Generate Knowledge

# What is the pathway for approval of tests for measuring the specific anticoagulant activity of NOAC?

François Depasse

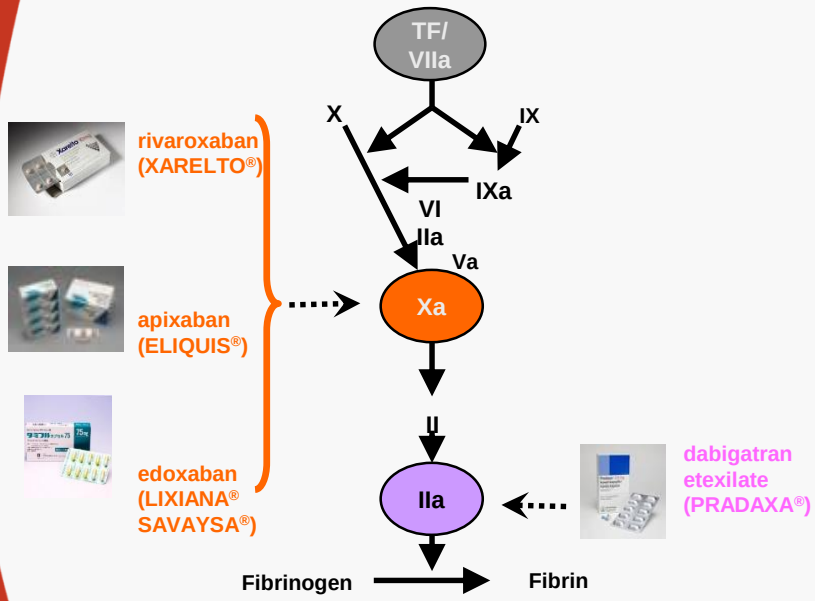
Cardiac Safety Research Consortium Meeting

December 3rd, 2015

Stago

# Background

*NOAC are changing the anticoagulation paradigm*




- **Non inferior to VKA or even superior in some patient subgroups**
  - Less intracranial bleeding
  - Increased risk of gastrointestinal bleeeding (but less severe)
- **No routine monitoring**
- **No dose adjustment based on test results**

Expert consensus that measurement can be of help in some situations

IVD companies including Stago have developed specific assays to measure NOAC anticoagulant activity

Stago

# Background

*When could NOAC measurement be useful?*

- **Emergency situations**
  - Severe bleeding
  - Invasive procedure / emergency surgery
  - Thrombotic episodes including stroke
    - Thrombolysis…
- **Reversal procedures**
  - Use of antidotes
- **Risk of overdosage**
  - Deterioration of renal / liver function
  - Drug-drug interactions
- **Treatment adherence**
- **Dose adjustment???**
  - Need for evidence-based decision

Stago

# What works well today

*NOAC meet a strong success*

- **NOAC precription steadily increases to the detriment of VKA**
  - NOAC ≅ 25% of all anticoagulant prescriptions in 2014
    - 1st NOAC marketed in 2010
  - NOAC > VKA for new patients
    - 55% NOAC vs 45% VKA

IMS Health National Prescription Audit, Data through 2/6/15

Stago

# What works well today

*Reliable IVD assays are available*

- **PT, APTT are not specific and CANNOT be used for accurate measurement**
- **LC-MS is the reference assay used during drug development**
  - Esoteric methodology
  - Limited availability
- **Specific quantitative assays for the measurement of NOAC are CE marked and available in many countries**
  - Europe, Asia, Middle-East, Australia, New Zealand, Latin America
  - Traceable to LC-MS
  - Assay performances are acknowledged

*Adcock-Funk D. FDA Public Worshop. In vitro Diagnostic Testing for Direct Oral Anticoagulants, October 26th, 2015*
*Gosselin R. FDA Public Worshop. In vitro Diagnostic Testing for Direct Oral Anticoagulants, October 26th, 2015*

Stago

# What is missing, broken or does not work well today

*Drug-related considerations*

- **Bleeding cases, some of them fatal**
  - Rare situations
  - Often associated with risk factors
    - Elderly, renal impairment, drug-drug interactions
  - Treatment adherence
- **Pivotal studies conducted in selected patients**
  - « Real life » patients?
    - e.g.: elderly treated life long for SPAF are often polymedicated and may to some degree develop renal insufficiency
- **Emerging debate on the opportunity of testing from time to time patients on long term therapy**
- **Accumulating KOL communication on possible dose adjustment**
  - Limited approved dose adjustement options

Stago

# What is missing, broken or does not work well today

*Reference range, cut-offs, alert values*

- **No consensus on the time blood should be drawn**
  - Peak, trough, randomly?
    - Dramatic impact on drug level due to NOAC PK
- **No reference range for test result**
  - High inter- and intraindividual variability
  - Only observed values available from drug development
  - « On Therapy Range »:
    - 5th percentile trough level – 95th percentile peak level
- **No cut-offs, No alert values, No consensus on clinical decision based on test result**

**Consensus on the need for tests being made available rapidly as expressed during the FDA Public Workshop held on October 26th, 2015**

*Cuker A. FDA Public Worshop. In vitro Diagnostic Testing for Direct Oral Anticoagulants, October 26th, 2015*
*Korley F. FDA Public Worshop. In vitro Diagnostic Testing for Direct Oral Anticoagulants, October 26th, 2015*
*Moll S. FDA Public Worshop. In vitro Diagnostic Testing for Direct Oral Anticoagulants, October 26th, 2015*

Stago

# What is missing, broken or does not work well today

*Difficulties for an IVD company (1)*

- **Cut-offs and associated patient's management:**
  - Beyond the sole capabilities of an IVD company
- **NOAC assay market is limited**
  - SPAF = largest potential for NOAC measurement (~3M AF patients in the US[1])

| Treatment for SPAF | % of Patients | Nb of Patients | IVD Testing | Patients that may benefit from testing / year | Tests / Patient / Year | Potential nb of tests / year |
|---|---|---|---|---|---|---|
| No treatment | ~50% | 1 500 000 | 0% | / | / | / |
| VKA | ~25%[2] | 750 000 | 100% | 750 000 | > 12 | ~ 9 millions |
| NOAC | ~25%[2] | 750 000 | 10 -20%[3] | 75 000 to 150 000 (if tests available) | < 3 | ~ 450 000 |

→ Significant number of patients may benefit from NOAC measurements

BUT…

→ NOAC testing potential market is limited compared to VKA monitoring

1- Adcock DM, Gosselin R. Thromb Res 2015; 136: 7-12
2- IMS Health National Prescription Audit, Data through 2/6/15
3- Pernod G *et al.* Arch Cardiovasc Dis 2013; 106: 382-93

# What is missing, broken or does not work well today

*Difficulties for an IVD company (2)*

## Validation study (CE):

- Primary objective:
  - Demonstrate the performances of the assay for quantitative determination of NOAC concentration in plasma samples
- Study design: method comparison
  - Based on CLSI EP09-A2/3 guideline
  - Reference method: LC-MS
- Samples included in the study:
  - Plasma samples with NOAC concentration covering the assay measuring range
    - Plasma samples are native as far as possible, but
    - Contrived samples accepted to cover the high end of the measuring range:
      - These plasma samples are rare
      - Conducting HV trials would not solve the issue: ethical considerations + ceilling effect

# What is the highest priority short term (1 – 3 years)

- **Make assays available in the US**
  - Meet a clinical need
    - Tool for an improved patient'smanagement
  - FDA least burdensome pathway
    - Most efficient pathway for clearance
      - Balance investments/burden
      - Small portion of patients on DOAC will need testing
- **Initiation of Phase IV studies**
  - Pharma companies, KOL, Learning Societies
  - To document the clinical utility of NOAC testing

Stago

# What is the highest priority long term (3 – 5 years)

- **Phase IV studies**
  - Completion
  - Result analysis
- **Guideline for NOAC anticoagulant activity testing**
  - Which patient / clinical situation is **eligible for drug testing**?
  - Is there an indication for **periodic testing** in some patients? If yes in **which patients**?
  - At what time blood should be drawn *vs* drug intake?
  - Is it important to have **repeated measurement** and if yes in which **time frame** to estimate drug clearance?
  - **How to interpret** test results? reference range, “on therapy range”, cut-off / threshold / alert values (if defined)?
  - **How to manage** the patient based on test result? safe surgery / invasive procedure, NOAC reversal,..

Stago

# Conclusion

- **Management of patients receiving NOACs is still raising questions**
- **Although no routine monitoring is required, measurement can help improve patient's outcomes in special situations**
  - Benefit for patients, physicians and institutions
  - Even if no reference values nor thresholds are available
- **IVD specific assays are available outside US**

**IVD manufacturers look forward to work closely with the FDA to define the least burdensome pathway to have these assays cleared in a timely manner**

Stago