ENGAGE AF –TIMI 48

November 19, 2013

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Randomized, double-blind, double-dummy, noninferiority design comparing 2 exposure strategies of edoxaban 60 mg, 30 mg per day to warfarin

50% dose reduction at randomization or at any point of the trial if one of the following factors was present:

- **CrCl 30-50 mL/min,**
- **body weight ≤60 kg,**
- **or use of verapamil, quinidine, dronedarone**

High-exposure group: 60 mg→30 mg
Low-exposure group: 30 mg→15 mg

Baseline Characteristics AF Trials

	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF
N	**18,113**	**14,264**	**18,201**	**21,105**
Age, yrs	72	73	70	72
Prior stroke	20%	55%	19%	28%
Hypertension	79%	91%	87%	94%
HF	32%	62%	36%	57%
Diabetes	23%	39%	25%	36%
$CHADS_2$	2.1	3.5	2.1	2.8

KEY FEATURES

- CHADS score ≥ 2 (medium to high risk)
- Dynamic dose adjustment:

  25 % had dose reduced at randomization;
  ?? % dose reductions post randomization

- TTR, median 68.4%

RE-LY	median 66%;	mean 64%
ARISTOTLE	median 66%;	mean 62%
ROCKET	median 58%;	mean 55%

Intention to Treat Analysis Overall

		Edoxaban	Warfarin	HR (95% CI)	*P*
Stroke/SEE	High dose	1.57%	1.80%/yr	0.87 (0.73-1.04)	0.084
	Low dose	2.04%		1.13 (0.96-1.34)	0.10
Ischemic CVA	High dose	1.25%	1.25%	1.00 (0.83-1.19)	0.97
	Low dose	1.77%		1.41 (1.19-1.67)	<0.001
Hemorrhagic CVA	High dose	0.26%	0.47%	0.54 (0.38-0.77)	<0.001
	Low dose	0.16%		0.33 (0.22-0.55)	<0.001

Intention to Treat Analysis Overall

		Warfarin	Edoxaban		
Major Bleed	High Dose	3.43%	2.75%	0.80 (0.71-0.91)	<0.001
	Low dose		1.61%	0.47 (0.41-0.55)	<0.001
Fatal Bleed	High dose	0.38%	0.21%	0.55 (0.36-0.84)	0.006
	Low dose		0.13%	0.35 (0.21-0.57)	<0.001
GI hemorrhage	High dose	1.23%	1.51%	1.23 (1.02-1.50)	0.031
	Low dose		0.82%	0.67 (0.53-0.83)	<0.001

Intention to Treat Analysis Overall

		Edoxaban	Warfarin	HR (95% CI)	*P*
All cause mortality	High dose	3.99%	4.35%	0.92 (0.83-1.01)	0.082
	Low dose	3.80%		0.87 (0.79-0.96)	0.006
CV mortality	High dose	2.74%	3.17%	0.86 (0.77-0.97)	0.01
	Low dose	2.71%		0.85 (0.76-0.96)	0.008

SUMMARY

Edoxaban 60 mg once-daily was noninferior to warfarin for the prevention of stroke/SEE and ischemic stroke.

Edoxaban 60 mg once-daily was associated with significantly lower rates of intracerebral and overall intracranial bleeding, fatal bleeding, major bleeding, and death from cardiovascular causes.

Edoxaban 60 mg was associated with more GI hemorrhages compared to warfarin.

SUMMARY

Edoxaban 30 mg once-daily (low exposure strategy) lacked efficacy for prevention of ischemic stroke increasing the risk by approximately 40% compared to warfarin.

Presumably lower drug concentrations underlie the loss of efficacy and help to explain the very low bleeding rates compared to warfarin.

Dose reduction strategy decreased the risk of bleeding, but its effect on drug levels and efficacy in the setting of renal function recovery during the trial is uncertain.

The conduct of the ENGAGE AF TIMI trial was exemplary with its end of trial transition protocol, rigor of endpoint ascertainment, and vigilance regarding trial TTR.