2014 AHA/ACC/HRS Atrial Fibrillation Guideline Data Supplements

(Section numbers correspond to the full-text guideline.)

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AF indicates atrial fibrillation.

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AF indicates atrial fibrillation.

Data Supplement 3. Oral Anticoagulants (Dabigatran, Rivaroxaban, Apixaban) vs. Warfarin (Section 4.2.2)

Study Name, Author, Year	Study Aim	Study Type/Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints			P Values, OR: HR: RR: & 95% CI:	Adverse Events	Study Limitations
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint & Results*	*Safety Endpoint & Results*	*Secondary Endpoint & Results*			
RE-LY Randomized Connolly SJ, et al., 2009 (149) 19717844	To compare 2 fixed doses of dabigatran with open-label use of warfarin in pts with AF at increased risk of stroke	RCT, open-label, blinded doses of dabigatran (18,113)	Dabigatran 110 mg (6,015) Dabigatran 150 mg (6,076) Warfarin (6,021)	AF and ≥1 of the following: prior stroke or TIA; LVEF<40%, NYHA class II or higher HF Sx, age ≥75 y or an age of 65-74 y plus DM, HTN, or CAD Mean CHADS2 of 2.1	Severe heart-valve disorder, stroke within 14 d or severe stroke within 6 mo, condition that increased hemorrhage risk, CrCl <20 mL/min, active liver disease, pregnancy	Dabigatran in 2 fixed doses – oral prodrug, direct competitive inhibitor of thrombin Warfarin INR 2-3, mean TTR 64%	Stroke or SE Dabigatran110 mg 1.53%/y Dabigatran 150 mg 1.11%/y Warfarin 1.69%/y	Major Hemorrhage Dabigatran 110 mg 2.71%/y Dabigatran 150 mg 3.11%/y Warfarin 3.36%/y Intracranial Bleeding Dabigatran 110 mg 0.23%/y Dabigatran 150 mg 0.30%/y Warfarin 0.74%/y Major GI	Stroke Dabigatran 110 mg 1.44%/y Dabigatran 150 mg 1.01%/y Warfarin 1.57%/y Stroke, ST elevation, PE, MI, death, or major bleeding Dabigatran 110 mg 7.09%/y Dabigatran 150 mg 6.91%/y Warfarin 7.64%/y	Dabigatran 110 mg RR: 0.91; 95% CI: 0.74-1.11; p<0.001 for noninferiority, p=0.34 for superiority Dabigatran 150 mg RR: 0.66; 95% CI: 0.53-0.83; p<0.001 for noninferiority, p<0.001 for superiority	Dyspepsia	Open-label Median duration of FU 2 y

								Dabigatran 110 mg 1.12%/y Dabigatran 150 mg 1.51%/y Warfarin 1.02%/y				
ROCKET-AF Patel MR, et al., 2011 (150) 21830957	To compare QD oral rivaroxaban with dose-adjusted warfarin for the prevention of stroke and SE in pts with NVAF who were at moderate to high risk of stroke	RCT, double-dummy, double-blinded (14,264)	Rivaroxaban (7,131) Warfarin (7,133)	NVAF at moderate to high risk of stroke: Hx of stroke, TIA, or SE or ≥2 of the following (HF or LVEF<35% , HTN, age >75 y, DM (CHADS2 score of≥2) Mean CHADS2 score of 3.5	Severe valvular disease, transient AF caused by a reversible disorder, hemorrhage risk related criteria; severe, disabling stroke within 3 mo or any stroke within 14 d, TIA within 3 d; indication for anticoagulant Tx	Rivaroxaban Factor Xa inhibitor, 20 mg QD or 15 mg QD for those with CrCl of 39-40 mL/min Warfarin INR 2-3, mean TTR 55%	Any stroke or SE Per-protocol as treated Rivaroxaban 1.7%/y Warfarin 2.2%/y Intention to Treat Rivaroxaban 2.1%/y Warfarin 2.4%/y	Major and non-major clinically relevant bleeding Rivaroxaban 14.9/100 pt-years Warfarin 14.5/100 pt-years ICH Rivaroxaban 0.5/100 pt-years Warfarin 0.7/100 pt-years Major GI Rivaroxaban 3.15% Warfarin 2.16%	Stroke, SE, or VD Rivaroxaban 3.11/100 pt-years Warfarin 3.64/100 pt-years HR: 0.86; 95% CI: 0.74-0.99; p=0.034	Per-Protocol, as treated HR: 0.79; 95% CI: 0.66-0.96; p<0.001 for noninferiority Intention to treat HR: 0.88; 95% CI: 0.75-1.03; p<0.001 for noninferiority p=0.12 for superiority	N/A	Median duration of follow-up was 707 d Lower TTR in warfarin group 1° analysis was prespecified as a per-protocol analysis High-event rate after discontinuation of Tx

ARISTOTLE Granger CB, et al., 2011 (151) 21870978	To determine whether apixaban was noninferior to warfarin in reducing the rate of stroke (ischemic or hemorrhagic) or SE among pts with AF and ≥1 other risk factor for stroke	RCT, double-dummy, double-blinded (18,201)	Apixaban (9,120) Warfarin (9,081)	AF and ≥1 stroke risk factor (age >75 y; previous stroke, TIA or SE; symptomatic HF within the prior 3 mo or LVEF≤40% ; DM; or HTN) Mean CHADS2 score of 2.1	AF due to a reversible cause, moderate or severe mitral stenosis, conditions other than AF requiring OAC, stroke within the prior 7 d, a need for ASA>165 mg or for ASA and CP, or severe renal insufficiency (CrCl<25 mL/min)	Apixaban Factor Xa inhibitor 5 mg BID or 2.5 mg BID among pts with ≥2 of the following (≥80 y, body weight ≤60 kg, or serum Cr level of ≥1.5 mg/dL) Warfarin INR 2-3 Mean TTR 62.2%	Any stroke or SE Apixaban 1.27%/y Warfarin 1.6%/y	Major Bleeding Apixaban 2.13%/y Warfarin 3.09%/y ICH Apixaban 0.33%/y Warfarin 0.80%/y Major GI Apixaban 0.76%/y Warfarin 0.86%/y	Stroke, SE, major bleeding, or death from any cause Apixaban 6.13%/y Warfarin 7.20%/y	HR: 0.79; 95% CI: 0.66-0.95; p<0.001 for noninferiority, p=0.01 for superiority HR: 0.85; 95% CI: 0.78-0.92; p<0.001	No differences	Median duration of FU 1.8 y
AVERROES Connolly SJ, et al., 2011 (152) 21309657	To determine the efficacy and safety of apixaban, at a dose of 5 mg BID, as compared with ASA, at a dose of 81-324 mg QD, for the Tx of pts with AF for whom VKA Tx was considered unsuitable	RCT double-blind, double-dummy (5,559)	Apixaban (2,808) ASA (2,791)	≥50 y and AF and ≥1 of the following stroke risk factors: prior stroke or TIA, ≥75 y, HTN, DM, HF, LVEF≤35% , or PAD. Pts could not be receiving VKAs	Pts required long-term anticoagulation, VD requiring surgery, a serious bleeding event in the previous 6 mo or a high-risk bleeding, stroke	Apixaban Factor Xa inhibitor 5 mg BID or 2.5 mg BID among pts with ≥2 of the following (age ≤80 y, body weight ≤60 kg, or serum Cr level of ≥1.5 mg/dL) ASA	Any stroke or SE Apixaban 1.6%/y ASA 3.7%/y p<0.001	Major Bleeding Apixaban 1.4% ASA 1.2% Intracranial Bleeding Apixaban 0.4% ASA 0.4% Major GI	Stroke, SE, MI, VD or major bleeding event Apixaban 5.3%/y ASA 7.2%/y HR: 0.74; 95% CI: 0.60–0.90; p<0.003	HR: 0.45; 95% CI: 0.32-0.62; p<0.001	No differences	N/A

				because it had already been demonstrated to be unsuitable or because it was expected to be unsuitable. Mean CHADS2 of 2.0	within the previous 10 d, severe renal insufficiency (a sCr>2.5 mg/dL) or a calculated CrCl<25 mL/min	81-325 mg/dL		Apixaban 0.4% ASA 0.4%				

1° indicates primary; AF, atrial fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in AF; ASA, aspirin; AVERROES, Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; BID, twice daily; CAD, coronary artery disease; CHADS2, Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, Stroke; ; CP, codeine phosphate; Cr, creatinine; CrCl, creatinine clearance; DM, diabetes mellitus; FU, follow-up; GI, gastrointestinal; HF, heart failure; HR, hazard ratio; HTN, hypertension; Hx, history; ICH, intracranial hemorrhage; INR, international normalized ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not applicable; PAD, peripheral arterial disease; PE, pulmonary embolism; N/A, not applicable; NVAF, nonvalvular atrial fibrillation; NYHA, New York Heart Association; OAC, oral anticoagulation; pts, patient; QD, once daily; RCT, randomized controlled trial; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial; RR, relative risk; sCr, serum creatinine; SE, systemic embolism; Sx, symptom; TIA, transient ischemic attack; TTR, time in therapeutic range; Tx, therapy; VD, valvular disease; and VKA, vitamin K antagonist.

Data Supplement 4. Warfarin vs. Control (Section 4.2)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints			P Values, OR: HR: RR: & 95% CI:
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint & Results*	*Safety Endpoint & Results*	*Secondary Endpoint & Results*	
Aguilar MI, et al., 2005 (153) 16034869	To characterize the efficacy and safety of oral anticoagulants for the 1° prevention of stroke in pts with chronic AF	Cochrane Collaboration Systematic Review (AFASAK I, BAATAF, CAFA, SPAF I, SPINAF)	2,313 pts Warfarin 1,154 PC 1,159	AF (intermittent or sustained)	Prior stroke or TIA, mitral stenosis or prosthetic cardiac valves	Oral VKAs (warfarin) mean INR 2.0-2.6	All Stroke (ischemic or ICH) Warfarin 27 PC 71	ICH, Major extracranial bleeds ICH, Warfarin 5, PC 2 Extracranial bleeds, Warfarin	Stroke, MI or VD Warfarin 69 PC 118	All ischemic stroke or ICH OR: 0.39; 95% CI: 0.26-0.59 Ischemic stroke OR: 0.34; 95% CI: 0.23-0.52

								17, PC 16		Stroke, MI, VD OR: 0.57; 95% CI: 0.42-0.77 All ICH OR: 2.38; 95% CI: 0.54-10.50) Major extracranial bleeds OR: 1.07; 95% CI: 0.53-2.12

1° indicates primary; AF, atrial fibrillation; AFASAK, Atrial Fibrillation, Aspirin and Anticoagulant Therapy Study; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation ; ICH, intracranial hemorrhage; INR, international normalized ratio; MI, myocardial infarction; N/A, not applicable; OR, odds ratio; PC, placebo; Pts, patients; RR, relative risk; SPAF I, Stroke Prevention in Atrial Fibrillation Study; SPINAF, Stroke Prevention in Atrial Fibrillation; TIA, transient ischemic attack; VD, vascular death; and VKA, vitamin K antagonist.

Data Supplement 5. Warfarin vs. Antiplatelet Therapy (Section 4.2)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints			P Values, OR: HR: RR: & 95% CI:	Study Limitations
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint & Results*	*Safety Endpoint & Results*	*Secondary Endpoint & Results*		
Aguilar MI, et al., 2007 (154) 17636831	To characterize the relative effect of long-term oral anticoagulant Tx compared with antiplatelet Tx in pts with AF and no Hx of stroke or TIA	Cochrane Collaboration Systematic Review (ACTIVE-W, AFASAK I, AFASAK II, ATHENS, NASPEAF, PATAF, SPAF IIa, SPAF IIb,	9,598 pts OAC 4,815 Antiplatelet 4,783	AF (intermittent or sustained)	Prior stroke or TIA, mitral stenosis or prosthetic cardiac valves	Adjusted dose warfarin or other coumarins; antiplatelet therapies	All Stroke (ischemic or ICH) OAC 132/4,815 Antiplatelet 190/4,783	ICH, major extracranial bleeds	Stroke, MI, or VD	All Stroke OR: 0.68; 95% CI: 0.54-0.85; p=0.00069 Ischemic stroke OR: 0.53; 95% CI: 0.41-0.69 ICH OR: 1.98; 95% CI: 1.20-3.28 Major Extracranial OR: 0.97; 95% CI: 0.74-1.28	N/A

										Major Extracranial (exclude ACTIVE W with CP+A) OR: 1.90; 95% CI: 1.07-3.39 Stroke, MI, 485 VD OR: 0.74; 95% CI: 0.61-0.90	
Saxena R, et al., 2011 (155) 15494992	To compare the value of anticoagulants and antiplatelet Tx for the long term prevention of recurrent vascular events in pts with non-rheumatic AF and previous TIA or minor ischemic stroke	Cochrane Collaboration Systematic Review (EAFT, SIFA)	1,371 pts, warfarin 679, antiplatelet 692	AF and prior minor stroke or TIA	Rheumatic VD	Oral VKAs (warfarin) mean INR>2.0; Antiplatelets 300 mg ASA; indobufen 200 mg BID	All major vascular events (VD, recurrent stroke, MI, or SE)	Any ICH; major extracranial bleed	All fatal or nonfatal recurrent strokes	All Major Vasc Events OR: 0.67; 95% CI: 0.50-0.91 Recurrent Stroke OR: 0.49; 95% CI: 0.33-0.72 Any ICH OR: 1.99; 95% CI: 0.40-9.88 Major Extracranial bleed OR: 5.16; 95% CI: 2.08-12.83	N/A
Mant J, et al., 2007 BAFTA (156) 17693178	To compare the efficacy of warfarin with that of ASA for the prevention of fatal and nonfatal stroke, ICH, and other clinically significant arterial embolism in a 1° care	RCT (973 pts)	973 pts, ASA 485, warfarin 488	Age ≥75 y, AF or flutter by EKG within 2 y from 1° care practices	Rheumatic heart disease, a major nontraumatic hemorrhage within 5 y, ICH, documented peptic ulcer disease within the previous year, esophageal varices,	ASA 75 mg QD; Warfarin target INR 2.5, range 2-3	Fatal or nonfatal disabling stroke (ischemic or hemorrhagic), other ICH, or clinically significant arterial embolism Warfarin 24 (1.8%/y)	Hemorrhage Major extracranial Warfarin 18 (1.4%/y) ASA 20 (1.6%/y) All major hemorrhages Warfarin 25 (1.9%/y) ASA 25 (2.0%/y)	Major vascular events (stroke, MI, PE, VD) Warfarin 76 (5.9%/y) ASA 100 (8.1%/y) 1° events plus major hemorrhage Warfarin 39	RR: 0.48; 95% CI: 0.28-0.80; p=0.0027 Stroke RR: 0.46; 95% CI: 0.26-0.79; p=0.003 All major hemorrhages RR: 0.96; 95% CI: 0.53-1.75; p=0.90 Major vascular	Open-label with blind assessments 67% of the warfarin group remained on Tx TTR was 67%

	population of pts aged ≥75 y who had AF				allergic hypersensitivity to study drugs, terminal illness, surgery within the last 3 mo, BP>180/110		ASA 48 (3.8%/y)		(3.0%/y) ASA 64 (5.1%/y)	events (stroke, MI, PE, VD) RR: 0.73; 95% CI: 0.53-0.99; p=0.03 1° events plus major hemorrhage RR: 0.59; 95% CI: 0.38-0.89; p=0.008	

1° indicates primary; AF, atrial fibrillation; ACTIVE-W, Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events-W; AFASAK, Atrial Fibrillation, Aspirin and Anticoagulant Therapy Study; ATHENS, Primary Prevention of Arterial Thromboembolism in the Oldest Old with Atrial Fibrillation; BID, twice daily; BP, blood pressure; EAFT, European Atrial Fibrillation Trial; EKG, electrocardiogram; Hx, history; ICH, intracranial hemorrhage; MI, myocardial infarction; N/A, not applicable; NASPEAF, National Study for Prevention of Embolism in Atrial Fibrillation; PATAF, Primary Prevention of Arterial Thromboembolism in Nonrheumatic Atrial Fibrillation; PE, pulmonary embolism; pts, patients; QD, once daily; RR, relative risk; SE, systemic embolism; SIFA, Studio Italiano Fibrillazione Atriale; SPAF, Stroke Prevention in Atrial Fibrillation Study; TIA, transient ischemic attack; TTR, time in therapeutic range; Tx, therapy; and VD, vascular death.

Data Supplement 6. Beta Blockers (Sections 5.1.1)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints		P Values, OR: HR: RR: & 95% CI:	Adverse Events	Study Limitations
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint & Results*	*Secondary Endpoint & Results*			
Abrams J, et al., 1985 (157) 3904379	Evaluation of the efficacy and safety of esmolol in comparing to propranolol for the acute control of SVT	Randomized prospective, multicenter double-blind	IV esmolol vs. IV propranolol	Pts over age 18 y with ventricular rates >120 bpm 2° to AF, atrial flutter, SVT, atrial tachycardia, idiopathic sinus tachycardia and AV reentrant tachycardias	WPW syndrome, hypotension, sick sinus syndrome, AV conduction delay decompensated HF or noncardiac precipitated arrhythmias	Esmolol vs. propranolol	Composite endpoint of either ≥20% reduction from average baseline heart rate, reduction in heart rate to <100 bpm, or conversion to NSR esmolol 72% vs. propranolol 69%	N/A	No difference	Hypotension (esmolol 45% vs. propranolol 18%)	Small sample size Only 66% of pts had AF
Farshi R, et al., 1999 (158) 9973007	Comparison of the effects of 5 standard drug	Prospective, open-label crossover outpatient	N/A	Chronic AF pts who had a duration of ≥1 y	LVEF<0.35, WPW syndrome, sick sinus	Comparison of the effects of 5 standard drug	Comparison of 24 h mean ventricular rates	Peak ventricular response at 5 m of exercise:	p<0.01 for comparison of atenolol or atenolol and	N/A	N/A

	regimens: digoxin, diltiazem, atenolol, digoxin plus diltiazem, and digoxin + atenolol on the mean 24-h heart rate				syndrome, pacemaker or clinically significant renal, thyroid or hepatic disease	regimens: digoxin, diltiazem, atenolol, digoxin plus diltiazem, and digoxin + atenolol on the mean 24-h heart rate	Digoxin: 78.9±16.3 Diltiazem: 80.0±15 Atenolol: 75.9±11.7 Digoxin + Diltiazem: 67.3±14.1 Digoxin + atenolol: 65±9.4	Digoxin: 175±36 Diltiazem: 151±27 Atenolol: 130±34 Digoxin + Diltiazem: 146±40 Digoxin + atenolol: 126±29	digoxin compared to digoxin alone		

1° indicates primary; 2°, secondary; AF, atrial fibrillation; AV, atrioventricular; HF, heart failure; HR, hazard ratio; IV, intravenous; LVEF, left ventricular ejection fraction; N/A, not applicable; NSR, normal sinus rhythm; pts, patients; SVT, supraventricular tachycardia; Tx, therapy; and WPW, Wolff-Parkinson-White.

Data Supplement 7. Nondihydropyridine Calcium Channel Blockers (Sections 5.1.2)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints	P Values, OR: HR: RR: & 95% CI:	Study Limitations
				Inclusion Criteria	***Exclusion Criteria***		***Primary Endpoint & Results***		
Ellenbogen KA, et al., 1991 (159) 1894861	To demonstrate the safety and efficacy of a continuous IV diltiazem infusion for 24 h heart rate control	Randomized, double-blind, parallel, PC-controlled	IV diltiazem vs. PC	Pts >18 y with AF or atrial flutter with duration >24 h and HR>120 bpm	Severe CHF, sinus node dysfunction, 2nd or 3rd degree AV block, WPW syndrome or hypotension	IV diltiazem vs. PC	Therapeutic response (ventricular response <100 bpm, ≥20% decrease in heart rate from baseline or conversion to NSR 74% vs. 0%	p<0.001	Small sample size
Steinberg JS, et al., 1987 (160) 3805530	To determine the efficacy of diltiazem to control ventricular response at rest, during exercise, and during daily activities	Prospective, open-label	Oral diltiazem	Pts with chronic AF with a VR>100 bpm at 3 min of a standardized exercise test	UA, acute MI, WPW syndrome, hypotension, renal or hepatic failure, sick sinus syndrome without a pacemaker	Oral diltiazem	Ventricular response: Rest: 69±10 vs. 96±17 Exercise: 116±26 vs. 155±28+	p<0.001	Small sample size Most pts at entry were on digoxin and continued on digoxin

Siu CW, 2009 et al., (161) 19487941	To compare the clinical efficacy of IV diltiazem, digoxin, and amiodarone for acute VR in symptomatic AF	Randomized, prospective, open-label	IV diltiazem vs. IV amiodarone vs. IV digoxin	Hospitalized pts with symptomatic AF<48 h with ventricular response >120 bpm	Ventricular response >200 bpm, pre-excitation syndrome, hypotension, CHF, implanted pacemaker/defibrillator, recent MI, UA or stroke	IV diltiazem vs. IV amiodarone vs. IV digoxin	VR control (<90 bpm) within 24 h: ventricular response <90 bpm sustained for ≥4 h Diltiazem 90% vs. amiodarone 74% vs. digoxin 74%	p<0.47	N/A

AF indicates atrial fibrillation; AV, atrioventricular; CHF, congestive heart failure; IV, intravenous; MI, myocardial infarction; N/A, not applicable; NSR, normal sinus rhythm; PC, placebo; pts, patients; RR, relative risk; UA, unstable angina; VR, ventricular rate; and WPW, Wolff-Parkinson-White.

Data Supplement 8. Digoxin (Sections 5.1.3)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints		P Values, OR: HR: RR: & 95% CI:	Study Limitations
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint & Results*	*Secondary Endpoint & Results*		
IV Digoxin in Acute AF (162) 9129897	To examine the effects of IV digoxin in acute AF	Randomized, prospective, multicenter, double-blind PC-controlled	IV digoxin vs. PC	Pts >18 y with AF≤7d	Ongoing Tx with digoxin or antiarrhythmics, sick sinus syndrome or 2nd /3rd degree AV block without a pacemaker, WPW syndrome, heart rate <60 or >170 bpm, ongoing ischemia or recent MI	IV digoxin vs. PC	Conversion to sinus rhythm at 16 h Digoxin 46% vs. PC 51%	Effect on heart rate: 91.2±20 vs. 116.2±25	p=0.37 p<0.0001	N/A
AFFIRM Olshansky B, et al., 2004 (163) 15063430	To examine whether digoxin use was associated with adverse	Post hoc analysis	Nonrandomized comparison of digoxin vs. no digoxin	Pts with AF considered at high risk for stroke	N/A	Post hoc analysis including propensity analysis	Estimated HR of 1.41 for all-cause mortality for digoxin	Estimated HR of 1.61 for arrhythmic mortality Estimated HR	p<0.001 p<0.009 p<0.016	Post hoc analysis utilizing propensity scoring

	mortality and morbidity							of 1.35 for CV mortality		

AF indicates atrial fibrillation; AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management; AV, atrioventricular; HR, hazard ratio; IV, intravenous; MI, myocardial infarction; N/A, not applicable; PC, placebo; pts, patients; RR, relative risk; Tx, therapy; and WPW, Wolff-Parkinson-White.

Data Supplement 9. Other Pharmacological Agents for Rate Control (Sections 5.1.4)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints			P Values, OR: HR: RR: & 95% CI:	Adverse Events
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint & Results*	*Safety Endpoint & Results*	*Secondary Endpoint & Results*		
Delle Karth G, et al., 2001 (164) 11395591	To compare the efficacy of IV diltiazem bolus/infusion vs. IV amiodarone bolus vs. IV amiodarone bolus/infusion for immediate (4 h) and 24-h rate control during AF	Randomized prospective, controlled	IV diltiazem bolus/infusion vs. IV amiodarone bolus vs. IV amiodarone bolus/infusion	Critically ill pts with recent-onset AF with ventricular rate >120 bpm	N/A	IV diltiazem bolus/ infusion vs. IV amiodarone bolus vs. IV amiodarone bolus/infusion	Sustained heart rate reduction ≥30% within 4 h 70% vs. 55% vs. 75%	Bradycardia or hypotension 35% vs. 0% vs. 5%	Uncontrolled tachycardia 0% vs. 45% vs. 5%	1° endpoint: NS 2° endpoint p<0.00016 Safety endpoint p=0.01	N/A
Connolly SJ, et al., 2011 (165) 22082198	Assess impact of dronedarone on major vascular events in high-risk permanent AF	Randomized prospective, multicenter, double-blind, PC-controlled trial (3,236)	Dronedarone 400 mg po BID vs. PC	Permanent AF / flutter, age ≥65 y with ≥1 risk factor: CAD, CVA or TIA, CHF, LVEF≤0.40, PAD or age ≥75 y with HTN and DM	Paroxysmal or persistent AF, ICD, heart rate <50 bpm, QT interval corrected >500 ms	Dronedarone vs. PC	Composite of stroke, MI, SE, or CV death Composite of unplanned hospitalization for CV event/ death	N/A	N/A	HR: 2.29; 95% CI: 1.34-3.94 HR: 1.95; 95% CI: 1.45-2.62	Stroke HR: 2.32; 95% CI: 1.11-4.88 Unplanned hospitalization for CV event HR: 1.81; 95% CI: 1.44-2.70

1° indicates primary; 2°, secondary; AF, atrial fibrillation; BID, twice daily; CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; CVA, cerebrovascular accident; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; ICD, implantable cardioverter defibrillator; IV, intravenous; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not applicable; NS, not significant; PAD, peripheral artery disease; PC, placebo; po, orally; pts, patients; RR, relative risk; SE systemic embolism; and TIA, transient ischemic attack.

Data Supplement 10. AV Junction Ablation (Sections 5.2)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints *Primary Endpoint & Results*	P Values, OR: HR: RR: & 95% CI:	Study Limitations
				Inclusion Criteria	*Exclusion Criteria*				
Ozcan C, et al., 2001 (166) 11287974	Assess effect of radio-frequency ablation of the AV node and implantation of a permanent pacemaker on long-term survival in pts with AF refractory to drug Tx	Observational single site	Comparison to 2 control populations Age/sex matched from minnesota population Consecutive pts with AF who received drug Tx	All pts who underwent AV nodal ablation and pacemaker implantation for medically refractory AF between 1990 and 1998	N/A	AV nodal ablation pacemaker compared to 2 control groups	No difference in survival between ablation/pacemaker group and control group treated with drugs Excess observed death in ablation/ pacemaker group relative to age/sex matched population	N/A	Observation, nonrandomized trial

AF indicates atrial fibrillation; AV, atrioventricular; N/A, not applicable; pts, patients; RR, relative risk; and Tx, therapy.

Data Supplement 11. Broad Considerations in Rate Control (Sections 5.3.1)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints		P Values, OR: HR: RR: & 95% CI:	Adverse Events
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint & Results*	*Secondary Endpoint & Results*		
Van Gelder IC, et al., 2010 (167) 20231232	Lenient rate control is noninferior to strict rate control in permanent AF	Randomized, prospective, multicenter, open label N=614	Lenient rate control (resting heart rate <110) vs. strict rate control (resting heart rate <80)	Age <80 y, permanent AF, oral anticoagulant or ASA Tx	N/A	N/A	Composite of CV death and morbidity at 12.9% vs. 14.9%	Death, components of 1° endpoint, Sx, and functional status	1° endpoint, 3 y, HR: 0.84; 95% CI: 0.58-1.21	HF (3.8% vs. 4.1%); HR: 0.97; 95% CI: 0.48-1.96 Stroke 1.6% vs. 3.9%, HR: 0.35; 95% CI: 0.13-0.92 CV death 2.9% vs. 3.9%, HR: 0.79; 95% CI: 0.38-1.65

1° indicates primary; AF, atrial fibrillation; ASA, aspirin; CV, cardiovascular; HF, heart failure; HR, hazard ratio; N/A, not applicable; pts, patients; RACE, Rate Control Efficacy in Permanent Atrial Fibrillation; RR, relative risk; Sx, symptom; and Tx, therapy.

Data Supplement 12. Antiarrhythmic Drug Therapy (Section 6.2.1)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population	Endpoints		Adverse Events	Comments
					Primary Endpoint & Results	*Secondary Endpoint & Results*		
ADONIS, Singh BN, et al., 2007 (168) 17804843	To assess the efficacy of dronedarone in maintenance of SR in pts with AF	RCT, double-blind (625)	Dronedarone 400 mg BID (417) PC (208)	Age ≥21 y ≥1 episode AF in previous 3 mo	Time to the 1st recurrence of AF or atrial flutter Dronedarone 158 d PC 59 d (p=0.002)	Ventricular rate after recurrence, dronedarone 104.6 bpm PC 116.6 bpm (p<0.001).	N/A	Dronedarone was more effective than PC in maintaining SR and in reducing ventricular rate during recurrent AF
AFFIRM Substudy, 2003 (169) 12849654	To evaluate the efficacy of antiarrhythmic drugs for AF	RCT, open-label (410)	Amiodarone 200 mg/d vs. class I drug vs. sotalol	Substudy of pts randomized to rhythm control	1° – proportion at 1 y alive, on Tx drug, and in SR 62% amiodarone vs. 23% class I drug (p<0.001) 60% amiodarone vs. 38% sotalol (p=0.002) 34% sotalol vs. 23% class I drug (p=0.488)	N/A	AEs leading to drug discontinuation 12.3% amiodarone 11.1% sotalol 28.1% class I agent Amiodarone pulmonary toxicity 1.3% at 1 y and 2.0% at 2 y 1 case torsade de pointes - quinidine	Amiodarone more effective than sotalol or class I agent for SR without cardioversion AEs were common
Aliot E, et al., 1996 (170) 8607394	To assess the safety and efficacy of flecainide vs. propafenone in PAF or atrial flutter	RCT, open-label (97)	Flecainide 100-200 mg/d (48) Propafenone 600 mg/d (49)	Inclusion: >18 y with symptomatic PAF or atrial flutter Exclusion: AF last >72 h, Hx of MI or UA, Hx of VT, Hx of HF (NYHA class III or IV), LVEF<35%, PR>280 ms, QRS>150 ms, sick sinus syndrome or AV block in absence of pacemaker	Probability of SR at 1 y 0.619 flecainide 0.469 propafenone (p=0.79)	N/A	8.5% flecainide group had neurologic side effects 16.7% propafenone group GI side effects	Flecainide and propafenone similar efficacy (although small sample size and open-label design) Nonsignificant trend toward higher side-effects with propafenone

ANDROMEDA, Kober L, et al., 2008 (171) 18565860	To evaluate the efficacy of dronedarone in HF pts	RCT, double-blind (627)	Dronedarone (310) PC (317)	Age >18 y, hospitalized for HF, LVEF<35%, NYHA class III or IV (Did not require AF Dx, Hx of AF 37-40%)	Death from any cause or HF hospitalization 17.1% dronedarone 12.6% PC HR: 1.38; 95% CI: 0.92-2.09; p=0.12	N/A	Death 8.1% dronedarone 3.8% PC HR: 2.13; 95% CI: 1.07-4.25; p=0.03	Dronedarone is associated with increased mortality in pts with severe HF and reduced LVEF related to worsening of HF
ASAP, Page RL, et al., 2003 (172) 12615792	To assess the frequency of asymptomatic AF in pts treated with azimilide	RCT, double-blind (1,380)	Azimilide 35-125 mg/d (891) PC (489)	Inclusion: Symptomatic AF in SR at time of randomization Exclusion: Rest angina or UA, class IV CHF, Hx of torsade de pointes, QTc >440 ms, resting SR<50 bpm	Time to 1st documented asymptomatic AF – no significant difference 40% reduction in asymptomatic AF episodes in the 100 mg or 125 mg azimilide group vs. PC (p=0.03)	N/A	N/A	N/A
ATHENA, Hohnloser SH, et al., 2009 (173) 19213680	N/A	RCT, double-blind (4,628)	Dronedarone 400 mg BID (2,301) PC (2,327)	Inclusion: AF (paroxysmal or persistent) and ≥1 of these: >70 y, HTN, DM, LVEF<40%, LAD>50 mm, Hx of TIA/stroke/embolism	1° – 1st hospitalization due to CV event or death 31.9% dronedarone 39.4% PC HR: 0.76; p<0.001	Death due to any cause CV death CV hospitalization	N/A	N/A
Bellandi F, et al., 2001 (174) 11564387	To evaluate the long-term efficacy and safety of propafenone and sotalol for maintaining SR	RCT, double-blind (194)	Propafenone HCL 900 mg/d (102) Sotalol HCL 240 mg/d (106) PC (92)	≥18 y, recurrent AF (≥4 episodes previous 12 mo) and episode of AF at enrollment <48 h	Proportion of pts remaining in SR at 1 y FU 63% propafenone 73% sotalol 35% PC (p=0.001)	N/A	4% ventricular arrhythmia with sotalol Drug discontinuation due to AEs – 9% propafenone, 10% sotalol, 3% PC	Sotalol and propafenone appear to have similar efficacy and are superior to PC at maintaining SR at 1 y
Benditt DG, et al., 1999 (175) 10496434	To evaluate the efficacy of sotalol for maintaining of SR	RCT, double-blind (253)	Sotalol 80 mg BID (59) Sotalol 120 mg BID (63) Sotalol 160 mg	Inclusion: symptomatic AF or atrial flutter and SR at time of randomization Dose reduction in presence of renal dysfunction	Time to first recurrent symptomatic AF or atrial flutter after steady state (intention to treat) 27 d PC	Proportion of pts free of AF 12 mo 28% PC 30% sotalol 80 mg 40% sotalol 120	Bradycardia and fatigue most common AEs No cases of torsade de pointes in this study	Outpatient initiation in 27%

			BID (62) PC (69)	Exclusion: QT>450 ms, sinus rate <50, other QT prolonging drugs, renal failure (CrCl<40 mL/min), Hx of HF, uncorrected hypokalemia, asymptomatic AF, sick sinus syndrome without pacer, MI<2 mo, syncope, TIA/stroke	106 d sotalol 80 mg 229 d sotalol 120 mg 175 d sotalol 160 mg	mg 45% sotalol 160 mg		
Byrne-Quinn E, et al., 1970 (176) 4911757	To evaluate the efficacy of quinidine for maintenance of SR	RCT, double-blind (65)	Quinidine 1.2 g/d (28) PC (37)	Inclusion: Pts hospitalized for AF with plan for cardioversion Exclusion: digoxin stopped 24 h prior	Percentage of pts at FU in SR 24.3% PC 57% quinidine	N/A	1 death presumed related to quinidine	Small sample size, variable FU period (5-15 mo)
Carunchio A, et al., 1995 (177) 7642012	To evaluate the efficacy and safety of flecainide and sotalol for maintenance of SR	RCT, open-label (66)	Flecainide acetate 200 mg/d (20) Sotalol HCL 240 mg/d (20) PC (26)	N/A	Arrhythmia free survival at 12 mo 70% flecainide 60% sotalol 27% PC p=0.002 AAD vs. PC p=0.163 flecainide vs. sotalol	N/A	N/A	Flecainide and sotalol have similar efficacy in prevention of recurrence of AF Side effects common but serious AE uncommon in this FU period
Channer KS, et al., 2004 (178) 14720531	To evaluate the efficacy of amiodarone to prevent recurrent AF after cardioversion	RCT, double-blind (161)	Amiodarone (short-term) 200 mg/d for 8 wk after DCCV (62) Amiodarone (long-term) 200 mg/d for 52 wk after DCCV (61) PC (38)	Inclusion: Age >18 y and sustained AF>72 h Exclusion: LVEF<20%, significant valve disease, female <50 y, thyroid, lung or liver disease, contraindication to anticoagulation	Percentage in SR at 1 y 49% long-term amiodarone 33% short-term (8 wk after DCCV) amiodarone 5% PC	Spontaneous conversion to SR 21% amiodarone and 0% in PC SR rhythm at 8 wk after DCCV – 16% PC, 47% short-term amiodarone, 56% long-term amiodarone	AEs leading to discontinuation 3% PC 8% short-term amiodarone 18% long-term amiodarone	Amiodarone pre-Tx allows chemical cardioversion in 1/5 of pts with persistent AF and is more effective at maintaining SR after DCCV Given the long-term AEs with amiodarone, 8 wk of adjuvant Tx suggested as option by authors

CTAF, Roy D, et al., 2000 (179) 10738049	Low dose amiodarone would be more efficacious in preventing recurrent AF than sotalol or propafenone	RCT (403)	Amiodarone 200 mg/d (201) Sotalol 160 mg BID (101) Propafenone 150 QID (101)	Symptomatic AF within previous 6 mo but not persistent AF>6mo	Recurrence of AF during FU (mean 16 mo) 35% amiodarone 63% sotalol or propafenone (p<0.001)	N/A	AEs requiring drug discontinuation 18% amiodarone vs. 11% sotalol or propafenone group (p=0.06)	Amiodarone is more effective than sotalol or propafenone in preventing recurrent AF (with a trend toward higher side-effects)
DAFNE, Touboul P, et al., 2003 (180) 12919771	To determine the most appropriate dose of dronedarone for prevention of AF after DCCV	RCT, double-blind (199)	Dronedarone 800 mg/d (54) Dronedarone 1,200 mg/d (54) Dronedarone 1600 mg/d (43) PC (48)	Inclusion: age 21-85 y, pts with persistent AF (>72 h and <12 mo) scheduled for DCCV Exclusion: Hx of torsade de pointes, QT>500 ms, severe bradycardia, AV block, NYHA class III or IV HF, LVEF<35, ICD, WPW syndrome	Time to first documented AF recurrence at 6 mo 60 d for dronedarone 400 mg BID 5.3 d for PC (p=0.001)	Spontaneous conversion of AF with dronedarone 5.8 to 14.8% pts	Premature discontinuation 22.6% 1600 mg, 3.9% 800 mg	Small sample size, dose-finding study
DIAMOND, Pedersen OD, et al., 2001 (181) 11457747	To evaluate the efficacy of dofetilide to maintain SR in pt with LV dysfunction	RCT, double-blind (506)	Dofetilide 500 mcg/d (249) PC (257)	Inclusion: Persistent AF associated with either HF or recent acute MI Dose reduction for renal insufficiency Exclusion: HR: <50 bpm, QTc>460 ms (500 ms with BBB), K<3.6 or >5.5, CrCl<20 mL/min	Probability of maintaining SR at 1 y 79% dofetilide 42% with PC (p<0.001)	No effect on all-cause mortality Dofetilide associated with reduced rate of rehospitalization	Torsade de pointes occurred in 4 dofetilide pts (1.6%)	N/A
DIONYSOS, Le Heuzey JY, et al., 2010 (182) 20384650	To evaluate the efficacy and safety of amiodarone and dronedarone in pts with persistent AF	RCT, double-blind (504)	Amiodarone 600 mg QD for 28 d then 200 mg QD (255) Dronedarone 400 mg BID (249)	Age ≥21 y with documented AF for >72 h for whom CV and AAD were indicated and oral anticoagulation	Recurrence of AF (including unsuccessful CV) or premature study discontinuation at 12 mo 75.1% dronedarone, 58.8% amiodarone, HR: 1.59; 95% CI: 1.28-1.98; p<0.0001	N/A	Drug discontinuation less frequent with dronedarone (10.4 vs. 13.3%). MSE was 39.3% and 44.5% with dronedarone and amiodarone, respectively, at 12 mo (HR: 0.80;	Dronedarone was less effective than amiodarone in decreasing AF recurrence, but had a better safety profile

					Mainly driven by AF recurrence with dronedarone compared with amiodarone (63.5 vs. 42.0%)		95% CI: 0.60 to 1.07; p=0.129), and mainly driven by fewer thyroid, neurologic, skin, and ocular events in the dronedarone group	
Dogan A, et al., 2004 (183) 15255456	To evaluate the efficacy of propafenone for maintenance of SR after cardioversion	RCT, Single-blind (110)	Propafenone 450 mg/d (58) PC (52)	Recent onset or persistent AF Exclusion: MI, HF, CABG<6 mo, severe COPD, LA thrombus, thyroid disease, inability to consent to DCCV	Percentage of AF recurrences at 15 mo 39% propafenone 65% PC	Spontaneous conversion with drug predicted lower chance of recurrence	Discontinuation due to side effects: 4 pts on propafenone and 1 PC (p=0.36)	Propafenone is more effective than PC for prevention of recurrent AF
EURIDIS, Singh BN, et al., 2007 (168) 17804843	To assess the efficacy of dronedarone in maintenance of SR in pts with AF	RCT, double-blind (612)	Dronedarone 400 mg BID (411) PC (201)	≥1 episode AF in previous 3 mo, Age ≥2y	Time to the 1st recurrence of AF or atrial flutter 96 d dronedarone 41 d in the PC (p=0.01)	After AF recurrence, mean rate=117.5 bpm, PC=102.3 bpm, dronedarone (p<0.001)	N/A	Dronedarone was more effective than PC in maintaining SR and in reducing ventricular rate during recurrent AF
FAPIS, Chimienti M, et al., 1996 (184) 8607393	To compare the safety of flecainide to propafenone for Tx of PAF	RCT, open-label (200)	Flecainide acetate 200 mg/d (97) Propafenone HCL 450-900 mg/d (103)	Paroxysmal AF without structural heart disease	Probability of remaining free of AEs at 12 mo 77% flecainide 75% propafenone 1 VT in propafenone group 2 accelerated ventricular response with flecainide	Drug discontinuation 4 flecainide 5 propafenone	N/A	AEs appear occur at similar rate with propafenone and flecainide in this population with AF and without evidence of structural disease
GEFACA, Galperin J, et al., 2001 (185) 11907636	To evaluate the efficacy of amiodarone for restoration and maintenance of SR	RCT, double-blind (50)	Amiodarone 200 mg/d (47) PC (48)	Persistent AF>2 mo duration Exclusion: paroxysmal AF, age >75 y, HR<50 bpm, LA>60 mm	Recurrent AF in 37% amiodarone and 80% PC group Spontaneous conversion 34% with amiodarone and 0% PC	N/A	AEs 15% of pts on amiodarone	Amiodarone restored SR in 1/3 pts, increased success of DCCV, reduced and delayed recurrence of AF

Kalusche D, et al., 1994 (186) 7846939	To compare the efficacy of sotalol to a fixed combination of quinidine and verapamil	RCT, open-label (82)	Quinidine sulfate 1000 mg/d Sotalol HCL 240-400 mg/d	N/A	SR at 6 and 12 mo 75.7% and 67.3% quinidine/verapamil 63.4 and 49.9% sotalol p=NS	N/A	5 pts quinidine/verapamil discontinued Tx due to noncardiac AEs, 3 pts in sotalol discontinued due to bradycardia No proarrhythmia noted	N/A
Kochiadakis GE, et al., 2004 (187) 15589019	Compare the efficacy and safety of sotalol and propafenone for prevention of recurrent AF	RCT, single-blind (254)	Propafenone HCL 240 mg/d (86) Sotalol HCL 320 mg/d (85) PC (83)	Symptomatic AF, successful chemical or DCCV if persistent	Percentage recurrence AF during FU 69/85 sotalol 45/86 propafenone 73/83 PC (p<0.001)	N/A	N/A	Long-term results show superiority of propafenone (question methods of comparison)
Kuhlkamp, et al., 2000 (188) 10898425	To evaluate the efficacy of metoprolol XL to reduce AF recurrence after cardioversion	RCT, double-blind (394)	Metoprolol XL 100 mg/d (197) PC (197)	Inclusion: Persistent AF with successful cardioversion (DC or chemical) Exclusion: Concomitant Tx with any class I or class 3 AAD, beta blocker or CCB	Percentage of pts with recurrent AF during FU (up to 6 mo) 48.7% metoprolol XL 59.9% PC (p=0.005)	Mean HR was lower with recurrent AF in pts on metoprolol (107 vs. 98; p=0.015)	SAEs similar with metoprolol or PC	Metoprolol XL prevents recurrent AF after cardioversion Short duration of FU
Naccarelli GV, et al., 1996 (189) 8607392	To compare the efficacy of flecainide to quinidine for PAF	RCT, open-label (239)	Flecainide acetate 200-300 mg/d (122) Quinidine sulfate 1000-1500 mg/d (117)	Symptomatic PAF	Percentage of pts with reported episodes of symptomatic AF 72% flecainide 74.3% quinidine (p=0.54)	Combined endpoint efficacy and tolerability at 1 y 70% flecainide vs. 55.4% quinidine (p<0.007)	N/A	Flecainide and quinidine have similar efficacy but flecainide is better tolerated
PAFAC, Fetsch T, et al., 2004 (190) 15302102	To compare the efficacy of quinidine and sotalol to PC for maintenance of SR in pt with persistent AF	RCT, double-blind (848)	Quinidine sulfate 480 mg/d Sotalol HCL 320 mg/d	Persistent AF lasting >7 d (mean duration: 15 mo), N=848, male: 66%, age (mean, SD): 63, ±9, structural heart disease: NS, left anterior descending: 45 mm, LVEF: 60%	At 12 mo: Mortality Pro-arrhythmia AEs AF recurrence	N/A	N/A	N/A

			PC					
PALLAS, Connolly SJ, et al., 2011 (165) 22082198	To assess whether dronedarone would reduce major vascular events in high-risk permanent AF	RCT, double-blind (3236)	Dronedarone 400 mg BID PC	Age >65 y with permanent AF or atrial flutter with no plan to restore SR and high risk feature: CAD, previous stroke or TIA, HF class II or III Sx, LVEF<40%, PAD or age >75 y, HTN & DM	Coprimary outcomes: Stroke, MI, SE, or CV death, 43 pts receiving dronedarone and 19 receiving PC (HR: 2.29; 95% CI: 1.34-3.94; p=0.002 Unplanned CV hospitalization or death, 127 pts receiving dronedarone and 67 pts receiving PC (HR: 1.95; 95% CI: 1.45-2.62; p<0.001)	Hospitalization for HF occurred in 43 pts in the dronedarone group and 24 in the PC group (HR: 1.81; 95% CI: 1.10- 2.99; p=0.02)	Most common AEs were diarrhea, asthenic condition, nausea and vomiting, dizziness, dyspnea, and bradycardia ALT>3x upper limit normal range occurred in 22 of 1,481 (1.5%) pts receiving dronedarone and in 7 of 1,546 (0.5%) receiving PC p=0.02	Dronedarone increased rates of HF, stroke, and death from CV causes in pts with permanent AF who were at risk for major vascular events.
Piccini JP, et al., 2009 (191) 19744618	To evaluate randomized trials of amiodarone and dronedarone for safety and efficacy in AF	Meta-analysis	4 trials of amiodarone vs. PC 4 trials of dronedarone vs. PC 1 comparison of amiodarone vs. dronedarone	Randomized PC-controlled trials of amiodarone and dronedarone for maintenance of SR in pts with AF	OR: 0.12 amiodarone vs. PC (95% CI: 0.08-0.19) OR: 0.79 dronedarone vs. PC (95% CI: 0.33-1.87)	N/A	Amiodarone trend towards increased mortality Amiodarone greater number AEs than dronedarone	Dronedarone is less effective than amiodarone but has fewer AEs

Plewan A, et al., 2001 (192) 11482924	N/A	RCT, open-label (128)	Sotalol 160 mg/d Bisoprolol fumarate 5 mg/d	Persistent AF (mean duration: 9 mo). N=128 Male: 62%. Age (mean, SD): 59, ±10 Structural heart disease: 72%. LAD: 48 mm. LVEF: 41%	At 8 mo: Mortality Pro-arrhythmia AEs AF recurrence	N/A	N/A	N/A
PRODIS, Crijns HJ, et al., 1996 (193) 8842506	N/A	RCT, double-blind (56)	Disopyramide phosphate 750 mg/d Propafenone HCL 900 mg/d	Persistent AF (mean duration: 5 mo). N=56 Male: 68%. Age (mean, SD): 60, ±11 Structural heart disease: 65%. LAD: 46 mm. LVEF: NS	At 6 mo: Mortality Pro-arrhythmia AEs AF recurrence	N/A	N/A	N/A
RAFT, Pritchett EL, et al., 2003 (194) 14556870	Assess the efficacy and safety of sustained-released propafenone for maintenance of SR	RCT, double-blind (523)	Propafenone hydrochloride 450-850 mg/d (397) PC (126)	Inclusion: Symptomatic AF (type not specified) SR at time of randomization Exclusion: Permanent AF, NYHA class III or IV HF, cardiac surgery <6 mo, MI<12 mo, WPW syndrome, 2nd or 3rd degree AV block, QRS>160 ms, HR<50 bpm, Hx of VF, VT or ICD	At 9 mo: Mortality Pro-arrhythmia AEs AF recurrence	N/A	N/A	N/A
Reimold SC, et al., 1993 (195) 8438741	To compare the efficacy of propafenone and sotalol for maintenance of SR	RCT, open-label (100)	Propafenone HCL 675 mg/d (50) Sotalol HCL 320 mg/d (50)	Pts with AF with previous AAD failure	Percentage with SR at 3, 6, and 12 mo 46%, 41%, 30% propafenone 49%, 46% sotalol	N/A	N/A	Propafenone and sotalol similar efficacy
Richiardi E, et al., 1992 (196) 1600529	To evaluate the efficacy and safety of oral propafenone vs. quinidine at preventing AF	RCT, open-label (200)	Propafenone 900 mg/d Quinidine 1000 mg/d	≥3 AF episodes in past 6 mo Exclusion: LA size >55 mm, hepatic or renal insufficiency, MI<30 d, pregnant, decompensated HF, thyroid dysfunction	SR at 6 mo 60% propafenone 56% quinidine SR at 1 y 48% propafenone 42% quinidine	p=NS	N/A	10% side effects propafenone 24% side-effects quinidine (p=0.02)
SAFE-T, Singh BN, et	To assess the efficacy of	RCT, double-blind	Amiodarone 300 mg/d	Inclusion: Persistent AF>72 h including at time of	Pharmacological Conversion to SR	Sustained SR improved QOL	NS difference in AEs among the 3 groups	N/A

al., 2005 (197) 15872201	amiodarone and sotalol in converting AF and maintenance of SR	(665)	Sotalol 320 mg/d PC	randomization & on oral anticoagulation Exclusion: Paroxysmal AF or atrial flutter, NYHA class III or IV HF, CrCl<60 mL/min, intolerance to beta blockers, Hx of long QT syndrome	27.1% amiodarone 24.2% sotalol 0.8% PC Median Time to Recurrence AF (intention to treat) 487 d amiodarone 74 d sotalol 6 d PC p<0.001	and exercise capacity		
SAFIRE-D, Singh S, et al., 2000 (198) 11067793	To determine the efficacy and safety of dofetilide in converting AF or atrial flutter to SR and maintaining SR for 1 y	RCT, double-blind (250)	Dofetilide 250-1000 mcg/d PC	Inclusion: Age 18-85 y with AF or atrial flutter 2-26 wk duration Exclusion: Sinus node dysfunction, QRS>180 ms, QT interval>400 ms (QT>500 ms with BBB), sinus rate<50 bpm, Hx of renal or hepatic disease, use of verapamil, diltiazem, QT prolonging drugs	Pharmacological Conversion Rate 6.1% 125 mcg BID 9.8% 250 mcg BID 29.9% 500 mcg BID 1.2% PC p=0.015 250 mcg and p<0.001 500 mcg (vs. PC) Probability of SR at 1 y 0.40 125 mcg BID 0.37 250 mcg BID 0.58 500 mcg BID 0.25 PC	N/A	2 cases of torsade de pointes during initiation phase (0.8%) 1 sudden death (proarrhythmic) on Day 8 (0.4%)	In-hospital initiation and dosage adjustment based on QTc and CrCl to minimize proarrhythmic risk
SOPAT, Patten M, et al., 2004 (199) 15321697	To assess the effectiveness of 2 AAD on frequency of AF	RCT, double-blind (1033)	High-dose Quinidine sulfate 480 mg/d and verapamil 240 mg/d (263) Low-dose Quinidine sulfate 320 mg/d and	Age 18-80 y, symptomatic PAF Exclusion: cardiogenic shock, LA thrombus, MI or cardiac surgery <3 mo, UA, valve disease requiring surgery, ICD or pacemaker, sick sinus syndrome, 2nd or 3rd degree AV block, QTc>440 ms, bradycardia,	Time to 1st recurrence of symptomatic PAF or premature discontinuation 105.7 d PC 150.4 d high-dose quinidine/verapamil 148.9 d low-dose quinidine/verapamil	AF burden (% says with symptomatic AF) 6.1% PC 3.4% high dose 4.5% low dose 2.9% sotalol (p=0.026)	1 death and 1 VT event related to high-dose quinidine/verapamil 2 syncopal events related to sotalol	Quinidine/verapamil fixed combination similar efficacy to sotalol but with risk of SAEs

			verapamil 160 mg/d (255) Sotalol HCL 320 mg/d (264) PC (251)	renal or liver dysfunction, hypokalemia, bundle branch block Mean time under Tx 233 d	145.6 d sotalol (p<0.001)			
Stroobandt R, et al., 1997 (200) 9052343	To assess the efficacy of propafenone at maintaining sinus rhythm	RCT, double-blind (102)	Propafenone HCL 150 mg TID (77) PC (25)	Age >18 y with AF, enrolled in maintenance phase after attempt at pharmacological conversion with IV propafenone (and if unsuccessful DCCV)	Proportion of pts free from recurrent symptomatic AF at 6 mo 67% propafenone 35% PC (p<0.001)	N/A	NS difference in AEs	Evidence for the efficacy of propafenone in maintaining sinus rhythm after cardioversion. Short duration of FU (6 mo)
SVA-3, Pritchett EL, et al., 2000 (201) 10987602	To assess the effectiveness of azimilide in reducing symptomatic AF or atrial flutter	RCT, double-blind (384)	Azimilide 50 mg, 100 mg, or 125 mg PC	Inclusion: Age ≥18 y, Symptomatic AF in SR at time of randomization Exclusion: Rest angina or UA, class IV CHF, Hx of torsade de pointes, QTc>440 ms, resting SR<50 bpm	Time to 1st symptomatic AF recurrence Azimilide 100 mg/125 mg QD vs. PC, HR: 1.58; p=0.005	N/A	2 sudden deaths in azimilide groups and 1 case of torsade de pointes	Initiated in outpatient setting
Villani R, et al., 1992 (202) 1559321	To compare the efficacy of amiodarone to disopyramide	RCT, open-label (76)	Amiodarone 200 mg/d (41) Disopyramide phosphate 500 mg/d (35)		Recurrence of AF at end of FU 57% disopyramide (13 mo) 32% amidarone (14 mo)	N/A	Disopyramide discontinued due to AE 14% <1 wk and another 14% by end of trial 8.5% developed hyperthyroidism	Amiodarone is more effective than disopyramide for prevention of recurrent AF

AAD indicates antiarrhythmic drug; ADONIS, American-Australian-African Trial With Dronedarone in Patients With Atrial Fibrillation or Atrial Flutter for the Maintenance of Sinus Rhythm; AE, adverse event; AF, atrial fibrillation; AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management; ALT, alanine aminotransferase; ANDROMEDA, European Trial of Dronedarone in Moderate to Severe Congestive Heart Failure; ASAP, ASA and Plavix; ATHENA, A Trial With Dronedarone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation; AV, atrioventricular; BBB, bundle-branch block; BID, twice daily; CABG, coronary artery bypass graft; CCB, calcium channel blocker; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disorder; CrCl, creatinine clearance; CTA, Canadian Trial of Atrial Fibrillation; CV, cardiovascular; DAFNE, Dronedarone Atrial Fibrillation Study after Electrical Cardioversion; DC, direct current; DCCV, direct current cardioversion; DIAMOND, Danish Investigators of Arrhythmia and Mortality on Dofetilide; DIONYSOS, Efficacy & Safety of Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation; DM, diabetes mellitus; Dx, diagnosis; FAPIS, Flecainide and Propafenone Italian Study; FU, follow-up; GEFACA, Grupo de Estudio de Fibrilacion Auricular Con Amiodarona; GI, gastrointestinal; HCL, hydrochloride; HF, heart failure; HR, hazard ratio; HTN, hypertension; Hx, history; ICD, implantable cardioverter defibrillator; K, potassium; LA, left atrial; LAD, left atrial dimension; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MSE, main safety endpoint; N/A, not applicable; NS, not significant; NYHA, New York Heart Association; OR, odds ratio; PAF, paroxysmal atrial fibrillation; PALLAS, Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy; PC, placebo; pts, patients; QD,

once daily; QID, four times a day; QOL, quality of life; RAFT, Rythmol Atrial Fibrillation Trial; RCT, randomized controlled trial; RR, relative risk; SAFE-T, Sotalol Amiodarone Atrial Fibrillation Efficacy Trial; SAFIRE-D, Symptomatic Atrial Fibrillation Investigative Research on Dofetilide; SD, standard deviation; SOPAT, Suppression of Paroxysmal Atrial Tachyarrhythmias; SR, sinus rhythm; SVA, Supraventricular Arrhythmia Program; TIA, transient ischemic attack; TID, three times a day; Tx, therapy; UA, unstable angina; VF, ventricular fibrillation; VT, ventricular tachycardia; and WPW, Wolff-Parkinson-White.

Data Supplement 13. Outpatient Initiation of Antiarrhythmic Drug Therapy (Section 6.2.1.2)

Study Name, Author, Year	Study Type	Intervention (n)	Rhythm at Time of Initiation	Place of Initiation	Patient Population	Adverse Events
Benditt D, et al., 1999 (175) 10496434	Prospective dose finding study	Sotalol 80 BID (59) Sotalol 120 BID (63) Sotalol 160 BID (62) PC (69)	SR	50 pts - outpatient 134 pts - inpatient	Structural heart disease 57% Exclusion: Hx of torsade de pointes, CHF, QT>450 ms, hypokalemia hypomagnesemia, bradycardia	No cases of VT/VF/torsade QT>520 ms in 7 pts (4 in 120 mg BID and 3 in 160 mg BID) Premature discontinuation due to AEs 25% inpatients, but 6% of outpatients (bradycardia predominantly)
Chung MK, at al., 1998 (203) 9669266	Retrospective	Sotalol	Not documented	Inpatient	120 inpatients admitted for sotalol initiation Structural heart disease (80%)	7 (5.8%) new or increased ventricular arrhythmias, 2 with torsades de pointes (d 6 in pt with pacemaker and hypokalemia and d 4 in pts with ICD) 20 (16.7%) with significant bradycardia 8 (6.7%) excessive QT prolongation
SAFE-T, Singh BN, et al., 2005 (197) 15872201	Prospective RCT	Total 665 Amiodarone 267 Sotalol 261 Placebo 137	AF	Outpatient	Initiated sotalol or amiodarone in the outpatient setting during AF Excluded CHF class III or IV, Hx of long QT, CrCl<60	1 case torsade in sotalol group (nonfatal, time of occurrence not specified) 13 deaths/267 (6 sudden) amiodarone group 15 deaths/261 (8 sudden) sotalol group 3 deaths/137 (2 sudden) PC group (no significant difference)
Zimetbaum PJ, et al., 1999 (204) 10072241	Prospective	172 Amiodarone 66 (38%) Flecainide 45 (26%) Sotalol 20 (12%) Disopyramide 16 (9%) Propafenone 11 (6%) Quinidine 8 (5%) Procainamide 6 (4%)	SR	Outpatient	Pts with AF in sinus at time of initiation started on oral antiarrhythmic medication Received 1 or 2 doses of AAD in hospital or clinic and monitored for ≤8 h and then 10 d continuous loop event recorder Exlusion: QTc>550 ms, NYHA class III or IV CHF, or pacemaker	6 symptomatic AEs (none before d 4) Class Ic 3 atrial flutter with 1:1 d 6 or 7 1 symptomatic brady d 4 Sotalol 1 symptomatic bradycardia d 7 1 QT prolongation 370-520 ms d 4

Hauser TH, et al., 2003 (205) 12804730	Prospective	409 Amiodarone 212 (51.8%) Class Ic 127 (31.1%) Propafenone 64 (15.6%) Flecainide 63 (15.4%) Sotalol 37 (9.0%) Class IA 33 (8.1%) Quinidine 8 (2%) Disopyramide 16 (3.9%) Procainamide 9 (2.2%)	SR	Outpatient	Pts with AF in sinus at time of initiation started on oral AAD with daily 30 s recording or with Sx	Amiodarone 2 Death (sudden) d 7 and d 9 3 Bradycardia requiring pacemaker d 6, 7, and 8 9 Bradycardia requiring dose reduction Class Ic Bradycardia d 7 and d 9 dose reduction Sotalol – none Quinidine Death (sudden) d 3
CTAF, Roy D, et al., 2000 (179) 10738049	Prospective open-label RCT	403 Amiodarone 201 Sotalol 101 Propafenone 101	Sinus≈60%	Outpatient	Exclusion: QTc>480, bradycardia <50 bpm	Arrhythmic deaths – 3 amiodarone group (2 had been off the drug >1 y) and 1 in sotalol/propafenone group Cardiac arrest due to torsade – propafenone Serious bradyarrhythmias – 6 amiodarone 7 in sotalol/propafenone group Time to event after initiation not specified All events occurred beyond 2 d of drug initiation mostly bradyarrhythmias
Kochiadakis GE, et al., 2004 (187) 15589019	N/A	254 Sotalol 85 Propafenone 86 PC 83	Sinus	Inpatient	N/A	No torsades noted Sotalol - 3 bradycardia during loading phase Propafenone – 1 bradycardia, 1 QRS widening

AAD indicates antiarrhythmic drug; AE, adverse event; AF, atrial fibrillation; BID, twice daily; CHF, congestive heart failure; CrCl, creatinine clearance; CTAF, Canadian Trial of Atrial Fibrillation; Hx, history; ICD, implantable cardioverter-defibrillator; IV, intravenous; NYHA, New York Heart Association; pts, patients; RCT, randomized controlled trial; RR, relative risk; SAFE-T, Sotalol Amiodarone Atrial Fibrillation Efficacy Trial; SR, sinus rhythm; Sx, symptom; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Data Supplement 14. Upsteam Therapy (Section 6.2.2)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population	Endpoints		Comments
					Primary Endpoint & Results	*Secondary Endpoint & Results*	

ANTIPAF, Goette A, et al., 2012 (206) 22157519	Effect of olmesartan on AF burden in pts with paroxysmal AF and no structural heart disease	Prospective, PC-controlled RCT	Olmesartan 40 mg QD (214) PC (211)	Pts with PAF and no other indication for ACE inhibitor or ARB Tx	No difference in the 1° endpoint of AF burden (p=0.770)	No difference in QOL, time to 1st AF recurrence, time to persistent AF and hospitalizations	In pts with AF (2° prevention) but without structural disease, 1 y of ARB does not appear to decrease AF burden
GISSI-AF, 2009 (207) 20435196	N/A	Prospective, PC-controlled, RCT	Valsartan (722) PC (720)	AF and underlying CV disease, diabetes, or left atrial enlargement	Co-primary endpoints: Time to first recurrence of AF, 295 d valsartan, 271 d PC Proportion of pts who had >1 recurrence of AF>12 mo, 26.9% valsartan, 27.9% PC OR: 0.95; p=0.66	N/A	Tx with valsartan not associated with reduced AF
Healey JS, et al., 2005 (208) 15936615	Systematic review of all RCT evaluating the benefit of trials of ACE inhibitor and ARBs in prevention of AF	Meta-analysis	N/A	11 studies included with 56,308 pts	ACE inhibitor and ARB reduced incidence of AF (RR: 0.28; p=0.0002) Reduction in AF greatest in pts with HF (RR: 0.44; p=0.007) No significant reduction in pts with HTN (RR: 0.12; p=0.4) although 1 study 29% reduction in pts with LVH (RR: 0.29)	N/A	ACE inhibitor and ARBs appear to be effective in prevention of AF probably limited to pts with systolic LV dysfunction or HTN LVH
J-RHYTHM II, Yamashita T, et al., 2011 (208, 209) 21148662	N/A	Open label, RCT	Candesartan Amlodipine	Pts with PAF (2° prevention) and HTN	N/A	N/A	Tx of HTN by candesartan was not superior to amlodipine for reduction in AF frequency
Schneider MP, et al., 2010 (210) 20488299	N/A	Meta-analysis	N/A	23 studies included with 87,048 pts	N/A	N/A	N/A

1° indicates primary; 2°, secondary; ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ANTIPAF, Angiotensin II-Antagonist in Paroxysmal Atrial Fibrillation; ARB, angiotensin-receptor blockers; CV, cardiovascular; GISSI-AF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation; HF, heart failure; HTN, hypertension; J-RHYTHM, Japanese Rhythm Management Trial for Atrial Fibrillation; LV, left ventricular; LVH, left ventricular hypertrophy; N/A, not applicable; OR, odds ratio; PAF, paroxysmal atrial fibrillation; PC, placebo; pts, patients; QD, once daily; QOL, quality of life; RCT, randomized controlled trial; RR, relative risk; and Tx, therapy.

Data Supplement 15. AF Catheter Ablation to Maintain Sinus Rhythm (Section 6.3)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Type of AF	Ablation Technique	Endpoints	AF Free at 1 y			Crossover Rate to RFA	Adverse Events	Study Limitations
						Primary Endpoint & Results	**Ablation**	**AAD**	**P value**			
Krittayaphong R, et al., 2003 (211) 12866763	To compare the efficacy of amiodarone to RFA for maintenance of SR	RCT (30)	RFA Amiodarone	Paroxysmal and persistent	Circumferential PVI with anatomic isolation	Freedom from AF at 12 mo	79%	40%	0.018	Not stated	1 stroke in RFA arm 46.7% AE in amiodarone arm	Small sample size, single center
RAAFT, Wazni OM, et al., 2005 (212) 15928285	To determine whether PVI is feasible as 1st line Tx for symptomatic AF	RCT (70)	RFA (33) AAD (37)	Paroxysmal	Segmental PVI with electrical isolation	Freedom from AF at 12 mo (Any recurrence of symptomatic AF or asymptomatic AF>15 s) 87% RFA 37% AAD	87%	37%	p<0.001	49%	Pulmonary vein stenosis 2 (6%) in RFA group	N/A
CACAF, Stabile G, et al., 2005 (213) 16214831	Compare RFA to AAD for prevention of AF in pts who failed AAD	RCT (137)	RFA (68) AAD – primarily amiodarone (69)	Paroxysmal and persistent	Circumferential PVI with anatomic isolation	Freedom from AF at 12 mo 55.9% RFA 8.7% AAD p<0.001	56%	9%	p<0.001	57%	4.4% major complications RFA	N/A

Oral H, et al., 2006 (214) 16908760	Persistent AF Compare RFA to AAD for prevention of AF	RCT (146)	RFA (77) Cardioversion with short-term amiodarone (69)	Persistent	Circumferential PVI with anatomic isolation	Monthly freedom from AF off AAD 74% RFA 58% control (intention to treat) p=0.05 70% RFA 4% control (on-Tx analysis) p<0.001	70% 74%	4% (on-Tx analysis) 58% (intention to treat analysis)	p<0.001 p=0.05	77%	N/A	77% AAD crossed over to RFA
APAF Pappone C, et al., 2006 (128) 14707026	Paroxysmal AF	RCT (198)	RFA (99) AAD (99)	Paroxysmal	Circumferential PVI with anatomic isolation	Freedom from AF at: 12 mo 86% RFA 22% AAD	86%	22%	p<0.001	42%	RFA: 1 TIA, 1 pericardial effusion not requiring drainage AAD: 3 proarrhythmia flecainide, 7 thyroid disfunction amiodarone, 11 sexual dysfunction sotalol	Single center, high crossover rate (42 of 99, 42%)
A4 Jais P, et al., 2008 (215) 19029470	Compare RFA to AAD in paroxysmal AF	RCT (112)	RFA (53) AAD (59)	Paroxysmal	Circumferential PVI with electrical isolation	Freedom from AF at 12 mo	89%	23%	p<0.001	63%	RFA: (155 ablation procedures, 2 tamponade, 2 groin, hematoma) AAD: 1 hyperthyroidism	N/A
Forleo GB, et al., 2009 (216) 19443515	Compare RFA to AAD in pts with	RCT (70)	RFA (35) AAD (35)	Paroxysmal and persistent	Circumferential PVI with electrical	N/A	80%	43%	p=0.001	Not stated	N/A	N/A

	diabetes				isolation							
Thermocool Wilber DJ, et al., 2010 (217) 20103757	Compare RFA to AAD in paroxysmal AF	RCT (167)	RFA (106) AAD (61)	Paroxysmal	Circumferential PVI with electrical isolation	Freedom from protocol-defined Tx failure (documented symptomatic AF, repeat ablation >80 d after initial, changes in drug regimen post blanking, absence of entrance block)	66%	16%	p<0.001	59%	4.9% RFA 8.8% AAD	Catheter ablation is more effective than medical Tx alone in preventing recurrent Sx of paroxysmal AF in pts who have already failed Tx with 1 AAD
STOP-AF Packer DL, et al., 2013 (218) 23500312	Assess efficacy of cryoballoon catheter ablation to AAD Tx in PAF	RCT (245)	Cryoballoon ablation (163) AAD (flecainide, propafenone, sotalol) (82)	Paroxysmal	Circumferential PVI with electrical isolation	Freedom from CTF (no detected AF, no AF interventions, no use of non-study drugs) 3-mo blanking period 69.9% cryoballoon (57.7% off drug) vs. 7.3% AAD (intention to treat) 60.1% single ablation (n=98)	70%	7.3%	p<0.001	79%	All events: cryoablation 12.3%, AAD 14.6% Procedure event rate 6.3% Phrenic nerve paralysis 11.2% (29) with 86.2% (25) resolved at 12 mo	N/A
RAAFT2 Morillo C, et al., 2014 (219)	Compare RFA to AAD as first-line therapy for pts with AF	RCT (127)	RFA (66) AAD (61)	Paroxysmal (98%%) and Persistent	Circumferential PVI with electrical isolation	AF, atrial flutter, or atrial tachycardia >30 s at 24 months	45%	28%	p=0.02	47%	9% RFA 5% AAD	>20% additional ablation
MANTRA-PAF	Compare	RCT (294)	RFA (146)	Symptomati	Circumferen	Cumulative	13%	19%	p=0.10	36%	RFA group – 1	No difference

Cosedis Nielsen J, et al., 2012 (220) 23094720	RFA to AAD as 1st-line Tx for pts with AF		AAD (class Ic or class III) (148)	c Paroxysmal AF prior to AAD Tx	tial PVI with voltage abatement	burden of AF Per visit burden at 24 mo Freedom from AF at 24 mo	 9% AF burden at 24 mo 85%	 18% AF burden at 24 mo71%	 p=0.007 p=0.01		death due to procedural stroke and 3 tamponade	in cumulative burden of AF endpoint and no difference in burden at 3, 6, 12 or 18 mo

A4 indicates Catheter Ablation Versus Antiarrhythmic Drugs for Atrial Fibrillation; AAD, antiarrhythmic drug; AE, adverse event; AF, atrial fibrillation; APAF, Ablate and Pace in Atrial Fibrillation; CACAF, Catheter Ablation for the Cure of Atrial Fibrillation; CTF, chronic treatment failure; N/A, not applicable; PAF, paroxysmal atrial fibrillation; Pt, patient; PVI, pulmonary vein isolation; RAAFT, Radiofrequency Ablation for Atrial Fibrillation Trial; RCT, randomized controlled trial; RFA, radiofrequency ablation; RR, relative risk; SR, sinus rhythm; STOP-AF, Sustained Treatment of Paroxysmal Atrial Fibrillation; Sx, symptom; TIA, transient ischemic attack; and Tx, therapy.

Data Supplement 16. Meta-Analyses and Surveys of AF Catheter Ablation (Section 6.3)

Study Name, Author, Year	Study Aim	Study Size (N)	Patient Population	Study Intervention	Endpoints	Follow-Up	Adverse Events
Bonnano C, et al., 2010 (221) 19834326	Systematic review of RCT of RFA vs. AAD	8 studies (844 pts)	N/A	N/A	98 (23.2%) of 421 pts in the Tx group and 324 (76.6%) of 423 pts in the control group had atrial tachyarrhythmia recurrence	N/A	N/A
Calkins H, et al., 2009 (222) 19808490	Systematic review of radiofrequency ablation for AF	63 studies included (8789 pts)	Mean age 55.5 y	N/A	Single-procedure success rate of ablation off AAD Tx was 57% (95% CI: 50% to 64%) Multiple procedure success rate of AAD was 71% (95% CI: 65% to 77%) Multiple procedure success rate on AAD or with unknown AAD usage was 77% (95% CI: 73% to 81%)	Major complication rate 4.9% Stroke/TIA 0.5% Mortality 0.7% Cardiac tamponade 0.8% PV stenosis 1.6% LA/esophageal fistula 0.0%	N/A
Parkash R, et al., 2011 (223) 21332861	Systematic review of RCT to assess optimal technique for RFA of AF	N/A	N/A	N/A	Freedom from AF after a single procedure RFA was found to be favorable in prevention of AF over AADs in either paroxysmal (5 studies, RR: 2.26; 95% CI: 1.74-2.94) or persistent AF (5 studies, RR: 3.20; 95% CI: 1.29-8.41)	Wide-area PVI appeared to offer the most benefit for both paroxysmal (6 studies, RR: 0.78; 95% CI: 0.63-0.97) and persistent AF (3 studies, RR: 0.64; 95% CI: 0.43-0.94)	N/A
Piccini JP, et al., 2009 (224) 20009077	Meta-analysis of all RCTs comparing PVI and medical Tx for the	N/A	N/A	N/A	Freedom from recurrent AF at 12 mo PVI was associated with markedly increased odds of freedom	N/A	Among those randomly assigned to PVI, 17% required a repeat PVI ablation before 12 mo. The

	maintenance of sinus rhythm				from AF at 12 mo of FU (n=266/344 [77%] vs. n=102/346 [29%]; OR: 9.74; 95% CI: 3.98-23.87)		rate of major complications was 2.6% (n=9/344) in the catheter ablation group

AAD indicates antiarrhythmic drug; AF, atrial fibrillation; ; FU, follow-up; LA, left atrial; N/A, not applicable; OR, odds ratio; pts, patients; PV, pulmonary vein; PVI, pulmonary vein isolation; RCT, randomized controlled trial; RFA, radiofrequency ablation; RR, relative risk; TIA, transient ischemic attack; and Tx, therapy.

Data Supplement 17. Specific Patient Groups (Section 7)

Study	Aim of study	Study Size	Patient Population / Inclusion & Exclusion Criteria	Endpoint(s)	Statistical Analysis Reported	CI and/or P values	OR/HR/RR/ Other	Study Conclusion
Roy D, et al., 2008 (225) 18565859	To investigate maintenance of SR (rhythm control) with ventricular rate control in pts with LVEF≤35% and Sx of CHF, and a Hx of AF	1,376 (682 in rhythm-control group and 694 in rate-control group)	Inclusion criteria: LVEF≤35% (measured by nuclear imaging, echocardiography, or cardiac angiography, with testing performed ≤6 mo before enrollment); Hx of CHF (defined as symptomatic NYHA class II or IV within the previous 6 mo, asymptomatic condition that pt had been hospitalized for HF during the previous 6 mo, or LVEF≤25%; Hx of AF (with EKG documentation), defined as 1 episode lasting for ≥6 h or requiring cardioversion within the previous 6 mo or an episode lasting for ≥10 min within the previous 6 mo and previous electrical cardioversion for AF; and eligibility for long-term Tx in either of the 2 study groups Exclusion criteria: Persistent AF for ≥12 mo, a reversible cause of AF or HF, decompensated HF within 48 h prior to intended randomization, use of AADs for other arrhythmias, 2nd degree or 3rd degree AVB (bradycardia of <50 bpm), Hx of the long-QT syndrome, previous ablation of an AV node, anticipated cardiac transplantation within 6 mo, renal failure requiring dialysis, lack of birth control in women of child-bearing potential, estimated life expectancy of <1 y, and an age <18 y	1° outcome was time to death from CV causes	The 1° outcome, death from CV causes, occurred in 182 pts (27%) in the rhythm-control group and 175 pts (25%) in the rate-control group Death from any cause (32% in the rhythm-control group and 33% in the rate-control group) Ischemic or hemorrhagic stroke 3% and 4%, respectively Worsening HF (defined as HF requiring hospitalization, administration of an IV diuretic, or change in Tx strategy) Composite outcome of death from CV causes, stroke, or worsening HF	None of the 2° outcomes differed significantly between the Tx groups 95% CI: 0.86-1.30; p=0.53 95% CI: 0.80-1.17; p=0.73 95% CI: 0.40-1.35; p=0.32 95% CI: 0.72-1.06; p=0.17 95% CI: 0.77-1.06; p=0.20	HR: 1.06 HR: 0.97 HR: 0.74 HR: 0.87 HR: 0.90	The routine strategy of rhythm control does not reduce the rate of death from CV causes, as compared with a rate-control strategy in pts with AF and CHF

AFFIRM, Olshansky B, et al., (163) 15063430	To evaluate and compare several drug classes for long-term ventricular rate control	2027	Inclusion criteria: (All criteria must have been met). Episode of AF documented on EKG or rhythm strip within last 6 wk, ≥65 y or <65 y + ≥1 clinical risk factor for stroke (systemic HTN, DM, CHF, TIA, prior cerebral vascular accident, left atrium ≥50 mm by echocardiogram, fractional shortening <25% by echocardiogram (unless paced or LBBB present), or LVEF<0.40 by radionuclide ventriculogram, contrast angiography, or quantitative echocardiography), duration of AF episodes in last 6 mo must total ≥6 h, unless electrical and/or pharmacologic cardioversion was performed prior to 6 h, duration of continuous AF must be <6 mo, unless normal SR can be restored and maintained ≥24 h, in opinion of clinical investigator, pt (based on clinical and laboratory evaluation before randomization) must be eligible for both Tx groups, based on pt Hx, pt must be eligible for ≥2 AADs (or 2 dose levels of amiodarone) and ≥2 rate-controlling drugs Exclusion criteria: Not presented. Based on the judgment that certain therapies are contraindicated or inclusion would confound the result. Criteria included cardiac, other medical, and nonmedical	Overall rate control with various drugs (average FU 3.5±1.3 y)	Overall rate control was met in 70% of pts given beta blockers as the 1st drug (with or without digoxin), vs. 54% with CCBs (with or without digoxin), and 58% with digoxin alone Multivariate analysis revealed a significant association between 1st drug class and several clinical variables, including gender, Hx of CAD, pulmonary disease, CHF, HTN, qualifying episode being the 1st episode of AF, and baseline heart rate	N/A	N/A	In pts with AF, rate control is possible in the majority of pts. In the AFFIRM FU study, beta blockers were most effective. The authors noted frequent medication changes and drug combinations were needed

ANDROMEDA, Kober L, et al., 2008 (171) 18565860	To evaluate the efficacy of dronedarone in reducing hospitalization due to CHF in pts with symptomatic HF	627	Inclusion criteria: Pts ≥18 y hospitalized with new or worsening HF and who had ≥1 episode of SOB on minimal exertion or at rest (NYHA III or IV) or paroxysmal nocturnal dyspnea within the month before admission Exclusion criteria: LV wall motion index of >1.2 (approximating an EF of >35%), acute MI within 7 d prior to screening, a heart rate <50 bpm, PR interval >0.28 s, sinoatrial block or 2nd or 3rd degree AV block not treated with a pacemaker, Hx of Torsades de pointes, corrected QT interval >500 ms, a serum potassium level <3.5 mmol/L, use of class I or III AADs, drugs known to cause Torsades de pointes, or potent inhibitors of the P450 CYP3A4 cytochrome system, other serious disease, acute myocarditis, constrictive pericarditis, planned or recent (within the preceding mo) cardiac surgery or angioplasty, clinically significant obstructive heart disease, acute pulmonary edema within 12 h before randomization, pregnancy or lactation, expected poor compliance, or participation in another clinical trial	The 1° endpoint was the composite of death from any cause or hospitalization for HF	After inclusion of 627 pts, the trial was prematurely terminated for safety reasons. A median FU of 2-mo death occurred in 8.1% of dronedarone group and 3.8% of PC group After additional 6 mo, 42 pts in dronedarone group (13.5%) and 39 pts in PC group (12.3%) died The 1° endpoint did not differ significantly between the 2 groups; there were 53 events in the dronedarone group (17.1%) and 40 events in the PC group (12.6%)	p=0.03; 95% CI: 1.07-4.25 p=0.60; 95% CI: 0.73-1.74 p=0.12; 95% CI: 0.92-2.09	HR: 2.13 HR: 1.13 HR: 1.38	Dronedarone increased early mortality in pts recently hospitalized with symptomatic HF and depressed LV function. 96% of deaths were attributed to CV causes, predominantly progressive HF and arrhythmias

RACE II Van Gelder IC, et al., 2010 (167) 20231232	To investigate if lenient rate control is not inferior to strict control for preventing CV morbidity and mortality in pts with permanent AF	614	Inclusion criteria: Permanent AF up to 12 mo, age ≤80 y, mean resting heart rate >80 bpm, and current use of oral anticoagulation Tx (or ASA, if no risk factors for thromboembolic complications present) Exclusion Criteria: Paroxysmal AF; contraindications for either strict or lenient rate control (e.g., previous adverse effects on negative chronotrophic drugs); unstable HF defined as NYHA IV HF or HF necessitating hospital admission <3 mo before inclusion; cardiac surgery <3 mo; any stroke; current or foreseen pacemaker, ICD, and/or cardiac resynchronization Tx; signs of sick sinus syndrome or AV conduction disturbances (i.e., symptomatic bradycardia or asystole >3 s or escape rate <40 bpm in awake Sx-free pts; untreated hyperthyroidism or <3 mo euthyroidism; inability to walk or bike	Composite of death from CV causes, hospitalization for HF, and stroke, SE, bleeding and life-threatening arrhythmic events. FU duration 2 y, with a maximum of 3 y	1° outcome incidence at 3 y was 12.9% in the lenient-control group and 14.9% in the strict-control group. Absolute difference with respect to the lenient-control group of -2.0 percentage points More pts in the lenient-control group met the heart rate target or targets (304 [97.7%] vs. 203 [67.0%] in the strict-control group) Frequencies of Sx and AEs were similar in the 2 groups	Absolute risk difference, -2.0% Absolute risk difference, CI: -7.6-3.5; p<0.001 90% CI: 0.58-1.21; p=0.001 p<0.001	HR: 0.84	Lenient rate control is as effective as strict rate control and easier to achieve in pts with permanent AF
Gaita F, et al., 2007 (226) 17531584	Assess usefulness and safety of transcatheter ablation of AF in pts with HCM	26	Pts with HCM with paroxysmal (n=13) or permanent (n=13) AF refractory to antiarrhythmic Tx Characteristics: age 58±11 y, time from AF onset 7.3±6.2 y, left atrial volume 170±48 mL, 19±10 mo clinical FU	Pulmonary vein isolation at RFCA plus linear lesions	64% overall success rate 10 of these 16 success pts were off AAD Tx at final evaluation 77% success rate in PAF compared with 50% in the subgroup with permanent AF	NYHA FC in those achieving NSR 1.2±0.5 vs. 1.7±0.7 before the procedure, p=0.003	N/A	RFCA proved a safe and effective therapeutic option for AF, improved functional status, and was able to reduce or postpone the need for long-term pharmacologic Tx

Kilicaslan F, et al., 2006 (227) 16500298	The purpose of this study was to report the results and outcome of PV antrum isolation in pts with AF and HOCM	27	27 pts with AF and HOCM who underwent PV antrum isolation between February 2002 and May 2004 Mean age 55±10 y Mean AF duration was 5.4±3.6 y AF was paroxysmal in 14 (52%), persistent in 9 (33%), and permanent in 4 (15%) Mean FU of 341±237 d	Maintenance of sinus rhythm after PV antrum isolation	13 pts (48%) had AF recurrence 5 of the 13 with recurrence maintained sinus rhythm with AADs, 1 of 13 remained in persistent AF, 7 of 13 underwent a second PV antrum isolation. After 2nd ablation: 5 pts remained in SR Final success rate=70% (19/27) 2 pts had recurrence after 2nd ablation; 1 maintained SR with AADs and 1 remained in persistent AF	N/A	N/A	AF recurrence after the 1st PV antrum isolation is higher in pts with HOCM. However, after repeated ablation procedures, long-term cure can be achieved in a sizable number of pts. PV antrum isolation is a feasible therapeutic option in pts with AF and HOCM
Bunch TJ, et al., 2008 (228) 18479329	Assess efficacy of RFCA for drug-refractory AF in HCM	32	Consecutive pts (25 male, age 51±11 y) with HCM underwent PV isolation (n=8) or wide area circumferential ablation with additional linear ablation (=25) for drug-refractory AF Paroxysmal AF=21 (64%) pts had paroxysmal AF Persistent/permanent AF=12 (36%) had persistent/permanent AF Duration AF=6.2±5.2 y Average EF=0.63±0.12 Average left atrial volume index was 70±24 mL/m^2 FU of 1.5±1.2 y	Survival with AF elimination and AF control	N/A	1-y survival with AF elimination was 62% (95% CI: 0.66-0.84) and with AF control was 75% (95% CI: 0.66-0.84)	N/A	AF control was less likely in pts with a persistent/chronic AF, larger left atrial volumes, and more advanced diastolic disease. Additional linear ablation may improve outcomes in pts with severe left atrial enlargement and more advanced diastolic dysfunction. 2 pts had a periprocedureal TIA, 1 PV stenosis, and 1 died after mitral valve replacement from prosthetic valve thrombosis. QOL scores improved from baseline at 3 and 12 mo

Di Donna P, et al., 2010 (229) 20173211	Assess the outcome of a multicentre HCM cohort following RFCA for symptomatic AF refractory to medical Tx	61	Age 54±13 y; Time from AF onset 5.7±5.5 y Paroxysmal AF=35; (57%) Recent persistent AF=15; (25%) Long-standing persistent AF=11; (18%) Ablation scheme: pulmonary vein isolation plus linear lesions 32 of 61 pts, 32 (52%) required redo procedures. Antiarrhythmic Tx was maintained in 22 (54%) FU: 29±16 mo 41 (67%) NSR at FU	N/A	In pts in NSR there was marked improvement in NYHA class (1.2±0.5 vs. 1.9±0.7 at baseline; p<0.001). In pts (33%), with AF recurrence, there was less marked, but still significant, improvement following RFCA (NYHA class 1.8±0.7 vs. 2.3±0.7 at baseline; p=0.002)	Independent predictors of AF recurrence: increased left atrium volume HR per unit increase 1.009, 95% CI: 1.001-1.018; p=0.037, and NYHA class (HR: 2.24; 95% CI: 1.16 to 4.35; p=0.016)	N/A	RFCA was successful in restoring long-term sinus rhythm and improving symptomatic status in most HCM pts with refractory AF, including the subset with proven sarcomere gene mutations, although redo procedures were often necessary. Younger HCM pts with small atrial size and mild Sx proved to be the best RFCA candidates, likely due to lesser degrees of atrial remodelling

1° indicates primary; 2, secondary; AAD, antiarrhythmic drug; AE, adverse event; AF, atrial fibrillation; AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management; ANDROMEDA, European Trial of Dronedarone in Moderate to Severe Congestive Heart Failure; ASA, aspirin; AV, atrioventricular; AVB, atrioventricular block; CAD, coronary artery disease; CCB, calcium channel blocker; CHF, congestive heart failure; CV, cardiovascular; DM, diabetes mellitus; EF, ejection fraction; EKG, electrocardiogram; FU, follow up; HCM, hypertrophic cardiomyopathy; HF, heart failure; HOCM, hypertrophic obstructive cardiomyopathy; HR, hazard ratio; HTN, hypertension; Hx, history; ICD, implantable cardioverter defibrillator; IV, intravenous; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; N/A, not applicable; NSR, normal sinus rhythm; NYHA, New York Heart Association; pts, patients; PV, pulmonary vein; QOL, quality of life; RACE, Rate Control Efficacy in Permanent Atrial Fibrillation; RFCA, radio frequency catheter ablation; RR, relative risk; SOB, shortness of breath; SR, sinus rhythm; Sx, symptom; TIA, transient ischemic attack; and Tx, therapy.

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