# Oral Anticoagulants – New Regulatory Considerations

Martin Rose, MD

FDA/CDER Division of Cardiovascular and Renal Products

The views expressed in this presentation are those of the presenter and do not necessarily represent the views of the FDA.

# Topics

- Results of the trials of novel agents by stroke type
- Dabigatran – selection of marketed dose
- Thrombotic events after discontinuation of study drug in the major trials
- Antidotes for the novel agents
- Choice of comparator in future trials

# Effects on Stroke

## HR (95% CI) vs. Warfarin or Aspirin

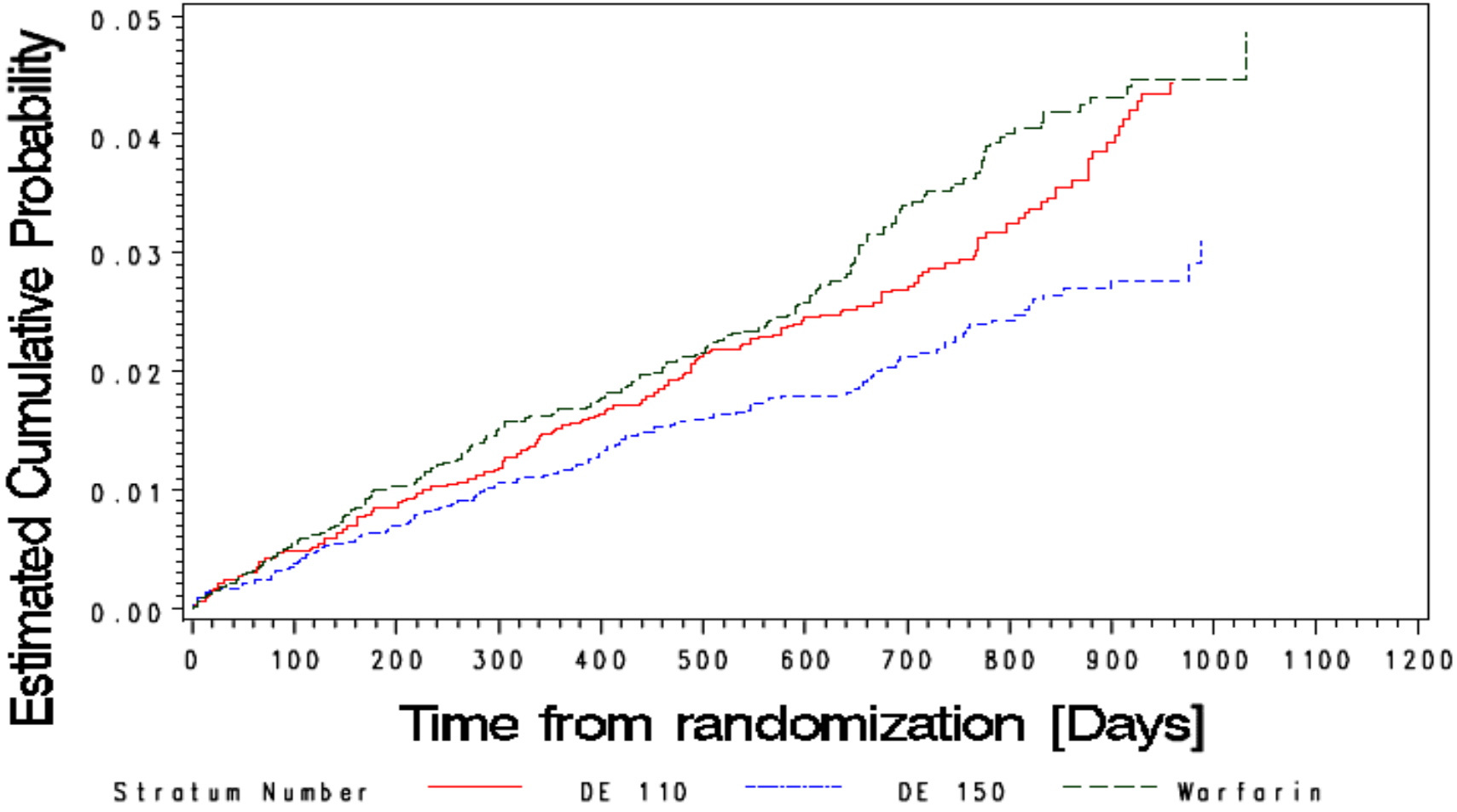
| | Stroke Type | | | |
|---|---|---|---|---|
| | All | Ischemic | Hem. | Unknown |
| Dabigatran 150 mg | 0.64 (0.51, 0.81) | 0.75 (0.58, 0.81) | 0.26 (0.14, 0.49) | - |
| Dabigatran 110 mg | 0.91 (0.89, 1.42) | 1.13 (0.89, 1.42) | 0.31 (0.17, 0.56) | - |
| Rivaroxaban | 0.85 (0.70, 1.03) | 0.94 (0.75, 1.17) | 0.59 (0.37, 0.93) | 0.65 (0.25, 1.67) |
| Apixaban ARISTOTLE | 0.79 (0.65, 0.95) | 0.92 (0.74, 1.13) | 0.51 (0.35, 0.75) | - |
| Apixaban AVERROES | 0.46 (0.33, 0.65) | 0.37 (0.25, 0.55) | 0.67 (0.24, 1.88) | 2.24 (0.69, 7.27) |



Data from FDA Reviews of RE-LY, ARISTOTLE, AVERROES

# Dabigatran – Dose Selection

## Results of RE-LY – Time to Stroke/SE




**D 150 mg vs. D 110 mg: HR=0.72 (0.58, 0.90), p=0.004**

# Dabigatran – Dose Selection

## Results of RE-LY – Risk-Benefit

| | Events per 1000 patient-years | | |
|---|---|---|---|
| | D 110 mg | D 150 mg | Δ |
| Mortality: Total | 37 | 36 | -1 |
| Vascular | 24 | 23 | -1 |
| Stroke/SE | 15 | 11 | -4 |
| Major Bleeds: Total | 29 | 33 | 4 |
| Life-Threatening | 12 | 15 | 3 |
| Fatal | 2.4 | 2.7 | 0.3 |
| Myocardial Infarction | 7 | 7 | 0 |

# RE-LY – Stroke/Systemic Emboli (SSE) and Major Bleeds (MB) in Vulnerable Subgroups Per 1000 Patient-Years

| Subgroup | D 110 | D 150 | Δ |
|---|---|---|---|
| Age ≥ 75 yrs SSE | 19 | 14 | -5 |
| Age ≥ 75 yrs MB | 44 | 51 | +7 |
| CrCl 30-50 mL/min SSE | 24 | 13 | -11 |
| CrCl 30-50 mL/min MB | 57 | 53 | -4 |

# Significant Bleeding Subsequent to an Initial Bleeding Event (%)

| | |
|---|---|
| Dabigatran 110 | 16% |
| Dabigatran 150 | 14% |
| Warfarin | 12% |



7

# Dabigatran – Dose Selection

## Results of RE-LY – Risk-Benefit

- D 150 superior to D 110 for primary endpoint
- Risk-benefit favors D 150 overall and in vulnerable subgroups based on age, renal function (and gender and aspirin use)

"Ultimately, the FDA's decision to approve only the 150-mg strength was based on our inability to identify any subgroup in which use of the lower dose would not represent a substantial disadvantage."

*Beasley et al. NEJM 364;19: 1788-90 (2011)*

# ROCKET – Stroke/SE From Day 3 To Day 30 after Last Dose of Study Drug in Completers

| | Rivaroxaban | Warfarin |
|---|---|---|
| Days after last dose | n/N | n/N |
| 3-30 | 22 / 4637 (6.42%)* | 6 / 4691 (1.73%)* |

* Events per 100 patient–years

*HR=3.72 (1.51, 9.16) p=0.004*

# Apixaban – Stroke/SE from Day 1 To Day 30 after Last Dose of Study Drug in Completers

| Study | Apixaban | | Control | | |
|---|---|---|---|---|---|
| | n/N | Rate* | n/N | Rate* | HR (95% CI) |
| **ARISTOTLE** | 21 / 6791 | 4.02 | 5 / 6569 | 0.99 | 4.07 (1.54, 10.81) |
| **AVERROES** | 9 / 1472 | 10.55 | 1 / 1421 | 1.20 | 8.78 (1.11, 69.34) |

* **Events per 100 patient-years**

# Other Topics

- Antidotes to Factor IIa and Xa inhibitors
- Choice of comparator in future studies

# ADDITIONAL SLIDES

# Bleeding definitions – only need one

| Definitions | Major[1] | LT[1] | GUSTO severe | ICH |
|---|---|---|---|---|
| Bleeding with hemoglobin (g/dL) reduction | ≥ 2 | ≥ 5 | | |
| Bleeding leading to blood transfusion | 2 U | 4 U | | |
| Symptomatic bleeding in critical area/organ | ✓ | | | |
| Symptomatic intracranial bleed | ✓ | ✓ | ✓ | ✓ |
| Bleeding associated with hypotension requiring intravenous inotropes | ✓ | ✓ | ✓ | |
| Necessitated surgical intervention | ✓ | ✓ | ✓ | |
| Fatal | ✓ | ✓ | | |

LT=life threatening, GUSTO=Global Use of Strategies to Open Occluded Coronary Arteries,

ICH=intracranial hemorrhage

1. adjudicated