ROCKET-AF: Rivaroxaban vs Warfarin in patients with Atrial Fibrillation [1]

Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in AF

BOTTOM LINE

In atrial fibrillation (AF) patients with an ↑ risk of stroke (mean $CHADS_2$ score 3.5), rivaroxaban 20mg po daily:

- Was non-inferior (i.e. no worse than) to warfarin for ↓ stroke or systemic embolism
- Had less hemorrhagic strokes, systemic embolism & bleeding (critical, fatal & intracranial) versus warfarin
- Had more drops in hemoglobin ≥20 g/L, tranfusions, gastrointestinal bleeding, epistaxis & hematuria versus warfarin
- At time of publication, rivaroxaban for AF is approximately $100/month; 15mg, 20mg tablets. ☂A Fib,⊗ Warfarin + monitoring ~$35/month.

BACKGROUND

- Vitamin K antagonists (VKA) are used to ↓ the risk of stroke in AF patients; however, these agents require frequent monitoring, interact with drugs/food, & require several days of therapy to become therapeutic/discontinuation before clearing the body.
- New oral anticoagulants (apixaban ELIQUIS,[2,3] dabigatran PRADAX [4,5] & rivaroxaban XARELTO) are alternatives to VKA, such as warfarin.
- **Rivaroxaban** XARELTO is a new oral direct factor Xa inhibitor.
- **ROCKET-AF** is the first Phase III study assessing the use of rivaroxaban for stroke prevention in AF patients.

TRIAL BACKGROUND [6]

DESIGN: randomized, multi-centre 45 countries, double-blinded, double-dummy controlled trial with concealed allocation; non-inferiority with pre-designed superiority, intention-to-treat & per-protocol analysis. Funded by Johnson & Johnson and Bayer.

INTERVENTION: rivaroxaban 20mg* po daily vs dose-adjusted warfarin (INR 2-3 measured ≤1 month)
* rivaroxaban 15mg po daily in patients with CrCl 30-49 mL/min see page 2 for subgroup analysis

INCLUSION: persistent/paroxysmal AF on ≥ 2 episodes 1 documented on ECG within 30 days of enrolment; age ≥ 18 yrs; risk of future stroke: history of stroke/TIA or systemic embolism **OR** ≥ 2 of the following: HF or LVEF≤35%, HTN (on BP meds 6 months before or SBP>140 mmHg or DBP >90 mmHg), age ≥75 yr, or DM (i.e. $CHADS_2$ score of ≥ 2). Only 10% could have a $CHADS_2$ score of 2, with the remainder having a score of ≥3 or prior stroke, TIA or systemic embolism.

EXCLUSION: Cardiac-related conditions AF due to reversible disorders, active endocarditis, mitral stenosis, presence of atrial myxoma or LV thrombus, planned cardioversion, prosthetic heart valve, BP ≥ 180/100 mmHg; **Hemorrhage risk-related criteria** active internal bleeding, hx of major surgical procedure or trauma within 30 days, GI bleed within 6 months, hx of intracranial/intraocular/spinal/atraumatic intraarticular bleeding, chronic hemorrhagic disorder, known intracranial neoplasm, arteriovenous malformation, or aneurysm, planned invasive procedure with potential for uncontrolled bleeding, including major surgery; anemia Hgb <100g/L; any **stroke within 14 days (severe within 90 days)** or **TIA within 3 days**; indication for anticoagulant therapy for a condition other than AF (e.g. VTE); tx with ASA>100mg/d, ASA/thienopyridine or IV antiplatelets within 5 days; fibrinolytics within 10 days; anticipated need for long-term tx with NSAID; systemic treatment with a strong inhibitor/inducer of CYP P450 3A4 within 4 days or planned treatment during the study; pregnancy/breastfeeding; HIV; **CrCl<30mL/min**; liver disease or ALT>3x ULN.

POPULATION at baseline: n=14,264 non-valvular AF patients at risk of stroke

- AF ~81% persistent, ~17.6% paroxysmal, 1.4% newly diagnosed/onset; $CHADS_2$ mean = 3.5, median=3, $CHADS_2$ score ~13% =2, 43% =3, 29% =4, 13% =5, rivaroxaban 1.7% vs warfarin 2.2% = 6 ($p<0.05$ for $CHADS_2$ score of 6).
- ~60% ♂; median age 73yrs 25% ≥78yrs, BMI 28 kg/m^2, BP 130/80 mmHg, CrCl 67mL/min
- History of stroke/TIA 55%, HF 63%, HTN 91%, DM 40%, MI 17%
- Baseline medications: β-blocker ~65%, diuretics 60%, ACE-I 55%, statins 43%, digoxin 39%, ASA 38%. Previous use of vitamin K antagonist 62%.

RESULTS

median follow-up: per-protocol (PP) & safety population = 590 days, intention-to-treat (ITT) = 707 days

TABLE: EFFICACY & SAFETY NON-INFERIOR DATA SUPERIORITY DATA

PRIMARY ENDPOINTS	RIVAROXABAN		WARFARIN		HAZARD RATIO (95% CI)		NNT/NNH		Comments
	PER-PROTOCOL (n=6958)	ITT (n=7081)	PER-PROTOCOL (n=7004)	ITT (n=7090)	PER-PROTOCOL	ITT	PP/ 1.6yr	ITT/ 1.9yr	
Stroke or Systemic Embolism	2.70% {n=188} 1.7%/yr	3.80% {n=269} 2.1%/yr	3.44% {n=241} 2.2%/yr	4.32% {n=306} 2.4%/yr	0.79 (0.66-0.96)	0.88 (0.75-1.03)	135	-	**RIVAROXABAN VS WARFARIN:** - Non-inferior (i.e. no worse than) to warfarin for stroke or systemic embolism. - ↓ hemorrhagic stroke, systemic embolism & bleeding (critical, fatal & intracranial). - ↑ drop of hemoglobin ≥20g/L, transfusion, GI bleed, epistaxis & hematuria. **WARFARIN VS RIVAROXABAN:** - ↑ concurrent ASA use: warfarin (36.2%) vs rivaroxaban (34.9%) - ↑ baseline $CHADS_2$ score of 6: warfarin (2.2%) vs rivaroxaban (1.7%), $p<0.05$. - Warfarin TTR= mean 55%, median 58%. North American sites: 64%.[7] **OTHER COMMENTS:** - Lost to follow-up: 32 - 93 patients excluded (50 rivaroxaban & 43 warfarin) from all efficacy analyses before unblinding because of violations in Good Clinical Practice. - Subgroup analyses: NS
SECONDARY ENDPOINTS	**RIVAROXABAN** (n=7061)		**WARFARIN** (n=7082)		**HAZARD RATIO (95% CI)**		**NNT/NNH /1.6YR**		
EFFICACY: Based on safety population, rivaroxaban n=7061 vs warfarin n=7082 excluded violating site & those who did not receive a dose									
Stroke	2.61% {n=184} (1.65%/yr)		3.12% {n=221} (1.96%/yr)		NS		-		
Hemorrhagic Stroke	**0.41% {n=29} (0.26%/yr)**		**0.71% {n=50} (0.44%/yr)**		**0.59 (0.37-0.93)**		**333**		
Systemic Embolism	**0.07% {n=5} (0.04%/yr)**		**0.31% {n=22} (0.19%/yr)**		**0.23 (0.09-0.61)**		**417**		
Myocardial Infarction	1.43% {n=101} (0.91%/yr)		1.78% {n=126} (1.12%/yr)		**NS**		-		
All Cause Mortality	2.95% {n=208} (1.87%/yr)		3.53% {n=250} (2.21%/yr)		NS		-		
BLEEDING: Based on safety population, rivaroxaban n=7111 vs warfarin n=7082 excluded those who did not receive a dose									
Major Bleed*	5.6% {n=395} (3.6%/yr)		5.4% {n=386} (3.4%/yr)		NS		-		
Hemoglobin ↓≥20g/L	4.3% {n=305} (2.8%/yr)		3.6% {n=254} (2.3%/yr)		1.22 (1.03-1.44)		143		
Transfusion	2.6% {n=183} (1.6%/yr)		2.1% {n=149} (1.3%/yr)		1.25 (1.01-1.55)		200		
Critical Bleeding	1.3% {n=91} (0.8%/yr)		1.9% {n=133} (1.2%/yr)		0.69 (0.53-0.91)		167		
Fatal Bleeding	0.4% {n=27} (0.2%/yr)		0.8% {n=55} (0.5%/yr)		0.50 (0.31-0.79)		250		
Intracranial bleed	**0.8% {n=55} (0.5%/yr)**		**1.2% {n=84} (0.7%/yr)**		**0.67 (0.47-0.93)**		**250**		
Gastrointestinal Bleed†	3.2% {n=224}		2.2% {n=154}		P<0.05		100		
Epistaxis	10.1% {n=721}		8.6% {n=609}		P<0.05		67		
Hematuria	4.2% {n=296}		3.4% {n=242}		P<0.05		125		
Discontinuation Rates	23.7%		22.2%		-		-		

* Major Bleed = Hemoglobin ↓≥20g/L, transfused ≥2units, or symptomatic bleeding critical area or organ (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome), fatal outcome or permanent disability.
† Gastrointestinal Bleed = upper, lower, rectal gastrointestinal bleeding

PUBLISHED SUBGROUP ANALYSES

Note: subgroup analyses are not powered to detect a conclusive difference between treatments groups; however, the following subgroup analyses were similar to the overall trial results with the entire patient population.

1) Pre-Designed Subgroup Analysis of ROCKET-AF Patients with Moderate Renal Impairment (=CrCl 30-49 mL/min at baseline)[8]

- Background: patients with CrCl 30-49 mL/min have a 25-30% ↑ rivaroxaban serum concentration → 25% ↓ in rivaroxaban =15mg
- N=2950 (20.7% of ROCKET-AF patient population), rivaroxaban 15mg po daily (n=1474) vs dose-adjusted warfarin (INR 2-3, n=1476)
- Population: compared to the ROCKET-AF patients with CrCl ≥50 mL/min, patients with a CrCl 30-49 mL/min:
  - ↑ age (median 79 years), $CHADS_2$ score (mean 3.7 ±1), history of HF ~66%, PAD ~7.5% & MI ~19%
  - ↓♂ 45%, BMI (median 25 kg/m^2), history of stroke/TIA ~50% & DM ~32%
- Compared to the ROCKET-AF patients with CrCl ≥50 mL/min, patients with a CrCl 30-49 mL/min had an↑ risk of stroke & systemic embolism (primary endpoint) & ↑ risk of bleeding.
- Rivaroxaban 15mg po daily vs warfarin had consistent results when compared to patients with preserved renal function.

2) Pre-Designed Subgroup Analysis of ROCKET-AF Patients with Previous Stroke or TIA[9]

- N=7468 (52% of ROCKET-AF patient population), previous stroke (n=4907) or TIA (n=2561)
- Median time from previous stroke or TIA to randomization was 551 days (interquartile range 126-1702 days)
- Rivaroxaban (n=3754) versus warfarin (n=3714)
- Population: compared to ROCKET-AF patients *without* a history of stroke/TIA, patients *with* a history of stroke/TIA (p<0.05):
  - ↑ CrCl (median 69 mL/min), $CHADS_2$ score (median 4), previous ASA (38%) or vitamin K antagonist (59%) use
  - ↓ age (median 71 years), BMI (median 27.5 kg/m^2), persistent AF (80%), HTN 85%, HF 51%, DM 25%, MI 15%, PAD 5%, COPD 9%
- Regardless of study group, patients *with* a history of stroke/TIA had ↑ risk of stroke & systemic embolism (primary endpoint) & ↓ risk of major bleeding (compared to ROCKET-AF patients *without* a history of stroke/TIA):
  - Stroke & systemic embolism: *without* history of stroke/TIA 1.66% vs *with* a history of stroke/TIA 2.87%, HR 1.7 (95% CI 1.44-2.02), p<0.0001
  - Major bleeding: *without* history of stroke/TIA 3.89% versus *with* a history of stroke/TIA 3.18%, HR 0.81 (95% CI 0.7-0.93), p=0.0037
- The comparison of rivaroxaban versus warfarin was similar, regardless of whether the anticoagulants were used as primary or secondary stroke prevention.

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:
- Important clinical endpoints (e.g. stroke & bleed)
- Double blind, double dummy with sham INRs
- Moderate to high risk of stroke (mean $CHADS_2$ score = 3.5)
- Used both per-protocol & intention-to-treat analysis
- Similar discontinuation rates in both groups (rivaroxaban 23.7% versus warfarin 22.2%)
- Only 32 patients lost to follow-up (0.22%)

LIMITATIONS:
- Warfarin was within therapeutic range only 55% North American sites 64% of the study period ACTIVE-W 63.8%, ARISTOTLE 66%, RELY 64%
- Short study duration
- One site violated Good Clinical Practice
- ~ 35% of patients in each arm of the trial were on concomitant aspirin treatment

UNCERTAINITIES:
- Drug not yet studied in patients with CrCL<30 mL/min or in liver disease
- Drug interactions?
- ↑stroke after rivaroxaban stopped 28 days later
- No antidote for reversing bleeding with rivaroxaban
- Lack long-term follow-up & real-world experience with rivaroxaban

RELATED STUDIES

J-ROCKET AF[10]
- Japan was not included in the original ROCKET-AF trial because:
  - Pharmacokinetic data: Cmax & area under the curve for rivaroxaban 15mg po daily in Japanese patients ≈ rivaroxaban 20mg po daily in Caucasians.
  - Japanese clinical practice guidelines recommend a target INR of 1.6 – 2.6 in patients' ≥70 years of age.
- N=1280; randomized, double-blind, double-dummy, multicentre 167 sites non-inferiority trial in Japan.
- Intervention: rivaroxaban 15mg* po daily versus dose-adjusted warfarin (INR 2-3 in patients <70 years of age & INR 1.6-2.6 in patients ≥70 years old).
  *rivaroxaban 10mg po daily in patients with CrCl 30-49 mL/min → 22% of the patient population
- **Safety**: rivaroxaban was non-inferior to warfarin for the composite of major & non-major bleeding; individual composite endpoints not statistically significant when separated. Differences in location of bleeds were not tested for statistical significance.
- **Efficacy:** not powered for efficacy stroke & systemic embolism was NS (p=0.05).
- Overall, the J-ROCKET AF study results were similar to the global ROCKET-AF study.

RxFILES RELATED LINKS
- Atrial Fibrillation Treatment Overview http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-Atrial-Fibrillation.pdf
- Oral Antiplatelet & Antithrombotic Agents Comparison Chart http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-AntiThrombotics.pdf
- Canadian Family Physician RxFiles: Article Oral anticoagulation in atrial fibrillation http://www.cfp.ca/content/58/8/850.full
- ARISTOTLE (apixaban ELIQUIS vs warfarin in AF) Trial Summary http://www.rxfiles.ca/rxfiles/uploads/documents/ARISTOTLE-AF-Apixaban.pdf
- RELY (dabigatran PRADAX vs warfarin in AF) Trial Summary http://www.rxfiles.ca/rxfiles/uploads/documents/RE-LY-Trial-Dabigatran.pdf
- ACTIVE-A (ASA ± clopidogrel PLAVIX in AF) & ACTIVE-W (ASA + clopidogrel PLAVIX vs warfarin in AF) Trial Summary http://www.rxfiles.ca/rxfiles/uploads/documents/ACTIVE-A-Trial-Summary.pdf
- RACE-II (lenient vs strict rate control in AF) Trial Summary http://www.rxfiles.ca/rxfiles/uploads/documents/RACE-II-trial.pdf
- PALLAS (dronedarone MULTAQ in permanent AF) Trial Summary http://www.rxfiles.ca/rxfiles/uploads/documents/PALLAS-trial%20summary.pdf

♂=male ☎ = requires EDS in SK ⊗= not covered by NIHB **ACE-I**=angiotensin converting enzyme inhibitor **AF**=atrial fibrillation **ALT**=alanine aminotransferase **ASA**=acetylsalicylic acid **β-blocker**=beta blocker **BMI**=body mass index **BP**=blood pressure **CI**=confidence interval **COPD**=chronic obstructive pulmonary disease **CrCl**=creatinine clearance **CYP**=cytrochrome **DBP**=diastolic blood pressure **DM**=diabetes **EDS**=exceptional drug status **ECG**=electrocardiogram **GI**=gastrointestinal **HF**=heart failure **Hgb**=hemoglobin **HIV**=human immunodeficiency virus **HR**=hazard ratio **HTN**=hypertension **hx**=history **INR**=international normalized ratio **ITT**=intention-to-treat **IV**=intravenous **LV**=left ventricle **LVEF**=left ventricular ejection fraction **MI**=myocardial infarction **NNT**=number needed to treat **NNH**=number needed to harm **NS**=not significant **NSAID**=nonsteroidal anti-inflammatory drug **PAD**=peripheral artery disease **PP**=per-protocol **SBP**=systolic blood pressure **TIA**=transient ischemic attack **tx**=treatment **ULN**=upper limit of normal **VKA**=vitamin K antagonist **VTE**=venous thromboembolism **yrs**=years

Additional references:

ACCF- AHA-HRS Atrial Fibrillation 2011 Focused Update. Circulation 2011. http://circ.ahajournals.org/cgi/reprint/CIR.0b013e3181fa3cf4v1 Wann LS, Curtis AB, January CT, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2010; DOI: 10.1161/CIR.0b013e3181fa3cf4.)

Avorn Jerry. The Relative **Cost-Effectiveness of Anticoagulants**: Obvious, Except for the Cost and the Effectiveness. Circulation 2011, 123: 2519-2521.

Bansilal S, Bloomgarden Z, Halperin JL, et al. Efficacy and safety of rivaroxaban in patients with **diabetes** and nonvalvular atrial fibrillation: the ROCKET AF trial. Am Heart J. 2015.

Beasley BN, Unger EF, Temple R. Anticoagulant options- Why the FDA approved a **higher but not a lower dose of dabigatran**. New Engl J Med 2011; DOI: 10.1056/NEJM/1103050.

Bovio JA, Smith SM, Gums JG. **Dabigatran** etexilate: a novel oral thrombin inhibitor for thromboembolic disease. Ann Pharmacother. 2011 May;45(5):603-14.

Büller HR et al. for the **EINSTEIN–PE** Investigators. Oral **rivaroxaban** (15mg po bid x 3 wk, then 20mg od) for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012 Mar 26.

Cairns JA, Connolly S, McMurtry S, et al. CCS Atrial Fibrillation Guidelines Committee. **Canadian cardiovascular society atrial fibrillation guidelines 2010**: prevention of stroke and systemic thromboembolism in atrial fibrillation and flutter. Can J Cardiol. 2011 Jan-Feb;27(1):74-90.

Callahan T, Baranowski B. **Managing newly diagnosed atrial fibrillation**: Rate, rhythm, and risk. Cleve Clin J Med. 2011 Apr;78(4):258-64.

Camm AJ, Amarenco P, Haas S, et al. **XANTUS**: A **real-world**, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. *Eur Heart J* 2015.

Canadian Agency for Drugs and Technologies in Health. Common Drug Review. CEDAC Final Recommendation – Dabigatran Etexilate. http://www.cadth.ca/media/cdr/complete/cdr_complete_Pradax_June-27-11.pdf, accessed September 2, 2011

Cohen D. Data on trial of anticoagulant is to be reanalyzed after discovery that investigators used **faulty device**. (**Rocket-AF)** BMJ. 2015 Dec 3;351:h6431.

Cohen D. Rivaroxaban: **Can we trust the evidence**? *BMJ* 2015.

Cohen D. **Manufacturer failed to disclose faulty device in rivaroxaban** trial. BMJ 2016;354:i5131.

Cohen D. **Rivaroxaban: can we trust the evidence**?BMJ 2016;352:i575. doi:10.1136/bmj. i575 pmid:26843102.

Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L; Randomized Evaluation of Long-Term Anticoagulation Therapy Investigators. Newly identified events in the RE-LY trial. N Engl J Med. 2010 Nov 4;363(19):1875-6.

Diener, Hans-Christoph, Connolly, Stuart J, Ezekowitz Michael D. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial .The Lancet Neurology, Early Online Publication, 8 November 2010 doi:10.1016/S1474-4422(10)70274.

Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation. Circulation 2011; 123:2363-2372.

EINSTEIN investigators. Oral **rivaroxaban** for symptomatic **venous thromboembolism**. N Engl J Med 2010; DOI:10.1056/NEJMoa1007903.

Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. **Reversal of Rivaroxaban** and Dabigatran by **Prothrombin Complex Concentrate**: A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects. Circulation. 2011 Sep 6.

Ezekowitz MD, et al.. Dabigatran and Warfarin in Vitamin K Antagonist–Naive and –Experienced Cohorts With Atrial Fibrillation. Circulation. 2010 Nov 30; 122: 2246-2253.

FDA draft briefing document for the Cardiovascular and Renal Drugs Advisory Committee: **Xarelto (rivaroxaban)** tablets (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM270796.pdf). It was noted that the hazard ratio increased sharply as the center TTR rose to above 65%, and at a TTR above 67%, the hazard ratio crossed 1.0. Thus, the noninferiority of rivaroxaban over warfarin, when used carefully by skilled clinicians, is not apparent.

Fleming TR, Emerson SS. Evaluating rivaroxaban for nonvalvular atrial fibrillation--**regulatory considerations**. N Engl J Med 2011; DOI:10.1056.NEJMp1110639.

Fordyce CB, Hellkamp AS, Lokhnygina Y, et al; On-Treatment Outcomes in Patients With **Worsening Renal Function** With **Rivaroxaban** Compared With Warfarin: Insights From **ROCKET AF**. Circulation. 2016 Jul 5;134(1):37-47.

Freeman James V., Zhu Ruo P., Owens Douglas K., et al. **Cost-Effectiveness of Dabigatran Compared With Warfarin** for Stroke Prevention in Atrial Fibrillation. Ann Intern Med January 4, 2011 154:1-11; published ahead of print Nov 1, 2010, doi:10.1059/0003-4819-154-1-201101040-00289.

Goodman SG, Wojdyla DM, Piccini JP, MD; et al. Factors associated with **major bleeding events**: insights from the rivaroxaban once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF). J Am Coll Cardiol 2013.

Halperin JL, Hankey GJ, Wojdyla DM, et al; on behalf of the **ROCKET AF** Steering Committee and Investigators. Efficacy and Safety of **Rivaroxaban** Compared with Warfarin among **Elderly** Patients with Nonvalvular Atrial Fibrillation in the ROCKET AF Trial. Circulation. 2014 Jun 3.

Hankey GJ, Eikelboom JW. **Dabigatran** etexilate: a new oral thrombin inhibitor. Circulation. 2011 Apr 5;123(13):1436-50.

Hankey GJ, Patel MR, Stevens SR, et al, for the **ROCKET AF** Steering Committee and Investigators. Rivaroxaban compared with warfarin in patients with atrial fi brillation and **previous stroke or transient ischaemic attack**: a subgroup analysis of ROCKET AF. Lancet Neurol 2012; online March 7.

Hankey GJ, Stevens SR, Piccini JP, et al; **ROCKET AF** Steering Committee and Investigators. **Intracranial hemorrhage** among patients with atrial fibrillation anticoagulated with **warfarin or rivaroxaban**: the rivaroxaban once daily, oral, direct factor xa inhibition compared with vitamin k antagonism for prevention of stroke and embolism trial in atrial fibrillation. Stroke. 2014 May;45(5):1304-12.

Mahaffey KW, Wojdyla D, Hankey GJ, et al. Clinical outcomes with rivaroxaban in patients **transitioned from vitamin k antagonist therapy**: a subgroup analysis of a randomized trial. (Rocket AF) Ann Intern Med. 2013 Jun 18;158(12):861-8.

Mahaffey KW, Hellkamp AS, Patel MR, et al. End of Study Transition From **Study Drug to Open-Label Vitamin K Antagonist** Therapy: The ROCKET AF Experience. Circ Cardiovasc Qual Outcomes. 2013 Jun 11.

Nagarakanti R, Ezekowitz MD, Oldgren J, et al. Dabigatran versus warfarin in patients with atrial fibrillation: An analysis of patients undergoing **cardioversion**. Circulation 2011; DOI:10.1161/CIRCULATIONAHA.110.977546.

Nessel C, Mahaffey K, Piccini J, et al. Incidence and Outcomes of **Gastrointestinal Hemorrhage** in Patients With Atrial Fibrillation Treated With Rivaroxaban or Warfarin: Results From the ROCKET AF Trial. Chest 142.4_MeetingAbstracts (2012): 84A-84A.

Patel MR, Hellkamp AS, Lokhnygina Y, et al. Outcomes of **Discontinuing Rivaroxaban** Compared With Warfarin in Patients With Nonvalvular Atrial Fibrillation: Analysis From the **ROCKET AF** Trial (Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation). J Am Coll Cardiol. 2013 Feb 12;61(6):651-8.

Patel MR, Hellkamp AS, Fox KA; ROCKET AF Executive Committee and Investigators. **Point-of-Care Warfarin Monitoring in the ROCKET AF** Trial. N Engl J Med. 2016 Feb 3.

Piccini JP, Hellkamp AS, Washam JB, et al. **Polypharmacy** and the Efficacy and Safety of **Rivaroxaban versus Warfarin** in the Prevention of Stroke in Patients With Nonvalvular Atrial Fibrillation. (**Rocket-AF**) Circulation. 2015 Dec 16.

Pisters R, Lane DA, Nieuwlaat R, et al. A novel userfriendly score (**HAS-BLED**) to assess one-year risk of major bleeding in atrial fibrillation patients: The Euro Heart Survey. Chest 2010; published online March 18. DOI:10.1378/chest.10-013 4.

Shah Shimoli V., Gage Brian F.. **Cost-Effectiveness of Dabigatran** for Stroke Prophylaxis in Atrial Fibrillation. Circulation 123: 2562-2570.

Shah R, Hellkamp A, Lokhnygina Y, et al. Use of **concomitant aspirin** in patients with atrial fibrillation: Findings from the ROCKET AF trial. Am Heart J. 2016 Sep;179:77-86.

Sherwood MW, Douketis JD, Patel MR, et al; on behalf of the ROCKET AF Investigators. Outcomes of **Temporary Interruption of Rivaroxaban Compared with Warfarin** in Patients with Nonvalvular Atrial Fibrillation: Results from ROCKET AF. Circulation. 2014 Feb 19.

Sherwood M, Nessel C, Hellkamp A, et al. **Gastrointestinal bleeding** in patients with atrial fibrillation treated with rivaroxaban or warfarin. (**Rocket-AF)** J Am Coll Cardiol 2015; 66:2271-2281.

Steinberg BA, Hellkamp AS, Lokhnygina Y, et al; ROCKET-AF Steering Committee and Investigators. Higher risk of **death** and stroke in patients with **persistent vs. paroxysmal** atrial fibrillation: results from the ROCKET-AF Trial. Eur Heart J. 2015 Feb 1;36(5):288-96.

Washam JB, Stevens SR, Lokhnygina Y, et al; for the ROCKET AF Steering Committee and Investigators. **Digoxin** use in patients with atrial fibrillation and adverse cardiovascular outcomes: a retrospective analysis of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). Lancet. 2015 Mar 5.

Wallentin L et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: An analysis of the RE-LY trial. Lancet 2010 Aug 29; [e-pub ahead of print]. (http://dx.doi.org/10.1016/S0140-6736(10)61194-4)

Wann L. Samuel, Curtis Anne B., Ellenbogen Kenneth A., et al. **2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Update on Dabigatran):** A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Circulation published February 14, 2011, doi:10.1161/CIR.0b013e31820f14c0 http://circ.ahajournals.org/cgi/reprint/CIR.0b013e31820f14c0v1

ROCKET-AF TRIAL SUMMARY REFERENCES:

[1] Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. August 10, 2011. http://www.nejm.org/doi/full/10.1056/NEJMoa1009638 (**ROCKET-AF**)

[2] Granger CB, Alexander JH, McMurray JJV et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med August 28, 2011 http://www.nejm.org/doi/pdf/10.1056/NEJMoa1107039 (**ARISTOTLE)**

[3] Jin M. RxFiles Trial Summary – **ARISTOTLE**: Apixaban versus warfarin in patients with atrial fibrillation. Saskatoon, SK: RxFiles; 2011. Available from: www.rxfiles.ca. Accessed April 30th, 2012.

[4] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. NEJM 2009;361. (**RELY**)

[5] Dumont, Z. RxFiles Trial Summary – **RELY**: Dabigatran versus warfarin in patients with atrial fibrillation. Saskatoon, SK: RxFiles; 2009. Available from: www.rxfiles.ca. Accessed April 30th, 2012.

[6] ROCKET AF Study Investigators. Rivaroxaban – once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: **Rationale and Design of the ROCKET AF** study. Am Heart J 2010;159:340-7.e1

[7] FDA Advisory Committee Briefing Document: Rivaroxaban for the Prevention of Stroke and Non-Central Nervous System (CNS) Systemic Embolism in Patients With Atrial Fibrillation. August 2011. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM270797.pdf

[8] Fox KAA, Piccini JP, Wojdyla D, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and **moderate renal impairment (ROCKET-AF)**. European Heart Journal. Advance access published August 28, 2011.

[9] Hankey GJ, Patel MR, Stevens SR et al; ROCKET AF Steering Committee Investigators. Rivaroxaban compared with warfarin in patients with atrial fibrillation and **previous stroke or TIA**: a subgroup analysis of ROCKET AF. Lancet Neurol. 2012 Apr;11(4):315-22.

[10] Hori M, Matsumoto M, Tanahashi N et al; J-ROCKET AF study investigators. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation – the **J-ROCKET AF study**. Circ J. 2012;76(9):2104-11.