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Cardiology Update
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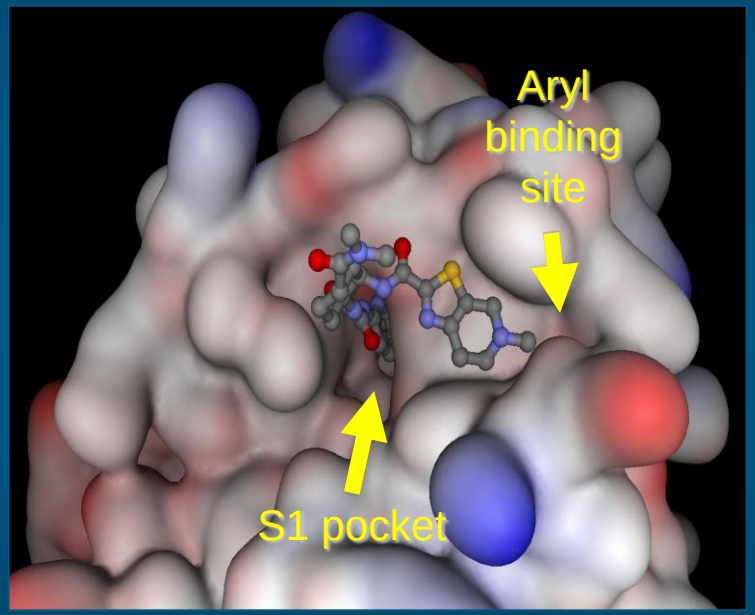

Engage AF-TIMI 48

Edoxaban in AF: What can we expect?

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4 Phase III Trials of Novel Anticoagulants in AF

	RE-LY	ROCKET-AF	ARISTOTLE	ENGAGE AF
Drug	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Dose (mg) Freq	150, 110 BID	20 (15) QD	5 BID	60, 30 QD
N	18,113	14,266	15,000	21,500
Design	Open	2x blind	2x blind	2x blind
Endpoint	Stroke/SEE	Stroke/SEE	Stroke/SEE	Stroke /SEE
HR	1.46	Not publ.	1.38	1.38

SEE = systemic embolic event (i.e., non-CNS)

Phase III AF Trials: Results To Date

	RE-LY[1]		ROCKET-AF[2]	ARISTOTLE[3]	ENGAGE AF-TIMI 48[4]
Drug	Dabigatran		Rivaroxaban	Apixaban	Edoxaban
N	18,113		14,264	18,201	21,105
Dose	110 BID	150 BID	20 QD	5 BID	60, 30 QD
Stroke + SEE	Non-inferior	Superior	ITT : non-inferior On Rx : superior	Superior	
ICH	Superior	Superior	Superior	Superior	
Bleeding	Lower	Similar	Similar	Lower	
Mortality	Similar	P=0.051	Similar	Sup: p=0.047	
Ischemic stroke	Similar	Lower	Similar	Similar	
Mean TTR	64 %		55 %	62 %	
Stopped drug	21 %		23 %	23 %	
WD consent	2.3 %		8.7 %	1.1 %	

ENGAGE AF-TIMI 48

Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation

AHJ
American Heart Journal

American Heart Journal is online at www.mosby.com/ahj

Reprinted from Volume 160, Issue 4, October 2010, Pages 635-641.e2

Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: Design and ratio... lation with factor xA ... Fibrillation-Thrombolysis ... 48 (ENGAGE AF-TIM...

Christian T. Ruff, Robert P. Giugl... Tomas Bocanegra, Michele Mer... Minggao Shi, Dan Salazar, Car...

Mosby

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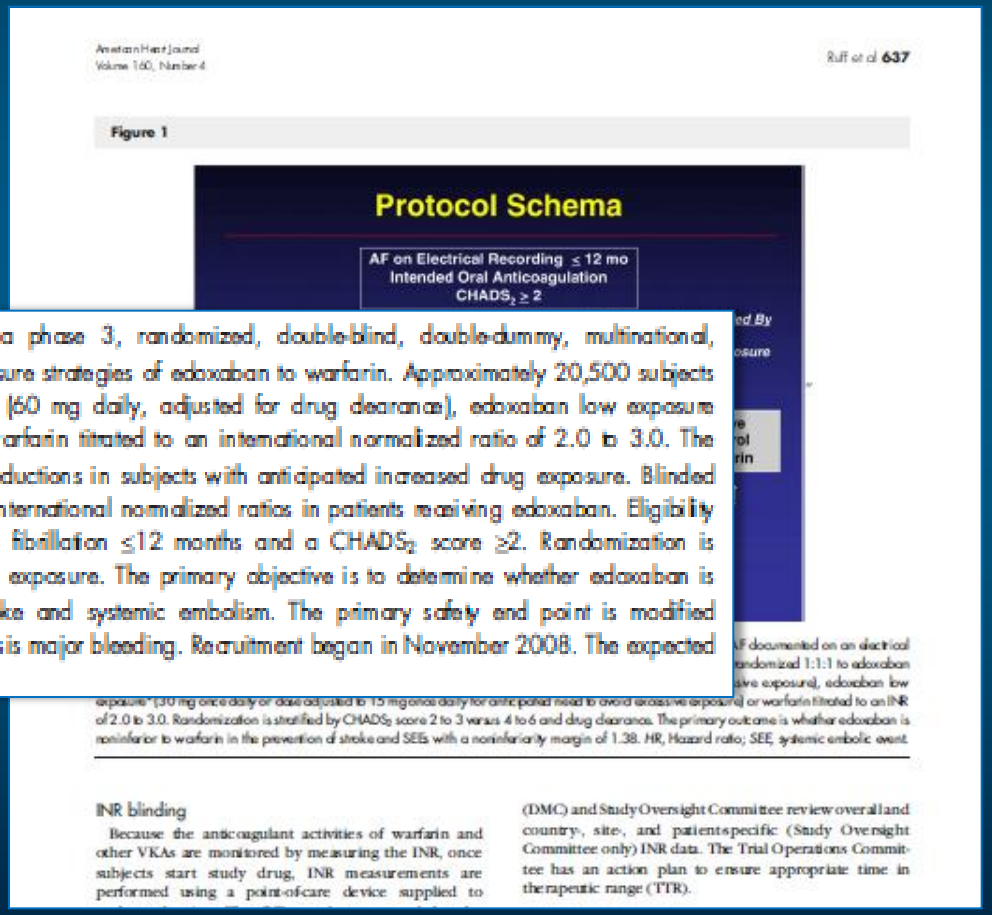
Study Design ENGAGE AF–TIMI 48 is a phase 3, randomized, double-blind, double-dummy, multinational, noninferiority design megatrial comparing 2 exposure strategies of edoxaban to warfarin. Approximately 20,500 subjects will be randomized to edoxaban high exposure (60 mg daily, adjusted for drug clearance), edoxaban low exposure (30 mg daily, adjusted for drug clearance), or warfarin titrated to an international normalized ratio of 2.0 to 3.0. The edoxaban strategies provide for dynamic dose reductions in subjects with anticipated increased drug exposure. Blinded treatment is maintained through the use of sham international normalized ratios in patients receiving edoxaban. Eligibility criteria include electrical documentation of atrial fibrillation ≤12 months and a $CHADS_2$ score ≥2. Randomization is stratified by $CHADS_2$ score and anticipated drug exposure. The primary objective is to determine whether edoxaban is noninferior to warfarin for the prevention of stroke and systemic embolism. The primary safety end point is modified International Society on Thrombosis and Haemostasis major bleeding. Recruitment began in November 2008. The expected median followup is 24 months.



American Heart Journal
Volume 160, Number 4

Ruff et al 637

Figure 1

Protocol Schema

AF on Electrical Recording ≤ 12 mo
Intended Oral Anticoagulation
$CHADS_2 \geq 2$

...F documented on an electrical ...randomized 1:1:1 to edoxaban ...sive exposure), edoxaban low ... or warfarin titrated to an INR of 2.0 to 3.0. Randomization is stratified by $CHADS_2$ score 2 to 3 versus 4 to 6 and drug clearance. The primary outcome is whether edoxaban is noninferior to warfarin in the prevention of stroke and SEEs with a noninferiority margin of 1.38. *HR*, Hazard ratio; *SEE*, systemic embolic event.

INR blinding

Because the anticoagulant activities of warfarin and other VKAs are monitored by measuring the INR, once subjects start study drug, INR measurements are performed using a point-of-care device supplied to

(DMC) and Study Oversight Committee review overall and country-, site-, and patient-specific (Study Oversight Committee only) INR data. The Trial Operations Committee has an action plan to ensure appropriate time in therapeutic range (TTR).

Ruff et al. Am Heart J 2010;160:635-641

Study Design

N=21,105

AF on electrical recording ≤ 12 mo
Intended oral anticoagulant
$CHADS_2 \geq 2$

Exposure strategy: patients anticipated to have increased drug exposure received a 50% dose reduction

R

Randomization stratified by
1. CHADS2 2-3 vs 4-6
2. Increased Drug Exposure

Low exposure strategy
Edoxaban 30 mg QD

High exposure strategy
Edoxaban 60 mg QD

Active control:
warfarin
(INR 2.0 – 3.0)

Median duration of follow up 24-months

Primary objective

Edoxaban: therapeutically as good as warfarin

1º endpoint = stroke or SEE (non-inferiority boundary HR 1.38)
2º endpoint = stroke or SEE or all-cause mortality
Safety endpoints = major bleeding, hepatic function

AF, atrial fibrillation, mo, months; QD, once daily; HR, hazard ratio
SEE, systemic embolic event; INR, International Normalised Ratio

Ruff et al. Am Heart J 2010;160:635-641

Global Participation

Inclusion Criteria

- Male or female, age ≥21 years
- AF documented by an electrical tracing within the prior 12 months and for which anticoagulation is indicated and planned
- Subjects with paroxysmal, persistent or permanent AF
- Subjects with or without previous VKA experience
  - Anticipated that ~40% of subjects will be VKA naïve (< 60 days of continuous anticoagulation at anytime before randomization)
- $CHADS_2$ index score ≥2

AF, atrial fibrillation; VKA, vitamin K antagonist

Ruff et al. Am Heart J 2010;160:635-641

Major Exclusions

- Rheumatic mitral stenosis or mechanical valve
- Anticoagulation contraindicated or not planned
- Patients at high-risk of bleeding
- Need for dual antiplatelet therapy (e.g., recent stent, ACS, stroke) or strong PGP inhibitors
- Pregnancy, severe comorbidities (e.g., cancer, severe renal failure, life-expectancy < 12 mths)

Dosing Strategy

- Patients randomized to either of the two edoxaban groups anticipated to have an increased drug exposure received a 50% dose reduction (e.g. from 30 mg to 15 mg)

ARISTOTLE dose reduction only at randomization:
Apixaban 5 mg b.i.d. to 2.5 mg b.i.d.
***≥2 of the following**:*

- ***age ≥80 years,***
- ***body weight ≤60 kg***
- ***serum creatinine level ≥1.5 mg/dL (133 µmol/L)***

- Total of 3 doses studied with over a 4-fold range of doses (60, 30, 15 mg)

Ruff et al. Am Heart J 2010;160:635-641

CrCl, creatinine clearance; P-gp, P-glycoprotein

ENGAGE AF- TIMI 48
TTR Approach

- Reviewed worldwide experience with VKA
- Monthly monitoring of TTR at level of
  - Trial, Region, Country, Individual Center
- Review of centers with TTR <40 %
- Letters to centers with TTR <60 % and >80 %
- Lessons learned:
  - Fixed (usually too low) initial dose selection
  - Insufficient, infrequent INR monitoring
  - Excessively cautious dose adjustment when INR sub-therapeutic
- Solutions: Reporting, Education, Algorithm

Baseline Characteristics First 15,000 Patients

Characteristic	Value
Demographics – Mean age (years)	72 (64-77)
– Age ≥75 years (%)	39
– Female (%)	38
$CHADS_2$ 2-3 (%)	81
$CHADS_2$ 4-6 (%)	19
Warfarin naïve (%)	39
AF category – Paroxysmal (%)	26
– Persistent (%)	23
– Permanent (%)	52
Dose adjustment* – Any reason (%)	25
– Weight ≤60 kg (%)	10
– CrCl ≤50 mL/min (%)	19
– Concomitant p-gp inhibitors (%)	4

*May have >1 reason for dose adjustment, thus, the total of the individual reasons is >25%. AF, atrial fibrillation; CrCl, creatinine clearance

Ruff et al. Am Heart J 2010;160:635-641

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Additional Scientific Investigations

Name	Objective
Pharmacokinetics/ Pharmacodynamics in all patients	Characterise the relationship between exposure and response to edoxaban
Health economics/Quality of life	Cost-effectiveness of edoxaban therapy
Pharmacogenetics	Identify genetic polymorphism that identify patients at higher risk for recurrent AF, thromboembolism and bleeding
Biomarker	Correlate concentrations of biomarkers of thrombosis, inflammation, necrosis and haemodynamic status with efficacy and safety
Continuous and static electrocardiography	Determine the varying risk associated with different burdens of AF
Echocardiography	Determine if left atrial size predicts thromboembolic risk

Ruff et al. Am Heart J 2010;160:635-641

ENGAGE AF-TIMI 48
Expected strengths

1. Scientifically sound design incorporates
   - Two doses (30 mg, 60 mg) selected on phase II PK data
   - Dosing is adjusted for drug clearance
   - Entry criteria identify moderate-high risk patients

2. Posing several interesting questions
   - Doses that are as safe (or safer) than current Rx
   - Built in investigations of PK, PD, genetics, health economics
   - Ancillary studies of biomarkers, echo, holter, ECG

3. Investigation of two dose regimens could result in superior net clinical benefit (efficacy/bleeding) compared to other oral anticoagulants, especially to other direct factor Xa inhibitors.

ENGAGE AF- TIMI 48
Unique features

- The largest (>21,000) single RCT in AF with a novel oral anticoagulant
- Longest follow-up (median 2.5-3.0 yrs)
- 2 once-daily dosing regimens (60 & 30 mg)
- First study with dose adjustment after titration
  - 60 → 30 mg
  - 30 → 15 mg
- Data on 3 doses spanning a 4-fold range

Summary

- High unmet needs for the replacement of VKAs in AF from physician's and patient's perspective
- Predictable pharmacological profile and convenient once-daily dosing regimen of edoxaban
- Edoxaban the only Factor Xa inhibitor with a large Phase II dose finding study in AF
- Largest Phase III study programme in AF
- Strategy with 2 dose regimens and dose adjustments might allow selection of best dose on an individual basis

Thank you for your attention

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