Η Σημασία των «Πραγματικών Δεδομένων» στην Καθημερινή Κλινική Πράξη

Real World Data

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The Journey from Drug Discovery to Clinical Use is a Long One

Drug tested in a small and well-controlled patient population

(1) Does it work?
(2) Is it safe (benefit to patient greater than risk)?

Interventional Clinical Trials

Protocol dictates which approved drug the patient will receive

(1) Compare the effectiveness of two or more interventions in real-world settings
(2) Seek clinically applicable evidence about the relative advantages and disadvantages of interventions to inform the decisions made by clinicians, patients, and others

Interventional Clinical Trials

Pragmatic Clinical Trials

(1) Does it still work?
(2) Is it still safe (benefit to patient greater than risk)?
(3) How is the drug being used?

Patient already taking the drug. Protocol dictates what information to collect

Non-Interventional Studies

Drug used in a large and less well-defined patient population

Drug Development

Knowledge Gap

Drug used by ‘Real Patients’
RCTs: The Gold Standard for Assessing Drug Efficacy and Safety
RCTs are Obviously Essential Steps but…

A standardized therapy in a selected group of patients…
RCTs are Obviously Essential Steps but…

Strict inclusion / exclusion criteria
...Under-representation of Subpopulations

“I feel guys like me are underrepresented in your sex life.”
What Happens in the Real World?
Phase III trial results do not always ‘translate’ well

The following drugs appeared to be ‘game changers’ in phase III but showed problems in the real world:

- Mibefradil (Posicor): Calcium channel blocker
- Rofecoxib (Vioxx): COX-2 inhibitor
- Rosiglitazone (Avandia): Thiazolidinedione
- Ximelagatran (Exanta): Direct thrombin inhibitor

After initial approval by agencies like the FDA and/or EMA, all were either withdrawn from the market or substantially limited in their use.
RWE clarifies whether results observed under RCTs are also observed in everyday clinical practice.

Nallamothu BK et al, Circulation 2008
Real World Data and Real World Evidence

Data collected from outside of trials

The insights that such data can generate
### Types of Real-life Observational Studies and Data Sources

- **Case series**
- **Cross-sectional studies or surveys**
- **Case–control studies**
- **Retrospective cohort studies**
- **Prospective cohort studies (longitudinal studies)**

<table>
<thead>
<tr>
<th>Data source</th>
<th>Examples</th>
<th>Patient selection</th>
<th>Data quality</th>
<th>Data amount</th>
<th>Outcomes</th>
<th>Other features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase IV studies</strong></td>
<td>XANTUS</td>
<td>Informed consent</td>
<td>eCRF</td>
<td>Prespecified</td>
<td>Adjudicated</td>
<td>Prospective design, independent endpoint adjudication</td>
</tr>
<tr>
<td><strong>Nationwide cohorts</strong></td>
<td>Danish cohort, Taiwan cohort</td>
<td>All</td>
<td>Diagnostic codes</td>
<td>Limited</td>
<td>Data linking</td>
<td>Rapid data collection, large N of patients</td>
</tr>
<tr>
<td><strong>Insurance claims datasets</strong></td>
<td>Medicare, US DoD, Truven MarketScan, Optum Insight</td>
<td>All</td>
<td>Disease codes</td>
<td>Limited</td>
<td>Data linking</td>
<td>Rapid data collection, large N of patients</td>
</tr>
<tr>
<td><strong>Societal registries</strong></td>
<td>EORP-AF Long Term, PINNACLE, FUSHIMI</td>
<td>Informed consent</td>
<td>eCRF</td>
<td>Prespecified</td>
<td>Investigator reported</td>
<td>Independent registries</td>
</tr>
<tr>
<td><strong>Industry sponsored registries</strong></td>
<td>ORBIT-AF, GARFIELD-AF, GLORIA</td>
<td>Informed consent</td>
<td>eCRF</td>
<td>Pre-specified, extensive</td>
<td>Investigator reported</td>
<td>Detailed, extensive information</td>
</tr>
</tbody>
</table>
Real-life Data Have an Important Role to Play…

…short- and long-term drug safety in clinical practice

More heterogeneous population,
higher rates of non-compliant patients
more subjects with significant comorbidities
Real-life Data Have an Important Role to Play...

..to assess the effectiveness of therapy in special populations
Real-life Data Have an Important Role to Play…

…to evaluate medication adherence and persistence
Phase IV Studies

Phase I
- Young healthy people
- Small group size (about 50)
- Tests: Possible harm, Side effects, Dosage

Phase II
- People affected by the disease
- Larger group size (up to 300)
- Tests: Whether treatment is effective in patients, Side Effects, Against a dummy treatment (called a placebo)

Phase III
- People affected by the disease
- Larger group size (up to thousands)
- Tests: Whether treatment is effective in patients, Over longer periods over many different countries, Often against other possible existing treatments

Treatment deemed safe / effective

Licensing
- Treatment licensed, and benefits weighed up by NICE against costs and limitations to help guide use in practice

Phase IV
- Tests over longer periods of time, in different groups of people and/or in combination with other treatments
- Ten to fifteen years later
XANTUS Programme

XANTUS
Europe, Israel and Canada

XANTUS-EL
Middle East, Eastern Europe, Africa and Latin America

XANAP
Asia Pacific

- XANTUS
- XANTUS-EL
- XANAP
XANTUS: Patients with AF in Real-World Clinical Practice

- XANTUS was an international, prospective, single-arm, observational phase IV study.

**Population:**
Adult patients with non-valvular AF receiving rivaroxaban for stroke/non-CNS SE prevention, who had provided written informed consent.

**Objectives:**
To collect data on adverse events in patients treated with rivaroxaban to determine its safety profile across the broad range of patient risk profiles.

**Primary outcomes:**
Major bleeding (ISTH definition), all-cause mortality, any other adverse events.

**N=6784**

**Data collection at initial visit, hospital discharge (if applicable) and quarterly:**

- **1 year**

**Final visit:**
1 year
Population: Adult patients with NVAF receiving rivaroxaban for stroke/non-CNS SE prevention

Rivaroxaban; treatment duration and dose at physician’s discretion

Data collection at initial visit, hospital discharge (if applicable) and quarterly*

N=16,187

N=11,121

1 year

Final visit: 1 year#

XANTUS pooled

XANTUS
Europe, Israel and Canada

XANTUS-EL
Middle East, Eastern Europe, Africa and Latin America

XANAP
Asia Pacific
XANTUS Major Strengths

An independent Central Adjudication Committee adjudicated major bleeding, stroke, SE, TIA, MI, and all-cause death

Prospective design
XANTUS Reaffirms the Safety and High Effectiveness of Rivaroxaban in the Real World

**Effectiveness**

- Stroke/S: 0.8%
- Death: 1.9%

**Safety**

- Major bleeding: 2.1%
- ICH: 0.4%
- GI bleeding: 0.9%

### Baseline Event Rate

<table>
<thead>
<tr>
<th>CHADS2 Value</th>
<th>Event Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>41%</td>
</tr>
<tr>
<td>2</td>
<td>30%</td>
</tr>
<tr>
<td>≥3</td>
<td>29%</td>
</tr>
</tbody>
</table>

- Heart failure: 19%
- Hypertension: 75%
- Age >75 years: 37%
- Diabetes: 20%
- Prior stroke*: 19%
- Prior MI: 10%

*Events per 100 patient-years; *includes prior stroke, SE or TIA
Cumulative rates for treatment-emergent major bleeding, stroke/non-CNS SE and all-cause death

Kirchhof et al, Poster presented at ESC 2017
The XANTUS program analyzed data from 11,121 patients globally and is currently the largest prospective, observational program of a single NOAC for stroke prevention in patients with NVAF.

Reaffirms the Safety and High Effectiveness of Rivaroxaban in the Real World.

Major strengths of the XANTUS pooled analysis include adjudication of all events by one Central Adjudication Committee to minimize reporting bias, and the prospective design with pre-planned analysis.
Registries

Registries represent a more unselected population compared to claims or national administrative data.

**Registry-based, centrally adjudicated**
- High specificity and sensitivity
- More detailed event information (i.e., ISTH major bleeding criteria)
- More costly
- Smaller and more selected populations
- May have less external validity

**Administrative claims or electronic health records**
- Larger populations can be efficiently included
- Less costly
- Shorter lag time (if retrospective)
- May have more external validity

**Strengths**

**Limitations**
- Less detailed event information
- Lower sensitivity and/or specificity
- Coding practices may change over time
Limitations and Challenges with RWD

- **Selection bias**: inadvertent or intentional differences in selection of patients for treatment
- **Performance bias**: the result of differences in adherence
- **Detection bias**: the result of differential assessment of outcomes
- **Attrition bias**: the result of differences in the groups that withdraw from a study
The amalgamation of RWD from multiple sources presents several issues.
Limitations and Challenges with RWD

✓ The lack of patient selection, one of the most distinctive characteristics of real life studies, makes it impossible to avoid unmeasured confounding factors.
Limitations and Challenges with RWD

> Quality of data is an important concern
> ✓ the accuracy of coding is variable and is not easily verified
> ✓ incompleteness of patients’ information
> ✓ only outcomes that lead to hospital visits and new billing codes can be captured
Limitations and Challenges with RWD

Inclusion/exclusion criteria not strictly monitored:

Ineligible patients enroll and weaken the generalizability of findings
The absence of blinding and randomization does not always allow factors potentially influencing the outcomes to be properly balanced.
Limitations and Challenges with RWD

Follow-up not standardized as in RCT
Ascertainment of outcomes incomplete or inaccurate

Missing data greater problem
But Wait! We Can Adjust for all that!..
...Limitations and Challenges with RWD

Even after sophisticated analysis, studies of this type are generally subject to bias.

...studies often match on ~30–50 ‘relevant’ characteristics, but many more diagnoses and drugs exist.
Limitations and challenges with RWD

- Electronic health records and administrative claims are generated for reimbursement and administrative purposes…
Real World of Registries: What Can Happen

- Physician assign patients who are more likely to have favorable outcomes to one treatment over another
- Physician favors one treatment over another due to their training or skill level
- A more demanding patient may receive more monitoring or additional care
- A patient who is more educated, information-seeking or affluent might engage in other behaviors that contribute to the outcomes
- Adherence is more likely to be poorer outside a controlled trial
- Patients may be taking other medications
What Have We Learned from Real World Studies on Direct Oral Anticoagulants?
Making Sense of the Data

- Randomized clinical trial
  - ROCKET AF
  - n=7111
- Prospective registry
  - Dresden NOAC
  - n=1204
- Retrospective
  - US DoD PMSS
  - n=27,467
- Prospective NIS
  - (adjudicated events)
  - XANTUS
  - n=6784

**Major bleeding event rate/100 patient-years**
- 3.6
- 3.0
- 2.9
- 2.1

**Mean CHADS² score**
- 3.5
- 2.4
- 2.2
- 2.0

**consistency of results**
Making Sense of the Data

Randomized clinical trial
ROCKET AF n=7111

Prospective registry
Dresden NOAC n=1204

Prospective NIS
(adjudicated events)
XANTUS n=6784

GI bleeding event rate/100 patient-years

Mean CHADS² score

2.0
1.2
0.9

3.5
2.4
2.0

consistency of results
Making Sense of the Data

Major bleeding event rate/100 patient-years

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean CHADS2</th>
<th>Major bleeding rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized clinical trial</td>
<td>3.5</td>
<td>3.6</td>
</tr>
<tr>
<td>Prospective registry</td>
<td>2.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Retrospective</td>
<td>2.2f</td>
<td>2.9</td>
</tr>
<tr>
<td>Study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective NIS</td>
<td>2.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Retrospective Medicare</td>
<td>2.7</td>
<td>6.3</td>
</tr>
</tbody>
</table>

CHADS2: Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and stroke, transient ischemic attack or thromboembolism in the past.
GARFIELD-AF: Underuse of OACs in pts with AF

Camm J et al. Heart 2017
NOAC Underdosing

**REVISIT US**
- Apixaban (n = 4083): 15.5%
  - Rivaroxaban (n = 11,411): 17.3%

**ORBİT-AF**
- Dabigatran (n = 425): 7.5%
  - Rivaroxaban (n = 3078): 8%
  - Apixaban (n = 2235): 11.8%
NOAC Off-Label Dosing

Benjamin A. Steinberg et al. JACC 2016
NOAC over- and Underdosing are Associated with Increased Risk for Adverse Events
NOACs Dosing in pts with AF and Renal Dysfunction

Yao et al, J Am Coll Cardiol 2017
# Real World Discontinuation Rates

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>NOAC</th>
<th>Design</th>
<th>N</th>
<th>Adh/Pers</th>
<th>pr outcome</th>
<th>Fup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forslund (76)</td>
<td>2015</td>
<td>Sweden</td>
<td>Dabigatran Rivaroxaban Apixaban</td>
<td>Observational Prospective</td>
<td>2,701</td>
<td>92.0% / 74.4%</td>
<td>Adherence &amp; Persistence Rate</td>
<td>1 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2,074 / 1,352</td>
<td></td>
<td>95.7% / 77.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>93.5% / 85.9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martinez (77)</td>
<td>2015</td>
<td>UK</td>
<td>All NOACs*</td>
<td>Observational Retrospective</td>
<td>914</td>
<td>79.2%</td>
<td>Persistence Rate</td>
<td>1 year</td>
</tr>
<tr>
<td>McHorney (75)</td>
<td>2015</td>
<td>United States</td>
<td>Dabigatran Rivaroxaban Apixaban</td>
<td>Observational Retrospective</td>
<td>6,548</td>
<td>67.2%</td>
<td>Adherence Rate</td>
<td>1 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11,095 / 3,532</td>
<td></td>
<td>72.7% / 69.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shiga (74)</td>
<td>2015</td>
<td>Japan</td>
<td>All NOACs*</td>
<td>Observational Retrospective</td>
<td>401</td>
<td>70.0%</td>
<td>Discontinuation Rate</td>
<td>12 months</td>
</tr>
<tr>
<td>Alberts (80)</td>
<td>2016</td>
<td>United States</td>
<td>All NOACs*</td>
<td>Observational Retrospective</td>
<td>38,868</td>
<td>70.3%</td>
<td>Ischemic Stroke</td>
<td>12 months</td>
</tr>
<tr>
<td>Beyer-Westendorf (78)</td>
<td>2016</td>
<td>Germany</td>
<td>Dabigatran Rivaroxaban</td>
<td>Observational Retrospective</td>
<td>821</td>
<td>47.6% / 47.3%</td>
<td>Adherence &amp; Persistence Rate</td>
<td>360 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1,317</td>
<td></td>
<td>62.6% / 53.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coleman (60)</td>
<td>2016</td>
<td>United States</td>
<td>Dabigatran Rivaroxaban</td>
<td>Observational Retrospective</td>
<td>10,878</td>
<td>38.0%</td>
<td>Adherence Rate</td>
<td>24 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10,878</td>
<td></td>
<td>49.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yao (79)</td>
<td>2016</td>
<td>United States</td>
<td>Dabigatran Rivaroxaban Apixaban</td>
<td>Observational Retrospective</td>
<td>10,235</td>
<td>38.5%</td>
<td>Stroke/TIA/SEE Major Bleeding</td>
<td>1.1 years (median)</td>
</tr>
</tbody>
</table>
Use of RWE to Compare the Efficacy and/or Safety of One Drug vs. Another

Therefore, comparisons in non-interventional studies, even with careful propensity score matching, remain less reliable than comparisons from randomised controlled trials.
Real World Studies Landscape...

US and Europe top locations for RWS

Drugs are the most popular technology studied
However RCTs Remain the Gold Standard...
Especially DOACs Randomised Controlled Trials

- over 80% of patients screened for participation were actually enrolled into the trials
- the enrolled population is representative of daily practice
Rivaroxaban plus aspirin improves survival and reduces stroke and heart attack in patients with stable coronary or peripheral artery disease.
<table>
<thead>
<tr>
<th>CV Patients – with AF</th>
<th>CV Patients – no AF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticoagulation Dose</strong></td>
<td><strong>Vascular Dose</strong></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>20 mg od</td>
<td>2.5 mg bid</td>
</tr>
<tr>
<td>15 mg od (CrCl 15–49 m/min)</td>
<td>Combined with aspirin</td>
</tr>
<tr>
<td><strong>Left atrial thrombus Formation</strong></td>
<td>Atherosclerosis &amp;</td>
</tr>
<tr>
<td></td>
<td>Plaque Rupture</td>
</tr>
<tr>
<td><strong>AF – Embolic Stroke</strong></td>
<td>Atherothrombotic Stroke</td>
</tr>
</tbody>
</table>

AF: Atrial Fibrillation
COMPASS represents an important step forward in thrombocardiology, and it is likely to change practice guidelines
OACs Real World Studies
OACs Real World Studies Evaluation...
…All that Glitters is not Gold