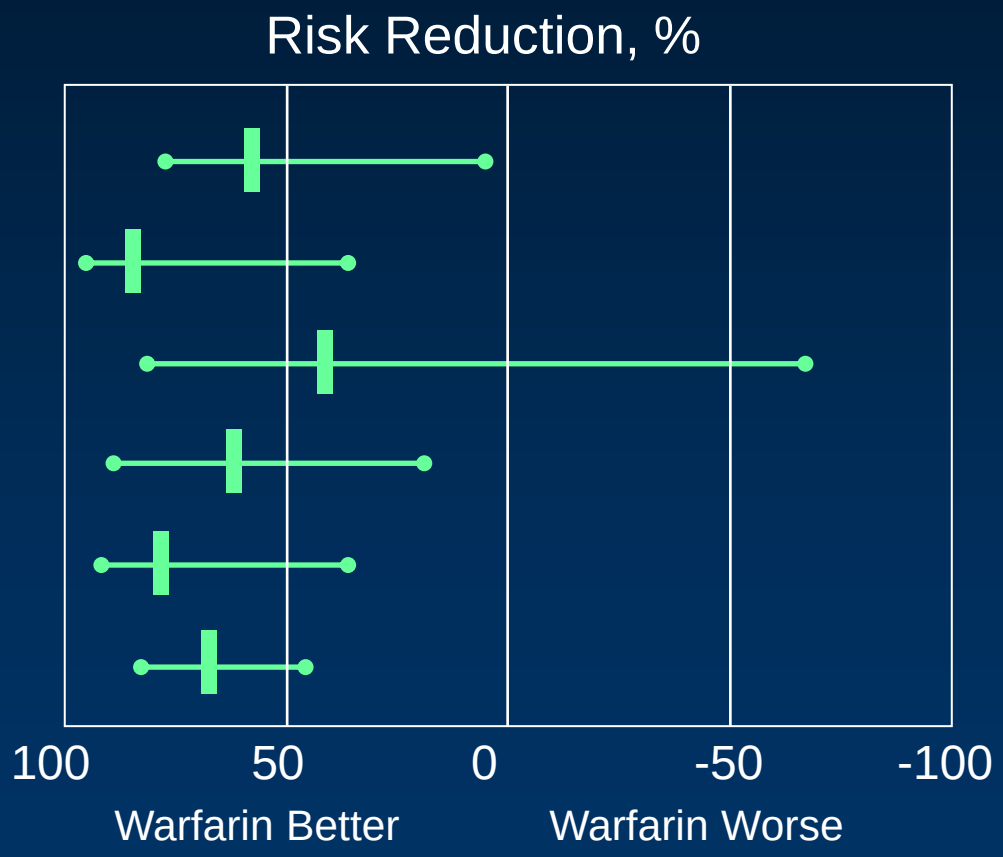
- SPAF
- RELY
- ROCKET AF
- ARISTOTLE
- ENGAGE-AF
- CRYSTAL-AF
- PROTECT-AF
- PREVAIL

Efficacy of Warfarin

Compared With Control in 5 Studies

62% to 67% RRR with warfarin vs placebo

	No. of Events	Patient-Years
AFASAK	**27**	**811**
BAATAF	**15**	**922**
CAFA	**14**	**478**
SPAF	**23**	**508**
SPINAF	**29**	**972**
Combined	**108**	**3691**



Atrial Fibrillation Investigators. Arch Intern Med. 1994;154(13):1449-1457.

Major Outcomes of NOACs vs. Adjusted Dose Warfarin

SUPERIOR INFERIOR NONINFERIOR

Outcome (RR ±95% CI)	RE-LY[1] (Dabigatran 150 mg BID)	ROCKET-AF[2] (Rivaroxaban 20 mg QDay)	ARISTOTLE[3] (Apixaban 5 mg BID)	ENGAGE-AF[4] (Edoxaban 60 mg QDay)
Stroke/SE	**0.66 (0.53-0.82)**	0.88 (0.75-1.03)	**0.79 (0.66-0.95)**	**0.79 (0.63-0.99)**
Ischemic stroke	**0.76 (0.60-0.98)**	0.94 (0.75-1.17)	0.92 (0.74-1.13)	1.00 (0.83-1.19)
Hemorrhagic stroke	**0.26 (0.14-0.49)**	**0.59 (0.37-0.93)**	**0.51 (0.35-0.75)**	**0.54 (0.38-0.77)**
Major bleeding	0.93 (0.81-1.07)	1.04 (0.90-1.20)	**0.69 (0.60-0.80)**	**0.80 (0.71-0.91)**
ICH	**0.40 (0.27-0.60)**	**0.67 (0.47-0.93)**	**0.42 (0.30-0.58)**	**0.47 (0.34 -0.63)**
GI	**1.50 (1.19–1.89)**	**1.39 (1.19–1.61)**	0.89 (0.70–1.15)	**1.23 (1.02–1.50)**
CV mortality	**0.85 (0.72-0.99)**	0.89 (0.73-1.10)	0.89 (0.76-1.04)	0.92 (0.83-1.01)
All-cause mortality	0.88 (0.77-1.00)	0.85 (0.70-1.02)	**0.89 (0.80-0.998)**	**0.86 (0.77-0.97)**

CV, cardiovascular; GI, gastrointestinal; ICH, intracranial hemorrhage. Black text indicates noninferior findings

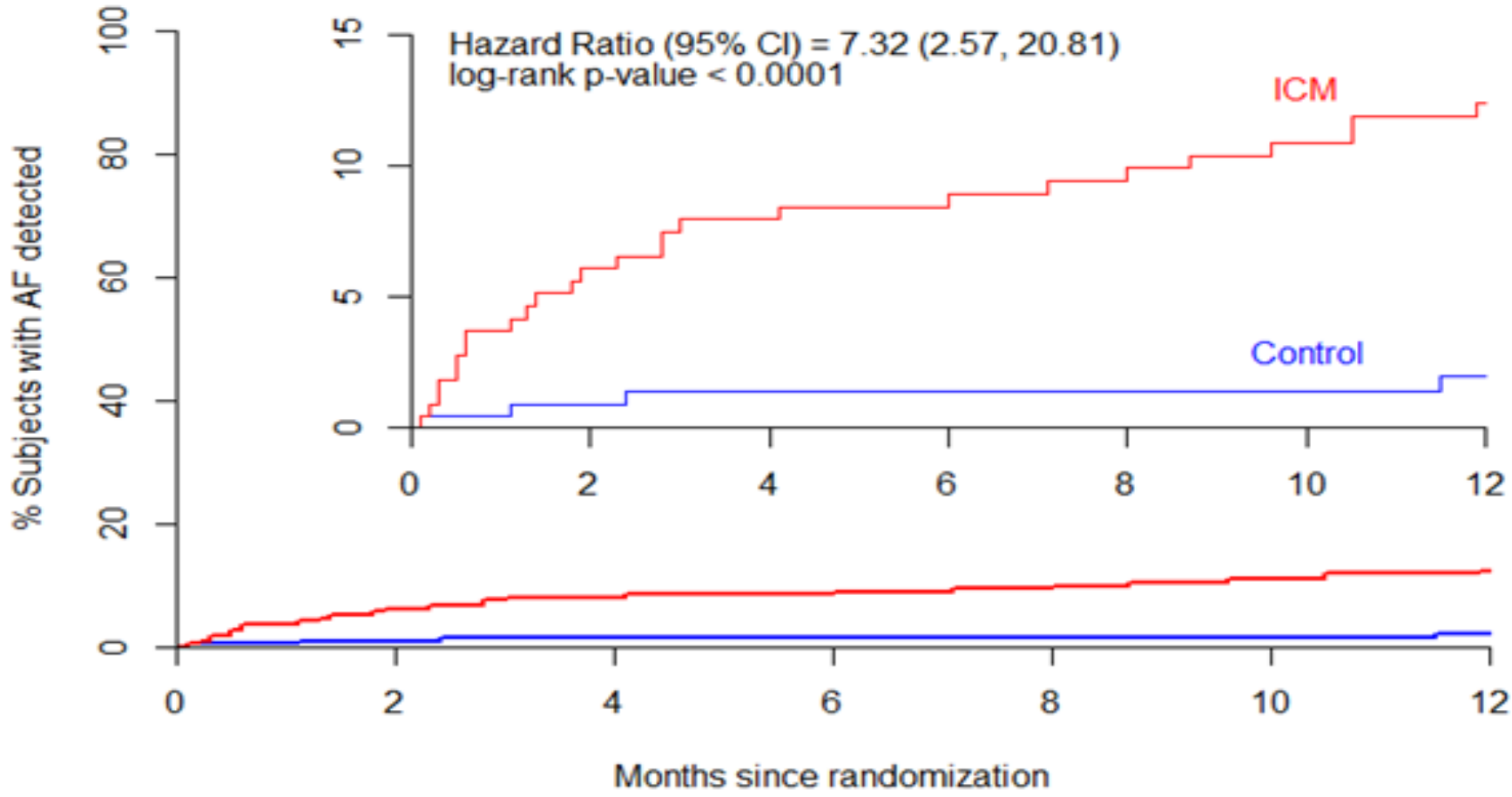
1. Connolly SJ et al. *N Engl J Med*. 2009;363:1175-1176. 2. Patel MR et al. *N Engl J Med* 2011;365:883-891.
3. Granger CB et al. *N Engl J Med*. 2011;365:981-992. 4. Giugliano RP et al. *N Engl J Med*. 2013;369:2093-2104.

Factor XI Inhibition

- Theoretic benefit over Xa
  - Less bleeding
  - Longer half- life - once a day dosing
  - Minimal drug interactions
- OCEANIC-AF (Asundexian vs. Apixaban)
- LIBREXIA-AF (Milvexian vs, Apixaban)

CRYSTAL-AF

Secondary Endpoint: AF Detection at 12 mos

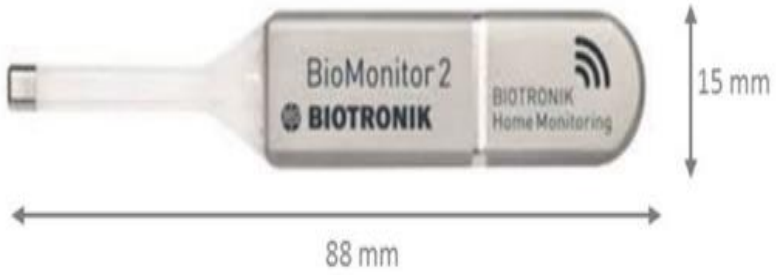


Rate of detection: ICM arm was 12.4% vs 2.0% control arm

Sanna T, et al. N Engl J Med 2014; 370:2478-2486

ILRs on the Market

BioMonitor 2 (Biotronik SE & Co, Berlin, Germany)



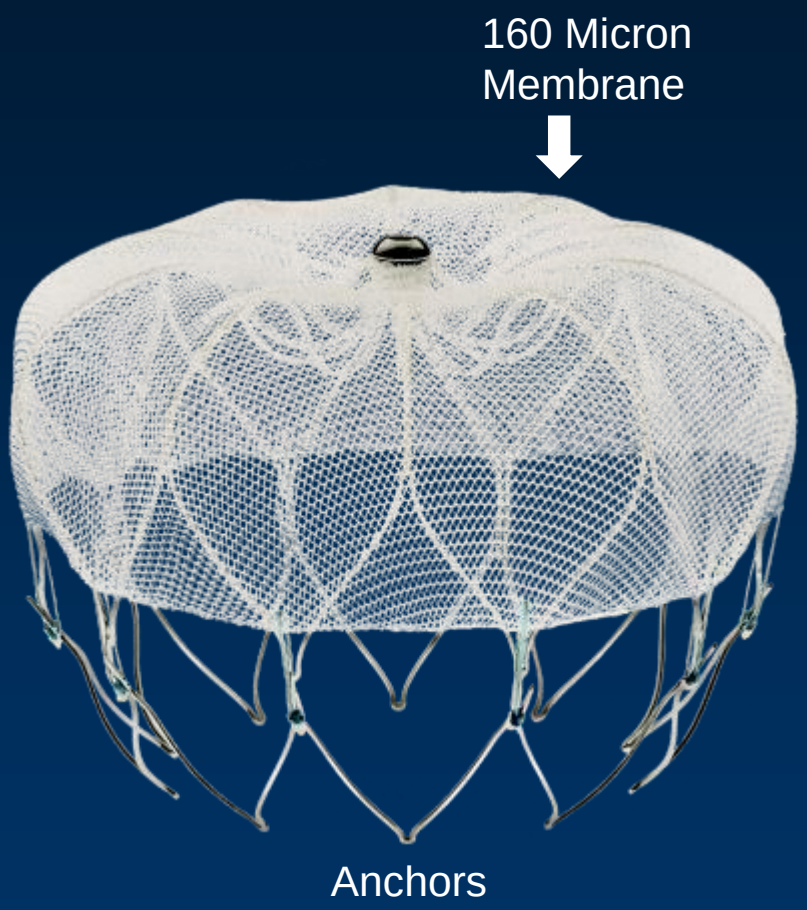
Reveal LINQ (Medtronic, Minneapolis, USA)

Reveal XT (Medtronic, Minneapolis, USA)

Confirm Rx ™ ICM (St Jude Medical, Minnesota, USA)

Bisignani A, et al. J Arrhythmia 2018

WATCHMAN™ LAAC Closure Device



Minimally Invasive, Local Solution
- Available sizes: 21, 24, 27, 30, 33 mm diameter

Intra-LAA design
- Avoids contact with left atrial wall to help prevent complications

Nitinol Frame
- Conforms to unique anatomy of the LAA to reduce embolization risk
- 10 active fixation anchors - designed to engage tissue for stability

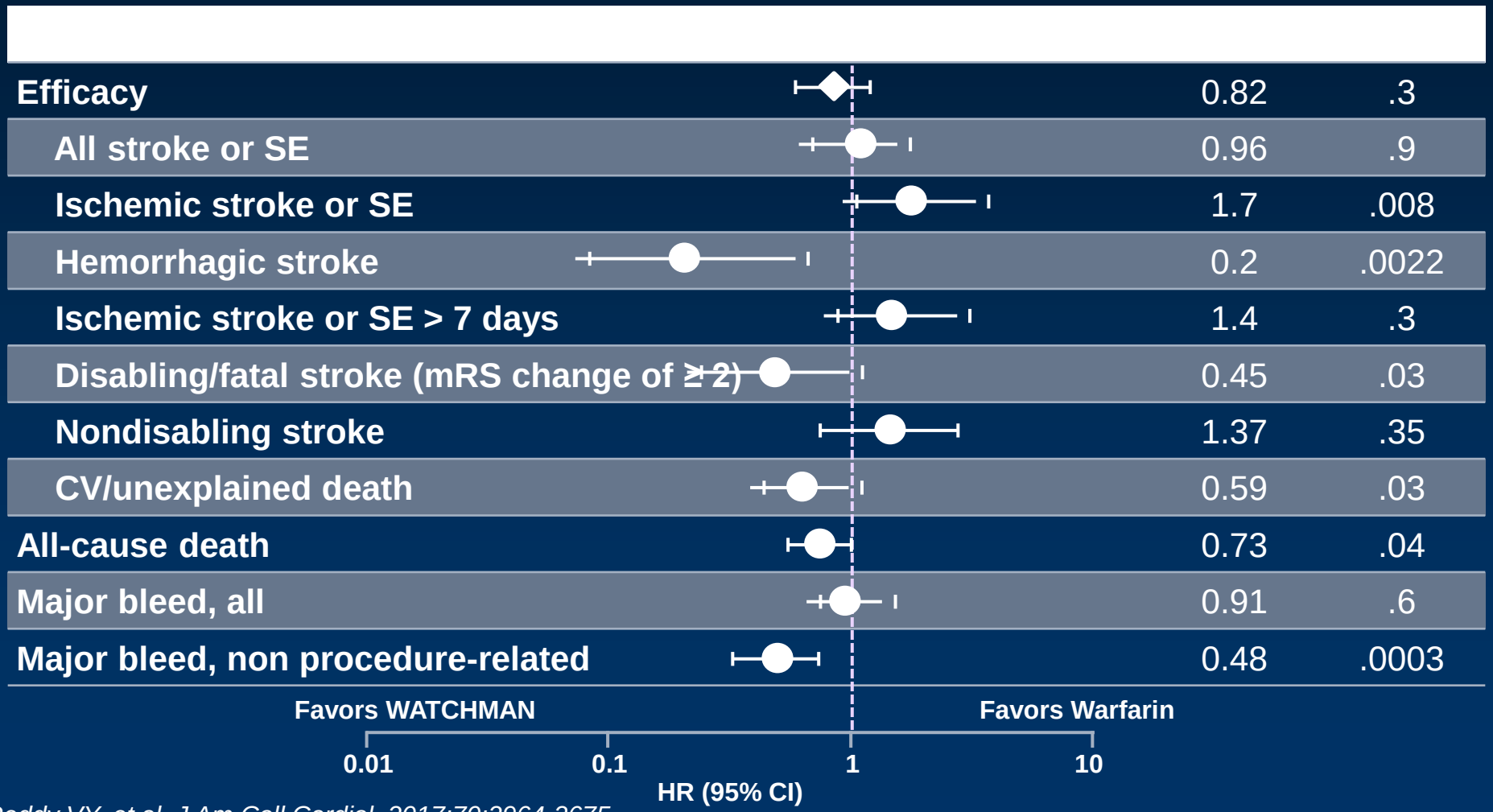
Proximal Face
- Minimizes surface area facing the left atrium to reduce post-implant thrombus formation
- 160 micron membrane PET cap designed to block emboli and promote healing

Warfarin Cessation
- 92% after 45 days, >99% after 12 months[1]
- 95% implant success rate[1]

Percutaneous LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation (IIB)

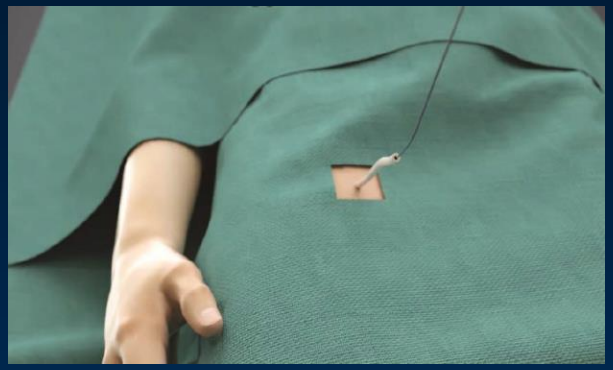
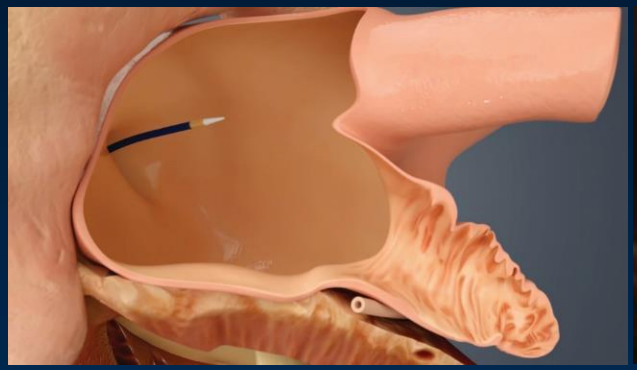
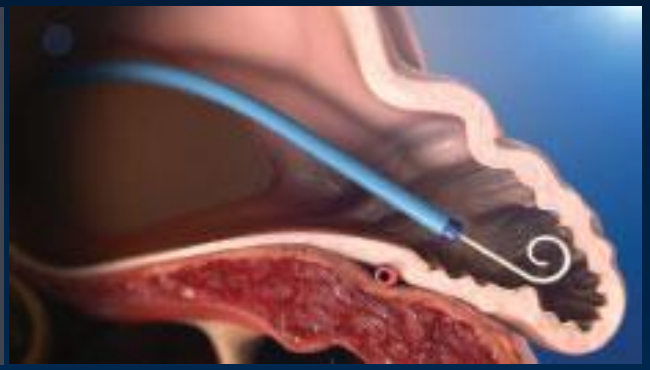
Holmes, DR et al. J Am Coll Cardiol 2014;64

WATCHMAN LAA Closure Device: 5-Year Meta-Analysis of PROTECT AF, PREVAIL



Reddy VY, et al. J Am Coll Cardiol. 2017;70:2964-2675

WATCHMAN FLX Implant Procedure: Percutaneous Access

Ongoing Indication Expansion Trials
CHAMPION-AF Trial

Expanding the Breath of Patients Who May Benefit from LAAC Therapy

Global Head-to-Head RCT comparing the safety and efficacy of WATCHMAN FLX to NOAs in a broader NVAF population, including of lower risk patients

Primary Endpoints:

- WATCHMAN FLX™ is non-inferior for the occurrence of stroke (including ischemic and/or hemorrhagic), cardiovascular (CV) death (including unexplained death), and systemic embolism at 36 months.
- WATCHMAN FLX is superior for non-procedural bleeding (ISTH major bleeding and clinically relevant non-major bleeding) at 36 months.
- WATCHMAN FLX is non-inferior for the occurrence of ischemic stroke and systemic embolism at 60 months.

ICD Trials That Altered Clinical Landscape over Last 40 Years

- AVID
- MADIT II
- SCD-HeFT
- COMPANION

Major ICD Trials for Prevention of Sudden Cardiac Death

Trial	Year	Patients (n)	LVEF	Additional Study Features	Hazard Ratio*	95% CI	p
MADIT I	1996	196	≤ 35%	NSVT and EP+	0.46	(0.26-0.82)	p=0.009
MADIT II	2002	1232	≤ 30%	Prior MI	0.69	(0.51-0.93)	p=0.016
CABG-Patch	1997	900	≤ 36%	+SAECG and CABG	1.07	(0.81-1.42)	p=0.63
DEFINITE	2004	485	≤ 35%	NICM, PVCs or NSVT	0.65	(0.40-1.06)	p=0.08
DINAMIT	2004	674	≤ 35%	6-40 days post-MI and Impaired HRV	1.08	(0.76-1.55)	p=0.66
SCD-HeFT	2006	1676	≤ 35%	Prior MI of NICM	0.77	(0.62-0.96)	p=0.007
AVID	1997	1016	Prior cardiac arrest	NA	0.62	(0.43-0.82)	NS
CASH†	2000	191	Prior cardiac arrest	NA	0.766	‡	1-sided p=0.081
CIDS	2000	659	Prior cardiac arrest, syncope	NA	0.82	(0.60-1.1)	NS

* Hazard ratios for death from any cause in the ICD group compared with the non-ICD group. Includes only ICD and amiodarone patients from CASH.
‡CI Upper Bound 1.112 CI indicates Confidence Interval, NS = Not statistically significant, NSVT = nonsustained ventricular tachycardia, SAECG = signal-averaged electrocardiogram.

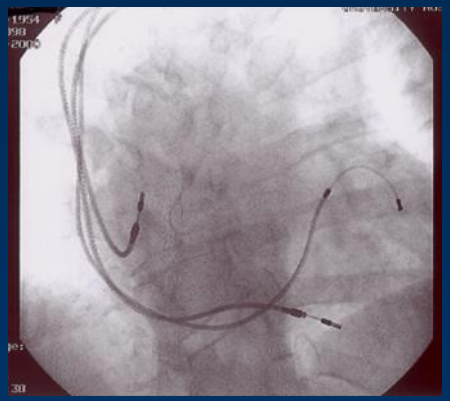
Epstein A, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. J Am Coll Cardiol 2008; 51:e1–62. Table 5.

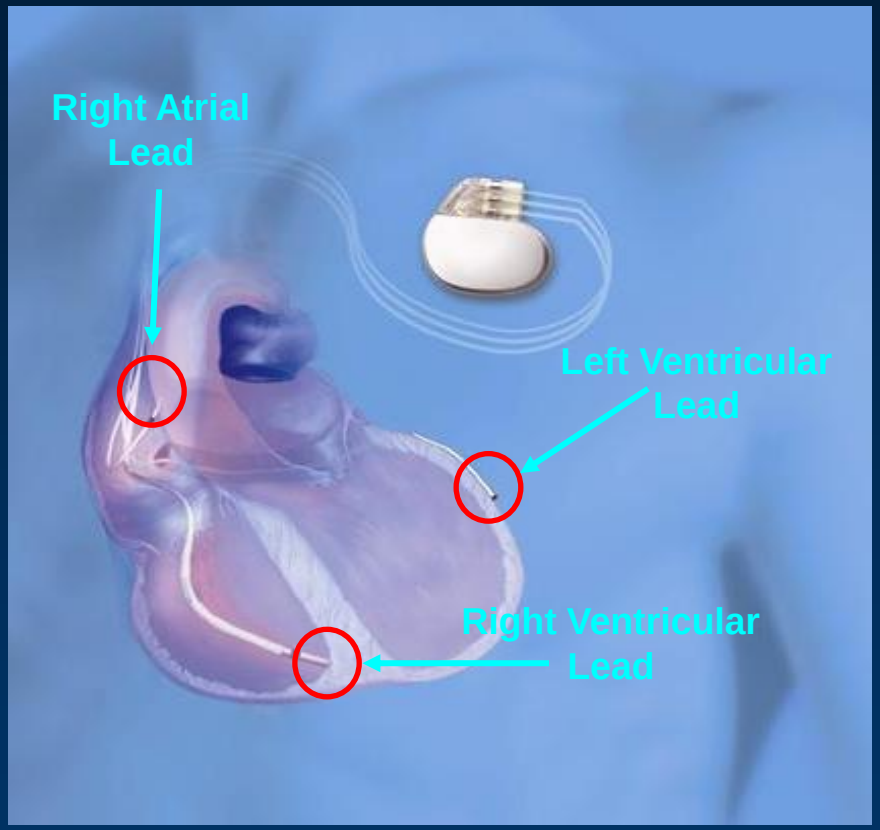
Achieving Cardiac Resynchronization

Goal: Atrial synchronous biventricular pacing

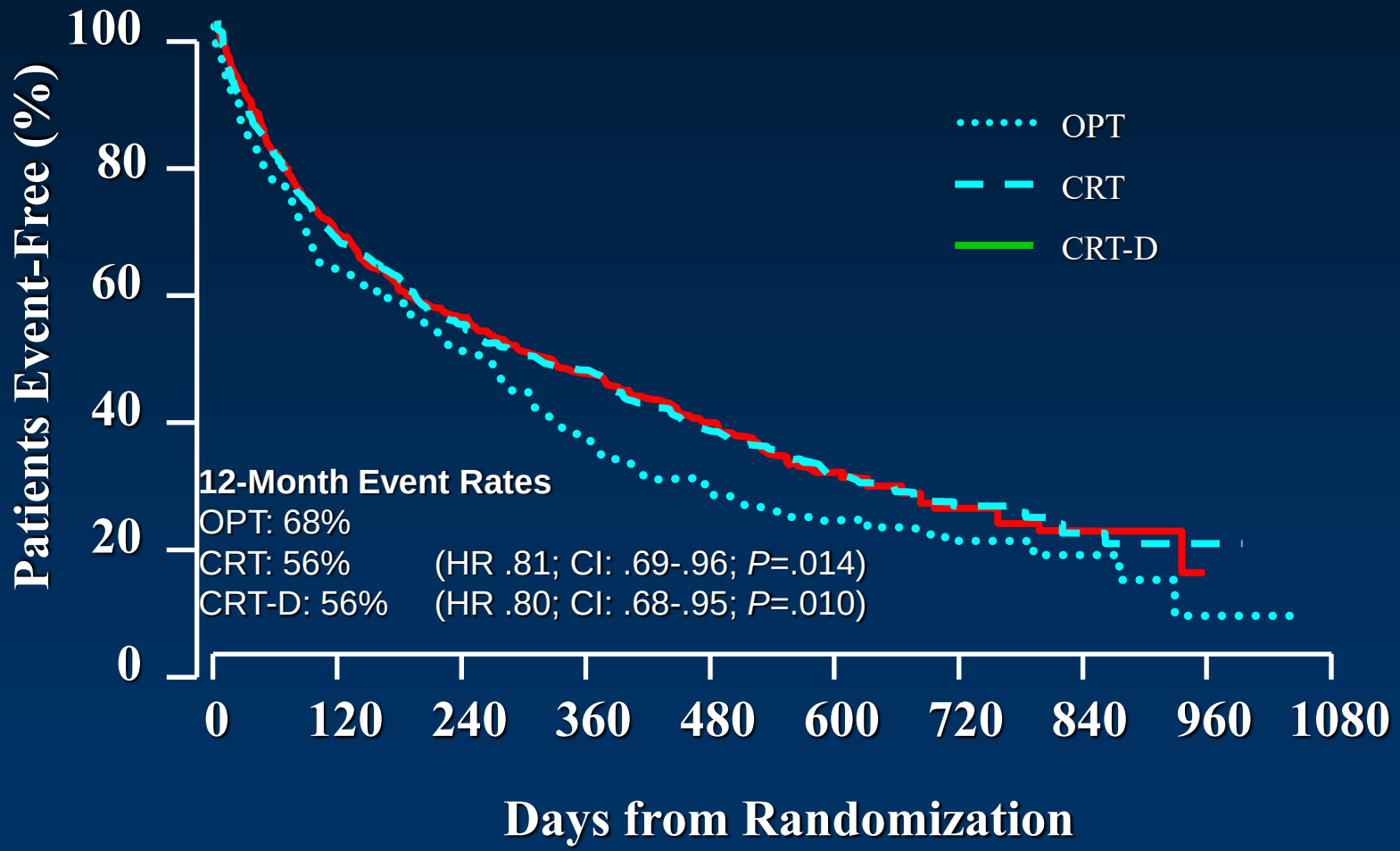
Transvenous approach for left ventricular lead via coronary sinus

Back-up epicardial approach





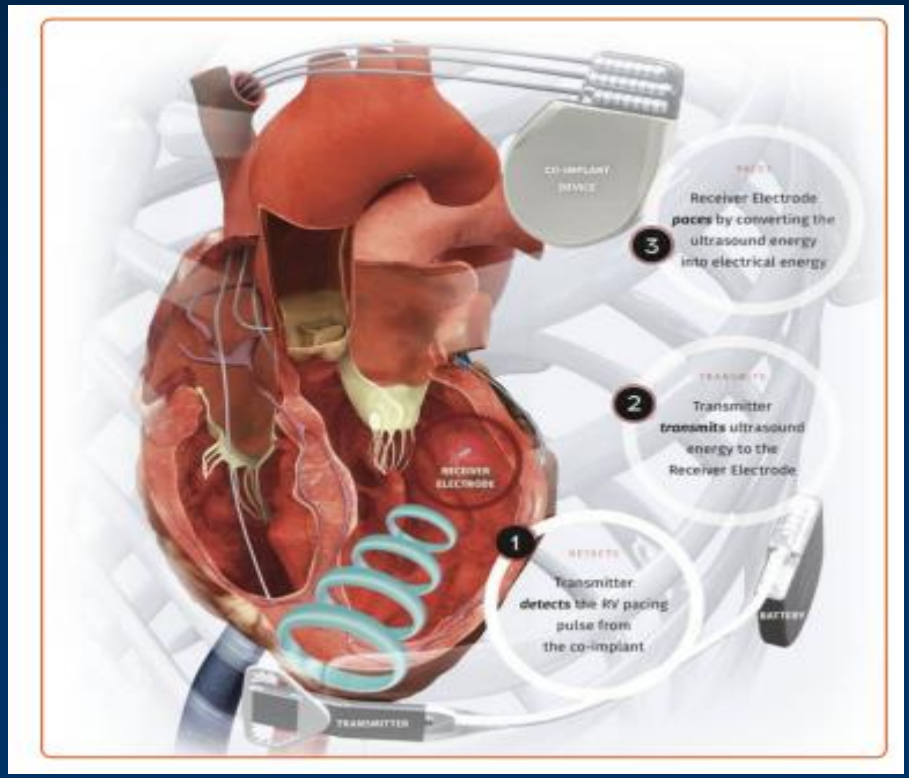
COMPANION: Primary Endpoint



Bristow MR, et al. N Engl J Med. 2004;350:2140-2150.

Options for CRT Candidate When CS Lead Not Attainable

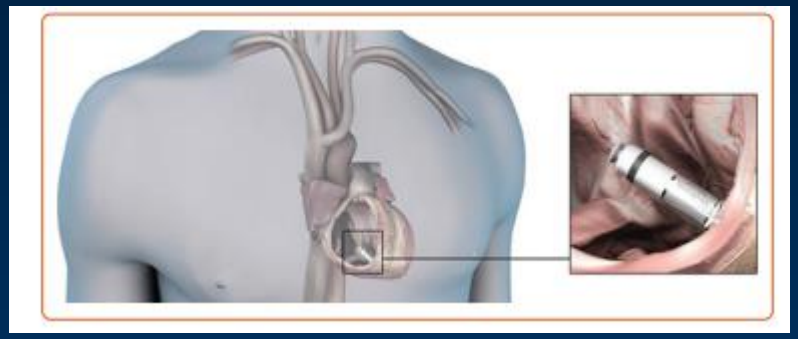
- Epicardial LV Lead with Biventricular pacing
  - Left anterior/lateral mini-thoracotomy
  - Video-assisted thoracoscopic approach
  - Robotically enhanced telemanipulation systems
- His Bundle Pacing (HBP)
- LBB Pacing
- WISE LV Lead System (Wireless LV Endocardial)

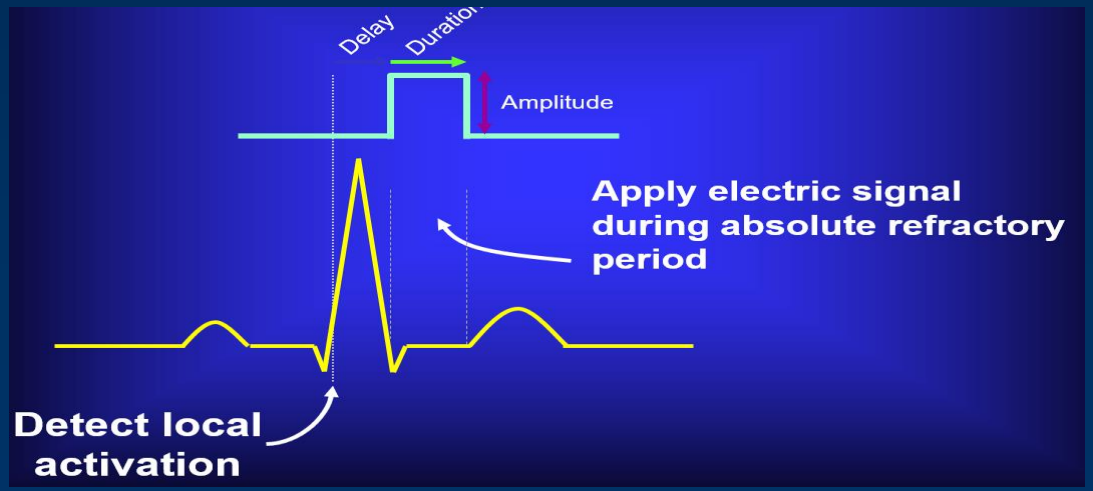


Wijesurlya N, et al. Front Phys 2022; 13:908

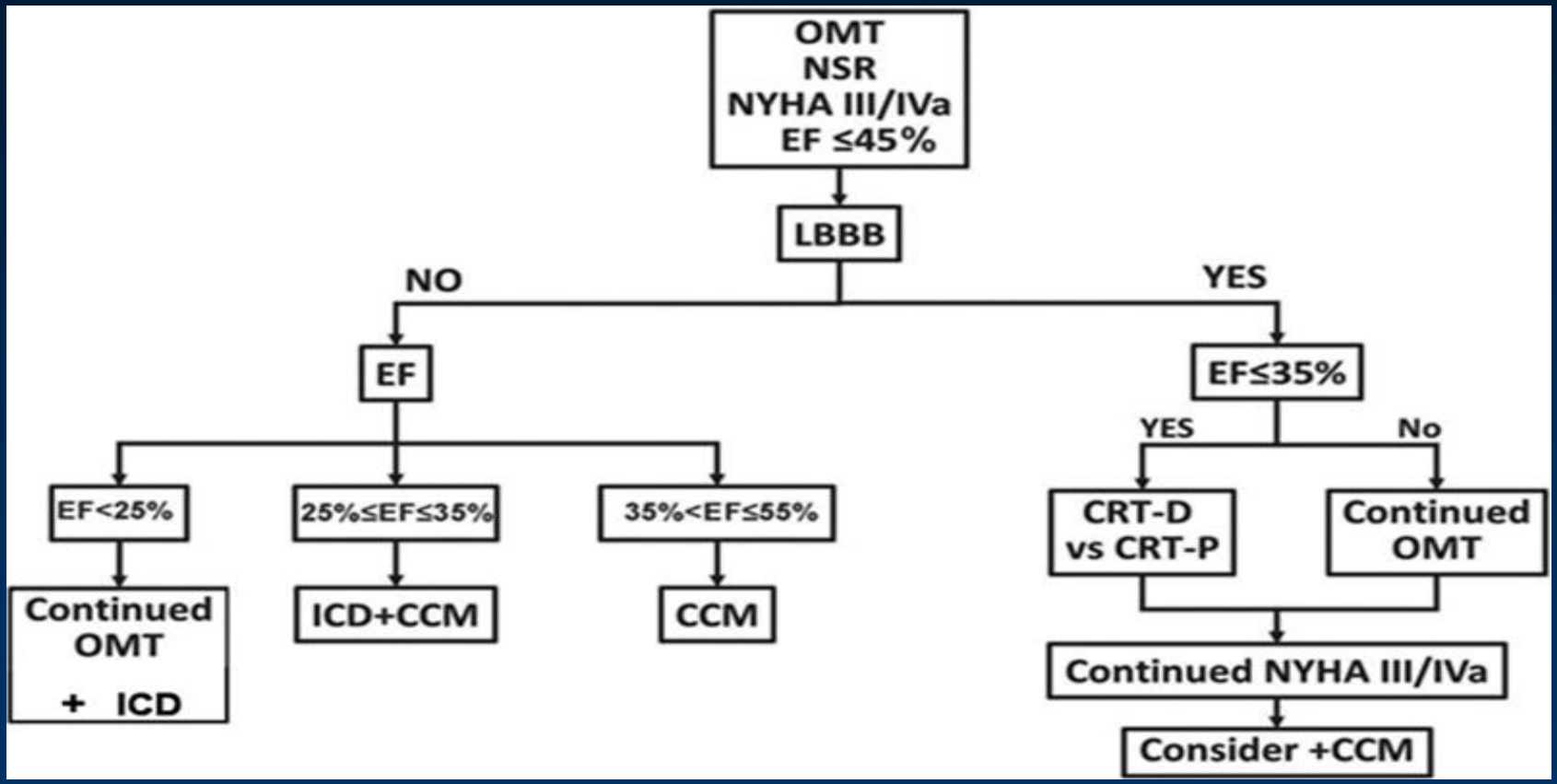
Future Advances in Pacing

- Better CRT lead systems
- Achieving CRT without complicated lead systems
  - His Bundle Pacing
  - Left Bundle Pacing
- Leadless pacemakers
  - Dual Chamber
  - Part of SQ-ICD system
- CCM





Potential Role of Cardiac Contractility Modulation (CCM)



Martin Borggrefe. Circulation. Cardiac Contractility Modulation in 2018, Volume: 138, Issue: 24, Pages: 2738-2740, DOI: (10.1161/CIRCULATIONAHA.118.036460)

Future Growth of EP

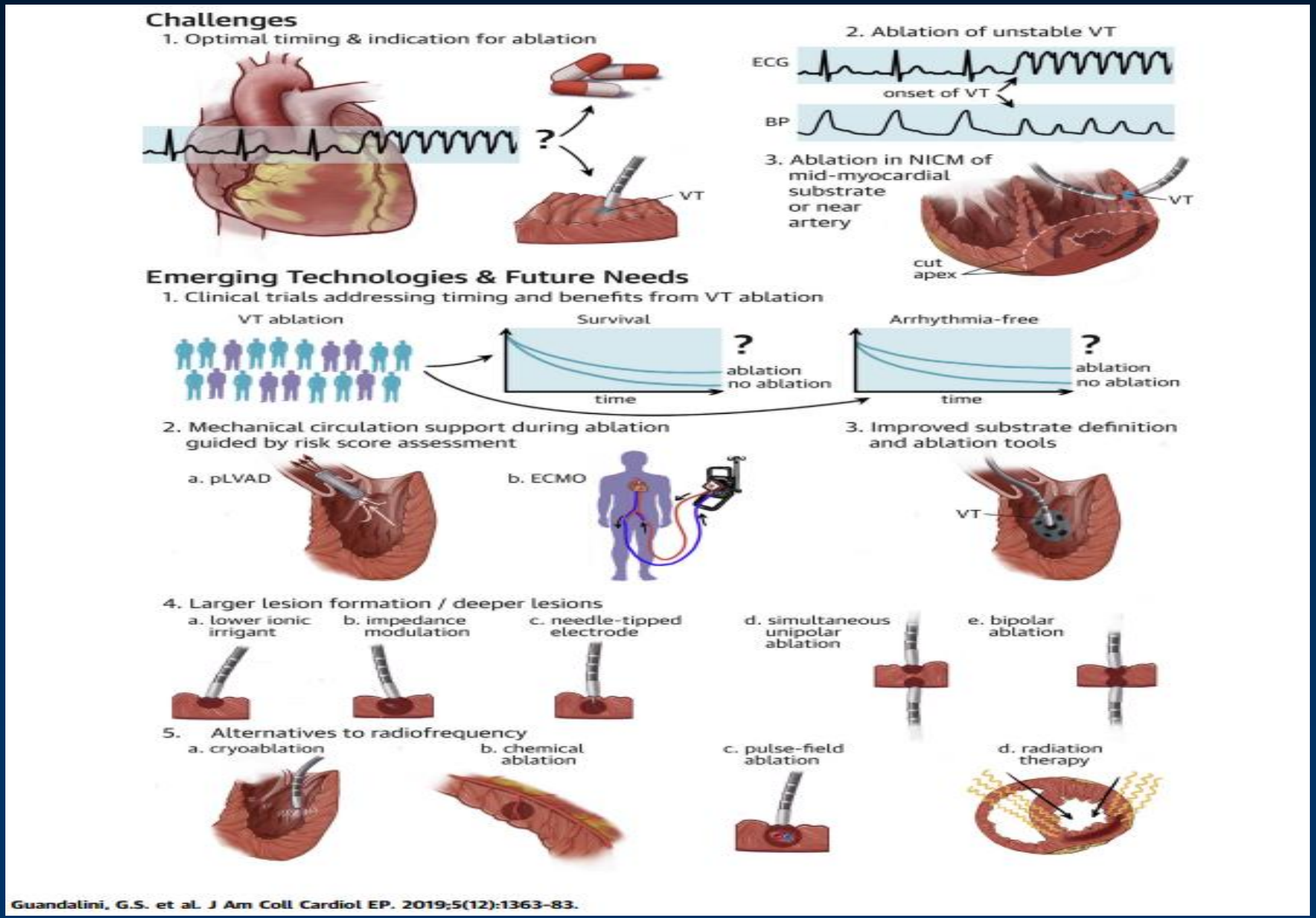
- AF Ablation
- VT Ablation
- Ablation of AT/VT in ACHD
- Improvement in Imaging and Mapping systems and novel energy delivery systems
- ILR
- Leadless Pacemakers and His Bundle/LBB pacing
- LAA Occlusion
- Lead extractions

VT Ablation: Novel Methods

	Novel Method/ Technology	Indications	Study Results	Advantages	Disadvantages/Issues
1	Higher impedance irrigant (HNS or D5W)	Bailout strategy when standard RFA with NS irrigant fails	UP to 83% acute success rate in patients with prior failed standard RFA[14]	No special tools or expertise needed Larger and deeper lesions compared to NS	Risk of steam pops Careful titration of power required Monitor impedance drops, abrupt rise in temperature/ impedance, unusual echogenicity on ICE
2	Simultaneous unipolar RFA	Failed sequential RFA	Limited clinical data[15]	Larger and deeper lesions (hourglass shaped)	Requires two ablation catheters and RF generators Paucity of clinical data
3	Bipolar RFA	Failed traditional RFA Deeper substrate	80 to 93% acute success in patients with prior failed RFA[16]	Larger and deeper lesions (cylindrical shaped). Larger necrotic core compared to SERF[25,26]	Requires two ablation catheters and non-standard cable set-up Limitations in lesion size when myocardial thickness exceeds 2 cm
4	Infusion needle ablation	Failed traditional RFA. Deep intramural substrate	73% acute success in patients with VA who failed prior RFA[22]	Deeper intramural lesions	Risk of myocardial dissection Epicardial blebs leading to tamponade
	Alternative energy modalities for ablation of VA				
1	Pulse field ablation		Preclinical only. Greater lesion depth compared to RFA in scar areas. Similar lesion depth to RFA in healthy myocardium[48–51]	Greater lesion depth while sparing neurovascular structures	Preclinical data only System parameters need optimisation for individual catheters Flash arcing and associated trauma Muscle contractions Coronary spasm
2	Ultrasound catheter ablation		Preclinical data only Deeper and larger lesions compared to RFA[55,56]	Greater lesion depth and penetration through epicardial fat	Preclinical data only Need further optimisation in catheter design to be viable alternative to RFA and be used for endocardial delivery
3	Stereotactic body radiation therapy	Patients who are not candidates for percutaneous intervention	Lower VA burden and ICD therapy[63] Improved quality of life in multiple small studies[63–65]	Non-invasive mapping and ablation	Lack of randomised data Needs further improvement in non-invasive diagnostic imaging and dosing protocols
4	Focused electrical field ablation		Preclinical only Lesion depth up to 1.4 mm[70] Lower peak temperature	Uses standard RF generator Larger lesions than RFA	Requires perpendicular catheter tip tissue orientation Potential collateral thermal injury from large lesions
5	Alcohol ablation therapy	Bailout ablation for intramural foci, intraventricular septum	56– 84% acute non inducibility in small studies.[78]	Transarterial or retrograde coronary venous approach to reach intramural and epicardial foci	Success depends on proximity of vessels to target tissue Risk of reentrant VT Inadequate occlusion could limit ethanol delivery Collateral injury
6	Ultra-low temperature cryoablation		Preclinical for VA Clinical study under way	Contiguous, transmural and durable lesions in preclinical studies	Limited clinical data

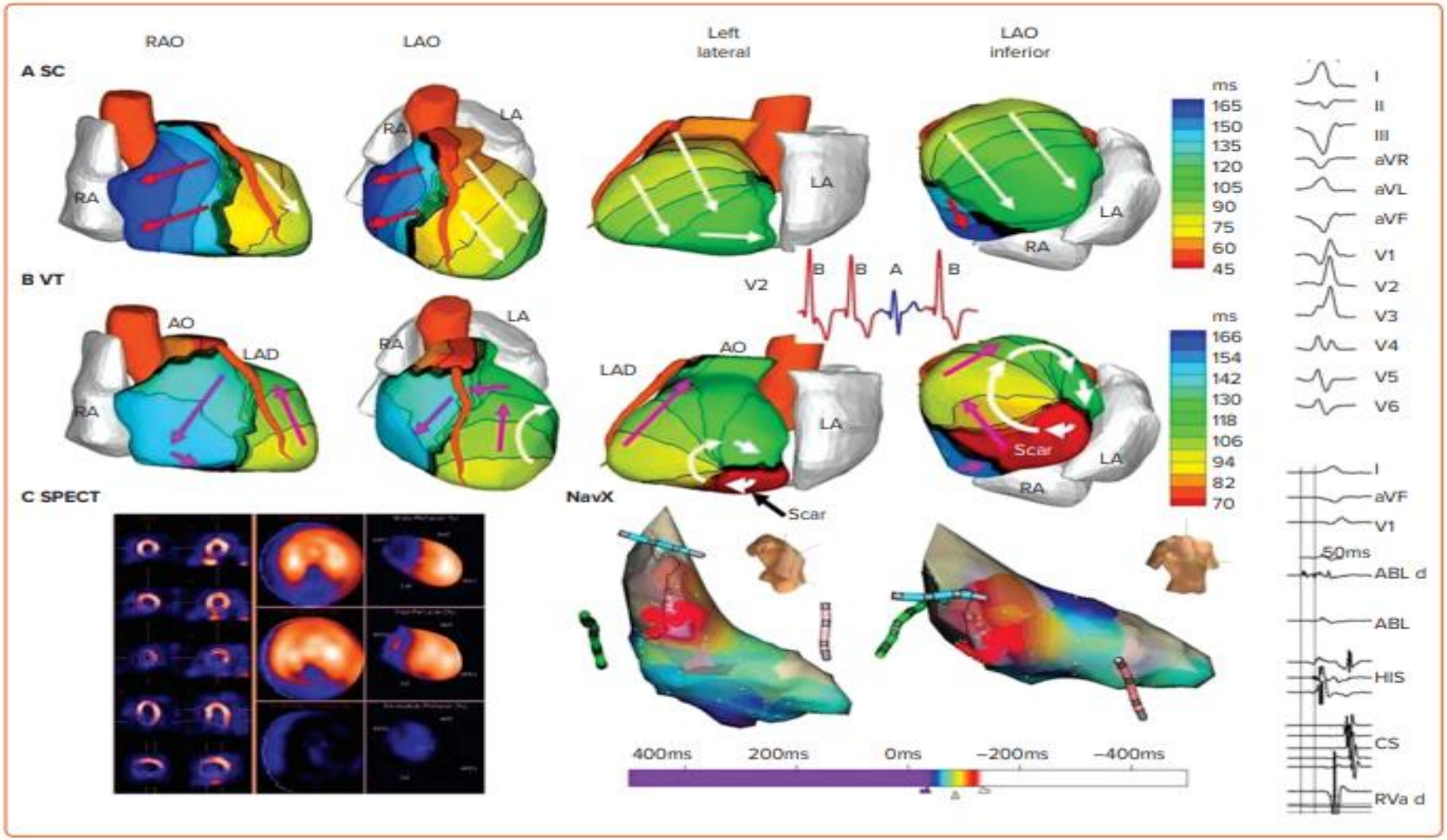
Ravi V, et al. AER 2023;12e04

VT Ablation: Current Challenges/Emerging Technologies



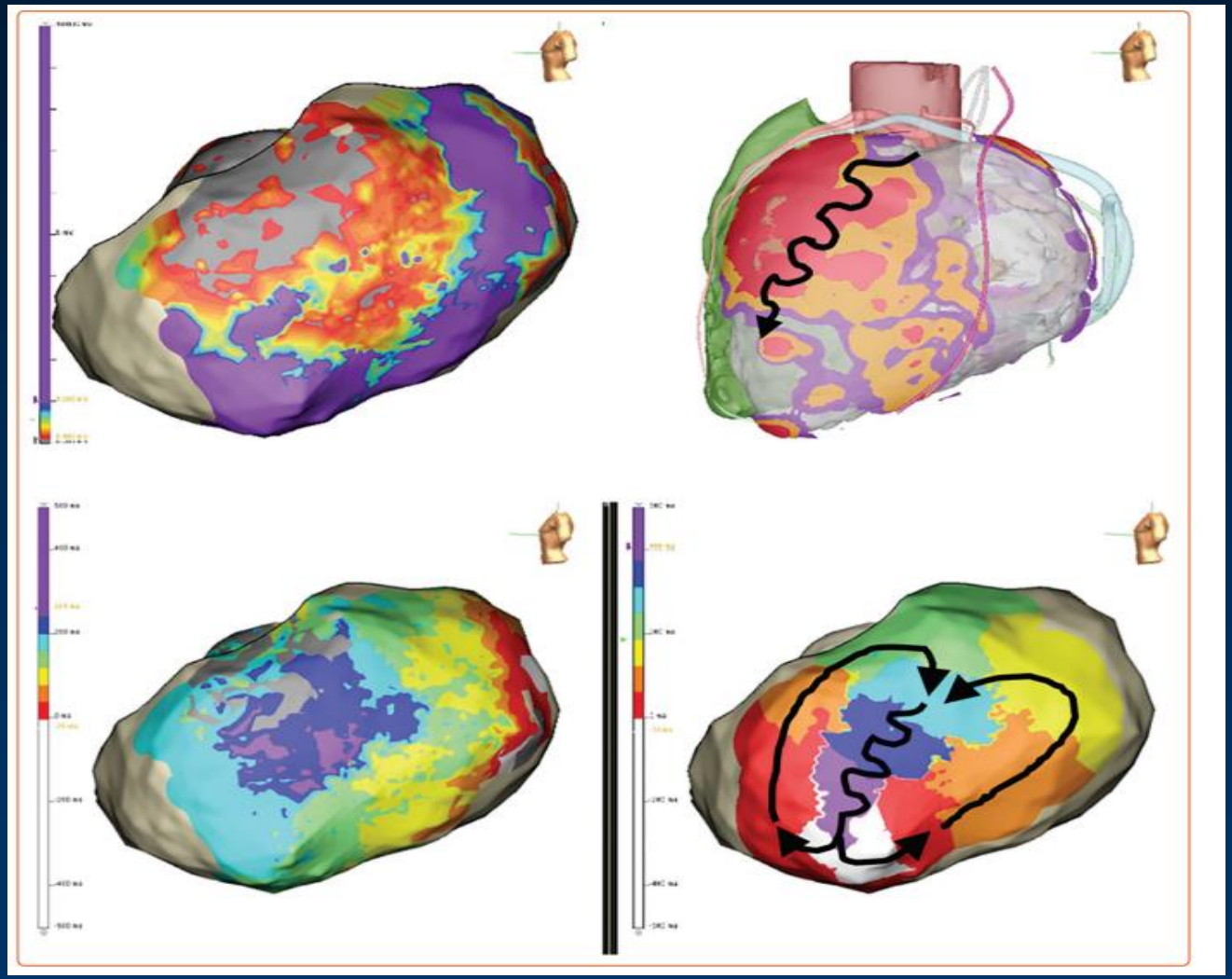
Guandalini, G.S. et al. J Am Coll Cardiol EP. 2019;5(12):1363-83.

Imaging of Reentrant VT From a InferoBasal Scar



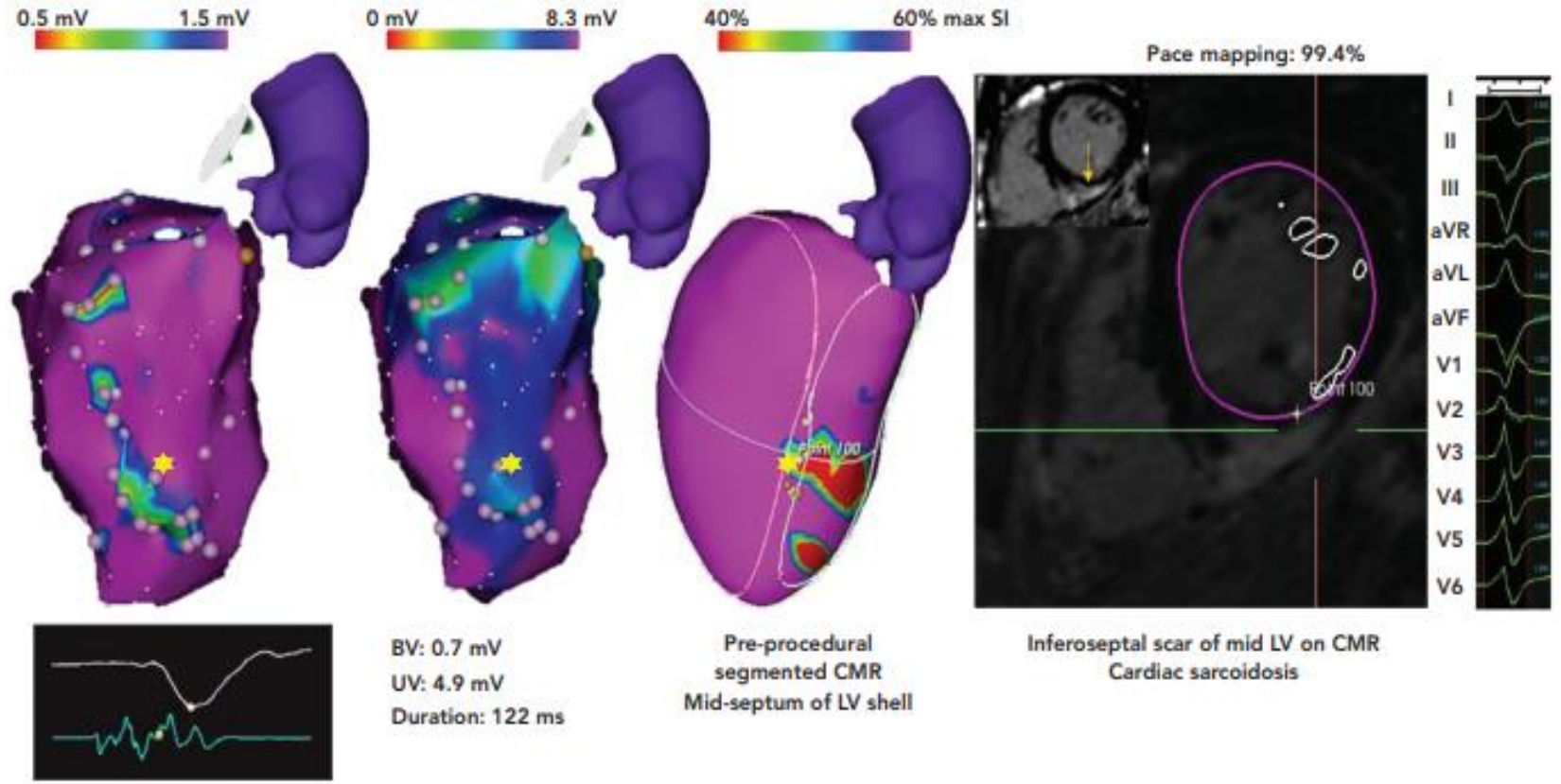
Wang Y, et al. Sci Transl Med 2011

Epicardial High Density Bipolar Voltage Maps versus Integrated CT Images after Post-Image Processing to Guide Ablation



Ravi V, et al. AER 2023;12e04

Fractionated Electrograms in Late Gadolinium Enhancement Region by Cardiac MRI



Small area of abnormal bipolar voltage at septum of mid-LV and extensive abnormal unipolar voltage from basal, perivalvular, inferoseptal wall to mid-LV are noted on electroanatomical voltage mapping. Pre-procedural late gadolinium enhancement-CMR segmented LV shell displays inferoseptal scar at mid-septum of mid LV. The good pace-mapping point on electroanatomical voltage mapping is projected to late gadolinium enhancement region on CMR. BV = bipolar voltage; CMR = cardiac magnetic resonance; LV = left ventricle; SI = signal intensity; UV = unipolar voltage.

Kuo L, et al. AER 2019; 8(4): 255-264

EP Today and Tomorrow: What Has Not and Will Not Change

- Basic Electrocardiography and anatomy of the conduction system
- Proper training in basic and clinical electrophysiology
  - With a strong foundation, future changes can easily be learned
- Arrhythmic, cardiology and bedside consultative skills
- Proper training for all procedures
- Continued growth of new ablation techniques and therapies
- Given the large number of patients with arrhythmias, antiarrhythmic drugs will continue to be a major antiarrhythmic strategy