RENal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation (RENAL-AF)

November 16, 2019

Sean D. Pokorney, MD, MBA
on behalf of the RENAL-AF Investigators

RENAL-AF

Duke Clinical Research Institute

Bristol-Myers Squibb

Pfizer

Stanford MEDICINE

Frenova Renal Research

RENAL-AF was an investigator-sponsored research study supported by grant from the BMS/Pfizer Alliance

Atrial Fibrillation in Patients on Hemodialysis

- AF is more common in patients with end-stage renal disease (ESRD) on hemodialysis than in the general population
  - Prevalence of 11-13%
- Increased risk of stroke and bleeding among patients with AF and ESRD
  - 1.5 fold increase in stroke
  - 2 fold increase in bleeding

Winkelmayer *JASN* 2011; 22: 349-357.
Olesen NEJM 212; 367: 625-635.

Stroke Prevention in AF and ESRD

- Uncertainty about risk-benefit of warfarin in AF and ESRD
  - Bleeding risk in patients on anticoagulation
  - Warfarin control is challenging
  - Warfarin is associated with calciphylaxis
- Apixaban has dosing recommendations in the US label
  - 5mg BID unless age $\geq$ 80 years and/or weight $\leq$ 60kg
- Increasing clinical use of NOACs in patients with ESRD
- No randomized data of NOAC in patients with AF and ESRD

Yang F. Heart. 2017; 103: 818-826.

Study Objective of RENAL-AF

- Assess the safety of apixaban versus warfarin with respect to major bleeding or clinically relevant non-major bleeding in patients with AF and with ESRD on hemodialysis

Original Study Design

Selected inclusion criteria
- **Atrial fibrillation**
- **CHA2DS2-VASc ≥2**
- **Hemodialysis**
- **Candidate for OAC**

Randomize
(n ≈ 760)

Selected exclusion criteria
- **Moderate or severe mitral stenosis**
- **OAC needed for reason other than AF**
- **Need for aspirin > 81 mg**
- **Need for dual antiplatelet therapy**
- **Life expectancy < 3 months**

Apixaban 5 mg oral twice daily
(2.5 mg BID in selected patients)

Warfarin
(target INR 2–3)

Open label with blinded event adjudication

Primary outcome: ISTH major and clinically relevant non-major bleeding

Secondary outcomes:
- ***PK in patients randomized to apixaban***
- ***Stroke and systemic embolism***
- ***Death***
- ***Tolerability/persistence/adherence parameters***

Trial Organization

STEERING COMMITTEE

Christopher Granger (PI)

Glenn Chertow (PI)

Sean Pokorney (USA)

Renato Lopes (USA)

Nisha Bansal (USA)

Wolfgang Wikelmayer (USA)

John Middleton (USA)

Kevin Thomas (USA)

Hussein Al-Khalidi (USA)

David Garcia (USA)

Crystal Gadegbeku (USA)

STEERING COMMITTEE

Kenneth Mahaffey (USA)

Ravi Thadhani (USA)

Kurt Mussina (Frenova)

George Sands (Non-voting member, Pfizer)

CLINICAL EVENTS CLASSIFICATION (CEC) COMMITEE

Duke Clinical Research Institute

RESEARCH PARTNER

Frenova Renal Research

ACADEMIC COORDINATING CENTER

Duke Clinical Research Institute

DATA SAFETY MONITORING BOARD

Marc Pfeffer (Chair)

Roxana Mehran

Patrick Parfrey

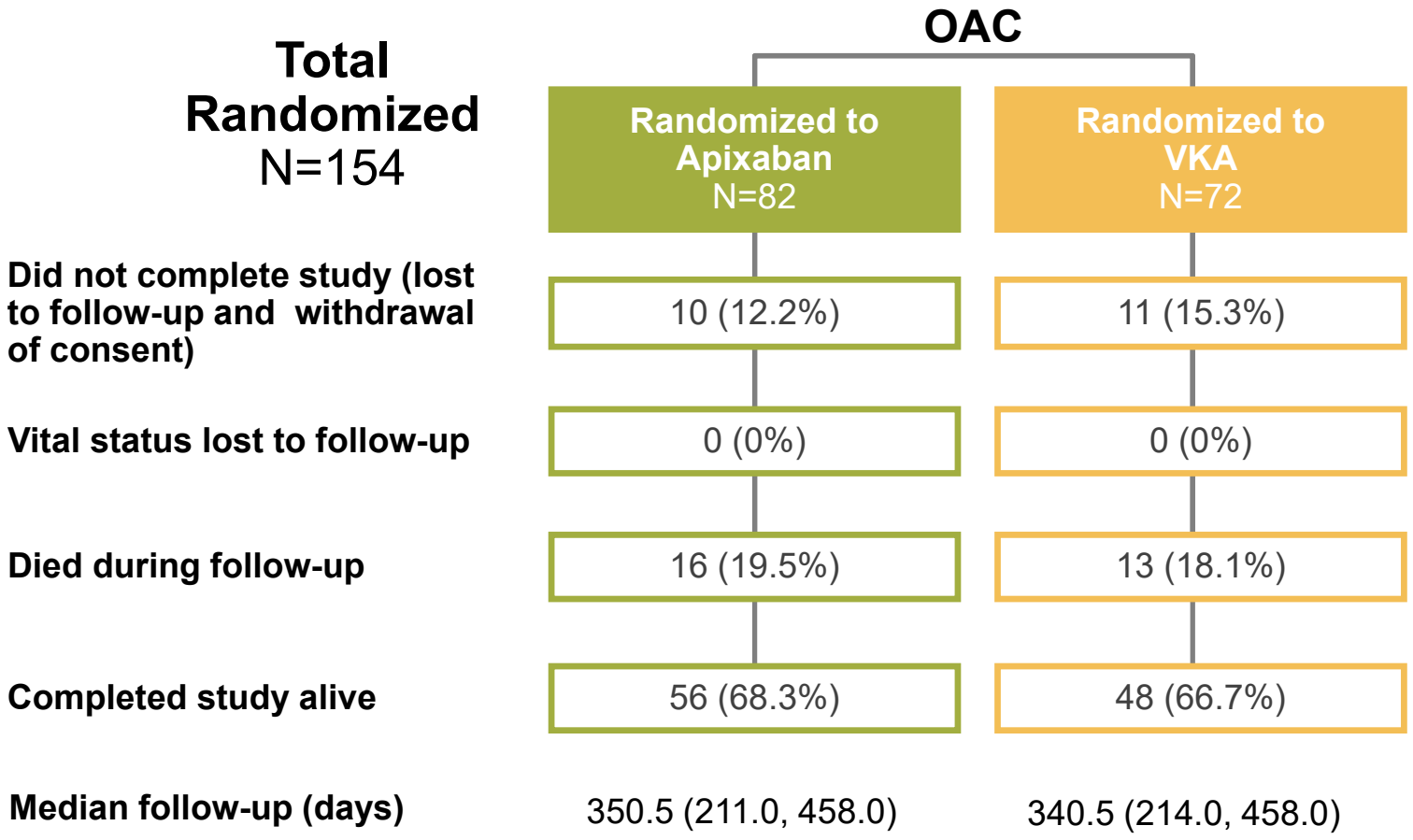
Kerry Lee

Statistical Support: Duke Clinical Research Institute

Study Stopped Early

- Given resources allocated to this investigator-initiated project, completing the trial as originally designed was not possible
- Slower than anticipated enrollment
  - Related to patient and dialysis center factors
- Enrollment had increased by the end

CONSORT Diagram



Patient Baseline Characteristics

	Apixaban (N=82)	Warfarin (N=72)
Age (years), Median	69.0 (61.0, 76.0)	68.0 (60.5, 72.5)
≥ 75 years old	24 (29.3%)	15 (20.8%)
Female	34 (41.5%)	22 (30.6%)
Black	35 (42.7%)	34 (47.2%)
CHA_2DS_2-VASc, Median (Q1, Q3)	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)
Stroke	17 (20.7%)	12 (16.7%)
Warfarin or NOAC naïve	10 (12.2%)	4 (5.6%)
Type of atrial fibrillation		
Paroxysmal	45 (54.9%)	40 (55.6%)
Persistent/Permanent	37 (45.1%)	32 (44.4%)
Prior clinically relevant or spontaneous bleeding	18 (22.0%)	14 (19.4%)
Bleeding the past year requiring hospitalization	8 (9.8%)	2 (2.8%)
Aspirin	29 (36.7%)	32 (45.7%)

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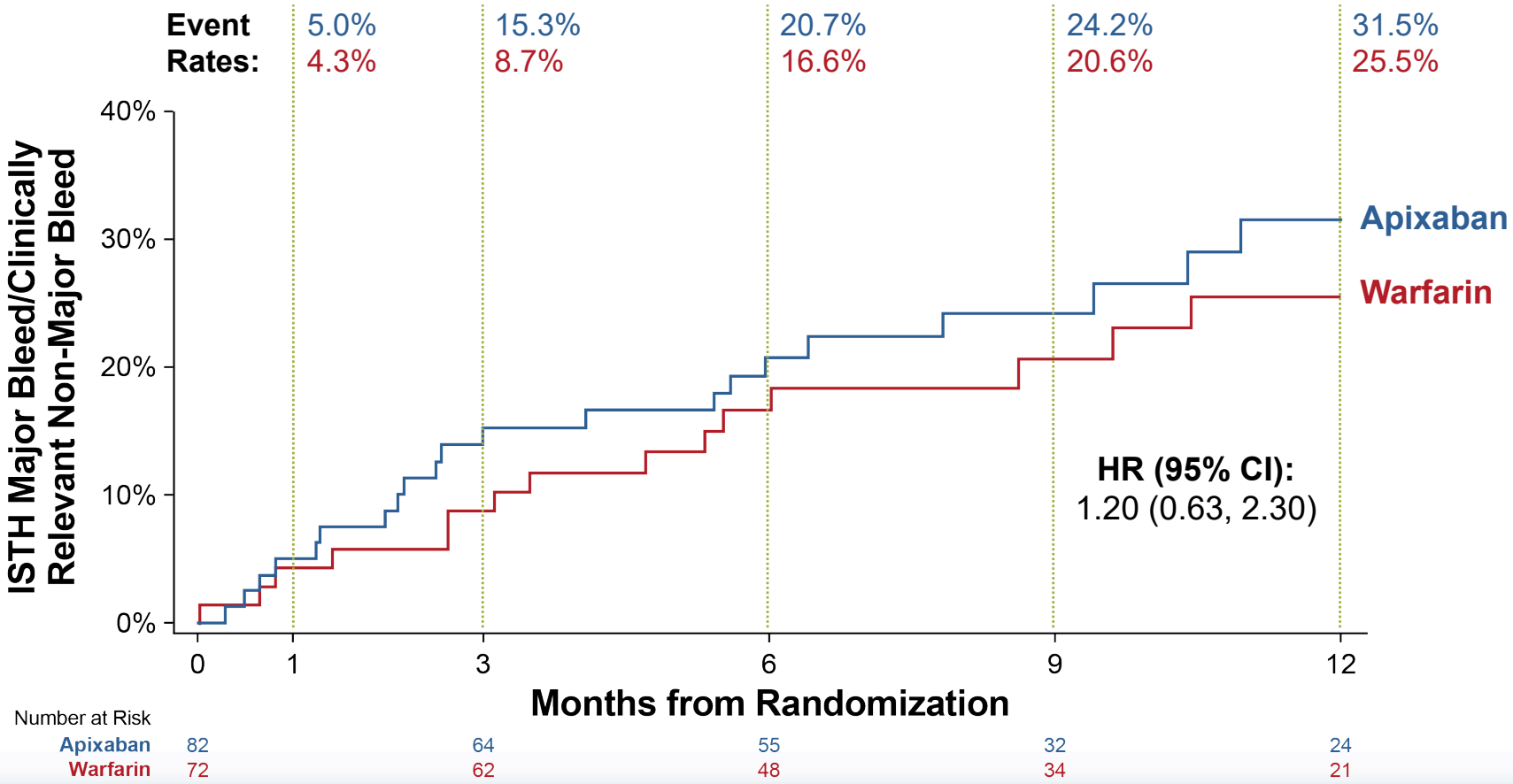
Apixaban and Warfarin Dosing in Modified ITT

Patients randomized to apixaban and received at least one dose	Apixaban N = 77
First apixaban dose	
2.5 mg BID	22 (28.6%)
5.0 mg BID	55 (71.4%)
Apixaban dose reduction from 5.0 mg to 2.5 mg BID	15 (27.3%)
Patients randomized to warfarin and received at least one dose	**Warfarin N = 68**
Time in therapeutic range (2.0-3.0), Median (Q1, Q3)[1]	44.3% (23.2%, 59.0%)

- Patients were 3 times as likely to be subtherapeutic (INR <2.0) relative to supratherapeutic (>3.0)

1 Time in therapeutic range was calculated by the Rosendaal method

Time to Major or Clinically Relevant Non-Major Bleed for Intention to Treat



RENAL-AF

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Primary Safety Endpoint: ITT Analysis

	Apixaban N = 82	Warfarin N = 72
ISTH major bleed/clinically relevant non-major bleed[1]	21 (25.6%)	16 (22.2%)
Intracranial	1 (1.2%)	1 (1.4%)
Gastrointestinal	2 (2.4%)	6 (8.3%)
Hemodialysis access site	11 (13.4%)	6 (8.3%)
ISTH major bleed[1]	7 (8.5%)	7 (9.7%)
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Ischemic	1 (1.2%)	2 (2.8%)
Hemorrhagic	1 (1.2%)	0 (0.0%)
Systemic embolism	0 (0.0%)	0 (0.0%)
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Conclusions

- This is the first randomized trial to assess the safety of a NOAC (apixaban) versus warfarin for patients with AF and ESRD on hemodialysis
- The study was terminated prematurely and the power was limited by small sample size
- In this exploratory study, there were similar rates of major and clinically relevant non-major bleeding with apixaban and warfarin
  - Large proportion of warfarin patients in sub-therapeutic range
- Hemodialysis patients are challenging to enroll and maintain in cardiovascular clinical trials
- These results suggest that apixaban may be a reasonable anticoagulant choice in patients on hemodialysis, and more data are needed to guide care for this high-risk population

Acknowledgement

- Thank you to the steering committee, investigators, study coordinators, and study participants who made RENAL-AF possible

Valley Nephrology Associates	Knoxville Kidney Center	West Virginia University	Nephrology and Hypertension Assoc.	Southland Renal Medical Group
Durham Nephrology Associates	Massachusetts General Hospital	Renal Medicine Associates	East Carolina University	Washington University School of Medicine, Division of Nephrology
South Carolina Nephrology and Hypertension	Advanced Kidney Care of Hudson Valley	HNC Dialysis, Ltd.	Lubbock Vascular Access Center	University of North Carolina at Chapel Hill
South Shore Nephrology, PC	Northwestern University	Washington Nephrology Associates	Eastern Nephrology Associates, PLLC	Summit Nephrology Medical Group, Inc
Northeast Clinical Research Ctr.	Southern Clinical Research Group, LLC	Satellite Healthcare	The Johns Hopkins University	Northwest Louisiana Nephrology
Southwest Mississippi Nephrology PLLC	University of Virginia Health System	The Medical Research Group, Inc.	Medical Professional Clinical Research Center	Nephrology Consultants
Paragon Health PC d/b/a Nephrology Centre, PC	University of Washington	Boise Kidney & Hypertension PLLC	Columbia Nephrology Associates	University of Utah
Nephrology & Hypertension Associates, Ltd	Valley Renal Medical Group Research	Polack Renal, LLC	NANI Research	Nuren Medical and Research Center
Aspirus Research Institute	Regional Health Clinical Research			