2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation Data Supplement

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Methodology and Evidence Review

The recommendations listed in this guideline are, whenever possible, evidence based. An extensive evidence review was conducted from August 2016 through October 2016, that included literature published through October 2016. Other selected references published through December 2017 were incorporated by the writing committee. Literature included was derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline. Key search words included but were not limited to the following: *acute coronary syndrome, anticoagulants, anticoagulation, antiplatelet agents, apixaban, atrial fibrillation, atrial high rate events, betrixaban, cardiac surgery, cardioversion, coronary artery disease, coronary heart disease, coronary stenting, cryptogenic stroke, dabigatran, device detection, devices, DOAC, dual therapy, edoxaban, hypertension, left atrial appendage closure, myocardial infarction, NOAC, obesity, percutaneous coronary intervention, renal dysfunction, risk factor modification, rivaroxaban, silent atrial fibrillation, sleep apnea, stroke, thromboembolism, TSOAC, triple therapy, unstable angina, warfarin, Watchman*

Abbreviations: 1° indicates primary; 2°, secondary; AC, anticoagulation; ACS, acute coronary syndrome; AF, atrial fibrillation; AFASAK, Atrial Fibrillation, Aspirin and Anticoagulant Therapy Study; AFCAS, Management of patients with Atrial Fibrillation undergoing Coronary Artery Stenting; AFSS, Atrial fibrillation severity scale; AHRE, atrial high rate episodes; ARREST AF, Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ASA, aspirin; ASD, atrial septal defect; ASSERT, Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial; AT, atrial tachycardia; ATRIA, Anticoagulation and Risk factors In Atrial fibrillation; AVERROES, Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; AVR, aortic valve replacement; AUCinf, area under the curve extended to infinity; BARC, Bleeding Academic Research Consortium; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; BID, twice daily; bpm, beats per minute; BMI, body mass index; BRIDGE, Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery; CABG, coronary artery bypass graft; CAD, coronary artery disease; CAFA, Canadian Atrial Fibrillation Anticoagulation; $CHADS_2$, Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, Stroke; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years, sex category; CHF, congestive heart failure; CI, confidence interval; CIED, cardiac implantable electronic device; CKD, chronic kidney disease; Cmax, maximum observed plasma concentration; CP, codeine phosphate; Cr, creatinine; CrCl, creatinine clearance; CRT-D, cardiac resynchronization therapy defibrillator; CRYSTAL AF, Cryptogenic Stroke and Underlying AF; CV, cardiovascular; CVA, cerebrovascular accident; DAPT, dual antiplatelet therapy; DC, direct current; DES, drug-eluting stent; DM, diabetes mellitus; ECG, electrocardiogram; ED, emergency department; ENGAGE AF-TIMI 48, Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48; ER, emergency room; ESRD, end-stage renal disease; EWOLUTION, Registry on WATCHMAN Outcomes in Real-Life Utilization; FDA, Food and Drug Administration; FU, follow-up; GI, gastrointestinal; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol Concomitantly; HF, heart failure; HR, hazard ratio; HTN, hypertension; Hx, history; ICD, implantable cardioverter-defibrillator; ICH, intracranial hemorrhage; ICM, implantable cardiac monitor; IMPACT, The IMPACT of BIOTRONIK Home Monitoring Guided Anticoagulation on Stroke Risk in Patients With ICD and CRT-D Devices; INR, international normalized ratio; IQR,

interquartile range; IRR, Incidence Rate Ratio; ISAR-TRIPLE, Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation; LA, left atrium; LAA, left atrial appendage; LAAO, left atrial appendage occlusion; LAC, left atrial cavity; LEGACY- Long-Term Effect of Goal directed weight management on Atrial Fibrillation Cohort: A 5 Year follow-up study; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac event; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; MOST, Mode Selection Trial; N/A, not applicable; NGR, nongender-related; NOAC, non-vitamin K oral anticoagulant; NS, not significant; NVAF, nonvalvular atrial fibrillation; NYHA, New York Heart Association; OAC, oral anticoagulation; OR, odds ratio; pts, patient; PAD, peripheral arterial disease; PC, placebo; PCI, percutaneous coronary intervention; PE, pulmonary embolism; PIONEER AF-PCI- Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention; PFO, patent foramen ovale; PRCT, prospective randomized controlled trial; PREVAIL, Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy; PROACT, Prospective Randomized On-X Anticoagulation Clinical Trial; PROTECT AF, WATCHMAN Left Atrial Appendage System for Embolic protection in Patients With Atrial Fibrillation; pt., patient; QD, every day; RCT, randomized controlled trial; RE-ALIGN, Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement; RE-CIRCUIT, Uninterrupted Dabigatran Etexilate in Comparison to Uninterrupted Warfarin in Pulmonary Vein Ablation; RE-DUAL PCI, Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; RE-VERSE AD, Reversal Effects of Idarucizumab on Active Dabigatran; RFM, risk factor management; 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 or risk ratio; sCr, serum creatinine concentration; SE, systemic embolism; SOS AF, Stroke Prevention Strategies based on Atrial Fibrillation Information from Implanted Devices; SPAF I, Stroke Prevention in Atrial Fibrillation Study; SPINAF, Stroke Prevention in Atrial Fibrillation; STEMI, ST-Elevation Myocardial Infarction; SVT, supraventricular tachycardia; Sx, symptom; TE, thromboembolism/thromboembolic; TEE, transesophageal echocardiogram/echocardiography; TIA, transient ischemic attack; TIMI, Thrombolysis In Myocardial Infarction; TRANSLATE- ACS, Treatment with Adenosine Diphosphate Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome; TRENDS, A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics; TTR, time in therapeutic range; Tx, treatment; VD, vascular death; and VKA, vitamin K antagonist; WOEST, What is the Optimal antiplatElet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary StenTing; X-VeRT, Explore the Efficacy and Safety of Once-daily Oral Rivaroxaban for the Prevention of Cardiovascular Events in Subjects With Nonvalvular Atrial Fibrillation Scheduled for Cardioversion.

Data Supplement 1. RCTs, Nonrandomized Trials, Observational Studies, and/or Registries of Studies Comparing Risk-Based Anticoagulant Therapy (Section 4.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Bonde AN, et al. 2014 (1) 25500231	**Aim:** Test hypothesis that CKD would be associated with a higher risk of stroke/TE in all stroke risk strata of non-anticoagulated patients with AF. Test hypothesis that the benefits of warfarin would outweigh its risks in AF patients with CKD and a high risk of stroke/TE. **Study type:** Observational cohort **Size:** 4,519 patients (2.9% total screened) with non-end-stage CKD. 1,142 (0.7%) receiving renal replacement therapy.	**Inclusion criteria:** • National Danish Registry patients discharged from hospital with nonvalvular AF from 1997 to 2011. • CKD. **Exclusion criteria:** FU began 7 d after discharge. Pts that experienced stroke/TE, major bleeding, or died during this 7-d period were excluded. Pts receiving antiplatelet drugs other than ASA (i.e., clopidogrel, prasugrel, or dipyridamole) were excluded.	N/A	**1° endpoint:** 1) Hospitalization/death from stroke/TE (i.e., peripheral arterial TE, ischemic stroke, and TIA); 2) death/hospitalization from stroke/TE/bleeding (i.e., GI, intracranial, urinary tract, and airway bleeding); 3) fatal stroke/fatal bleeding; 4) CV death; or 5) death from any cause. **Results:** CKD is associated with a higher risk of stroke/TE in AF patients. High-risk CKD patients (CHA_2DS_2-VASc ≥2) with AF benefit from warfarin Tx for stroke prevention.	• Observational trial. • Limited renal function data in some patients. • ASA use may be underestimated.

Siontis KC, et al. 2018 (2) 29954737	**Aim:** To determine patterns of apixaban use and its associated outcomes in dialysis-dependent ESRD in patients with AF compared with AF patients receiving warfarin. **Study type:** Retrospective cohort study of Medicare beneficiaries included in the United States Renal Data System (October 2010 to December 2015). Eligible patients were those with ESRD and AF undergoing dialysis who initiated treatment with an oral anticoagulant. **Size:** The study population consisted of 25,523 patients (45.7%	**Inclusion criteria:** AF diagnosis within 1 y before the anticoagulant prescription. **Exclusion criteria:** Because of the small number of dabigatran and rivaroxaban users, outcomes were assessed only in patients treated with apixaban or warfarin. Also excluded were patients with mitral stenosis or heart valve replacement/repair procedure before the anticoagulant prescription in accordance with the 2014 ACC/AHA/HRS definition of "valvular" AF. Patients with repaired or bioprosthetic heart valves were also excluded.	**Intervention:** Apixaban. **Comparator:** Warfarin.	**1° endpoint:** Differences between groups in survival free of stroke or systemic embolism, major bleeding, gastrointestinal bleeding, intracranial bleeding, and death were assessed using Kaplan-Meier analyses. HR and 95% CI were derived from Cox regression analyses. **Results:** In matched cohorts, there was no difference in the risks of stroke/systemic embolism between apixaban and warfarin (HR 0.88, 95% CI 0.69-1.12; P=0.29), but apixaban was associated with significantly lower risk of major bleeding (HR 0.72, 95% CI 0.59-0.87; P<0.001). In sensitivity analyses, standard dose apixaban (5 mg twice a day; n=1,034) was associated with significantly lower risks of stroke/systemic embolism and death as compared with either reduced dose apixaban (2.5 mg twice a day; n=1,317; HR 0.61, 95% CI 0.37-0.98, P=0.04 for stroke/systemic embolism; and HR 0.64, 95% CI 0.45-0.92, P=0.01 for death) or warfarin (HR 0.64, 95% CI 0.42-0.97, P=0.04 for stroke/systemic embolism; and HR 0.63, 95% CI 0.46-0.85, P=0.003 for death).	N/A

	women; age 68.2±11.9 years), including 2,351 patients on apixaban and 23,172 patients on warfarin.				
Andersson T, et al. 2014 (3) 25499348	**AIM:** To estimate the risk of stroke or TIA, HF, MI and all-cause mortality in patients hospitalized with incidental AF as the only diagnosis and in matched controls in a comprehensive nation-wide study. **Study type:** Observational matched control cohort. **Size:** 9,510 AF patients and 12,468 matched controls.	**Inclusion criteria:** National Swedish registry patients diagnosed with incidental AF between 1995 and 2008. Controls were matched for age, sex, and calendar y of the diagnosis of AF in patients. All subjects were free of any in-hospital diagnosis from 1987 and until patients were diagnosed with AF and also free of any diagnosis within 1 y from the time of inclusion. **Exclusion criteria:** • Other in-hospital diagnoses including 1 y of	N/A	**1° endpoint:** Stroke or TIA, HF, MI and all-cause mortality. **Results:** Pts with AF and no co-morbidities at inclusion had at least a doubled risk of stroke or TIA and a tripled risk of HF, through all age categories, as compared to controls. Women were at higher RR of stroke or TIA than men.	• Observational trial. • Some diseases (i.e., HTN) may be under represented. • Anticoagulation status of AF patients unknown. • Type of AF (i.e., paroxysmal, persistent or permanent) is known as is AF progression.

		FU (AF patients and controls). • AF patients without matched controls. • Controls without a matched AF patient.			
ATRIA Fang MC, et al. 2005 (4) 16157766	**Aim:** Test the hypothesis of whether women are at higher risk for atrial AF–related TE. **Study type:** Observational cohort. Kaiser Permanente of Northern California **Size:** 13,559 adults.	**Inclusion criteria:** Pts assembled between July 1, 1996 and December 31, 1997 by searching automated inpatient, outpatient, and ECG databases for physician-assigned diagnosis of AF. **Exclusion criteria:** Pts with diagnosed mitral stenosis, valvular repair or replacement, transient postoperative AF, or concurrent hyperthyroidism were excluded.	N/A	**1° endpoint:** Rates of ischemic stroke and peripheral embolism between male and female patients not taking anticoagulants while controlling for other known risk factors for TE. **Results:** Women are at higher risk than men for AF-related TE off warfarin. Warfarin therapy appears be as effective in women, if not more so, than in men, with similar rates of major hemorrhage. Female sex is an independent risk factor for TE and should influence the decision to use anticoagulant therapy in persons with AF.	• Observational study. • Women on average older than men.

Pancholy SB, et al. 2014 (5) 24315113	**Aim:** Systematic review and meta-analysis of gender differences in residual risk of CVA/SE and major bleeding outcomes in patients with nonvalvular AF treated with either warfarin or NOAC. **Study type:** Meta-analysis. **Size:** 6 RCT studies included (5 with gender data on warfarin and 5 with gender data on NOACs).	**Inclusion criteria:** Searched indexed studies recorded in major databases (PubMed, EMBASE, Cochrane Library, and Google Scholar) for keywords "atrial fibrillation," "gender," "anticoagulation," and "outcomes". **Exclusion criteria:** Did not meet inclusion criteria.	N/A	**1° endpoint:** CVA/SE and major bleeding. **Results:** Women with AF taking warfarin were at a greater risk of CVA/SE compared with men (OR: 1.279; 95% CI: 1.111–1.473; p=0.001). No gender difference in residual risk of CVA/SE was noted in patients with AF receiving NOAC agents (OR: 1.146; 95% CI: 0.97–1.354; p=0.109). Major bleeding was less frequent in women with AF treated with NOAC. Results suggest an increased net clinical benefit of NOAC agents compared with warfarin in treating women with AF.	• Meta-analysis (pooled analysis) design with limited number of studies meeting inclusion criteria. • Results indicate that the NOAC agents are associated with significantly less major bleeding in the female cohort compared with male cohort. The mechanism of this observed decrease in major bleeding risk in women compared with men is unclear.
Mikkelsen AP, et al. 2012 (6) 22805071	**Aim:** To investigate the risk of stroke/TE associated with female sex in non-valvular AF in non-anticoagulated patients. **Study type:** Observational cohort. **Size:** 87,202 AF patients; 44,744	**Inclusion criteria:** National Danish Registry patients discharged from hospital with nonvalvular AF from 1997 to 2008 subdivided by age.	**Exclusion criteria:** Pts were excluded if they died, had a stroke/TE event or experienced a major bleeding in a 7-d period following hospital discharge, or if they had received anticoagulation (VKA or heparin) up to 180 d before and 7 d after hospital discharge.	**1° endpoint:** Stroke/TE event resulting in either hospitalization or death. Pts who died from causes other than stroke/TE in the FU period were censored. **Results:** The rate of stroke/TE for females aged <65 and 65–74 y was not increased as compared with men, whereas the rate for females aged ≥75 y was increased. At both 1-y and 12-y FU, female sex did not increase the risk of stroke for patients aged <75 y.	• Observational cohort. • This study suggested that female sex should not be automatically included as an independent stroke/TE risk factor in guidelines or in the CHA_2DS_2-VASc score, without careful prior consideration of the 'age <65 and lone AF' criterion.

	(51.3%) were female.				• Pt baseline characteristics were not fully available. • Only hospitalized AF patients were studied.
Wagstaff AJ, et al. 2014 (7) 24633256	**Aim:** Systematic meta-analysis of the available evidence to establish if female sex is a risk factor for stroke/TE among patients with AF. **Study type:** Meta-analysis. **Size:** 17 studies (5 RCTs and 12 prospective observational studies).	**Inclusion criteria:** The search term 'atrial fibrillation' was used in combination with 'stroke risk', 'thromboembolism', 'female' and 'gender differences' and returned 735 articles, of which 17 were appraised and included.	**Exclusion criteria:** • Duplicates excluded. • Case-control studies excluded. • Studies with male-only populations excluded. • Studies focusing primarily on subjects with paroxysmal AF excluded. • Studies with population size <200 excluded. • Papers not in English excluded.	**1° endpoint:** Stroke or TE (ischemic, hemorrhagic, or unspecified stroke, TIA and SE). **Results:** Women with AF are at increased risk of stroke, particularly elderly women.	• Stroke risk assessment, including female sex as a risk factor, should be undertaken in all AF patients to inform decisions on thromboprophylaxis. • Significant heterogeneity between included studies.

Data Supplement 2. RCTs, Nonrandomized Trials, Observational Studies, and/or Registries of Studies Comparing Non-vitamin K-dependent Oral Anticoagulants (NOACs) (Section 4.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events

RE-LY Connolly SJ, et al. 2009 (8) 19717844	**Aim:** To compare 2 fixed doses of dabigatran with open-label use of warfarin in pts with AF at increased risk of stroke **Study type:** RCT, open-label, blinded doses of dabigatran **Size:** 18,113	**Inclusion criteria:** AF and ≥1 of the following: prior stroke or TIA; LVEF <40%, NYHA class II or higher HF Sx, age ≥75 y or age 65–74 y plus DM, HTN, or CAD Mean $CHADS_2$: 2.1 **Exclusion criteria:** 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	**Intervention:** Dabigatran in 2 fixed doses – oral prodrug, direct competitive inhibitor of thrombin Dabigatran 110 mg (N=6,015) Dabigatran 150 mg (N=6,076) **Comparator:** Warfarin INR: 2–3, mean TTR: 64% N=6,021	**1° endpoint:** Stroke or SE- • Dabigatran 110 mg 1.53%/y • Dabigatran 150 mg 1.11%/y • Warfarin 1.69%/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 **Safety endpoint (if relevant):** 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	• Secondary endpoints: 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 • Limitations: open-label, median duration of FU 2 y • Adverse events: Dyspepsia

				0.30%/y • Warfarin 0.74%/y Major GI- • Dabigatran 110 mg 1.12%/y • Dabigatran 150 mg 1.51%/y • Warfarin 1.02%/y	
ROCKET AF Patel MR, et al. 2011 (9) 21830957	**Aim:** 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 **Study type:** RCT, double-dummy, double-blinded **Size:** 14,264	**Inclusion criteria:** 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 $CHADS_2$ score of ≥2 Mean $CHADS_2$ score of 3.5 **Exclusion criteria:** 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	**Intervention:** Rivaroxaban Factor Xa inhibitor, 20 mg QD or 15 mg QD for those with CrCl of 39–40 mL/min (N=7,131) **Comparator:** Warfarin INR 2-3, mean TTR 55% (N=7,133)	**1° endpoint:** 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 • 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 **Safety endpoint (if relevant):**	• Secondary endpoints: Stroke, SE, or VD Rivaroxaban: 3.11/100 pt-y Warfarin: 3.64/100 pt-y HR: 0.86; 95% CI: 0.74–0.99; p=0.034 • Limitations: Median duration of FU was 707 d. Lower TTR in warfarin group 1° analysis was prespecified as a per-protocol analysis. High-event rate after discontinuation of Tx.

				• Major and non-major clinically relevant bleeding Rivaroxaban: 14.9/100 pt-y Warfarin: 14.5/100 pt-y • ICH Rivaroxaban: 0.5/100 pt-y Warfarin: 0.7/100 pt-y • Major GI Rivaroxaban: 3.15% Warfarin: 2.16%	
ARISTOTLE Granger CB, et al. 2011 (10) 21870978	**Aim:** 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 **Study type:** RCT, double-dummy, double-blinded **Size:** 18,201	**Inclusion criteria:** 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 $CHADS_2$ score of 2.1 **Exclusion criteria:** 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)	**Intervention:** 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 sCr ≥1.5 mg/dL (N=9,120) **Comparator:** Warfarin INR 2–3 Mean TTR 62.2% (N=9,081)	**1° endpoint:** Any stroke or SE Apixaban: 1.27%/y HR: 0.79; 95% CI: 0.66–0.95; p<0.001 for noninferiority, p=0.01 for superiority Warfarin: 1.6%/y **Safety endpoint (if relevant):** • 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	• Secondary endpoints: stroke, SE, major bleeding, or death from any cause Apixaban: 6.13%/y Warfarin: 7.20%/y • Adverse events: no differences • Limitations: median duration of FU 1.8 y

ENGAGE AF-TIMI 48 Giugliano RP, et al. 2013 (11) 24251359	**Aim:** Compare 2 dose regimens of once-daily edoxaban with warfarin in patients with atrial fibrillation who were at moderate-to-high risk for stroke. **Study type:** RCT, noninferiority design. **Size:** 21,105 patients, 1:1:1 randomization.	**Inclusion criteria:** Age ≥21 y and had atrial fibrillation documented by means of an electrical tracing within the 12 mo preceding randomization, a score of 2 or higher on the $CHADS_2$ risk assessment, and anticoagulation therapy planned for the duration of the trial. **Exclusion criteria:** Key exclusion criteria were atrial fibrillation due to a reversible disorder; an estimated Cr clearance of less than 30 mL/min; a high risk of bleeding; use of DAPT; moderate-to-severe mitral stenosis; other indications for anticoagulation therapy; ACS, coronary revascularization, or stroke within 30 d before randomization; and an inability to adhere to study procedures.	**Intervention:** 60 mg (high dose) or 30 mg (low dose) edoxaban. **Comparator:** Warfarin (adjusted by INR).	**1° endpoint:** During the Tx period, a stroke or systemic embolic event occurred in 232 patients in the warfarin group (1.50% per y), 182 patients in the high dose edoxaban group (1.18% per y; HR vs. warfarin, 0.79; 97.5% CI: 0.63–0.99; p<0.001 for noninferiority, p=0.02 for superiority), and 253 patients in the low dose edoxaban group (1.61% per y; HR vs. warfarin: 1.07; 97.5% CI: 0.87–1.31; p=0.005 for noninferiority; p=0.44 for superiority). **Safety endpoint (if relevant):** The annualized rate of major bleeding events was 3.43% with warfarin, 2.75% with high-dose edoxaban (HR: 0.80; 95% CI: 0.71–0.91; p<0.001) and 1.61% with low-dose edoxaban (HR: 0.47; 95% CI: 0.41–0.55; p<0.001).The	• 1,393 centers in 46 countries.

				rates of life-threatening bleeding, intracranial bleeding, and major bleeding plus clinically relevant nonmajor bleeding were 0.78%, 0.85%, and 13.02%, respectively, with warfarin, as compared with 0.40%, 0.39%, and 11.10%, respectively, with high-dose edoxaban, and 0.25%, 0.26%, and 7.97%, respectively, with low-dose edoxaban ($p<0.001$ for the comparison of warfarin with each dose of edoxaban). The annualized rate of major GI bleeding was higher with high-dose edoxaban than with warfarin (1.51% vs. 1.23%), but the rate was lowest with low-dose edoxaban (0.82%).	
Aguilar M, et al. 2005 (12) 16034869	**Aim:** To characterize the efficacy and safety of oral anticoagulants for the 1° prevention of stroke in pts with chronic AF **Study type:**	**Inclusion criteria:** AF (intermittent or sustained) **Exclusion criteria:** Prior stroke or TIA, mitral	**Intervention:** Oral VKAs (warfarin) mean INR 2.0–2.6 N=1,154	**1° endpoint:** All stroke (ischemic or ICH) • Warfarin 27 • PC 71	**Secondary endpoint:** Stroke, MI, or VD Warfarin 69 PC 118 **Safety endpoint:**

	Cochrane Collaboration systematic review (AFASAK I, BAATAF, CAFA, SPAF I, SPINAF) **Size:** N=2,313 pts	stenosis or prosthetic cardiac valves	**Comparator:** PC N=1,159	**Results:** • 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 • 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	ICH, major extracranial bleeds • ICH, Warfarin 5, PC 2 • Extracranial bleeds, Warfarin 17, PC 16
Hart RG, et al. 2007 (13) 17577005	**Aim:** Determine the efficacy and safety of antithrombotic therapy for stroke prevention in patients with AF **Study type:** Meta-analysis of 13 randomized trials with previous meta-analysis **Size:** 29 trials with 28,044 participants	**Inclusion criteria:** • Randomized trials with a mean FU of 3 mo or longer that tested antithrombotic agents in patients who have nonvalvular atrial fibrillation • 1966 to March 2007 • Unrestricted by language **Exclusion criteria:** Trials that included patients who have prosthetic	**Intervention:** Adjusted-dose warfarin (6 trials, 2900 participants) and antiplatelet agents (8 trials, 4876 participants) **Comparator:** Placebo	**1° endpoint:** Stroke reduction **Results:** Adjusted-dose warfarin and antiplatelet agents reduce stroke by approximately 60% and by approximately 20%, respectively, in patients who have AF.	Adjusted-dose warfarin is more effective than antiplatelet therapy, but it doubles the risk for major extracranial and ICH

		cardiac valves or mitral stenosis were not considered			
PROACT Puskas J, et al. 2014 (14) 24512654	**Aim:** To compare different INR targets in patients at high risk factor to prevent TE in the 3 mo after AVR. **Study type:** RCT **Size:** 375 aortic valve replacement patients	**Inclusion criteria:** 1. Pts with a clinical indication for isolated AVR 2. Pts with the following conditions, which place a patient in the ''high-risk'' group: chronic AF, left ventricular ejection fraction <30%, enlarged LA >50 mm in diameter, spontaneous echocardiographic contrasts in the LA, vascular pathologic features, neurologic events, hypercoagulability, left or right ventricular aneurysm, lack of a platelet response to ASA or clopidogrel, and women receiving estrogen replacement therapy 3. Concomitant cardiac surgery, including coronary artery bypass grafting, mitral or tricuspid valve repair, ascending aortic replacement, maze procedure, and so forth, were allowed 4. Adult patients	**Intervention:** Lower dose warfarin (INR: 1.5–2.0) and 81 mg ASA daily. **Comparator:** Warfarin (INR: 2.0–3.0) and ASA 81 mg.	**1° endpoint:** The mean INR was 2.50 ± 0.63 for the control and 1.89 ± 0.49 for the test groups (p<0.0001). The low INR group experienced significantly lower major (1.48% vs. 3.26%/pt-y; p=0.047) and minor (1.32% vs. 3.41%/pt-y; p=0.021) bleeding rates without an increase in TE events.	

		Exclusion criteria: 1. Right-sided valve replacement 2. Double (aortic plus mitral) valve replacement 3. Pts with active endocarditis at implantation			
Winkelmayer WC, et al. 2011 (15) 21959598	**Aim:** Assess the risks and benefits of warfarin in chronic dialysis patients with new AF. **Study type:** Observational cohort. **Size:** 2,313 patients. Healthcare claims data (1994 to 2006) from Medicare beneficiaries aged >65 y who received prescription coverage through 1 of 3 specified state-sponsored programs (New Jersey and Pennsylvania).	**Inclusion criteria:** Dialysis patients were ≥66 y on their first ESRD service date followed for first hospitalization with diagnosis of AF. **Exclusion criteria:** Not enrolled in the New Jersey or Pennsylvania prescription programs. Prior diagnosis of AF or warfarin use for any reason. Pt survival <30 d after index AF hospital admission.	**Intervention:** Warfarin. **Comparator:** Propensity-matched warfarin nonusers.	**1° endpoint:** Occurrence of ischemic stroke was similar (HR: 0.92; 95% CI: 0.61–1.37), whereas warfarin users experienced twice the risk of hemorrhagic stroke (HR: 2.38; 95% CI: 1.15–4.96). The risks of stroke, GI hemorrhage, and mortality did not differ between groups. **Safety endpoint (if relevant):** Association between warfarin use and increased hemorrhagic stroke in dialysis patients with AF was confirmed; however, there was no association between warfarin use and ischemic stroke.	• Limited size of study. • Observation cohort.

ENGAGE AF-TIMI 48 Bohula EA, et al. 2016 (16) 27358434	**Aim:** To analyze the efficacy and safety of edoxaban vs. warfarin across the range of baseline CrCl in the ENGAGE AF-TIMI 48 trial (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction Study 48) **Study type:** RCT subgroup analysis **Size:** 14,071	**Inclusion criteria:** Eligible patients were ≥21 y with AF within 12 mo and a $CHADS_2$ risk score ≥2 **Exclusion criteria:** CrCl <30 mL/min estimated with the Cockcroft-Gault method, a high risk of bleeding, and the use of DAPT.	**Intervention:** Edoxaban 60 mg/d **Comparator:** Warfarin (INR 2.0–3.0)	**1° endpoint:** The relative risk of stroke and SE with edoxaban 60 mg vs. warfarin in patients with CrCl >50 mL/min (HR: 0.87; 95% CI: 0.72–1.04) was similar to that in patients with CrCl ≤50 mL/min (HR: 0.87; 95% CI: 0.65–1.18; p for interaction=0.94). **Safety endpoint (if relevant):** Bleeding rates were lower at all levels of CrCl with Edoxaban (p for interaction=0.11).	N/A
Wang X, et al. 2016 (17) 26331581	**Aim:** To assess the pharmacokinetics, pharmacodynamics, and safety of apixaban in patients on hemodialysis. **Study type:** Open-label, parallel-group, single-dose pharmacokinetic/pharmacodynamics study. **Size:** 16 subjects (n=8 on hemodialysis and n=8 healthy controls)	**Inclusion criteria:** Male and female subjects, aged 18 to 65 y with either normal renal function (as determined by calculated CrCl >80 mL/min using the method of Cockcroft and Gault 10) or ESRD and on chronic and stable hemodialysis **Exclusion criteria:** Significant Hx of uncontrolled or unstable CV, respiratory, hepatic, GI, endocrine, hematopoietic,	**Intervention:** N/A **Comparator:** N/A	**Results:** Compared with healthy subjects, apixaban Cmax and AUCinf were 10% lower and 36% higher, respectively, in subjects with ESRD off hemodialysis. Hemodialysis in subjects with ESRD was associated with reductions in apixaban Cmax and AUCinf of 13% and 14%, respectively.	N/A

		psychiatric, and/or neurological disease in the 6 mo prior to study participation; Hx or evidence of abnormal bleeding or coagulation disorder; ICH, abnormal bleeding, or coagulation disorder in a first-degree relative; Hx of GI-related disorders that would impact absorption of the study drug; and use of concomitant medications likely to impair hemostasis or alter apixaban pharmacokinetics or pharmacodynamics.			
Stanton BE, et al. 2017 (18) 28117916	**Aim:** To evaluate the safety and effectiveness of apixaban vs. warfarin in patients with severe renal impairment **Study type:** Retrospective, matched-cohort study **Size:** 146 adults who received at least 1 dose of apixaban (n=73) or warfarin (n=73).	**Inclusion criteria:** Pts aged 18 y or older who received at least 1 dose of apixaban or warfarin while admitted to the study institution between January 30, 2014, and December 31, 2015 were screened for inclusion. Pts with a CrCl <25 mL/min or a sCr >2.5 mg/dL, or those receiving peritoneal dialysis or hemodialysis were included **Exclusion criteria:** Pts were excluded if an accurate assessment of	**Intervention:** N/A **Comparator:** N/A	**1° endpoint:** A nonsignificant difference in the occurrence of major bleeding and composite bleeding was observed between patients who received apixaban compared with those who received warfarin (9.6% vs. 17.8%; p=0.149, and 21.9% vs. 27.4%; p=0.442, respectively) **Safety endpoint (if relevant):** The	N/A

		dose or renal function could not be made (i.e., weight or sCr was missing). Pts receiving continuous renal replacement therapy were also excluded.		occurrence of stroke was similar between the groups (7.5% in each group)	
Mavrakanas TA, et al. 2017 (19) 28302754	**Aim:** To determine apixaban pharmacokinetics at steady state in patients on hemodialysis. **Study type:** Observational **Size:** n=7	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**Intervention:** N/A **Comparator:** N/A	**Results:** Apixaban 2.5 mg BID in patients on hemodialysis resulted in drug exposure comparable with that of the standard dose (5 mg BID) in patients with preserved renal function. Apixaban 5 mg BID led to supratherapeutic levels. **Safety endpoint (if relevant):** N/A	N/A
Hariharan S, et al. 2012 (20) 21956605	**Aim:** To derive a dosing regimen for dabigatran in patients with severe renal impairment by modeling and simulation. **Study type:** Statistical modeling **Size:** N/A	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**Intervention:** N/A **Comparator:** N/A	**Results:** Dabigatran 150 mg given once daily resulted in 35% higher average steady state peak dabigatran plasma concentration, whereas a 75 mg once daily regimen resulted in 42% lower average trough dabigatran plasma concentration, relative to that observed with 150 mg administered BID in	N/A

				subjects with moderate renal impairment.	
AVERROES Connolly SJ, et al. 2011 (21) 21309657	**Aim:** To determine the efficacy and safety of apixaban, 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 **Study type:** RCT, double-blind, double-dummy **Size:** N=5,559	**Inclusion criteria:** Age ≥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 because it had already been demonstrated to be unsuitable or because it was expected to be unsuitable. Mean $CHADS_2$ of 2.0 **Exclusion criteria:** Pts required long-term anticoagulation, VD requiring surgery, a serious bleeding event in the previous 6 mo or a high-risk bleeding, stroke within the previous 10 d, severe renal insufficiency (a sCr >2.5 mg/dL) or a calculated CrCl <25 mL/min	**Intervention:** 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 sCr ≥1.5 mg/dL (N=2,808) **Comparator:** ASA 81–325 mg/dL (N=2,791)	**1° endpoint:** Any stroke or SE Apixaban: 1.6%/y ASA: 3.7%/y p<0.001 HR with apixaban: 0.45; 95% CI: 0.32–0.62; p<0.001 **Safety endpoint (if relevant):** • Major bleeding Apixaban: 1.4% ASA: 1.2% • Intracranial bleeding Apixaban: 0.4% ASA: 0.4% • Major GI Apixaban: 0.4% ASA: 0.4%	• Secondary endpoint: 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 • Adverse events: no differences
Fauchier L, et al. 2016 (22) 27231269	**Aim:** To determine the net clinical benefit of OAC in AF patients with 1 NGR CHA_2DS_2-VASc stroke risk factor. **Study type:** Observational	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**Intervention:** N/A **Comparator:** N/A	**1° endpoint:** The yearly rate of stroke/SE in non-anticoagulated AF patients with 1 NGR stroke risk factor was 2.09% (95% CI: 1.37–	N/A

	Size: 8,962 patients with AF			3.18). This corresponded to an adjusted HR: 2.82 (95% CI: 1.32–6.04) relative to the group with no NGR stroke risk factors. The net clinical benefit was positive in favor of OAC use in patients with 1 NGR. **Safety endpoint (if relevant):** N/A	
RE-ALIGN Eikelboom JW, et al. 2013 (23) 23991661	**Aim:** Evaluated the use of dabigatran in patients with mechanical heart valves **Study type:** Phase 2 dose-validation study **Size:** 252 patients	**Inclusion criteria:** Pts were eligible for inclusion if they were between the ages of 18 and 75 y and were undergoing implantation of a mechanical bileaflet valve in the aortic or mitral position or both (population A) or if they had undergone implantation of a mechanical bileaflet mitral valve (with or without mechanical bileaflet aortic-valve replacement) more than 3 mo before randomization (population B). **Exclusion criteria:** N/A	Randomly assigned in a 2:1 ratio to receive either dabigatran or warfarin **Intervention:** The selection of the initial dabigatran dose (150, 220, or 300 mg BID) was based on kidney function. **Comparator:** Warfarin	**1° endpoint:** TE and bleeding events	• Trial was stopped early because of an excess of TE and bleeding events

Data Supplement 3. RCTs, Nonrandomized Trials, Observational Studies, and/or Registries of Studies Comparing Interruption and Bridging Anticoagulation (Section 4.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
BRIDGE Douketis JD, et al. 2015 (24) 26095867	**Aim:** To determine whether bridging therapy using heparin improves periprocedural outcomes **Study type:** Randomized, double-blind, placebo-controlled trial **Size:** 1,884 pts were enrolled	**Inclusion criteria:** Pts with AF who had warfarin Tx interrupted for an elective operation or other elective invasive procedure **Exclusion criteria:** A mechanical heart valve; stroke, systemic embolism, or TIA within the previous 12 wk; major bleeding within the previous 6 wk; CrCl >30 mL/min; platelet count of less than 100×10^3 per cubic millimeter; or planned cardiac, intracranial, or intraspinal surgery	**Intervention:** 934 assigned to receive bridging therapy **Comparator:** 950 assigned to receive no bridging therapy	**1° endpoint:** Forgoing bridging anticoagulation was noninferior to perioperative bridging with low-molecular-weight heparin for the prevention of arterial TE and decreased the risk of major bleeding	N/A
RE-VERSE AD Pollack CV, et al. 2017 (25) 28693366	**Aim:** Determine whether 5 g of intravenous Idarucizumab would be able to reverse the anticoagulant effect of dabigatran in patients who had	**Inclusion criteria:** Adults, ≥18 y, who were receiving dabigatran **Exclusion criteria:** N/A	**Intervention:** Surrogate marker thrombin **Comparator:** N/A	**1° endpoint:** Either the diluted thrombin time or the ecarin clotting time; measured the activity of those markers **Results:**	• Doesn't work for brain hemorrhage

	uncontrolled bleeding (Group A) or were about to undergo an urgent procedure (Group B). **Study type:** Multicenter, prospective, open-label study **Size:** 503 pts			• In Group A, median time to the cessation of bleeding was 2.5 h • In Group B, the median time to the initiation of the intended procedure was 1.6 h	
ANNEXA-A and ANNEXA-R Siegal DM, et al. 2015 (26) 26559317	**Aim**: To test efficacy and safety of Andexanet Alfa reversal of the anticoagulant effects of the factor Xa inhibitors apixaban and rivaroxaban. **Study type:** Two-part randomized, double blind, placebo-controlled study. **Size:** 145 patients.	**Inclusion criteria:** Healthy volunteers 50 to 75 years of age. **Exclusion criteria:** None identified.	**Intervention:** ANNEXA-A: Apixaban (5 mg twice daily for 3.5 days) followed by 3:1 randomization to Andexanet Alfa or placebo. ANNEXA-R: Rivaroxaban (20 mg daily for 4 days) followed by 2:1 randomization to Andexanet Alfa or placebo. **Comparator:** Placebo.	**1° endpoint:** Primary end point for both studies was the percent change in anti–factor Xa activity. **Results:** Andexanet Alfa, compared with placebo, rapidly reversed the anticoagulant activity of apixaban and rivaroxaban.	• Secondary endpoints included comparison of Andexanet Alfa bolus administration without and with a 2 hr continuous infusion, and measurements of clotting parameters and unbound-drug (apixaban or rivaroxaban) concentrations.
ANNEXA-4 Connolly SJ, et al. 2016 (27) 27573206	**Aim**: ANNEXA-4 is an ongoing, multicenter, prospective,	**Inclusion criteria:** Patients 18 years of age or older who received (prior 18 hours) one of	**Intervention:** Andexanet alfa bolus and 2-hour infusion. **Comparator: None.**	**1° endpoint:** Follow-up drug levels and measures of clinical hemostasis and complications.	• Thrombotic complications occurred in 12 of 67 patients during the 30-day follow-up period.

	open-label, single-group study of Andexanet Alfa in patients with acute major bleeding. **Study type:** Multicenter, prospective, open-label, single-group **Size:** 67 patients 47 patients in efficacy analysis).	four factor Xa inhibitors — apixaban (31 patients), rivaroxaban (32 patients), edoxaban (no patients), or enoxaparin (4 patients) meeting criteria for acute major bleeding (mainly GI and intracranial). **Exclusion criteria:** Multiple criteria were outlined. Of 67 patients considered, 20 were excluded due to low serum drug levels or missing data.		**Results:** Twelve hours after the Andexanet alfa infusion, clinical hemostasis was adjudicated as excellent or good in 37 of 47 patients in the efficacy analysis (79%; 95% CI, 64 to 89). Thrombotic events occurred in 12 of 67 patients (18%) during the 30-day follow-up.	

Data Supplement 4. RCTs, Nonrandomized Trials, Observational Studies, and/or Registries of Studies Comparing Percutaneous Approaches to Occlude the LAA (Section 4.4.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population Study Intervention (# patients) Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)
PROTECT AF Reddy VY, et al. 2014 (28) 25399274	**Aim:** To determine whether LAA closure was noninferior to warfarin **Study type:** Multicenter, RCT, unblinded **Size:** 707 pts	**Inclusion criteria:** Age >18 y, paroxysmal or persistent nonvalvular AF, 1 or more $CHADS_2$ risk factors and eligibility for long-term anticoagulation with warfarin **Exclusion criteria:** PFO with atrial septal aneurysm, ASD, mechanical valve prosthesis, LVEF <30%, mobile aortic atheromata, and symptomatic carotid disease	**1° endpoint:** Composite efficacy of stroke, SE, or CV death. **Results**: Device group: 39 events/1720.2 pt-y; warfarin group: 34 events/900.8 pt-y; rate ratio, 0.60; 95% credible interval, 0.41-1.05

		Intervention: WATCHMAN LAA closure device with warfarin and ASA for 45 d; followed by clopidogrel until the 6 mo visit if 45 d TEE revealed successful LAAO **Comparator:** Warfarin with INR monitoring at least every 2 wk for 6 mo and at least monthly thereafter, targeting an INR between 2 and 3.	
PREVAIL Holmes Jr, DR, et al. 2014 (29) 24998121	**Aim:** Assess safety and efficacy of LAA occlusion for stroke prevention in pts with NVAF compared to long-term warfarin therapy **Study type:** Multicenter RCT **Size:** 407 pts (PREVAIL trial borrowed 618 pt-y from the PROTECT-AF trial in addition to randomizing 269 pts to Watchman and 138 to warfarin) in a pre-specified Bayesian analysis plan	**Inclusion criteria:** Age >18 y, NVAF (paroxysmal, persistent, or permanent) and a $CHADS_2$ ≥2. Pts with $CHADS_2$ >1 with any of the following: female, age ≥75 y, baseline LVEF ≥30% but ≤35%, age 65–74 y and DM or CAD, and age ≥65 y with CHF **Exclusion criteria:** Need for long-term AC therapy for reasons other than AF, contraindications to warfarin or ASA, previous stroke or TIA within 90 d of enrollment, symptomatic carotid disease, or a PFO or ASD requiring Tx, and pts with an indication for clopidogrel. **Intervention:** WATCHMAN LAA closure device with warfarin and ASA for 45 d; followed by clopidogrel until the 6 mo visit if 45 d TEE revealed successful LAAO **Comparator:** Warfarin with INR monitoring at least every 2 wk for 6 mo and at least monthly thereafter, targeting an INR: 2–3.	**1° endpoint:** 3 co-primary endpoints: 1.) Primary efficacy – composite of hemorrhagic or ischemic stroke, systemic embolization, and CV/unexplained death was not met 2.) Late-ischemic efficacy, composite of systemic embolization or ischemic stroke, excluding the first 7 d of randomization 3.) Early safety, a composite of all-cause death, ischemic stroke, systemic embolization, or device/procedure-related events requiring open CV surgery, or major endovascular Tx. **Safety endpoint:** See above Results: • Coprimary efficacy endpoint Device 18 mo rate: 0.064, control 18 mo rate: 0.063; 18 mo RR: 1.07 (95% CI: 0.57–1.89); 95% RR noninferiority criterion 95% credible interval upper bound <1.75 • Late-ischemic coprimary endpoint Device 18 mo rate: 0.0253, control: 0.0200, 18 mo rate ratio: 1.6 (95% CI: 0.5–4.2) 18 mo rate difference: 0.0053 (95% CI: -0.0190–0.0273). Rate difference noninferiority criterion 95% CI upper bound <0.0275.

			• Safety primary endpoint result: % (n/N) 2.2% (6/269) 95% CI upper bound=2.652%
Holmes Jr. DR, et al. 2015 (30) 26088300	**Study type:** Meta-analysis **Size:** 2,406 patients	**Inclusion criteria:** • PROTECT AF: ≥18 y, paroxysmal or permanent AF with $CHADS_2$ risk ≥1 • PREVAIL: $CHADS_2$ ≥2, or $CHADS_2$ ≥1 with more than 1 of the following: female ≥75 y, baseline LVEF ≥30% but ≤35%, 65–74 y with DM or CAD, and ≥65 y with HF **Exclusion criteria:** • PROTECT AF; absolute contraindication to warfarin, LAA thrombus, PFO with atrial septal aneurysm and right to left shunt, mobile aortic atheroma, or symptomatic carotid disease • PREVAIL: Similar to PROTECT except pts with clopidogrel indication	**1° endpoint:** All-cause stroke (hemorrhagic and ischemic), systemic embolization and CV death **Results:** The combined data set of all PROTECT AF and PREVAIL - Watchman pts vs. chronic warfarin pts show: 1) similarity in overall stroke or SE; 2) ischemic stroke slightly increased with Watchman but hemorrhagic stroke significantly decreased with warfarin; 3) all-cause mortality and major nonprocedural bleeding both significantly improved with Watchman.
Price MJ, et al. 2015 (31) 26627989	**Study type:** Pooled, pt-level analysis of PROTECT AF and PREVAIL trials **Size:** 1,114 pts	**Inclusion criteria:** • PROTECT AF: age ≥18 y, paroxysmal or permanent AF with $CHADS_2$ risk ≥1 • PREVAIL: $CHADS_2$ ≥2, or $CHADS_2$ ≥1 with more than 1 of the following: female age ≥75 y, baseline LVEF ≥30% but ≤35%, 65–74 y with DM or CAD, and ≥65 y with HF **Exclusion criteria:** • PROTECT AF; Absolute contraindication to warfarin, LAA thrombus, PFO with atrial septal aneurysm and right to left shunt, mobile aortic atheroma, or symptomatic carotid disease • PREVAIL: Similar to PROTECT except pts with clopidogrel indication	**1° endpoint:** • The primary efficacy endpoint of both trials was a composite of CV or unexplained death, stroke, and SE. • Major bleeding was defined as an adverse event that was assigned 1 of several bleeding codes and was adjudicated by the clinical events committee as significant (life-threatening or resulting in hospitalization, prolongation of hospitalization, substantial disability, or death). **Results:** • The bleeding rates from randomization to the end of FU were similar between pts randomly assigned to device and long-term warfarin therapy (3.5 events vs. 3.6 events/100 pt-y; rate ratio: 0.96; 95% CI: 0.66–1.40; p=0.84). Approximately one-half

			of the bleeding events in the device group (48%) occurred within the first 7 d after randomization (i.e., during the periprocedural period). • LAA closure significantly reduced the rate of major bleeding compared with long-term warfarin beyond 7 d post-randomization (1.8 events vs. 3.6 events/100 pt-years; RR: 0.49; 95% CI: 0.32–0.75; p<0.001), beyond 45 d (1.3 events vs. 3.6 events/100 pt-years; RR: 0.37; 95% CI: 0.23–0.60; p<0.001); and beyond 6 mo (1.0 events vs. 3.5 events/100 pt-years; RR: 0.28; 95% CI: 0.16–0.49; p<0.001). • The decrease in bleeding with LAA closure was driven by reductions in both GI bleeding and hemorrhagic stroke.
EWOLUTION Boersma LVA, et al. 2016 (32) 26822918	**Study type:** Prospective, multicenter registry **Size:** 1,025 pts	**Inclusion criteria:** Subjects eligible to receive WATCHMAN device who were of legal age to provide consent	**Endpoints:** Data on procedural success and complications and long-term pt outcomes, including bleeding and incidence of stroke/TIA/SE **Results:** • 1,004 of 1,019 subjects (98.5%) successful device deployment. • 988 of 974 pts (99.3%) with TEE data available had successful procedural closure of LAA **Conclusions:** WATCHMAN device has a high implant and sealing success. Registry European real-world data demonstrating appearance of safety and efficacy, including a large % of pts unable to tolerate anticoagulation **Limitations:** Lack of control group, clinical FU and responsibility of complete reporting left to participating centers; postprocedural antithrombotic regimen was not uniform

EWOLUTION Boersma LV, et al. 2017 (33) 28577840	**Study type:** Prospective, multicenter registry **Size:** 1,025 pts	**Inclusion criteria:** Subjects eligible to receive WATCHMAN device who were of legal age to provide consent **Population:** Mean CHA_2DS_2-VASc score 4.5; mean age 73.4; 73% were deemed unsuitable for OAC therapy	**Results:** • WATCHMAN implant successful in 1,005 (98.5%) • Antiplatelet therapy only was used in 784 (83%) • Vitamin K antagonists were used in only 75 (8%). • At 1 y, mortality was 98 (9.8%) • Device thrombus was observed in 28 pts at routine TEE (3.7%) and not correlated with the drug regimen (p=0.14). • Ischemic stroke rate was 1.1% (RR: 84% vs. estimated historical data) • Major bleeding rate was 2.6% and was predominantly nonprocedure /device related.
Reddy VY, et al. 2017 (34) 27816552	**Study type:** Manufacturer collected data 3,822 consecutive Watchman 3/2015–5/2016, by 382 operating physicians at 169 U.S. centers	**Proceduralists:** Implanting physicians performing these procedures (n=382) included 71% new, nonclinical trial implanters, who performed 50% of the procedures.	**Results:** 3,822 consecutive cases, implantation was successful in 3,653 (95.6%) Complications: • Pericardial tamponades - 39 (1.02%) (24 treated percutaneously, 12 surgically, and 3 fatal) • Stroke: 3 procedure-related strokes (0.078%); • Device embolizations 9 (0.24%) Deaths: 3 procedure-related deaths (0.078%) **Summary/Conclusion:** • Procedural success was high and complication rates were low in the “real-world” U.S. dataset collected by manufacturer at the time of implant • Included a large fraction of previously inexperienced operators **Limitations:** Underestimates rates of procedure-related complications/events occurring beyond procedural period

Data Supplement 5. RCTs of Studies of Surgical LAA Occlusion/Excision (Section 4.4.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Friedman DJ, et al. 2018 (35) 29362794	**Study type/design:** Retrospective analysis multicenter STS ACSD registry data linked to Medicare claims data. **Study size:** 10,524 pts with a Hx of AF undergoing 1st time cardiac surgery (January 14, 2011 through June 1, 2012).	**Inclusion criteria:** Pts (age ≥65 y) with a Hx of AF or atrial flutter undergoing first-time cardiac surgery (CABG, mitral valve surgery ± CABG, or aortic valve surgery ± CABG). **Exclusion criteria:** Pts with planned off pump operations, endocarditis, double valve (aortic + mitral) procedures, congenital heart disease, cardiac transplant, left ventricular assist device, cardiogenic shock, missing data on LAA occlusion, inability to link to Medicare claims, missing anticoagulation data, those without information on the primary surgical procedure, and those with a duplicate Medicare record number.	**Endpoints:** The primary outcome was readmission within 3 y of operation for TE (stroke, TIA, or SE) with secondary outcomes including hemorrhagic stroke, all-cause mortality, and a composite endpoint of TE, hemorrhagic stroke, or all-cause mortality. **Results:** 10,524 pts who underwent a cardiac procedure with 3,892 (37%) having surgical LAA occlusion (surgical atrial ablation rate in the LAA occlusion group was 94% vs. 12% in the non-LAA occlusion group). Mean FU 2.6 y. Surgical LAA occlusion, compared with no LAA occlusion, was associated with lower unadjusted rates of readmission for TE (4.2% vs. 6.2%), all-cause mortality (17.3% vs. 23.9%), and the composite endpoint (20.5% vs. 28.7%), but no significant difference in rates of hemorrhagic stroke (0.9% each). Using an inverse probability weighting (IPW) analysis, pts with LAA occlusion, compared with pts who did not have LAA occlusion, had significantly lower risk of readmission for TE (sub distribution HR: 0.67; 95% CI: 0.56–0.81; p<0.001), all cause-mortality (HR: 0.88; 95% CI: 0.79–0.97; p=0.001), and the composite endpoint (HR: 0.83; 95% CI: 0.76–0.91; p<0.001). At hospital discharge, 68.9% of pts with AF (n=2,680) who underwent surgical LAA occlusion and 60.3% of pts with a Hx of AF (n=3,996) who did not receive LAA occlusion were prescribed	**Conclusions:** Findings suggest that surgical LAA occlusion (often with concurrent surgical atrial ablation) may be of benefit in reducing post-operative TE events in older pts with a Hx of AF. The data also support a role for anticoagulation, particularly in pts not receiving LAA occlusion. Future controlled randomized trials may be valuable. **Limitations:** This is a non-randomized, observational, multiple comparative database study with incomplete data. Pts under age 65 y were not included. The pt population characteristics (STS ASCD registry) are diverse. The surgical techniques and success rates for LAA occlusion are not defined. The long-term anticoagulation rates and effectiveness in the AF pt dataset are not known, as are the anticoagulant drugs used. Owing to differences in procedure characteristics, the results from this study may not be generalizable to pts who undergo LAA occlusion via a percutaneous approach.

			anticoagulation. In subgroup analyses stratified by anticoagulation status at hospital discharge, AF pts who received LAA occlusion without postoperative anticoagulation had a significantly lower TE rate compared with those who received neither LAA occlusion or anticoagulation (sHR: 0.26; 95% CI: 0.17–0.40; p<0.001). There was no significant difference in the risk of TE among AF pts discharged with anticoagulation therapy (adjusted HR: 0.88; 95% CI: 0.56–1.39; p=0.59), whether they received surgical LAA occlusion or not.	

Data Supplement 6. RCTs, Nonrandomized Trials, Observational Studies, and/or Registries of Studies Comparing Prevention of Thromboembolism (Section 6.1.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Gallagher MM, et al. 2002 (36) 12225717	**Study type:** Multicenter retrospective cohort study **Size:** 1,950 pts Assessed likelihood of embolic event after cardioversion	**Inclusion criteria:** All pts who underwent DC cardioversion of atrial arrhythmias between January 1, 1990 and June 30, 1997 **Exclusion criteria:** Not meeting above criteria	**1° endpoint:** Embolic event **Results:** • There were 14 TE events. Embolic events occurred between 6 h and 22 d after cardioversion (median 1.9 d, mean 5.1 d). • Embolism was significantly more common at an INR of 1.5–2.4 than at an INR ≥2.5 (0.93% vs. 0%; p=0.012).	• Cardioversion was performed <48 h of the apparent onset of the arrhythmia in 443 episodes, 352 without subsequent prolonged anticoagulation with 1 embolic complication. • The risk of embolism with cardioversion is substantially lower when the INR is >2 and very low at >2.5
Jaber WA, et al. 2000 (37) 10874278	**Study type:** Retrospective cohort study **Size:** 9,058	**Inclusion criteria:** We used a TEE database of 9,058 consecutive studies performed between January 1996 and	**Results:** • 174 pts with thrombi in the LAC and LAA were identified (1.9% of transesophageal studies performed).	• Study provides an estimate of the relative incidence of LAA and LAC thrombi. Left atrial cavity thrombi are rare and generally are found in the setting of mitral valve pathology.

		November 1998 to identify all pts with thrombi reported in the LA cavity and/or LAA. **Exclusion criteria:** Not meeting above criteria	• Anticoagulation of 47±18 d was associated with thrombus resolution in 80.1% of the pts on FU TEE.	• In addition, anticoagulation appears to be facilitating LAC and LAA thrombus resolution, with an 80% short-term success rate. • Authors recommend a TEE in the FU of thrombi once visualized in the LA
RE-LY Nagarakanti R, et al. 2011 (38) 21200007	**Study type:** Post-hoc analysis from RCT **Size:** 1,983 cardioversions were performed in 1,270 pts (647 on dabigatran 110 mg BID, 672 on dabigatran 150 mg BID, and 664 in the warfarin group.)	**Inclusion criteria:** All pts who underwent cardioversion during their participation in the RE-LY trial were included in this analysis. TEE was encouraged if cardioversion was planned within the first 60 d after randomization. **Exclusion criteria:** The protocol recommended against cardioversion of pts with left atrial thrombus.	**1° endpoint:** Rate of stroke and SE rates at 30 d. **Results:** • Stroke and SE were 0.8%, 0.3%, and 0.6% in the dabigatran 110 mg, 150 mg, and warfarin groups respectively. • TEE was performed before 25.5%, 24.1%, and 13.3% of cardioversions, of which 1.8%, 1.2%, and 1.1% were positive for left atrial thrombi, in the dabigatran 110 mg, 150 mg, and warfarin groups respectively. Stroke and SE were similar with and without TEE.	**Conclusion:** • Incidence of stroke and major bleeding <30 d of cardioversion on dabigatran were low and comparable to those on warfarin with or without TEE guidance. • Dabigatran is a reasonable alternative to warfarin in pts requiring cardioversion.
ROCKET AF Trial Piccini JP, et al. 2013 (39) 23500298	**Study type:** Post hoc analysis from an RCT **Size:** 143 pts underwent electrical cardioversion, 142 underwent pharmacological cardioversion Mean $CHADS_2$ score 3	**Inclusion criteria:** Pts in the ROCKET AF trial undergoing electrical or pharmacological cardioversion. Pts undergoing AF ablation were also included.	**1° endpoint:** Composite of all strokes (both ischemic and hemorrhagic) and SE Safety endpoint: Major or non-major clinically relevant bleeding **Results:** Event rate for electrical cardioversion were similar	**Limitations:** Post hoc analysis, sample size small limiting power to detect small differences in outcomes. **Conclusions:** Outcomes were similar in pts treated with cardioversion in the setting of rivaroxaban or warfarin.

			between the warfarin and rivaroxaban group (0.6% vs. 0.69%; p=0.398)	
ARISTOTLE Flaker G, et al. 2014 (40) 24211508	**Study type:** Retrospective analysis from RCT **Size:** 743 cardioversions were performed in 540 pts: 265 first cardioversions in pts assigned to apixaban and 275 in those assigned to warfarin	**Inclusion criteria:** For this post hoc analysis, all pts who underwent cardioversion for AF in the ARISTOTLE trial were identified by a case report form completed at the center of enrollment TEE data were available in 86 pts (97 cardioversions) assigned to apixaban and 85 pts (106 cardioversions) assigned to warfarin. None of the pts had evidence of a left atrial thrombus.	**1° endpoint:** Stroke or SE. There were no strokes or systemic emboli occurred in the 30-d FU period. **Secondary endpoints:** Myocardial infarction occurred in 1 pt (0.2%) receiving warfarin and 1 pt receiving apixaban (0.3%). Major bleeding occurred in 1 pt (0.2%) receiving warfarin and 1 pt receiving apixaban (0.3%). Death occurred in 2 pts (0.5%) receiving warfarin and 2 pts receiving apixaban (0.6%).	**Limitations:** Post hoc analysis. Also, small pt number with statistical power to evaluate rare endpoints is excessively low. **Conclusion:** Major CV events after cardioversion of AF are rare and comparable between warfarin and apixaban.
X-VeRT Cappato R et al. 2014 (41) 25182247	**Aim:** Evaluate efficacy and safety of rivaroxaban in pts with AF undergoing elective cardioversion **Study type:** Multinational, randomized, open-label, parallel-group phase IIIb study of pts **Size:** 1,504 pts	**Inclusion criteria:** Age ≥18 y scheduled for elective electrical or pharmacological cardioversion were eligible for the trial. **Exclusion criteria:** Hemodynamically significant mitral valve stenosis, prosthetic heart valves, known LA thrombi, severe disabling stroke within the previous 3 mo, and any stroke or TIA up to	**1° endpoint:** Composite of stroke, TIA, peripheral embolism, myocardial infarction, and CV death 5 (2 strokes) of 978 pts (0.51%) rivaroxaban vs. 5 (2 strokes) of 492 pts (1.02%) in the VKA group (RR: 0.50; 95% CI: 0.15–1.73) **Safety endpoint:** Major bleeding, which occurred in 6 pts (0.6%) in the rivaroxaban group and 4 pts (0.8%) in the	• Rivaroxaban was associated with a significantly shorter time to cardioversion compared with VKAs (p<0.001). **Study Limitations:** X-VeRT was underpowered to provide statistically noninferiority. **Conclusion:** Oral rivaroxaban appears to be an effective and safe alternative to VKAs.

		2 wk or 3 d, respectively, prior to randomization. **Intervention:** 20 mg once daily (15 mg if CrCl was between 30 and 49 mL/min) (N=1,002) **Comparator:** Dose-adjusted vitamin K antagonists (VKA) (N=502) 2:1 ratio of rivaroxaban to VKA The decision regarding early cardioversion with TEE or delayed cardioversion (rivaroxaban or VKA for 3–8 wk prior to the procedure) was made by the local investigator.	VKA group (RR: 0.76; 95% CI: 0.21–2.67)	
ENSURE-AF Goette A, et al. 2016 (42) 27590218	**Aim:** Evaluate the safety and effectiveness of use of edoxaban peri-cardioversion for AF **Study type:** Multicenter, prospective, randomized, open-label, blinded-endpoint evaluation **Size:** 2,199 pts	**Inclusion criteria:** Pts with persistent AF >48 h and <12 mo duration scheduled for cardioversion **Patient population**: Mean age 64 y and mean CHA_2DS_2-VASc score was 2.6 (±1.4) **Intervention:** Edoxaban 60 mg/d (N=1,095)	**1° endpoint:** Composite of stroke, systemic embolic event, myocardial infarction, and CV mortality, analyzed by intention to treat occurred in 5 (<1%) edoxaban and 11 (1%) enoxaparin/warfarin group (OR: 0.46; 95% CI: 0.12–1.43) **Safety endpoint:** Major and clinically relevant non-major bleeding occurred in 16 (1%) edoxaban vs. 11 (1%)	• FU was 28 d on study drug after cardioversion plus 30 d to assess safety • The results were independent of the TEE-guided strategy and anticoagulation status **Limitations:** Trial was not adequately powered to show statistically significant differences for efficacy or safety endpoints **Conclusion:** Rates of major and clinically relevant non-major bleeding and TE were low in the 2 treatment groups

		Comparator: Enoxaparin–warfarin (N=1,104) [NOTE: dose of edoxaban was reduced to 30 mg/d if 1 or more: CrCl 15–50 mL/min, low bodyweight (≤60 kg), or concomitant use of P-glycoprotein inhibitors]	enoxaparin/warfarin (OR: 1.48; 95% CI: 0.64–3.55)	
Pallisgaard JL, et al. 2015 (43) 26513589	**Study type:** Nationwide Danish registry data **Size:** 1,230 pts	**Inclusion criteria:** Oral anticoagulation naïve pts with first time non-valvular AF and first-time cardioversion from 2011 to 2012	**1° endpoint:** The cumulative incidence of composite endpoint of stroke, bleeding or death at 30 wk were 2.0% and 1.0% in the warfarin and dabigatran groups respectively, HR: 1.33; 95% CI: 0.33–5.42. Median time to cardioversion was 4.0 (IQR: 2.9–6.5) and 6.9 (IQR: 3.9–12.1) wk in the dabigatran and warfarin groups, respectively	**Conclusion:** Anticoagulation Tx with dabigatran allows shorter time to cardioversion for AF than warfarin, and appears to be an effective and safe alternative Tx strategy to warfarin.
ENGAGE AF-TIMI 48 Plitt A, et al. 2016 (44) 27028520	**Study type:** Retrospective analysis from RCT **Size:** 632 electrical cardioversion attempts performed in 365 pts Compared warfarin vs. once-daily higher dose edoxaban (60 mg) regimen or a lower-dose edoxaban (30 mg)	**Inclusion criteria:** Pts undergoing cardioversion in the ENGAGE AF-TIMI 48 trial **Exclusion criteria:** Major exclusion criteria were AF due to reversible cause, severe renal impairment, increased bleeding risk, mechanical heart valve, or moderate to severe mitral stenosis. Also, excluded	**1° endpoint:** Composite of stroke or systemic embolic events within 30 d of cardioversion: 0 pts in the warfarin group, 2 pts on the lower-dose edoxaban regimen and 0 pts on higher-dose edoxaban Major bleeding occurred in 0 pts within 30 d of cardioversion	**Conclusion:** Thromboembolic and major bleeding events post cardioversion were infrequent and similar with edoxaban and warfarin in the ENGAGE AF-TIMI 48 trial.

	regimen (pts with moderate renal dysfunction, weight ≤60 kg, or concomitant use of P-glycoprotein inhibitors received a 50% dose reduction of edoxaban)	from this analysis were cardioversions that occurred >3 d after the most recent dose of blinded study anticoagulant		
Dentali F, et al. 2015 (45) 25791094	**Study type:** Meta-analysis of 4 trials **Size:** 3,635 pts with 4,517 cardioversions (2,869 with NOACs and 1,648 with warfarin)	**Inclusion criteria:** Randomized control trials of NOAC vs. warfarin in which outcomes of cardioversion were reported	**1° endpoint:** Rate of stroke or SE (0.41% NOAC vs. 0.61% warfarin; RR: 0.7; 95% CI: 0.31–1.72; p=0.48) **Safety endpoint:** Major bleeding complications (0.81% vs. 0.60%; RR: 1.23; 95% CI: 0.55–2.71).	**Conclusion:** NOAC or warfarin appeared equally effective in the prevention of stroke/SE
FinCV Study Airaksinen KE, et al. 2013 (46) 23850908	**Study type:** Retrospective registry analysis and medical record review **Size:** 5,116 successful cardioversions in 2,481 pts	**Inclusion criteria:** Pts (age >18 y) with acute (<48 h) AF who underwent successful cardioversion without peri-procedural and post-cardioversion OAC or heparin **Exclusion criteria:** Lived outside the hospital catchment area	**1° endpoint:** Thromboembolic event within 30 d of index cardioversion **Results:** 38 definite embolic events in 38 pts (0.7%; 95% CI: 0.5–1.0%) occurring 1–27 d after cardioversion (mean 4.6 d). Age (OR: 1.05; 95% CI: 1.02–1.08; p<0.001), female sex (OR: 2.1; 95% CI: 1–4.0; p=0.03), heart failure (OR: 2.9; 95% CI: 1.1–7.2; p=0.03), and DM (OR: 2.3; 95% CI: 1.1–4.9; p=0.03) were independent predictors of embolic events. No events with failed cardioversion (N=246).	**Limitations:** Retrospective; symptom-based onset. • The incidence of post-cardioversion TE complications is high in certain subgroups of pts when no anticoagulation is used after cardioversion of acute AF. • Highest risk of TE (9.8%) was observed among pts with heart failure and DM. • Pts with no heart failure and age <60 y had the lowest risk of TE (0.2%)

Garg A, et al. 2016 (47)	**Study type:** Retrospective database analysis and medical record review **Size:** 1,591 DC cardioversions in 1,299 pts	**Inclusion criteria:** Pts undergoing DC cardioversion for AF <48 h. Group 1 (567 cardioversions in 484 pts): non-anticoagulated (no anticoagulation or INR <1.5) Group 2 (116 cardioversions in 106 pts): sub-therapeutic anticoagulation (INR 1.5–1.9). Group 3 (898 cardioversions in 709 pts): therapeutic anticoagulation (INR >2 or activated partial thromboplastin time >50 on heparin). **Exclusion criteria:** New oral anticoagulant drug (dabigatran)	**1° endpoint:** Thromboembolic event within 30 d of DC cardioversion **Results:** • In Group 1, 1.1% (6 pts) had neurologic event (mean CHA_2DS_2-VASc score, 3.3±1.2); no events with TEE-guided cardioversion. • In Group 2, there were no events (11 had TEE). In Group 3, 0.2% (2 pts) had neurologic event (CHA_2DS_2-VASc score, 4, 6), both off anticoagulation; no events with TEE-guided cardioversion (N=140). • Post cardiac surgery pts had no events (mean CHA_2DS_2-VASc score, 3.0±1.9).	**Limitations:** Retrospective; loss of FU, NOACs not included. • In pts with acute-onset AF, odds of TE complications were almost 5 times higher in pts without therapeutic anticoagulation at the time of cardioversion. • No events occurred in post-op pts and in those with CHA_2DS_2-VASc scores of <2. • This study supports the use of anticoagulation in pts undergoing cardioversion for acute-onset AF with a CHA_2DS_2-VASc with score ≥2
von Besser K, et al. 2011 (48) 22098994	**Study type:** Literature review **Size:** 5 studies with 1,151 pts undergoing electrical cardioversion	**Inclusion criteria:** studies investigating the safety of cardioversion for AF <48 h in the ER **Exclusion criteria:** not meeting above	**1° endpoint:** Embolic event **Results:** No pts experienced a TE event.	• Appears to be acceptable to discharge home stable pts with recent-onset AF after cardioversion in the ED with adequate FU. • It should be noted that although this strategy is safe and effective, the return visit rate for relapsed AF is 3% to 17%
EMANATE Ezekowitz, et al. 2018 (49) 29659797	**Study type:** multinational, RCT, open- labelled study in patients with recently	**Inclusion criteria:** patients with ECG confirmed AF and ≤48 h of prior anticoagulation were	**1° endpoint:** stroke, systemic embolism, and death **Results:**	**Secondary/Safety Endpoint:** Comparing apixaban to heparin/VKA, there were 3/735 vs. 6/721 major (RR 0.49; 95% CI 0.10–2.07; p=0.338) and 11 vs. 13

	diagnosed AF scheduled for cardioversion **Size:** 1,500 pts **Purpose:** To compare apixaban to heparin/VKA in AF undergoing cardioversion	randomized 1:1 to either apixaban or to usual care (IV heparin and/or an oral VKA) To expedite cardioversion, at the discretion of the investigator, TEE or CT and/or a loading dose of apixaban 10 mg (down-titrated to 5 mg) was allowed	Note that imaging (predominantly TEE) was performed in 855 patients, and 342 received a loading dose of apixaban Primary Endpoint: 0/753 (apixaban) vs. 6/747 (heparin/VKA) strokes (RR 0; 95% CI 0–0.64, p=0.015) 2 vs. 1 deaths (RR 1.98; 95% CI 0.19–54.00; p >0.999)	clinically relevant non-major bleeding events (RR 0.83; 95% CI 0.34–1.89; p=0.685) **Conclusions:** Rates of strokes, systemic embolism, deaths, and bleeds were low for both apixaban and heparin/VKA treated AF patients undergoing cardioversion and NOACs appear to be alternatives to VKA for cardioversion

Data Supplement 7. RCTs of Catheter Ablation in HF (Section 6.3.4)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
CASTLE AF Marrouche NF, et al. 2018 (50) 29385358	**Study type/design**: Multicenter RCT (33 sites). **Study size**: 363 pts were randomized to 2 study groups; 179 in the AF catheter ablation to restore sinus rhythm group and 184 in the medical therapy group.	**Inclusion criteria**: Heart failure (NYHA class II, III, IV) with LVEF ≤35% and a Biotronik ICD or CRT-D with remote-monitoring. Symptomatic paroxysmal, permanent or long-standing permanent AF and the absence of response to or could not take antiarrhythmic drugs. All pts received guidelines-based therapy for HF. **Exclusion criteria**: Candidacy for heart transplant or planned CV intervention (see also Supplemental Appendix).	**Endpoints**: The primary endpoint was a composite of death from any cause or worsening of HF that led to an unplanned overnight hospitalization. Several secondary endpoints were analyzed. **Results**: 3,013 pts were assessed for eligibility, 398 were enrolled, and after baseline screening 179 and 184 pts remained in the AF catheter ablation and medical therapy groups, respectively. Mean age was 64 y in both pt groups with predominantly male pts enrolled. Average duration of FU was 37.6 mo. The composite primary endpoint of death from any cause or hospitalization for worsening HF occurred in 51 pts (28.5%) vs. 82 pts (44.6%) in the AF catheter ablation vs. medical therapy groups (p= 0.006). Fewer pts in the AF catheter ablation group died from any cause (24 pts, 13.4% vs. 46 pts, 25.0%; p<0.009), died from CV causes (20 pts, 11.2% vs. 41 pts, 22.3%;p<0.008) or were hospitalized for worsening HF (37 pts, 0.7% vs. 66 pts, 35.9%; p<0.004). Cardiovascular hospitalization was more common in the medical therapy group (89 pts, 48.4%) compared to the AF catheter ablation group (64 pts, 35.8%; p= 0.04). Cerebrovascular accident was not statistically different between the 2 pt groups. Other data showed that at 60 mo of FU LVEF had significantly increased in the AF catheter ablation group (8.0% vs. 0.2%; p<0.005), and based on device interrogation more pts in the AF catheter	**Conclusions**: Findings suggest that AF catheter ablation to restore sinus rhythm was associated with lower rates of death from any cause and lower rates of hospital admission for HF along with a reduced burden of AF and improved LVEF. **Limitations**: Relatively small sample size, lack of blinded randomization and treatment allocation, and the fact that the procedures were performed by experienced operators in high-volume medical centers, a circumstance that probably reduced complication rates. The presence of an ICD or CRT-D may have affected mortality in the 2 pt groups. The authors also could not exclude the possibility that different or more aggressive approaches to medical management of these pts might have influenced the trial results.

			ablation group were in sinus rhythm (63.1% vs. 21.7%; p<0.001). Pts with an LVEF ≥25% had better outcomes with AF catheter ablation than pts with a lower LVEF. In the AF catheter ablation group, 3 pts had pericardial effusion with 1 requiring pericardiocentesis, 3 pts had bleeding/vascular complications, and there was 1 asymptomatic pulmonary vein stenosis.	
AATAC Di Biase L, et al. 2016. (51) 27029350	**Study type/design**: Open-label, multicenter RCT. **Study size**: AF catheter ablation (n=102) or amiodarone (n=101).	**Inclusion criteria**: Persistent AF, dual chamber ICD or CRTD, NYHA II-III and LV EF <40% within the last 6 mo **Exclusion criteria**: AF due to reversible etiology, valvular or coronary heart disease requiring surgical intervention, early post-operative AF (within 3 mo of surgery), or life expectancy <2 y, prolonged QT interval, hypothyroidism, Hx of severe pulmonary disease, liver failure, and pts receiving regular amiodarone ≥200 mg daily.	**Endpoints**: The primary endpoint was a long-term procedural-success (defined as freedom from AF, atrial flutter or atrial tachycardia of >30 s duration off AAD at FU. Several secondary endpoints included complications, all-cause mortality, AF and HF-related unplanned hospitalizations during the post-ablation FU, change in LVEF, 6-min walk distance, QOL. **Results**: Primary endpoint 71 (70% [95% CI: 60%–78%]) pts in AF ablation were recurrence-free after average 1.4±0.6 procedures as compared to 34 (34% [95% CI: 25%–44%]) in amiodarone (log-rank p<0.001). Over the 2-y FU, unplanned hospitalization rate was 32 (31%) in Group 1 and 58 (57%) in Group 2 (p <0.001), showing 45% reduction (RR: 0.55; 95% CI: 0.39–0.76). A significant lower mortality was observed in catheter ablation (8 [8%] vs. amiodarone (18 [18%]; p=0.037).	**Conclusions**: Findings suggest that AF catheter ablation is superior to amiodarone for maintenance of sinus rhythm. Secondary endpoints suggest that it also reduces unplanned hospitalization and mortality in pts with heart failure and persistent AF. **Limitations**: Study not blinded. Mortality and heart failure hospitalizations were not the primary endpoints. Small sample size and short duration of FU.

Data Supplement 8. RCTs, Nonrandomized Trials, Observational Studies, and/or Registries of Studies Comparing Dual Therapy (Warfarin Plus Clopidogrel) vs. Triple Therapy and 6 Weeks vs. 6 Months of Triple Therapy (Section 7.4)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
WOEST De Wilde WJ, et al. 2013 (52) 23415013	**Aim:** Evaluate the safety and efficacy of clopidogrel alone vs. clopidogrel plus ASA in pts who are taking OAC and who have undergone PCI **Study type:** RCT (multicenter, open-label) **Size:** N=573	**Inclusion criteria:** Pts taking OAC and with 75% coronary lesion with indication for coronary stenting; age 18-80 y **Exclusion criteria:** Hx of intracranial bleeding; cardiogenic shock; contraindication to use of ASA, clopidogrel, or both; peptic ulcer in the previous 6 mo; thrombocytopenia; major bleeding TIMI criteria in the past 12 mo; and pregnancy. **Intervention:** Clopidogrel alone (dual therapy) **Comparator:** Clopidogrel plus ASA (triple therapy)	**1° endpoint:** Any bleeding within 1 y HR: 0.36; 95% CI: 0.26–0.50; p<0.0001 Combined secondary endpoint of death, MI, stroke, target-vessel revascularization, and stent thrombosis HR: 0.60; 95% CI: 0.38–0.94; p=0.025	**Comments:** Only 69% received OAC for AF, ACS in 25-30%, not powered to assess risk of stent thrombosis **Conclusion**: Dual therapy (warfarin + clopidogrel) is associated with lower bleeding risk than triple therapy
Lamberts M, et al. 2013 (53) 23747760	**Study type:** National hospitalization registry in Denmark **Size:** N=12,165	**Inclusion criteria:** AF pts with hospitalization for MI or PCI **Exclusion criteria:** Hospitalization for MI or PCI within 1 y before index date.	**1° endpoint:** MI or coronary death, fatal or nonfatal ischemic stroke, and all-cause mortality at 1y. Safety outcome: fatal or nonfatal bleeding at 1 y. **Results:**	**Conclusion:** Warfarin and clopidogrel is equal or better on both benefit and safety outcomes compared to triple therapy.

			Warfarin + clopidogrel vs. triple therapy MI or coronary death (HR: 0.69; 95% CI: 0.48–1.00), bleeding (HR: 0.78; 95% CI: 0.55–1.12), fatal and nonfatal ischemic stroke and all-cause mortality (no significant difference)	
AFCAS Rubboli A, et al. 2014 (54) 24481953	**Study type:** Prospective multicenter registry **Size:** 914	**Inclusion criteria:** AF pts undergoing PCI with stenting **Exclusion criteria:** Unwillingness to give informed consent	**1° endpoint:** (1) MACCE including all-cause death, MI, repeat revascularization, stent thrombosis, and stroke/TIA; (2) bleeding **Results:** There were 3 groups: (1) triple therapy, (2) DAPT, (3) warfarin + clopidogrel 12 mo freedom from MACCE: 79.4% vs. 79.6% vs. 82.2%; p=0.75 12 mo freedom from BARC bleeding: 89.4% vs. 86.2% vs.92.5%; p=0.34	**Comments:** Group 3 only 8% of study population, variable durations of clopidogrel use **Conclusion:** Compared with triple therapy, dual therapy with warfarin and clopidogrel is not associated with higher ischemic event rates.
Braun OO, et al. 2015 (55) 25467434	**Study type:** Hospital-based retrospective cohort study **Size:** 266	**Inclusion criteria:** • Study group – age >18 y treated for an ACS at the Coronary Care Units at Helsingborg Hospital and Skåne University Hospital during 2013 and discharged on ticagrelor and warfarin. • Control group – all pts discharged on triple therapy from Skåne University Hospital in Lund after an ACS between 2005 and 2010	**1° endpoint:** Spontaneous major bleeding at 3 mo as defined in the HAS-BLED derivation study **Results:** • 7.5% vs. 7.0%; p=NS • Composite TE endpoint 4.7% vs. 3.2%; p=NS	**Comments:** Small retrospective cohort study, no statistical adjustment for potential confounders **Conclusion**: Compared with triple therapy, dual therapy with warfarin and ticagrelor is not associated with higher bleeding or TE event rates

PIONEER AF-PCI Gibson CM, et al. 2016. (56) 27959713	**Aim:** Compare the safety and efficacy of rivaroxaban plus 1 or 2 antiplatelet agents vs. vitamin K antagonist plus DAPT. **Study type:** RCT (multicenter, open-label) **Size:** 2,124	**Inclusion criteria:** Non-valvular AF pts who have undergone PCI; age ≥18 y. **Exclusion criteria:** Hx of stroke or TIA, clinically significant GI bleeding within 12 mo before randomization, CrCl <30 mL/min, anemia of an unknown cause with a hemoglobin concentration <10 g/dL, or any other condition known to increase the risk of bleeding. **Intervention:** • (Group 1) low-dose rivaroxaban (15 mg once daily) plus a $P2Y_{12}$ inhibitor for 12 mo (n=709) • (Group 2) very-low-dose rivaroxaban (2.5 mg BID) plus DAPT for 1, 6, or 12 mo (n=709) **Comparator:** (Group 3) dose-adjusted vitamin K antagonist (once daily) plus DAPT for 1, 6, or 12 mo (n=706)	**1° safety endpoint:** Clinically significant bleeding within 1 y (a composite of major bleeding or minor bleeding according to TIMI criteria or bleeding requiring medical attention) • Group 1 vs. 3 HR: 0.59; 95% CI: 0.47–0.76; p<0.001 • Group 2 vs. 3 HR: 0.63; 95% CI: 0.50–0.80; p<0.001 **2° efficacy endpoint:** Major adverse CV event within 1 y (a composite of death from CV causes, MI, or stroke) • Group 1 vs. 3 HR: 1.08; 95% CI: 0.69–1.68; p=0.75 • Group 2 vs. 3 HR: 0.93; 95% CI: 0.59–1.48; p=0.76	**Comments**: Not powered to assess risk of stent thrombosis, clopidogrel in >90% of participants, rivaroxaban 2.5 mg not available in the USA. **Conclusion**: Compared with warfarin plus DAPT for 1, 6, or 12 mo, low-dose rivaroxaban plus clopidogrel for 12 mo is associated with lower risk of bleeding
ISAR-TRIPLE Fiedler KA, et al. 2015 (57) 25908066	**Aim:** Determine whether shortening the duration of clopidogrel therapy from 6 mo to 6 wk after DES implantation is associated with a superior net	**Inclusion criteria:** Pts receiving OAC for at least 12 mo and receiving a DES for stable angina or ACS. **Exclusion criteria:** Age ≤18 y previous stent thrombosis, DES implantation in the left main stem, active bleeding or bleeding tendency, or a Hx of intracranial bleeding.	**1° endpoint:** Composite of death, MI, definite stent thrombosis, stroke, or TIMI major bleeding at 9 mo. HR: 1.14; 95% CI: 0.68–1.91; p=0.63 • Combined ischemic endpoint of cardiac death, MI, definite stent thrombosis, or ischemic stroke HR: 0.93; 95% CI: 0.43–2.05; p=0.87	**Comments**: 83-85% received OAC for AF, ACS in 31–33%, not powered to assess risk of stent thrombosis **Conclusion:** Compared with 6 mo of triple therapy, 6 wk of triple therapy is not associated with higher

	clinical outcome in pts receiving concomitant ASA and OAC. **Study type:** RCT (multicenter, open-label) **Size:** 614	**Intervention:** 6 wk clopidogrel therapy **Comparator:** 6 mo clopidogrel therapy	• Secondary endpoint of TIMI major bleeding HR: 1.35; 95% CI: 0.64–2.84; p=0.44	ischemic or bleeding event rates.
Koskinas KC, et al. 2016 (58) 27478115	**Study type:** Hospital-based PCI registry **Size:** 8,772	**Inclusion criteria:** Pts on anticoagulation who underwent PCI and who were discharged on triple therapy **Exclusion criteria:** None	**1° endpoint:** Composite endpoint of cardiac death, MI, stroke, definite stent thrombosis, or TIMI major bleeding within 1 y. **Results:** 1° endpoint: 1 mo vs. >1 mo triple therapy (adjusted HR: 1.07; 95% CI: 0.56–2.06)	**Comments:** AF comprised 55% of sample, stable CAD comprised >55% of sample **Conclusion:** No difference in net clinical outcomes between 1 mo of triple therapy vs. >1 mo of triple therapy.
Sarafoff N, et al. 2013 (59) 23524219	**Study type:** Prospective hospital-based cohort study **Size:** N=377	**Inclusion criteria:** Pts on warfarin who underwent PCI and DES and discharged with 6 mo of clopidogrel or prasugrel	**1° endpoint:** • TIMI major or minor bleeding at 6 mo • 2º endpoint: Composite endpoint of death, MI, ischemic stroke, or definite stent thrombosis at 6 mo **Results:** • 1° endpoint: warfarin + ASA + prasugrel vs. warfarin + ASA + clopidogrel (adjusted HR: 3.2; 95% CI: 1.1–9.1) • 2° endpoint: warfarin + ASA + prasugrel vs. warfarin + ASA + clopidogrel (unadjusted HR: 1.4; 95% CI: 0.3–6.1)	**Conclusion:** In triple therapy, prasugrel is associated with higher risk of bleeding than clopidogrel.

TRANSLATE-ACS Jackson LR, et al. 2015 (60) 26718518	**Study type:** Prospective cohort study (multicenter, hospital-based) **Size:** 11,756	**Inclusion criteria:** STEMI and non-STEMI pts treated with PCI and a $P2Y_{12}$ receptor inhibitor during the index MI hospitalization **Exclusion criteria:** Pts who were participating in another research study that specified use of either an investigational or approved $P2Y_{12}$ receptor inhibitor within the first 12 mo post-MI	**1° endpoint:** 6 mo adjusted risks of BARC bleeding **Results:** There were 4 groups: (1) ASA + OAC + clopidogrel, (2) ASA + OAC + prasugrel, (3) ASA + clopidogrel, (4) ASA + prasugrel • (2) vs. (1): IRR: 2.37; 95% CI: 1.36–4.15; p=0.003 • (1) vs. (3): IRR: 1.68; 95% CI: 1.29–2.18; p=0.0001 • (2) vs. (4): IRR: 1.88; 95% CI: 1.10–3.20, p= 0.02 • No significant differences in MACE among 4 groups	**Comments:** • Only 5% discharged on triple therapy • Among those on OAC, 58% was indicated by AF • Triple therapy with prasugrel used only in 0.8% of study population **Conclusion:** • Compared with triple therapy with clopidogrel, triple therapy with prasugrel is associated with higher incidence of BARC-defined bleeding events • Addition of an OAC is associated with a significantly greater risk of BARC-defined bleeding relative to DAPT, regardless of which $P2Y_{12}$ receptor inhibitor is used.

RE-DUAL PCI Cannon CP, et. al. 2017 (61) 28844193	**Aim:** Compare the incidence of major or clinically relevant non-major bleeding of dabigatran plus a $P2Y_{12}$ inhibitor vs. triple therapy with warfarin plus ASA and a $P2Y_{12}$ inhibitor. **Study type:** RCT (multicenter, open-label) **Size:** 2,725	**Inclusion criteria:** Non-valvular AF pts who have undergone PCI; age ≥18 y. **Exclusion criteria:** Bioprosthetic or mechanical heart valves, severe renal insufficiency (CrCl <30 mL/min), or other major coexisting conditions. **Intervention:** • (Group 1) dabigatran Etexilate (110 mg BID) plus either clopidogrel or ticagrelor • (Group 2) dabigatran Etexilate (150 mg BID) plus either clopidogrel or ticagrelor **Comparator:** (Group 3) warfarin plus ASA (≤100 mg daily) and either clopidogrel or ticagrelor	**1° endpoint:** Major or clinically relevant nonmajor bleeding event • Group 1 vs. Group 3 HR: 0.52; 95% CI: 0.42–0.63; p<0.001 for noninferiority • Group 2 vs. Group 3 HR: 0.72; 95% CI: 0.58–0.88; p<0.001 for noninferiority **Safety endpoint (if relevant):** Composite of MI, stroke, SE, or unplanned revascularization Group 1 and 2 combined vs. Group 3 HR: 1.04; 95% CI: 0.84–1.29; p=0.005 for noninferiority	**Comments**: Clopidogrel in 88% of participants, ACS in 50.5% of participants, not powered to assess risk of stent thrombosis, elderly pts outside the USA were randomized to Group 1 vs. Group 3 (were excluded from Group 2) **Conclusion**: Among pts with AF who had undergone PCI, the risk of bleeding was lower among those who received dual therapy with dabigatran and a $P2Y_{12}$ inhibitor than among those who received triple therapy with warfarin, a $P2Y_{12}$ inhibitor, and ASA.

Data Supplement 9. RCTs, Nonrandomized Trials, Observational Studies, and/or Registries of Studies Comparing Device Detection of AF and Atrial Flutter (Section 7.12)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
SOS AF Project Boriani G, et al. 2014 (62) 24334432	**Study type:** Pooled analysis of individual pt data from 3 prospective observational studies **Size:** 10,016 pts	**Inclusion criteria:** Implanted device capable of measuring AT/AF burden with at least 3 mo of FU and device diagnostic data available	**1° endpoint:** Ischemic stroke or TIA. **Results:** During a median FU of 24 mo, 43% of pts had at least 1 d with ≥5 min of AF burden. Median time to	• Device-detected AF burden is associated with an increased risk of ischemic stroke in a relatively unselected population of CIEDs pts. • Among the thresholds of AF burden that were evaluated, 1 h was associated

	AHRE: usually >175 bpm for ≥20 s.	**Exclusion criteria:** Permanent AF	maximum AF burden was 6 mo (IQR: 1.3–14). Cox regression analysis adjusted for the $CHADS_2$ score and anticoagulants at baseline showed AF burden was an independent predictor of ischemic stroke.	with the highest HR: 2.11; 95% CI: 1.22–3.64; p= 0.008.
MOST Glotzer TV, et al. 2003 (63) 12668495	**Study type:** Prospective, randomized trial of DDDR vs. VVIR pacing; retrospective subgroup analysis **Size:** 316 pts with AHREs (>220 bpm for 10 beats for detection; episodes of duration =5 min analyzed); mean FU 27 mo; 2,010 pts in main trial	**Inclusion criteria:** Pts at least 21 y; undergoing initial implantation of a dual-chamber, rate modulated pacing system for sinus-node dysfunction; and in sinus rhythm at assignment (VVIR vs. DDDR pacing) **Exclusion criteria:** Pts with serious concurrent illnesses	**1° endpoint:** Death from any cause or nonfatal stroke **Results:** 160 pts (51.3%) had at least 1 AHRE. AF documented by ECG in 38.9% pts with and 2.1% without AHREs. Any AHRE was an independent predictor of total mortality (HR: 2.48; 95% CI: 1.25–4.91; p=0.0092), death or nonfatal stroke (HR: 2.79; 95% CI: 1.51–5.15; p=0.0011), and AF (HR: 5.93; 95% CI: 2.88–12.2; p=0.0001).	• AHREs lasting 5 min in duration identify pts that are more than twice as likely to die or have a stroke, and are nearly 6 times as likely to develop AF as similar pts without AHRE. • Sensitivity and specificity for detection of AF using AHREs recorded by pacemakers was 100% and 97.6%, respectively. The false-positive rate was 2.4%. • Limitations: retrospective, small sample, 81% of pts with AHREs had prior supraventricular arrhythmias
TRENDS Glotzer TV, et al. 2009 (64) 19843914	**Study type:** Prospective, observational cohort study **Size:** 2,486 pts followed for 1.4 y AT/AF burden: Maximum daily duration in preceding 30 d; AT/AF detection: >175 bpm for 20 s	**Inclusion criteria:** At least 1 $CHADS_2$ stroke risk factor and new device and ≥30 d of monitoring; pts with and without AF were included **Exclusion criteria:** Replacement device, long-standing persistent AF, reentrant SVT, terminal illness	**1° endpoint:** Ischemic stroke, TIA, and SE. **Results:** Annualized TE rate was 1.1% for zero, 1.1% for low (<5.5 h), and 2.4% for high (≥5.5 h) burden subsets. Compared with zero burden, adjusted HRs in the low and high burden subsets were 0.98 (95% CI: 0.34–2.82; p=0.97) and 2.20 (0.96–5.05; p=0.06).	• TE rate was low in this study. • TE risk appears to be a quantitative function of AT/AF burden • AT/AF burden ≥5.5 h appeared to double TE risk • Limitations: Low event rate, no electrograms to verify AF, INR levels for pts treated with warfarin were not collected

ASSERT Healey JS, et al. 2012 (65) 22236222	**Study type:** Prospective, randomized trial of atrial overdrive pacing vs. conventional pacing **Size:** 2,580 pts followed for 2.5 y AHRE: ≥190 bpm for >6 min	**Inclusion criteria:** Age ≥65 y, HTN requiring medical therapy, and implantation of a first dual-chamber pacemaker or ICD **Exclusion criteria:** Hx of AF >5 min, taking oral anticoagulants	**1° endpoint:** Ischemic stroke, SE. Secondary outcome: Vascular death, MI, stroke from any cause, ECG documentation of AT **Results:** AHREs increased risk of clinical AF (HR: 5.56; 95% CI: 3.78–8.17; p<0.001) and of ischemic stroke or SE (HR: 2.49; 95% CI: 1.28–4.85; p=0.007).	• Subclinical atrial tachyarrhythmias, without clinical AF, occurred frequently in pts with pacemakers (34.7%) and were associated with a significantly increased risk of ischemic stroke or SE, as well as development of AF
IMPACT Martin DT, et al. 2015 (66) 25908774	**Study type:** Single blind, randomized trial of remote monitoring-based vs. conventional office-based anticoagulation **Size:** 2,718 pts AT: ≥6 of 48 beats ≥200 bpm. Randomized to start/stop of anticoagulation based on remote monitoring vs. usual care trial (stratified by $CHADS_2$ category and device type).	**Inclusion criteria:** Pts with ICD or CRT-D devices, $CHADS_2$ ≥1, ability to tolerate anticoagulation **Exclusion criteria:** Permanent AF or cannot take anticoagulation	**1° endpoint:** First occurrence of stroke, SE, or major bleeding **Results:** Trial stopped after 2 y median FU based on futility of finding a difference in primary endpoints (HR: 1.06; 95% CI: 0.75–1.51; p=0.732) between groups. Although AT burden was associated with TE, there was no temporal relationship between HTN and stroke.	• In pts with implanted defibrillators, the strategy of early initiation and interruption of anticoagulation based on remotely detected AT did not prevent TE and bleeding. • There was a clear relationship between AT burden and stroke risk. • There was no temporal association between AT and clinical events. • 3 embolic events that occurred after withdrawal of anticoagulation for pts with previously identified AT episodes. • Limitations: Poor compliance with the anticoagulation plan in the intervention group.

CRYSTAL AF Sanna T, et al. 2014 (67) 24963567	**Aim:** To assess whether long-term monitoring with an insertable cardiac monitor (ICM) is more effective than conventional FU to detect AF **Study type:** Randomized, parallel-group controlled study **Size:** 441 pts	**Inclusion criteria:** Pts ≥40 y with diagnosis of cryptogenic stroke or TIA within the previous 90 d. **Exclusion criteria:** Hx of AF/atrial flutter, indication or contraindication for OAC therapy, indication for pacemaker or ICD **Intervention:** Implantation of an ICM (REVEAL XT, Medtronic) that automatically detects and records AF **Comparator:** Conventional monitoring at discretion of the investigator 1:1 randomization	**1° endpoint:** Time to first detection of AF (>30 sec) at 6 mo of FU. By 6 mo, AF was detected in 8.9% in the ICM group vs. 1.4% in the control group (HR: 6.4; 95% CI: 1.9– 21.7; p<0.001).	• By 12 mo, AF was detected in 12.4% in the ICM group vs. 2.0% in the control group (HR: 7.3; 95% CI: 2.6–20.8; p<0.001). AF was asymptomatic in 79%. • At 36 mo of FU, the rate of detection of AF was 30.0% in the ICM group vs. 3.0% in the control group (HR: 8.8l 95% CI: 3.5–22.2; p<0.001). • Stroke/TIA occurred in 11 pts (5.2%) in the ICM group, as compared with 18 pts (8.6%) in the control group, at 6 mo, and in 15 pts (7.1%) vs. 19 pts (9.1%) at 12 mo. • Oral anticoagulants were used in 10.1% in the ICM group vs. 4.6% in the control group at 6 mo (p=0.04) and 14.7% vs. 6.0% at 12 mo (p=0.007). At 12 mo, 97.0% of pts in whom AF had been detected were receiving oral anticoagulants. • Limitations: Unclear relationship between newly-discovered AF and the index stroke; clinical significance of brief episodes of AF detected by ICM are unknown; not all episodes of AF can be accounted for (limited memory of ICM); accuracy of AF detection by ICM is not 100%.

Data Supplement 10. RCTs, Nonrandomized Trials, Observational Studies, and/or Registries of Studies Comparing Weight Loss (Section 7.13)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Abed HS, et al. 2013 (68) 24240932	**Aim:** Determine effect of weight reduction and management of cardiometabolic risk factors on AF burden and cardiac structure. **Study type:** Single center partially blinded prospective randomized trial **Size:** 150 (75 per arm)	**Inclusion criteria:** Symptomatic AF, BMI >27 y, age 21–75 y **Exclusion criteria:** Insulin-dependent DM, recent participation in weight loss program, significant cardiac valvular disease, inability to provide informed consent. **Intervention:** Physician-led weight loss program **Comparator:** Self-directed general lifestyle measures. HTN, hyperlipidemia, glucose intolerance, sleep apnea, alcohol, and tobacco were screened for and managed in both groups.	**1° endpoint:** AF symptom burden quantified by AFSS Intervention group showed a greater reduction in the AFSS vs. control (11.8 vs. 2.6 p<0.001).	• 7 d Holter AF episode and duration burden. • The AF episodes decreased by 2.5 vs. no change (p=0.01) and the cumulative duration of AF decreased by 692 min in treatment vs. increased by 419 min in control (p=0.002).
ARREST AF Pathak RK, et al. 2014 (69) 25456757	**Aim:** To evaluate impact of risk factor and weight management on AF ablation outcomes. **Study type:** Prospective comparison study.	**Inclusion criteria:** AF undergoing AF ablation, BMI >27 kg/m^2 **Exclusion criteria:** Permanent AF, Hx of myocardial infarction or cardiac surgery in the previous 12 mo, significant cardiac valvulopathy or ventricular dysfunction, active malignancy, autoimmune or systemic inflammatory	**1° endpoint:** AFSS burden Procedure success defined as AF freedom after 3 mo	• AF frequency, duration, symptoms, and symptom severity decreased more in the RFM group than in the control group. • RFM was an independent predictor of arrhythmia free survival

	Size: 149 consecutive pts undergoing AF ablation with BMI >27 kg/m^2 were offered risk factor and weight management. The outcomes of 61 pts who opted for RFM were compared to the 88 control subjects who declined.	diseases, severe renal or hepatic failure, and <24 mo of FU **Intervention:** Structured motivational and goal directed weight loss program **Comparator:** Control group given information on management of risk factors.		
LEGACY Pathak RK, et al. 2015 (70) 25792361	**Aim:** Evaluate long-term impact of weight loss and weight fluctuation on rhythm control in obese individuals with AF **Study type:** Observational **Size:** 355 pts	**Inclusion criteria:** BMI >27 kg/m^2. Weight loss during FU was characterized as Group 1 (>10%), Group 2 (3% to 9%), and Group 3 (<3%). Weight trend and/or fluctuation was determined by yearly FU. **Exclusion criteria:** Hx of myocardial infarction or cardiac surgery in the previous 12 mo; previous AF ablation; active malignancy; autoimmune or systemic inflammatory disease; severe renal or hepatic failure; and <12 mo FU after their procedure.	**1° endpoint:** AFSS and 7 d ambulatory monitoring **Results:** • Arrhythmia-free survival was greatest in Group 1 compared to Group 2 and 3. • Weight loss, and weight fluctuation were independent predictors of outcome. • >10% weight loss resulted in a 6-fold greater probability of arrhythmia-free survival than the other 2 groups.	• Arrhythmia-free survival was greatest in Group 1 compared to Group 2 and 3. • Weight loss, and weight fluctuation were independent predictors of outcome. • >10% weight loss resulted in a 6-fold greater probability of arrhythmia-free survival than the other 2 groups.

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