For whom are the current dosages optimal? Who might benefit from alternative dosing strategies?

CSRC Meeting
Role for pharmacokinetic/pharmacodynamics guided dosing for novel anticoagulant
Dec 3, 2015

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Disclosures

• Relationships with commercial interests: Bayer, Sanofi (honoraria/grants)

• Relationship with academic interests: New Investigator Fund, Hamilton Health Sciences
Stroke/SEE & major bleeding rates on warfarin and NOACs

Can we do better with alternative dosing strategies?

4. Ruff et al., Am Heart J 2010; 160:635-41
What factors affect clinical outcomes in NOAC-treated patients?
E.g., dabigatran

Possible dosing strategies:

• Dose adjustment based on clinical factors
  ▪ Age, renal function, body weight, co-medications
  ▪ Larger (absolute reduction) effect on bleeding, modest effect on stroke/SEE

• Dose adjustment based on drug level
  ▪ Testing strategy: test all or test selected patients
  ▪ Effect on clinical outcome is unclear
Who might benefit the most from dose adjustment based on laboratory monitoring?

Dabigatran

Rivaroxaban

Apixaban

Edoxaban

Patients at higher risk of bleeding
Steeper relationship
Higher absolute risk reduction

Figures obtained from:
FDA Medical Review documents & Ruff CT et al, Lancet March 2015
Note: y-axes use different scales
Factors to consider when adjusting dose based on a high drug level?

• Does “single” high drug level measurement remain consistently high?
  – can one measurement reliably identify patients with consistently high level?

• Will dose adjustment (within the constraint of dosing formulation approved) result in drug levels within the selected window?
Dabigatran variability study:

Aims:

1. Estimate inter- and intra-patient variability in dabigatran level

2. Explore whether one drug level can reliably identify patients with extreme levels

Can a single drug level measurement reliably identify patients with consistently high level (> 80th centile)?

- Proportion of patients with levels remaining above 129 ng/ml
  - At M2: 88.2% (95% CI, 64.4–97.9%)
  - At M4: 80.0% (95% CI, 47.9–95.4%)
  - At M6: 70.0% (95% CI, 39.2–89.7%)

- Up to 30% of dabigatran-treated patients did not have subsequent levels in upper extreme.

Unknowns:

• Does single high drug level remain consistently high in subsequent measurements for the other DOACs?

• Will dose adjustment (using approved doses) result in a higher proportion of drug levels within a selected window?

• Will dose adjustment improve clinical outcomes?