The Challenges of Big Data for European Agencies

Current status and future perspectives

Nikolai C Brun, MD,PhD

Director of Division, CMO, Medical Evaluation and Biostatistics

LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Real world data – current status

- Traditional clinical data are often limited by:
  - Few subjects
  - Highly selected population and limited follow up time.
  - In some cases, clinical trials are not even feasible.
- Real Word Data/Evidence ranges from existing databases such as patient and device registries, electronic health care records, medical administrative claims data, social media, etc.
- Real world data can add valuable insight at different stages during the product life cycle.

Real world data in regulatory decisions
Hematology, Oncology, and Rare Diseases -examples

- 76 unique medications were granted without RCT results during 1999-2014 (44 by EMA and 60 by FDA).
- The majority was for haematological malignancies, oncology and metabolic conditions.
- Post approval studies: registry studies used mainly for safety surveillance.

BMJ Open

Regulatory approval of pharmaceuticals without a randomised controlled study: analysis of EMA and FDA approvals 1999–2014

Anthony J Hatswell,[1] Gianluca Baio,[1] Jesse A Berlin,[2] Alar Irs,[3] Nick Freemantle[4]

PDS Pharmacoepidemiology & Drug Safety — Official Journal of the International Society for Pharmacoepidemiology

Explore this journal >

ORIGINAL REPORT

Registries in European post-marketing surveillance: a retrospective analysis of centrally approved products, 2005–2013

Jacoline C. Bouvy, Kevin Blake, Jim Slattery, Marie L. De Bruin, Peter Arlett, Xavier Kurz

First published: 26 March 2017 Full publication history

DOI: 10.1002/pds.4196 View/save citation

LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Examples: Historical controls from registries

- **Zalmoxis (Conditional approval 2016)**
  - Add-on treatment in adults, who have received a haematopoietic stem cell transplant from a partially matched donor.
  - Data of Zalmoxis-treated patients (n=37) have been compared with a 1-to-4 ratio to contemporaneous control patients (n=140) from the database of European Group for Blood and Marrow Transplantation (EBMT) Registry by a pair-matched analysis.
- **Alglucosidase alfa (Approved 2009)**
  - Myozyme is used to treat patients who have Pompe disease, a rare inherited disorder.
  - Two main studies involving a total of 39 babies and children up to the age of three and a half years with infantile-onset Pompe disease. These patients were compared with a ‘historical comparison group’ of babies and young children with Pompe disease who had not received treatment.

Post marketing approval: safety studies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 May 2013
EMA/329790/2013
EMEA/H/C/000309

Outcome of review of new safety data on insulin glargine

Data from population-based studies and the scientific literature do not indicate an increased risk of cancer

On 30 May 2013, the European Medicines Agency completed a review of new data on the cancer risk with insulin glargine-containing medicines. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the data do not show an increased risk of cancer and that the balance of the medicine's benefits and risks remains unchanged.

LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Registy data to support an extension of an indication

- Soliris (eculizumab)
  - To treat adults and children with paroxysmal nocturnal haemoglobinuria (PNH) or atypical haemolytic uraemic syndrome (aHUS).
  - A comparison of outcome recorded by the registry in patients with no transfusion history treated or not with eculizumab enabled a extension of the indication to patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history.

Real world evidence supporting withdrawals

Table 2 List of evidence used to support medicinal product withdrawals in all EU member states between 2002 and 2011 derived from EMA reports, PubMed literature search and websites of competent authorities

Drug name	Case reports	Animal studies	Case–control	Cohort	RCTs	Meta-analysis	*Others
Rofecoxib	X		x	x	x	X	
Thioridazine	X	X	x		x	X	
Valdecoxib	X				x	X	
Rosiglitazone	X		x	x	x	X	
Sibutramine	X				x		x
Orciprenaline	X				x		
Benfluorex	X		x	x	x		
Clobutinol	X	X			x		
Buflomedil	X	X					
Veralipride	X						
Rimonabant	X				x	X	
Carisoprodol	X	X		x	x		x
Aceprometazine+Acepromazine +Clorazepate	X						x
Dextropropoxyphene	X						x
Nefazodone	X						x
Ximelagatran/melagatran					x		
Lumiracoxib	X				x		
Sitaxentan	X	X					
Bufexamac	X	X					x

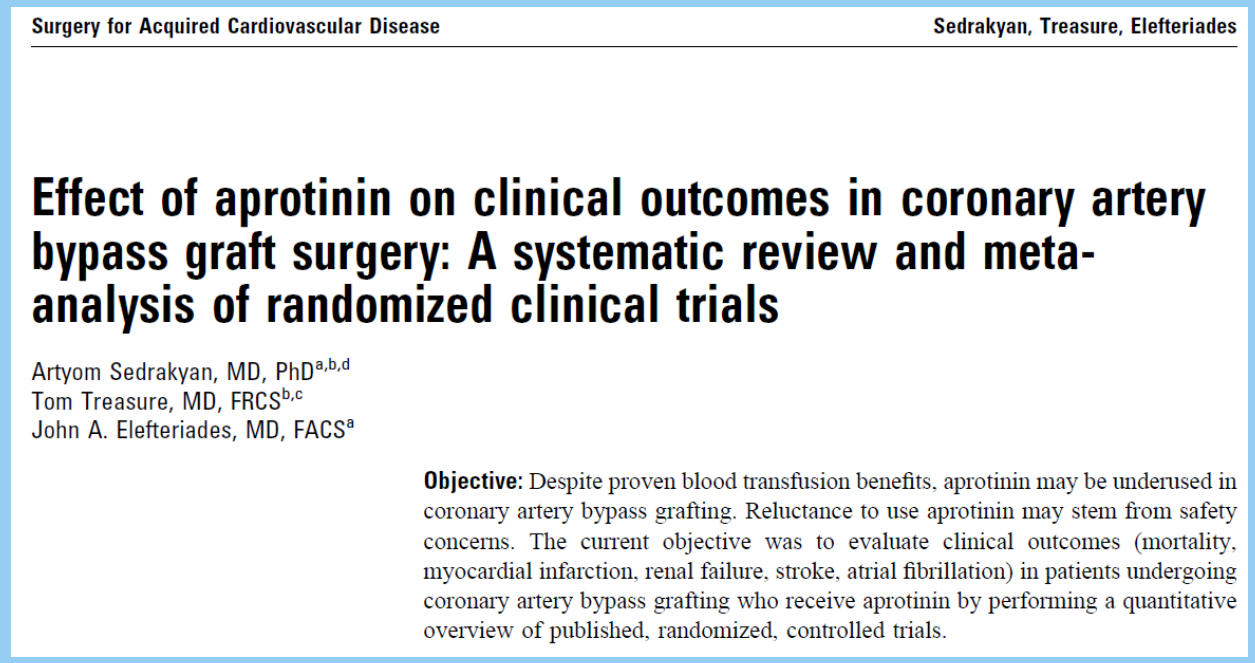
*Other studies include non-randomised and/or not controlled clinical trials and incidence studies.
EMA, European Medicines Agency; EU, European Union.

BMJ Open

An investigation into drug products withdrawn from the EU market between 2002 and 2011 for safety reasons and the evidence used to support the decision-making

Rhian McNaughton,[1,2] Gwenaël Huet,[1] Saad Shakir[1,2]

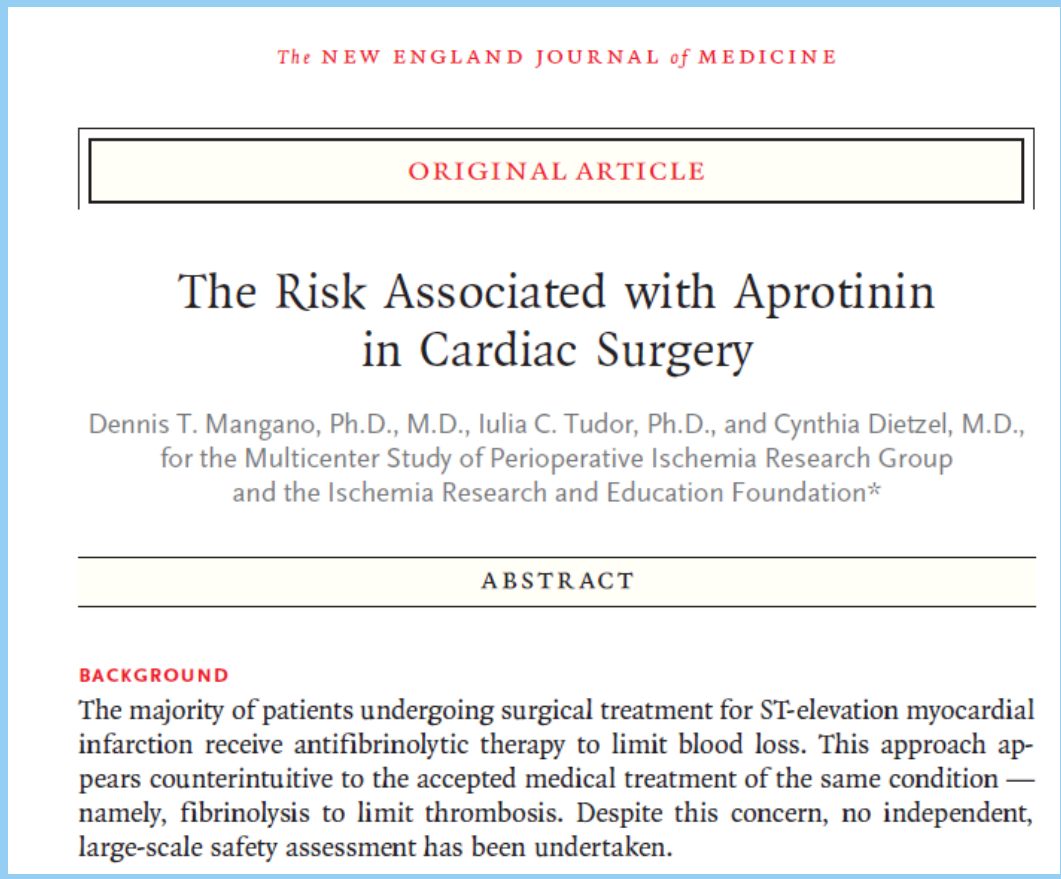
Withdrawal of aprotinin (Trasylol)



Effect of aprotinin on clinical outcomes in coronary artery bypass graft surgery: A systematic review and meta-analysis of randomized clinical trials

Artyom Sedrakyan, MD, PhD[a,b,d]
Tom Treasure, MD, FRCS[b,c]
John A. Elefteriades, MD, FACS[a]

Objective: Despite proven blood transfusion benefits, aprotinin may be underused in coronary artery bypass grafting. Reluctance to use aprotinin may stem from safety concerns. The current objective was to evaluate clinical outcomes (mortality, myocardial infarction, renal failure, stroke, atrial fibrillation) in patients undergoing coronary artery bypass grafting who receive aprotinin by performing a quantitative overview of published, randomized, controlled trials.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

The Risk Associated with Aprotinin in Cardiac Surgery

Dennis T. Mangano, Ph.D., M.D., Iulia C. Tudor, Ph.D., and Cynthia Dietzel, M.D., for the Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation*

ABSTRACT

BACKGROUND

The majority of patients undergoing surgical treatment for ST-elevation myocardial infarction receive antifibrinolytic therapy to limit blood loss. This approach appears counterintuitive to the accepted medical treatment of the same condition — namely, fibrinolysis to limit thrombosis. Despite this concern, no independent, large-scale safety assessment has been undertaken.

LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Effectiveness

Drugs (2017) 77:1461–1472
DOI 10.1007/s40265-017-0788-z

ORIGINAL RESEARCH ARTICLE

Factors Contributing to the Efficacy-Effectiveness Gap in the Case of Orphan Drugs for Metabolic Diseases

Y. Schuller[1] · C. E. M. Hollak[1] · C. C. Gispen-de Wied[2] · V. Stoyanova-Beninska[2] · M. Biegstraaten[1]

Key Points

Less than half of the authorized orphan drugs for metabolic diseases show good effectiveness in the real world.

Of drugs with an unclear efficacy at the time of authorization only 21% had good real-world effectiveness.

The use of a clinical or validated surrogate primary endpoint in the pivotal study seems to be the most important factor associated with good real-world effectiveness.

LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Challenges in using Real World Data

- Data usually collected for something else.
- Unstructured and heterogeneous.
- Bias: all sorts.
- Missing values, validity issues, etc.
- Access to data.
- Data protection issues.

Real world data applicable for all regulatory purposes?

– FDA guidance “Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices” (2017)

“*An existing RWD source, however, may have some inherent bias that could limit its value for drawing causal inferences between medical device exposures and outcomes. Therefore, to mitigate potential bias, careful study design is needed,* ***and a study protocol and analysis plan should be created prior to accessing, retrieving, and analyzing RWD****, regardless of whether the RWD are already collected (retrospective) or if they are to be collected in the future (prospective design). Protocols and analysis plans for RWD should address the same elements that a traditional clinical trial protocol and statistical analysis plan would cover. FDA recommends use of the pre-submission process when considering the development of a study using RWD in a regulatory submission.”*

Real World Data use today

- Real world data is already used during the product life cycle.
- There are several registries that have high enough quality to be used as information in regulatory decisions.
- Routine used in the post authorisation stage.
- Need for rules and framework about how to implement real word evidence in the regulatory environment.

Regulators vs. Big data

- Majority of NCA do not currently have big data dedicated resources
- Majority of NCAs believe it will be necessary to increase resources, BUT they have no definitive time scale for implementation.

  Access to relevant data is possible is the majority of countries, although challenges do exist:

  - Relatively few NCAs have academic collaborations in place to strategies
  - Big data is still rarely used as evidence to support regulatory processes
  - NCAs see the primary application of big data in the area of signal detection
  - Anticipated key challenges to the use of big data include data quality, access to relevant expertise and data harmonization

  Most NCAs find that big data is important, and increasingly so within the next 5 year and beyond

Thoughts from business pipeline and regulatory science meetings

Regulatory views/expectations on digital technologies – How will outcomes be assessed compared to standard measures? Use of digital technologies in dose adjustment, clinical trials

Regulatory convergence at a global level

Need for agile guidance mechanisms

More informal fora for engagement

Systems pharmacology approaches dose selection in orphan disease

Regulatory support for medicine and connected device combinations will be critical. Role of EMA Vs notified bodies

New approaches to pharmacovigilance

Novel data analytics
eg machine learning, AI, NLP

Acceptability of RWD across product life cycle

Validation requirements?

New modelling approaches especially for small populations

Acceptability of PROs

Need for standards e.g. gene editing field

Acceptability of biomarkers for efficacy and safety

Personalised medicine - genomic/proteomic biomarkers

Gold standards
Biopsy vs imaging – ground truth

New approaches for clinical trials

HMA/EMA joint taskforce on Big Data

- To map relevant sources of big data. **Completed Dec 2017**

- To describe the current state, future state and challenges regarding: regulatory expertise / competences in NCAs, need to specify legislation and guidelines, data analysing tools and systems needed to handle big data, and NCA/HMA/EMA responsibility for raw data analysis vs. sponsor responsibility. **Ongoing- Deadline Nov 2018**

- To generate a list of recommendations **Ongoing- Deadline Nov 2018**

HMA / EMA Joint Task Force Big Data

– **From the task force mandate:**

- The taskforce is co-led by Denmark and EMA
- **Big data** is a term for data sets that are so large or complex that traditional data processing applications are inadequate
- In the context of Medicines Regulation it could mean data in large amounts or of a complex nature reaching the NCAs (and EMA) in the margins of analysed and structured data, submitted for regulatory action. It could also mean data lying underneath the regulatory submissions, for which it would be crucial to understand their presence and their potential in order to make a competent evaluation
- In the area of medicines regulation, big data is already becoming a challenge, and in the short to mid-term future, this challenge will become even bigger.

HMA / EMA Joint Task Force Big Data

– **From the task force mandate(..continued):**

- The creation of a new Joint HMA/EMA Task Force focused on ***big data*** has been endorsed by HMA to address a number of issues regarding the emerging challenges on the big data.

HMA / EMA Joint Task Force Big Data

– **Activities (1/2):**

- The Task Force should ***map*** relevant sources of big data and define the main format, in which they can be expected to exist in
- HMA should ***describe*** the ***current state, future state and challenges*** when it comes for instance to:
  - Regulatory expertise / competences in NCAs when it comes to ability to evaluate / assess dossiers, clinical trials etc. in the context of big data underlying the submissions – this includes considerations of skill gaps of e.g. statisticians, big-data analysts etc.
  - Need to specify legislation and guidelines when it comes to which data will be accepted during regulatory approval procedure as well as during post marketing regulatory activities (e.g. PV).
  - Data analysing tools and systems needed to handle big data

–

HMA / EMA Joint Task Force Big Data

– **Activities (2/2):**

- A survey of current state in all NCAs as well as a HMA competency, tools and systems gap analysis will be included. Perform a gap analysis of current network expertise vs. needed expertise
- Design big data road-map for HMA (EMA) with clear milestones and recommendations.
- The Task Force should generate a list of recommendations regarding legislation, regulatory guidelines, ethical considerations incl. data security, competencies and tools/systems as well as an evaluation of the usefulness of big data in the regulatory setting.

–

HMA / EMA Joint Task Force Big Data

– Current status and next steps:

- Five subgroups were formed to map across the range of relevant datasets: **genomics, other 'omics, spontaneous ADR data, observational data, social media data and clinical trial data**. Each subgroup has mapped the relevant data sets to a common report template and is now considering the usability and applicability of the data for regulatory decision making across the product life cycle.
- Some of the subgroups are slightly behind schedule and therefore the timelines are under review
- **Two surveys** have been completed: one of National Competent Authorities and one of industry. The surveys explored the current state of expertise across NCAs, relevant to Big Data and its analysis in order to deliver a gap analysis of current network expertise vs. needed expertise. The industry survey explored their current plans, future directions and perceived opportunities and limitations.

HMA / EMA Joint Task Force Big Data

– **Current status and next steps:**

- A cross cutting data analytics subgroup has just been formed to determine data analytic needs in the light of the characterisation work performed by the subgroups.
- A two day stakeholder meeting is foreseen for May 2018: the first day will be reserved for internal discussions regarding the next steps on deliverables and the second day will be for external stakeholders
- The first set of concrete deliverables is expected in November 2018.

Initial findings in the HMA/EMA joint taskforce on Big data

- **Current status**
  - Good access to relevant big data sources across Europe, for example registry data, prescription data, and clinical trial data.
  - Genomics and other-omics data are very complex but have great potential.
  - Adverse event reporting system are very useful already today. However need to combine them with other data sources.

HMA/EMA Joint Task Force on Big Data

- Mandate: To explore a number of issues regarding the emerging challenges presented by big data. Reports will be presented in Nov 2018.
- Survey to ascertain current situation in the EU network regarding available expertise and competences to analyse big data.
- Surveys addressed to NCAs and pharma.
  - **NCAs** which responded (14th September to 9th October): **24 responses**
  - Member States (incl EEA) which did not respond: **9**
  - **Pharma Industry** (20th September to 20th October): **37 responses**

Initial findings in the HMA/EMA joint taskforce on Big data

Challenges

- Data privacy and security.
- Assessing the quality of data is key for regulatory decision making.
- Interoperability of data
- Lacking expertise in the agencies

Preliminary conclusions from the taskforce

- Unique opportunity to asses the capabilities of the European regulatory network to handle big data.

- Great opportunities for Europe to incorporate big data analyses in the regulatory life cycle of the drugs.

- Next step is to provide recommendations about how to implement big data in the regulatory process. **Deadline including presentations to HMA and EMA: November 2018**.

Thank you for your attention – Questions?
Follow us

LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY