Xarelto (Rivaroxaban)

Cardiovascular and Renal Drugs Advisory Committee Meeting

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Outline

- Brief Description of Clinical Development Program
- Integrated Analyses
  - Benefit
  - Bleeding Risk

Comparative Clinical Program - THR

- Two Active Control Studies (RECORD 1 and 2)
- Comparator: Enoxaparin
- Comparator Regimen in RECORD 1:
  - Approved and Considered Optimal
- Comparator Regimen in RECORD 2:
  - Shorter than Optimal Treatment Duration
  - Source of Bias potentially resulting in under-estimation of Enoxaparin Treatment effect

Comparative Clinical Program - TKR

- Two Active Control Studies (RECORD 3 and 4)
- Comparator: Enoxaparin
- Comparator Regimen in RECORD 3:
  - Unapproved Lower Dose for Enoxaparin
  - Source of Bias potentially resulting in under-estimation of Enoxaparin Treatment effect
- Comparator Regimen in RECORD 4:
  - Approved and Considered Optimal

Results

- Statistical superiority for Rivaroxaban achieved at 5% level
  - For the primary endpoint of “Total VTE”
  - Primarily due to venography based components
  - Low rates of Death and Non-fatal PE
- SAP did not include control of false positive rate for multiple secondary endpoints for anticipated claims based on statistical significance
- Nominal p-values for secondary endpoints
  - < 0.05 ONLY for RECORD 2 and 3, NOT for RECORD 1 and 4
  - Supportive of primary analysis

Agreement

The data from RECORD studies demonstrate efficacy of Rivaroxaban for prophylactic anticoagulation after THR/TKR surgery

What is the Extent of Benefit ?

An Evaluation

Symptomatic VTE or Death

- Clinically Important Endpoint
- No Confirmatory hypothesis test in the Statistical Analysis plan for each RECORD study
- Any comparison of rivaroxaban with enoxaparin in terms of this endpoint
  - exploratory
  - at best hypothesis-generating

Symptomatic VTE (DVT or PE)
in RECORD Study Safety Population

RECORD	Riva	Enox
1 (hip)	6/2209 (0.3%)	11/2224 (0.5%)
2 (hip) (Short Enox Duration)	3/1228 (0.2%)	15/1229 (1.2%)
3 (knee) (Lower Enox dose)	8/1220 (0.7%)	24/1239 (1.9%)
4 (knee)	11/1526 (0.7%)	18/1508 (1.2%)

Deaths (during treatment period) *in RECORD Study*

RECORD	Riva	Enox
1 (hip)	4 (n=2209, 0.2%)	4 (n=2224, 0.2%)
2 (hip) (Short Enox Duration)	2 (n=1228, 0.2%)	6 (n=1229, 0.5%)
3 (knee) (Lower Enox dose)	0 (n=1220, 0.0%)	2 (n=1239, 0.2%)
4 (knee)	2 (n=1526, 0.1%)	3 (n=1508, 0.2%)

Integrated Analyses

- Simple pooling
- Important study characteristics are ignored
  - Type of surgery
  - Dose
  - Duration
- No control of False Positive Rate
  - not built into the plan for pooled analyses for anticipated claims based on statistical significance.
- This type of analysis can yield spurious results.

Sponsor's Results for Symptomatic VTE or Death (*In RECORD Study Safety Population)*

RECORD	Riva	Enox	Hazard ratio (95% CI)
1	10/2209 0.45%	15/2224 0.67%	0.7 (0.3, 1.5)
2 (Shorter treatment duration for Enox)	5/1228 0.41%	20/1229 1.6%	0.2 (0.1, 0.7)
3 (unapproved dose regimen for Enox)	8/1220 0.66%	26/1239 2.1%	0.3 (0.1, 0.7)
4	12/1526 0.79%	21/1508 1.4%	0.6 (0.3, 1.2)
Pooled	35/6183 0.57%	82/6200 1.3%	0.4 (0.29, 0.63)

Statistical Methods Used by FDA Integrated Analysis

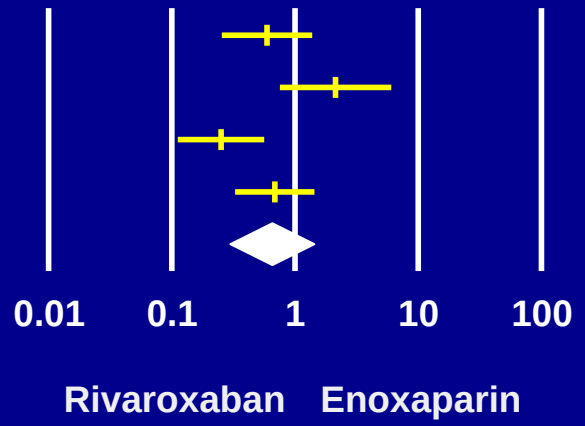
- **Meta-Analysis**
  - Provides ability to control between-study variation
  - Provides more precise estimate of the overall treatment effect
- **Proportional Hazard Regression adjusted for covariates**
  - Enables adjustment for the covariates or risk factors
  - Gives more precise analysis
  - Increases model power

Meta Analysis for Symptomatic VTE or Death for Pooled Study

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
RECORD 1	0.593	0.259	1.358	-1.236	0.216
RECORD 2	2.135	0.768	5.935	1.454	0.146
RECORD 3	0.251	0.114	0.554	-3.423	0.001
RECORD 4	0.685	0.331	1.418	-1.019	0.308
	0.654	0.298	1.438	-1.056	0.291

Statistics for each study

Hazard ratio and 95% CI



Meta Analysis

FDA Analyses Results for Symptomatic VTE or Death

- Proportional Hazard regression adjusting for 3 covariates:
  - Study
  - Treatment duration
  - Age

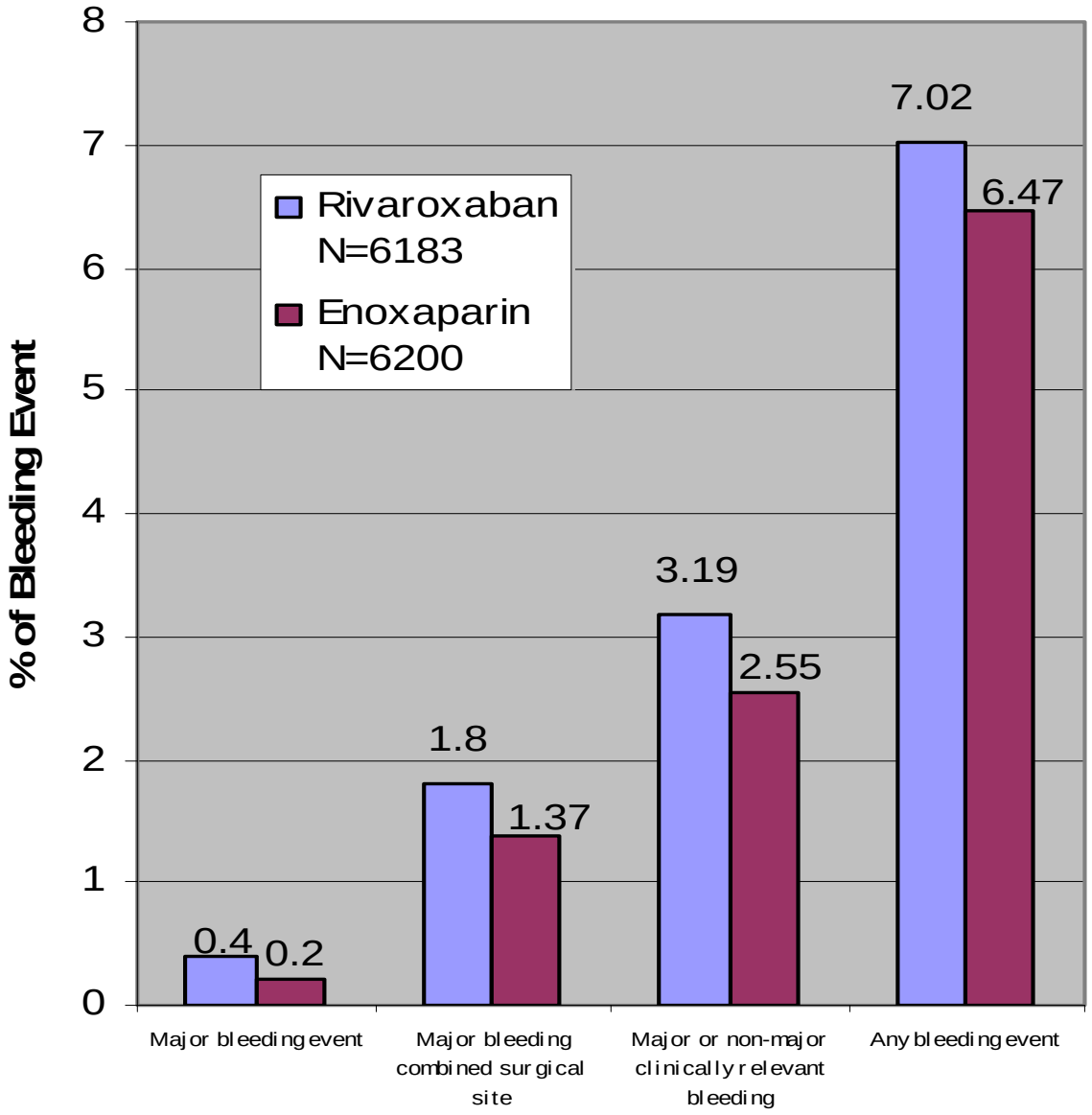
  P-value =0.07 Hazard Ratio=0.69

  95% Confidence Interval= (0.46, 1.04)

Bleeding Risk

An Evaluation

% of Bleeding Event for Total Duration in Pooled Study



FDA Analysis Results for Bleeding

Proportional Hazard Regression Model Adjusted for Covariates

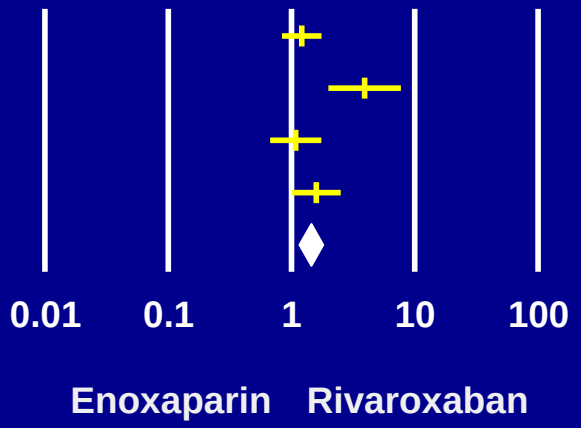
Type of Bleeding	P-value	HR	95% CI
Major or Non-Major Clinically Relevant Bleeding	<0.0001	1.56	(1.2, 1.9)
(sponsor's results)	(0.039)	(1.3)	(1.0, 1.5)
Major Bleeding	0.0037	3.0	(1.4, 6.2)
(sponsor's results)	(0.078)	(1.8)	(0.94, 3.6)
Major Bleeding Incl Surgical Site	0.0035	1.6	(1.1, 2.1)
(sponsor's results)	(0.063)	(1.3)	(1.0, 1.7)
Any Bleeding	0.0226	1.17	(1.0, 1.4)
(sponsor's results)	(0.26)	(1.1)	(0.9, 1.2)

Meta Analysis for Major or Non-major Clinical Relevant Bleeding Pooled Study

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
RECORD 1	1.210	0.850	1.722	1.058	0.290
RECORD 2	3.921	2.029	7.578	4.065	0.000
RECORD 3	1.082	0.680	1.721	0.333	0.739
RECORD 4	1.587	1.020	2.468	2.049	0.040
	1.446	1.157	1.807	3.240	0.001

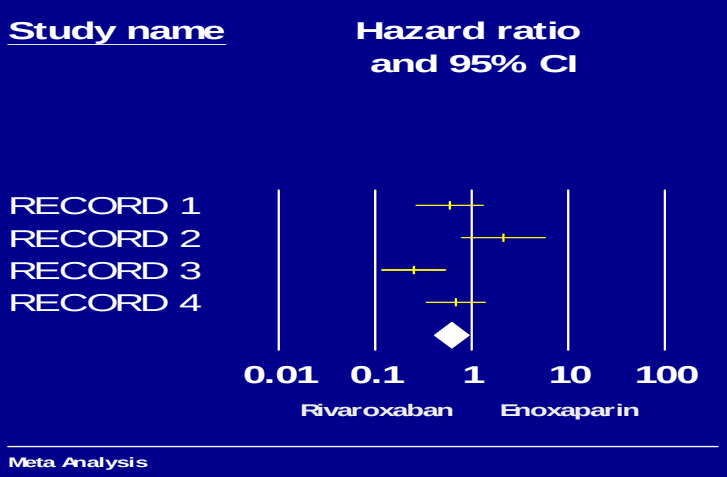
Statistics for each study

Hazard ratio and 95% CI

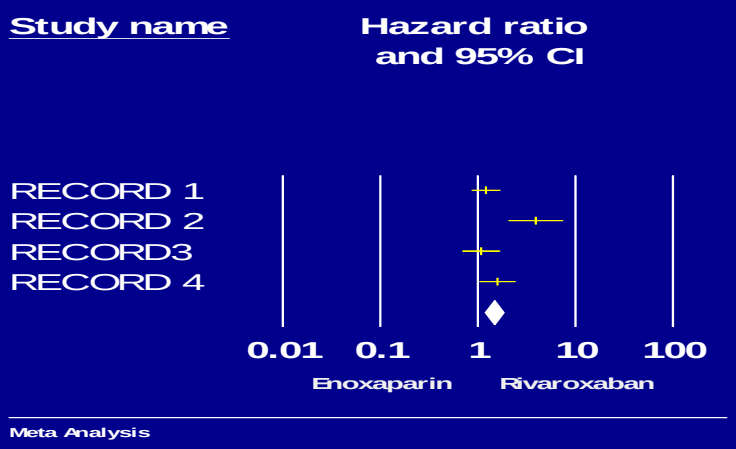


Meta Analysis

Mata Analysis for Symptomatic VTE or Death for Pooled Study



Meta Analysis for Major or Non-major Clincal Relevant Bleeding Pooled Study



Benefit/Risk

- Evidence of efficacy of Rivaroxaban for anticoagulation prophylaxis
  - In terms of Total VTE (Primary Efficacy Endpoint)
- No evidence of superiority of Rivaroxaban compared to Enoxaparin
  - For “Symptomatic VTE or Death”
- Consistent evidence of increased risk of bleeding for Rivaroxaban compared to Enoxaparin