CHALLENGES IN THE USE OF REAL-WORLD EVIDENCE FOR PHARMACOECONOMIC MODELLING

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Participants and disclosure




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- This project was funded by Bayer AG

Introduction

- **Economic evaluation**: estimation of ICERs to document comparative efficiency of healthcare technologies
- Evidence on 4 types of parameters requested
  - Epidemiological data
  - Resource use and treatment costs
  - Patient data (HRQL, adherence)
  - Relative treatment effects
- What is the most appropriate data to populate models, especially treatment effect ?
  - RCT data? → High internal validity, low external validity
  - What about effectiveness? Difficult to say at launching
  - RWD ≈ non-RCT data
- Which, when and how should RWE be used?
  - Current availability of RWE allows development of true cost-effectiveness models
- Many challenges remain
  - How to perform meta-analyses of RWD for treatment effect are needed?
  - How to cope with selection bias or missing data ?

ICER: Incremental Cost-Effectiveness Ratio, **RCT**: Randomized Controlled Trial, **RWE**: Real-World Data; **RWE**: Real-World Evidence

Objectives of the workshop

1. To summarize existing guidelines and recommendations for the use of RWE
   - in meta-analysis and,
   - in economic modelling
2. To share key learnings from experience in the context of stroke prevention in patients with NVAF
3. To benefit from audience experience

NOAC: Non-VKA Oral Anticoagulant, **NVAF** : Non-Valvular Atrial Fibrillation; **RWE**: Real-World Evidence

1. **Review of recommendations on RWE meta-analyses**
2. Illustrative example: rivaroxaban in SPAF
3. Review of recommendations on RWE cost-effectiveness models
4. Illustrative example: rivaroxaban in SPAF

Context, objective and methods

- Considering RWE in meta-analyses: potential benefits but also concerns

Objective: Summarize key recommendations of RWE use in meta-analyses

- SLR identified >1,500 citations
  1. Formal guidelines
  2. Recommendations
  3. Bias adjustment methods

RWE: Real-World Evidence; **SLR**: Systematic Literature Review

No guidelines, but some recommendations

1. Formal guidelines

- None

2. Main recommendations

Consensus on need for quality assessment but not consensus on how:

- No preferred instrument
  - Downs & Black, Chalmers, ROBINS-I, Newcastle-Ottawa Scale, GRACE, CriSTal, SIGN, GATE
- Quality assessment measure
- Risk of bias ≠ quality of evidence

Consensus on need for sensitivity analyses but no consensus on what:

- Study designs
- Follow-up
- Population
- Interventions
- Outcomes definitions
- Risk of bias

Several bias adjustment options exist

3. Bias adjustment methods

- Ioannadis summarized options on how to deal with biases in RWE meta-analyses:
  1. **Ignore** biases
  2. **Record** biases and **discuss** them qualitatively
  3. **Record** biases and **exclude** bad-quality studies
  4. **Record** biases and **avoid** performing meta-analysis
  5. **Record** biases, score them and **weigh** studies by overall quality in meta-analysis
  6. **Model** biases

Doi et al.

- Weigh studies based on their quality assessment and rank them
- Quality weight = ranking/N
- Final weight: quality weights x 1 / variance

- Options not validated empirically
- No consensus on best option

RWE: Real-World Evidence

What have we learnt?

- Lack of formal guidelines
- Existing recommendations
  - Need to assess quality of RWE... but how?
  - Need to conduct sensitivity analyses... but which ones?

➢ **Need for methodological guidance**

RWE: Real-World Evidence

1. Review of recommendations on RWE meta-analyses
2. **Illustrative example: rivaroxaban in SPAF**
3. Review of recommendations on RWE cost-effectiveness models
4. Illustrative example: rivaroxaban in SPAF

Context and objective

- AF is the most common cardiac arrhythmia (affects 1-2% of global population)
- Treatment recommendations: VKA, NOACs preferred
- Existing RWE overall in line with RCT results although conflicting results

Objective: Meta-analyse available RWE to evaluate the performance of rivaroxaban compared with VKA in patients with NVAF

- 3 steps
  1. Identification of studies
  2. Selection of base case
  3. Assessment of uncertainty

AF: Atrial Fibrillation; **NOAC**: Non-VKA Oral Anticoagulant; **NVAF** : Non-Valvular Atrial Fibrillation; **RWE**: Real-World Evidence; **VKA**: Vitamin K Antagonist

Identification of studies

P	Population	Adult patients with NVAF
I	Interventions	Rivaroxaban
C	Comparator	VKA
O	Outcomes	Ischemic Stroke (IS), Myocardial Infarction (MI), Intracranial Haemorrhage (ICH)
S	Study designs	Comparative non-randomized studies

NVAF : Non-Valvular Atrial Fibrillation; **RWE**: Real-World Evidence; **VKA**: Vitamin K Antagonist

Base case assumptions

Type of reference
- All studies (full texts + abstracts)

Patient population
- All studies (incident + prevalent)

Definition of outcomes
- All studies (although heterogeneity)

Adjustment
- All adjustment types (adjusted and crude HRs)

Dosage
- Use of pooled dosages

Follow-up
- Restriction to longest follow-up

Sample overlap
- Restriction to study with the highest precision

HR: Hazard Ratio

Scenarios to explore uncertainty

1. Patient population
- Exclusion of prevalent studies

2. Adjustment
- Exclusion of studies with no adjustment

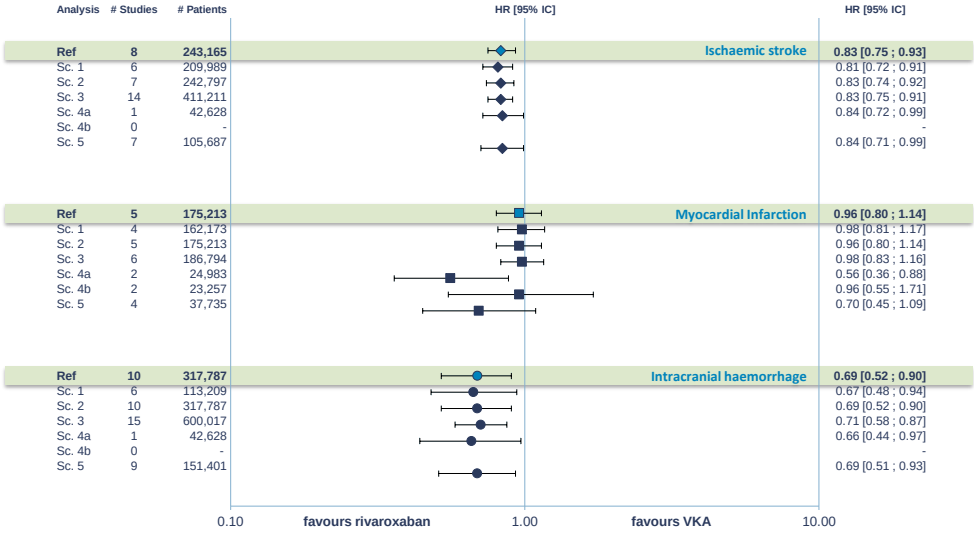
3. Sample overlap
- Inclusion of all studies independently of possible sample overlap

4. Dosage
- Distinction of HRs depending on dosage (low, high)

5. Quality assessment
- Doi et al. method to weigh the studies based on their quality assessment (Downs and Black checklist)

HR: Hazard Ratio

RWE meta-analysis results



HR: Hazard Ratio; **Sc**: Scenario (1-incident; 2-adjustment; 3-sample overlap; 4-dosage; 5-quality)

What have we learnt?

- RWE meta-analysis to be tailored to the intervention in scope
  - Assess population heterogeneity
  - Assess intervention and comparator heterogeneity
  - Assess outcome heterogeneity
- Conduct extensive sensitivity analyses
- Involve relevant experts (SLR, NMA, RWE, clinical, economist)

NMA: Network Meta-Analysis; **RWE**: Real-World Evidence; **SLR**: Systematic Literature Review;

1. Review of existing recommendations on conducting meta-analyses with RWE
2. Illustrative example: rivaroxaban in SPAF
3. **Review of existing recommendations and limitations on RWE cost-effectiveness models**
4. Illustrative example: rivaroxaban in SPAF

Context, objective and methods

- To support P&R decisions over time, use of RWE can provide more realistic estimates of cost-effectiveness
  - Does it work in routine clinical practice?
  - It is good value for money?
- How can we develop models based on RWE?

Objective: Summarize key recommendations and limitations regarding RWE cost-effectiveness analyses

- Identification of >1,500 citations
  1. Formal guidelines
  2. Examples of submission dossiers based on RWE
  3. Suggestions to address limitations

P&R: pricing and reimbursement; **RWE**: Real-World Evidence

Limited guidance exists

1. Formal guidelines (in studies comparing recommendations by HTA bodies)

- Most guidelines state RWE may be included or requested in many EU HTA agencies
  - Epidemiological data
  - Clinical practice (treatment pathways, comparators)
  - Resource use and costs
  - Patient data
- Recognition of potential biases associated with non-RCT data
- However, scope of guidance is limited or incomplete
- Consideration of the use of RWE for external validation of models
- For estimating relative treatment effects
  - RWD considered of lower quality than RCT data (EBM hierarchies of evidence)
  - Useful for extrapolation of data beyond period observed in RCTs

EBM: Evidence-Based Medicine; **EU**: European Union; **HTA**: Health Technology Assessment; **RCT**: Randomized Controlled Trial; **RWE**: Real-World Evidence

RWE already used in submission dossiers

2. Review of RWE cost-effectiveness models in submission dossiers

- Review of submission for melanoma drugs assessed by main EU HTA (Makady et al.)
  - Differences between agencies regarding RWE use
    - ZIN and IQWiG cited RWE for evidence on prevalence
    - NICE, SMC and HAS rather cited RWE use for drug effectiveness
    - In economic models, use for long-term extrapolation
- Review of submissions to NICE in solid tumours (Waser et al.)
  - 80% of STAs included RWE; effectiveness and safety informed by RWE in <10%
  - RWE frequently used to inform survival or resource utilization
- Examples of NICE acceptance of RWE for economic modelling (George)
  - Use of non-RCT efficacy data or other clinical evidence relevant in 3 situations:
    - For devices
    - For interventions where RCTs are difficult
    - For conditions with poor prognosis where single-arm studies are often carried out

HAS: Haute autorité de Santé; **IQWiG** : Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; **NICE**: National Institute For Health And Clinical Excellence; **RCT**: Randomized Controlled Trial; **RWE**: Real-World Evidence; **SMC:** Scottish Medicines Consortium; **STA**: Single Technology Appraisal; **ZIN**: Zorginstituut Nederland

Different types of evidence; Benefits and Limitations

3. Different types of evidence

- Impact of using different types of evidence to inform RWE cost-effectiveness models
  - Different types of evidence → different benefits and limitations: these must be considered and weighted when seeking to integrate them to inform decision making (Campbell et al.)

Pragmatic trials
- ✅ Prospective, randomized
- ✅ Larger & more diverse RW populations
- ❌ Often compare a trial intervention to the next best alternative

Registries
- ✅ Prospective, non-randomized
- ✅ Help understand the natural history of a disease and to assess, or monitor, safety, effectiveness, and cost-effectiveness

Administrative databases
- ✅ Retrospective, non-randomized
- ✅ To collect and track payments for healthcare services
- ❌ Limited socioeconomic and demographic characteristics
- ✅ Detailed data on billing, monies paid, and associated diagnostics

Health surveys
- ✅ Can collect important patient-centered outcomes data as well as patient-reported economic and clinical outcomes
- ✅ Can contribute greatly toward the representativeness of a disease population
- ❌ Limited by subjectivity
- ❌ May be prone to recall bias if not administered carefully

RW: Real-World; **RWE**: Real-World Evidence

Quality assessment tool for appraising CEAs that use observational data

3. Tools to address limitations

- Availability of different methods to address selection bias
  - Regression, matching (on propensity score, on individual covariates), instrument variable methods
- Choice of method can lead to different conclusions
- Development of a checklist to assess whether CEAs used appropriate statistical methods for addressing selection bias (Kreif et al.)

- Assumption of no unobserved confounding?
- Assumption of good overlap in the distribution of baseline covariates between arms?
- Assumption that the parametric regression model is correctly specified?
- Assumption that a matching method has balanced the matched samples?
- Structural uncertainty from the choice of statistical method for addressing selection bias?

CEA: Cost Effectiveness Analysis; **RWE**: Real-World Evidence

What have we learnt?

- Limited literature and lack of formal guidelines
  - Despite informal consensus
- Individual recommendation on identification of bias and quality assessment

➢ **Need for methodological guidance**

- **What can be called a RWE cost-effectiveness model?** All models use RWE
  - Based on RWE comparative treatment effect?
  - Based on RWE inputs only ?
  - How much does a cost-effectiveness model need to have to be called a RWE cost-effectiveness model?

RWE: Real-World Evidence

1. Review of recommendations on RWE meta-analyses
2. Illustrative example: rivaroxaban in SPAF
3. Review of recommendations on RWE cost-effectiveness models
4. **Illustrative example: rivaroxaban in SPAF**

Context and objective

- Authorities have expressed interest in RWE for the use of NOACs in patients with NVAF

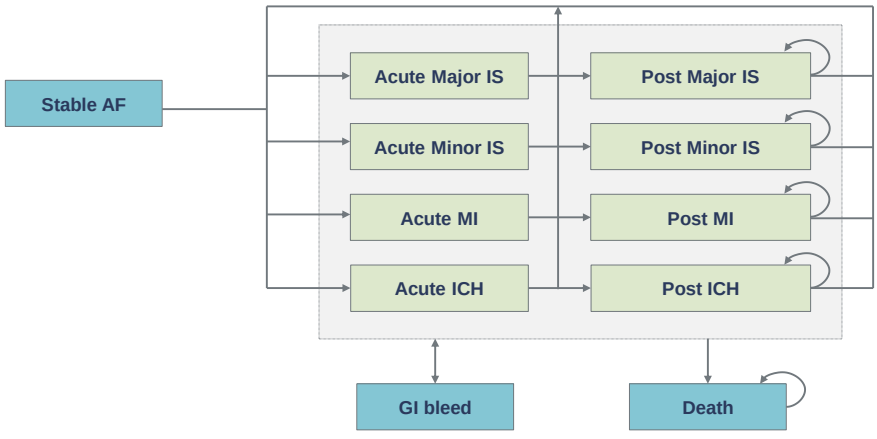
- France:
  - NOACs part of the national stroke plan
  - And increasing scrutiny regarding the cost of NOACs

Objective: Evaluate the RWE cost-effectiveness of rivaroxaban compared to VKA, for the prevention of stroke in patients with NVAF, using a French national healthcare insurance perspective

NOAC: Non-VKA Oral AntiCoagulant; **NVAF** : Non-Valvular Atrial Fibrillation; **RWE**: Real-World Evidence; **VKA**: Vitamin K Antagonist

Model developed in close collaboration with clinical and economic experts

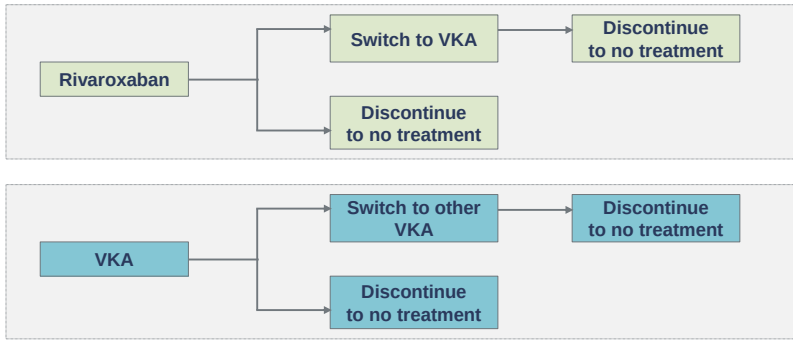
- Lifetime horizon and 3-month cycle length



AF: atrial fibrillation; **GI**: gastro-intestinal; **ICH**: intracranial haemorrhage; **IS**: ischaemic stroke; **MI**: Myocardial infarction

Two treatment options were evaluated

- Patients initiating a first-line treatment on rivaroxaban or VKA
- Possibility to switch and/or to discontinue



VKA: Vitamin K Antagonist

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RWE is a key source of inputs

Inputs	Sources
Patients characteristics	French RWE study
Clinical event rates for VKA	RWE studies
Persistence rates for VKA	RWE studies
Treatment effect for rivaroxaban	HRs from the RWE meta-analysis (incident and prevalent)
All-cause mortality	French life tables
Event-specific mortality	RWE studies
Utility	European RWE studies
Costs	French RWE studies

HR: Hazard Ratio; **RWE**: Real-World Evidence; **VKA**: Vitamin K Antagonist

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Rivaroxaban is cost-effectiveness vs VKA

	Rivaroxaban	VKA	Incremental
Total costs	€15,426	€14,867	€560
Total QALYs	6.87	6.74	0.13
Total LYs	9.94	9.78	0.15
Ischaemic strokes	0.374	0.398	-0.023
Myocardial infarctions	0.141	0.148	-0.007
GI bleeds + ICHs	0.115	0.095	0.019
Incremental cost/QALY gained	-	-	**€4,184**
Incremental cost/LY saved	-	-	€3,672

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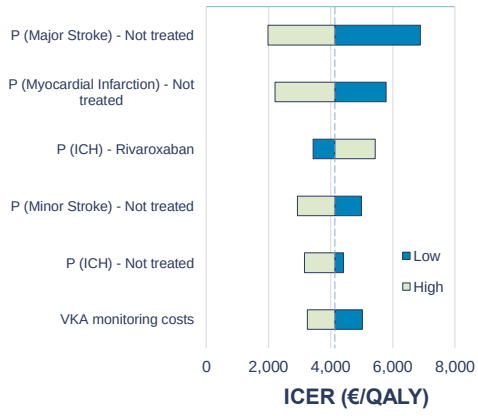
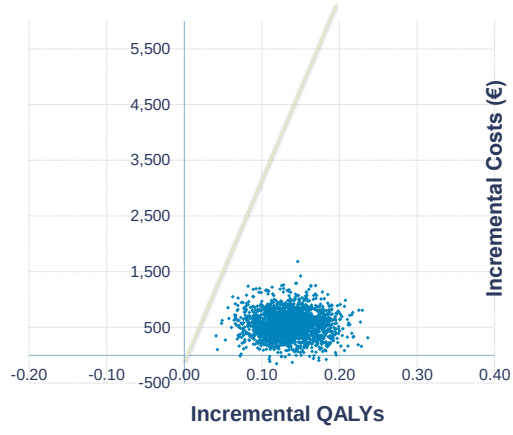
LY: life year; **QALYs**: Quality Adjusted Life Year; **GI**: gastro-intestinal; **ICH**: intracranial haemorrhage; **VKA**: Vitamin K Antagonist

Results are found to be robust

Deterministic sensitivity analysis



Probabilistic sensitivity analysis



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QALYs: Quality Adjusted Life Year; **ICH**: intracranial haemorrhage; **VKA**: Vitamin K Antagonist

What have we learnt?

- **So what is different?**
  - Model predominantly populated with RWE inputs
  - Captured the use of the treatment options in the real world
  - Better reflection of patient's characteristics and disease progression

- **Lessons learnt**
  - Collaboration with a wide range of economic, clinical, and methodological experts is essential
  - Several aspects require further refinement and research:
    - Necessity to adjust endpoints to RWE data reliability/consistency
    - RWE based on "On treatment" data therefore necessary to simulate persistence in some way

RWE: Real-World Evidence

Conclusion

Request is increasing, more research is required

- Request from HTA demonstrating the RW value of health technologies is increasing
  - Is the effort worth it ?
  - Little guidance available on use of RWE
  - ➢ More research is required
- What can be improved?
  - Transparency in reporting
    - Leads to better quality assessment and reduction in uncertainty
- Is the ultimate goal to merge RCT and RWE?
    - Complicated due to the different nature of the data (ITT, On treatment)
    - Requires investigation
- Current effort for framework development is being done
  - ISPOR and ISPE joint taskforce (2 other workshops)

HTA: Health Technology Assessment; **ISPE**: International Society of PharmacoEpidemiology; **ISPOR**: International Society of Pharmacoeconomics and Outcomes Research; **ITT**: Intention to Treat; **RCT**; Randomized Clinical Trial; **RWE**: Real-World Evidence

This work is being published

1. SLR on recommendations for RWE meta-analyses (Briere et al.)
2. SLR of RWE in patients with NVAF (Briere et al.)
3. Meta-analysis of RWE comparing NOACs and VKA in patients with NVAF (accepted)
4. Impact of methodological choices in a meta-analysis of RWE comparing NOACs with VKA in patients with NVAF (in development)
5. Cost-effectiveness analyses using real-world data: a systematic literature review of current considerations (submitted)
6. RWE cost-effectiveness of rivaroxaban compared with VKA in the context of stroke prevention in NVAF in France (in development)

NOAC: Non-VKA Oral AntiCoagulant; **NVAF** : Non-Valvular Atrial Fibrillation; **RWE**: Real-World Evidence; **SLR:** Systematic Literature Review; **VKA**: Vitamin K Antagonist

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Audience interaction