



# Exploiting Heterogeneous Open Data for Pharmacovigilance

Vassilis Koutkias<sup>1</sup>, Agnès Lillo-Le Louët<sup>2</sup> and Marie-Christine Jaulent<sup>1</sup>

<sup>1</sup> INSERM, U1142, LIMICS, F-75006, Paris, France;

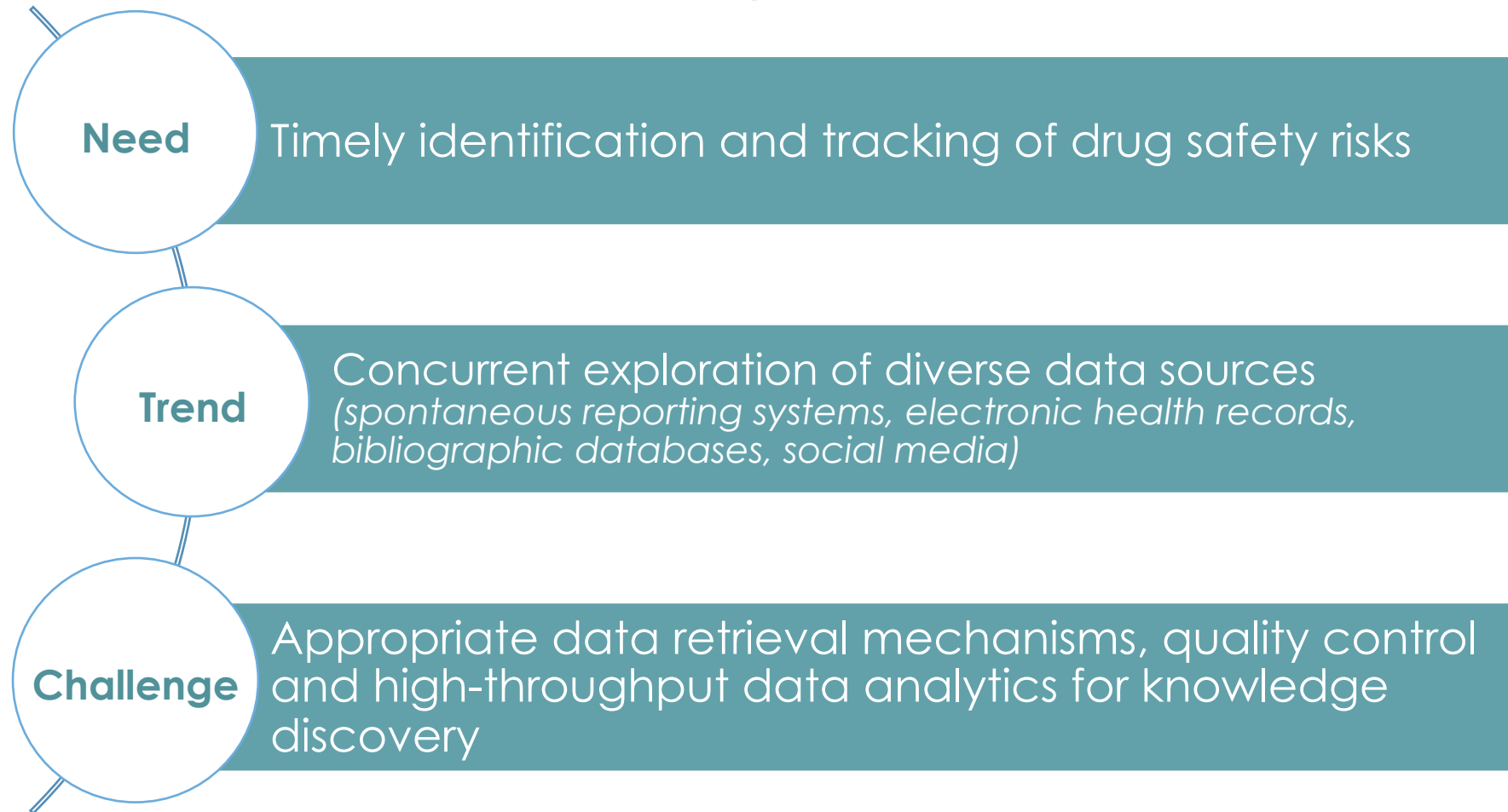
Sorbonne Universités, UPMC Univ Paris 06, UMR\_S 1142, LIMICS, F-75006, Paris, France;  
Université Paris 13, Sorbonne Paris Cité, LIMICS, (UMR\_S 1142), F-93430, Villetaneuse, France

<sup>2</sup> Centre Régional de Pharmacovigilance, Hôpital Européen Georges-Pompidou, AP-HP,  
F-75908, Paris, France



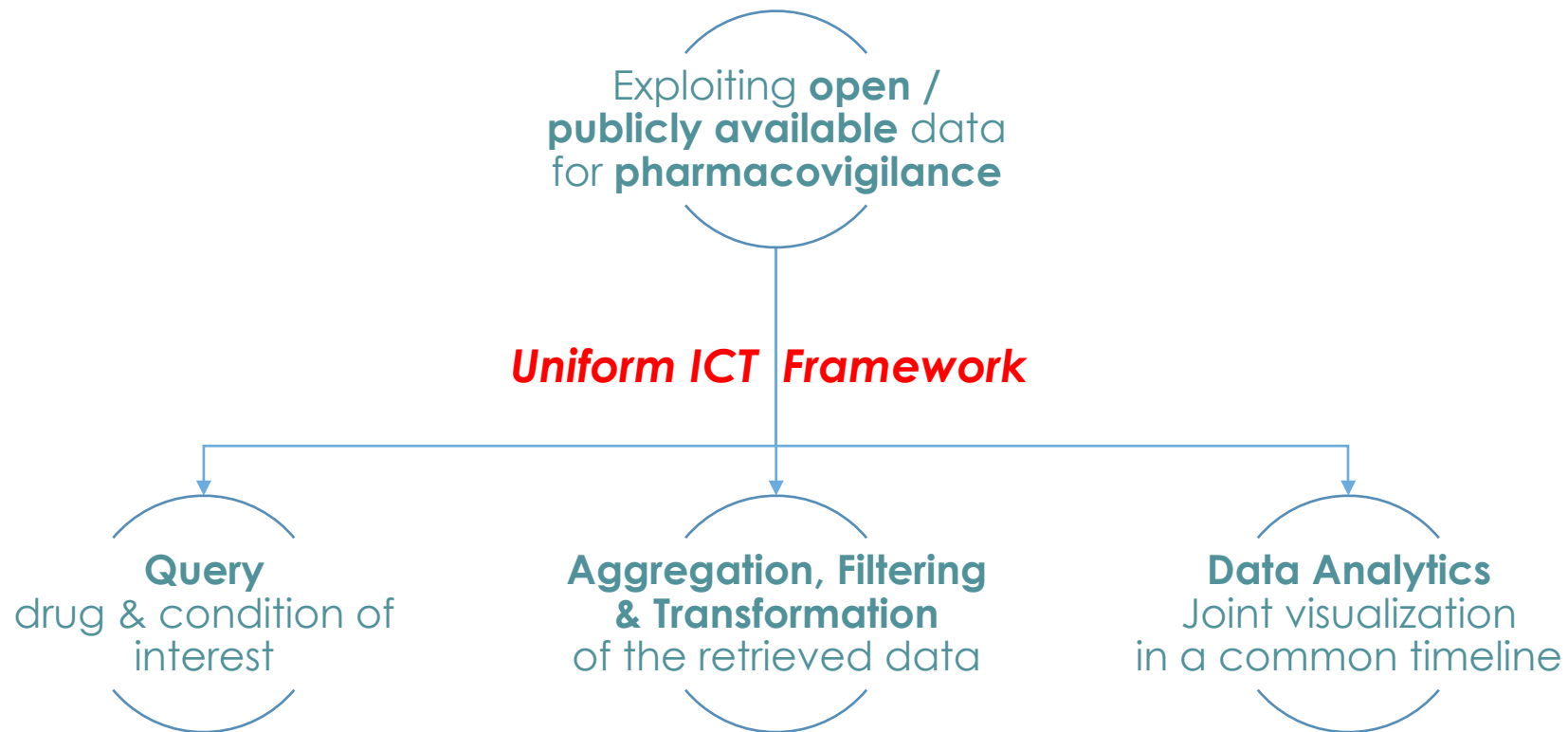


## Background





## Aim of the Study

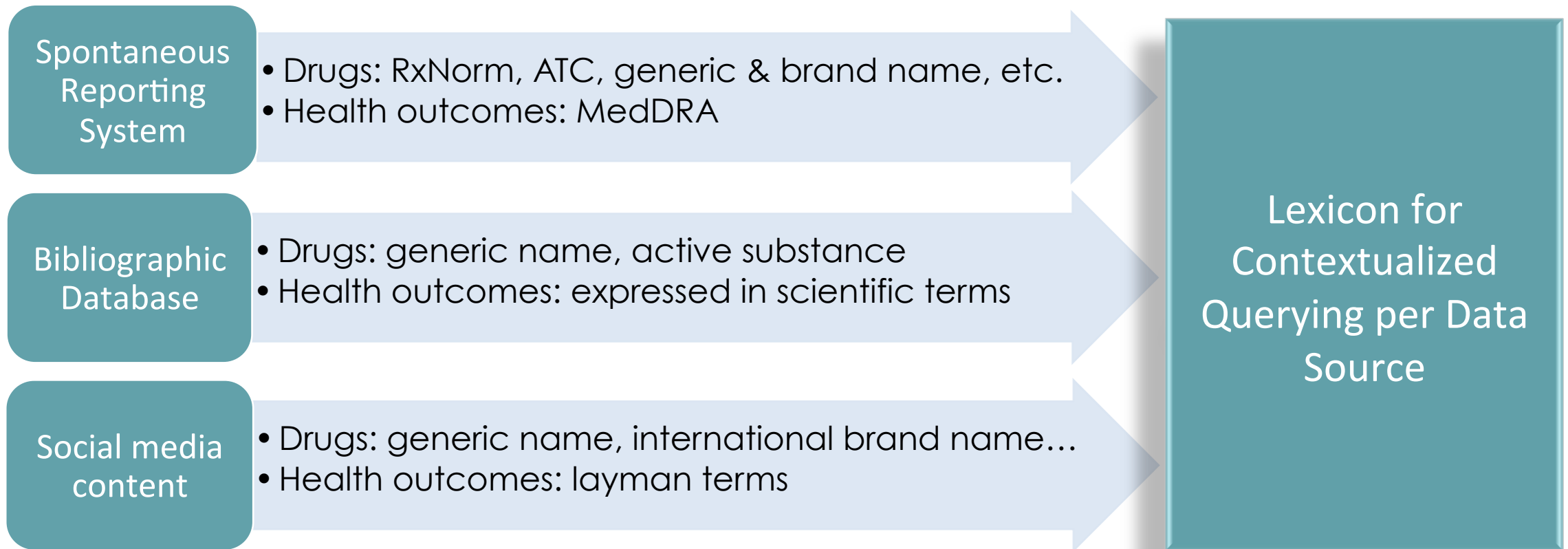




## Trend: Programmatic Access to Data Sources



## Query Formulation





# Data Aggregation: FAERS

## FAERS Data Files

Click on a link below to begin downloading.

- [FAERS ASCII 2015q2.zip \(ZIP - 36.4MB\)](#)  
April - June 2015
- [FAERS XML 2015q2.zip \(ZIP - 59.9MB\)](#)  
April - June 2015
- [FAERS ASCII 2015q1.zip \(ZIP - 37MB\)](#)  
January - March 2015
- [FAERS XML 2015q1.zip \(ZIP - 60.7MB\)](#)  
January - March 2015
- [FAERS ASCII 2014q4.zip \(ZIP - 26.8MB\)](#)  
October - December 2014
- [FAERS XML 2014q4.zip \(ZIP - 45.4MB\)](#)  
October - December 2014
- [FAERS\\_ASCII\\_2014q3.zip \(ZIP - 27MB\)](#)  
July - September 2014



```

results
├── 0
│   ├── fulfillpeditecriteria : "1"
│   ├── receivedateformat : "102"
│   ├── receiver
│   │   ├── reportduplicate
│   │   │   ├── reporttype : "2"
│   │   │   ├── receiptdateformat : "102"
│   │   │   └── receivedate : "20140221"
│   │   └── sender
│   │       └── @epoch : 1417466131.85916
│   └── patient
│       ├── reaction
│       │   ├── 0
│       │   │   ├── reactionmeddrapt : "Cerebral haemorrhage"
│       │   │   ├── reactionmeddraversionpt : "17.0"
│       │   │   └── reactionoutcome : "4"
│       │   └── patientonsetage : "59"
│       │       └── patientonsetageunit : "801"
│       └── drug
│           ├── 0
│           │   ├── drugstartdateformat : "102"
│           │   ├── drugcharacterization : "1"
│           │   ├── actiondrug : "1"
│           │   ├── drugindication : "THROMBOSIS PROPHYLAXIS"
│           │   ├── medicinalproduct : "APIXABAN"
│           │   ├── drugadministrationroute : "048"
│           │   ├── drugstructuredosagenum : "10"
│           │   └── openfda
│           │       ├── drugstartdate : "20101227"
│           │       ├── drugenddate : "20120309"
│           │       ├── drugstructuredosageunit : "003"
│           │       └── drugenddateformat : "102"
│           ├── 1
│           ├── 2
│           ├── patientsex : "1"
│           ├── receiptdate : "20140221"
│           ├── safetyreportversion : "2"
│           ├── serious : "1"
│           ├── companynumb : "ID-BRISTOL-MYERS SQUIBB COMPANY-16449811"
│           ├── safetyreportid : "9915508"
│           ├── duplicate : "1"
│           └── primarysource
│               ├── seriousnessother : "1"
│               ├── primarysourcecountry : "ID"
│               ├── transmissiondate : "20141002"
│               ├── transmissiondateformat : "102"
│               ├── occurcountry : "ID"
│               └── seriousnesshospitalization : "1"
  
```



# Data Aggregation: PubMed

The screenshot shows a PubMed search interface. The search query is "oral anticoagulant"[tiab] AND ("Cerebral haemorrhage"[tiab]). The results are sorted by Relevance. The first result is titled "Recurrence of ICH after resumption of anticoagulation with VK antagonists: CHIRONE study" by Poli D, Antonucci E, Dentali F, Erba N, Testa S, Tiraferri E, Palareti G, Italian Federation of Anticoagulation Clinics (FCSA). The second result is titled "Neurological complications of infective endocarditis: new breakthroughs in diagnosis and management" by Novy E, Sonnevile R, Mazighi M, Klein IF, Mariotte E, Mourvillier B, Bouadma L, Wolff M. The third result is titled "Edoxaban: A Review in Nonvalvular Atrial Fibrillation" by McCormack PL.



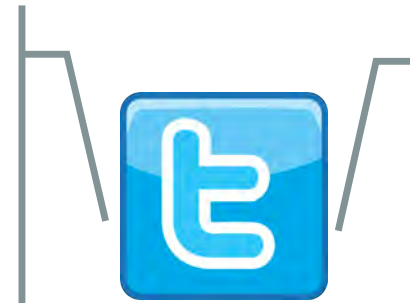
```

<result>
  <id>25715385</id>
  <source>MED</source>
  <pmid>25715385</pmid>
  <title>Patterns of oral anticoagulants use in atrial fibrillation.
  <authorString>Brais C, Larochelle J, Turgeon M, Tousignant A, Blai
  <journalTitle>J Popul Ther Clin Pharmacol</journalTitle>
  <issue>1</issue>
  <journalVolume>22</journalVolume>
  <pubYear>2015</pubYear>
  <journalIssn>1710-6222</journalIssn>
  <pageInfo>e90-5</pageInfo>
  <pubType>journal article</pubType>
  <inEPMC>N</inEPMC>
  <inPMC>N</inPMC>
  <citedByCount>0</citedByCount>
  <hasReferences>N</hasReferences>
  <hasTextMinedTerms>N</hasTextMinedTerms>
  <hasDbCrossReferences>N</hasDbCrossReferences>
  <hasLabsLinks>N</hasLabsLinks>
  <hasTMAccessionNumbers>N</hasTMAccessionNumbers>
  < luceneScore>698.85547</ luceneScore>
  <hasBook>N</hasBook>
</result>

```



# Data Aggregation: Twitter



```
{
  "metadata": {
    "iso_language_code": "en",
    "result_type": "recent"
  },
  "created_at": "Mon Oct 12 09:27:47 +0000 2014",
  "id": 653502312493789200,
  "id_str": "653502312493789184",
  "text": "RT @HJVJC: A comparison of the safety and effectiveness of dabigatran and warfarin in non-valvular atrial fibrill... http://t.co/LtT9QZmRaz...",
  "source": "<a href='\"http://twitter.com/#!/download/ipad\"' rel='\"nofollow\"'>Twitter for iPad</a>",
  "truncated": false,
  "in_reply_to_status_id": null,
  "in_reply_to_status_id_str": null,
  "in_reply_to_user_id": null,
  "in_reply_to_user_id_str": null,
  "in_reply_to_screen_name": null,
  "user": {
    "id": 299487527,
    "id_str": "299487527",
    "name": "Faur Mariana",
    "screen_name": "sorana1965",
    "location": "Romania",
    "description": "",
    "url": "http://t.co/fwIehmPFVu",
    "entities": {
      "url": {
        "urls": [
          {
            "url": "http://t.co/fwIehmPFVu",
            "expanded_url": "http://twitter.com/settings"
          }
        ]
      }
    }
  }
}
```



# Data Filtering & Transformation

```

JSON
├── results
│   ├── 0
│   ├── 1
│   ├── 2
│   ├── 3
│   ├── 4
│   ├── 5
│   ├── 6
│   └── 7
│       ├── safetyreportid : "5394148-5"
│       ├── fulfillxpeditecriteria : "1"
│       ├── receiver : null
│       ├── receivedateformat : "102"
│       ├── receiptdateformat : "102"
│       ├── receivedate : "20070723"
│       ├── primarysource
│       ├── sender
│       ├── seriousnessdeath : "1"
│       ├── @epoch : 1417048845.306429
│       └── patient
│           ├── reaction
│           │   ├── 0
│           │   ├── 1
│           │   └── 2
│           │       └── reactionmeddrapt : "MYOCARDITIS"
│           ├── patientonsetage : "64"
│           ├── patientondeath
│           └── patientonsetageunit : "801"
│               ├── drug
│               │   ├── 0
│               │   ├── 1
│               │   ├── 2
│               │   ├── 3
│               │   ├── 4
│               │   ├── 5
│               │   ├── 6
│               │   ├── 7
│               │   ├── 8
│               │   └── 9
│               │       ├── drugstartdateformat : "102"
│               │       ├── drugcharacterization : "2"
│               │       ├── medicinalproduct : "SERENACE"
│               │       ├── drugadministrationroute : "048"
│               │       ├── drugdosagetext : "FIRST THERAPY: UKN 1994"
│               │       └── drugstartdate : "19940101"

```



Reaction	medicinalproduct	drugcharacterization	Basic Drug Information
reactionmeddrapt	medicinalproduct	drugcharacterization	drugindication
MYOCARDITIS			
OBESITY			
PARANOSIA			
PULMONARY EMBOLISM			
PULMONARY OEDEMA			
RIGHT VENTRICULAR FAILURE			
SLEEP APNOEA SYNDROME			
SNOORING			
WEIGHT INCREASED			
ATRIAL FLUTTER	CLOZARIL	Suspected drug	SCHIZOPHRENIA
CARDIAC FAILURE	VALPROATE SODIUM	Suspected drug	
CELLULITIS	EFFEXOR	Suspected drug	
DEATH	HALOPERIDOL	Suspected drug	
DECREASED APPETITE			
DIFFICULTY IN WALKING	LORAZEPAM	Suspected drug	
FALL	OLANZAPINE	Suspected drug	
FLAT AFFECT	BENZTROPINE MESYLATE	Suspected drug	
GAIT DISTURBANCE			
HAEMOGLOBIN DECREASED			
HYPOTENSION			
INJURY			
LOBAR PNEUMONIA			
LYMPHOPENIA			
MALAISE			
MYOPLASMA INFECTION			
MYOCARDITIS			
OXYGEN SATURATION DECREASED			
PERONEAL NERVE PALSY			
PYREXIA			
RESTLESSNESS			
RIB FRACTURE			
SOMNOLENCE			
TACHYCARDIA			
THROMBOCYTOPENIA			
ABDOMINAL DISTENSION	TAMIFLU	Suspected drug	
CARDIO-RESPIRATORY APREST	VEGETAMIN B	Concomitant drug	
MYOCARDITIS	NEULEPTIL	Concomitant drug	
RESPIRATION ABNORMAL	SILECE	Concomitant drug	
	SEMINSIDE	Concomitant drug	
	HIRNAMIN	Concomitant drug	
	CREMIN	Concomitant drug	
	AKINETON	Concomitant drug	
	TRIHENXYPHENIDYL HYDROCHLORIDE	Concomitant drug	
	SERENACE	Concomitant drug	
	LIDOPIN	Concomitant drug	
	UNSPECIFIED DRUG	Concomitant drug	
	UNSPECIFIED DRUG	Concomitant drug	DRUG USE FOR UNKNOWN INDICATION
	WATER	Concomitant drug	DRUG USE FOR UNKNOWN INDICATION
MYOCARDITIS	CLOZAPINE	Suspected drug	SCHIZOAFFECTIVE DISORDER
	VALPROATE SODIUM	Concomitant drug	
	HALOPERIDOL DECANOATE	Concomitant drug	
MYOCARDITIS	FAZACLO ODT	Suspected drug	SCHIZOPHRENIA
	AMANTADINE HCL	Concomitant drug	
	NORVASC	Concomitant drug	



## Case Study: New Oral Anticoagulants & Risk of Cerebral Hemorrhage

Scope: What data are available for *Apixaban*, *Dabigatran* and *Rivaroxaban* and Cerebral Hemorrhage?

Sources: FAERS, PubMed and Twitter

Selection criteria: Interest & data availability

Study Context

Synonyms for drugs: DrugBank (<http://www.drugbank.ca/>)

Synonyms for cerebral hemorrhage: Layman terms and BioPortal (<http://bioportal.bioontology.org/>)

Query Lexicon

Identify common appearance of drug and health outcome of interest  
Focus on English terms only

Periodic search within a 3-month period (January-March 2015)

Search Protocol



## Case Study: New Oral Anticoagulants & Risk of Cerebral Hemorrhage

FAERS	PubMed*	Twitter
Apixaban AND Cerebral Haemorrhage		
10 (67)	1 / 59 / 33 (1 / 66 / 54)	8 (9)
Dabigatran AND Cerebral Haemorrhage		
17 (633)	10 / 93 / 54 (13 / 104 / 84)	188 (431)
Rivaroxaban AND Cerebral Haemorrhage		
18 (471)	5 / 73 / 40 (5 / 80 / 64)	57 (93)

**Notation: Reports/References/Posts retrieved via narrow term search (broad term search)**

\*Results in the form **N1 / N2 / N3**, where **N1**: number of papers in which the search terms (condition and/or drug) appear in their **title**, **N2**: number of papers in which the search terms (condition and/or drug) appear in their **title or abstract**, **N3**: number of papers that have been **annotated/classified by NLM librarians through MeSH with "adverse effects"[Subheading] OR "chemically induced"[Subheading] OR "Chemicals and Drugs Category"[Mesh]** and in which the search terms (condition and/or drug) appear in their **title or abstract**.





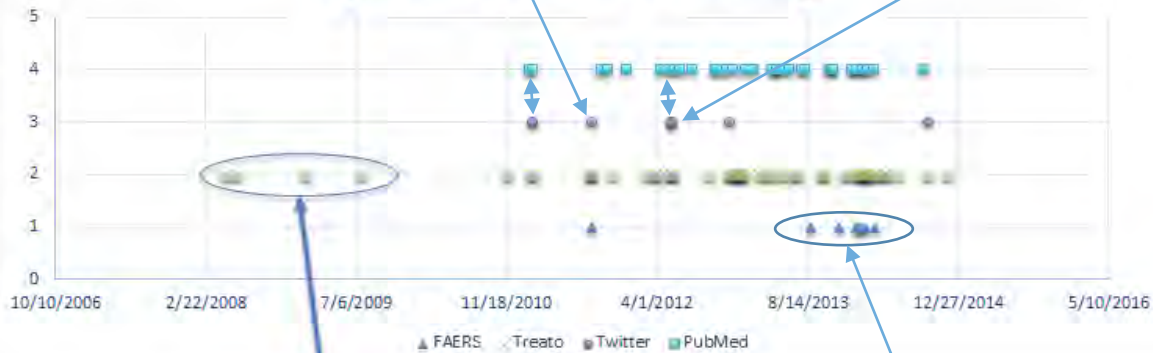
# Case Study: New Oral Anticoagulants & Risk of Cerebral Hemorrhage

## Healthcare professional experience

Recently saw another patient with [#brain](#) hemorrhage due to [#Warfarin](#). New alternatives like **Apixaban** with less bleed risk are welcome

The Lancet @TheLancet · 20 May 2012  
perhaps the most important advantage of **apixaban** over warfarin: less intracranial bleeding [awe.sm/5roOm](#)

## Apixaban and Cerebral Haemorrhage



## Reply #2

The oral anticoagulant will be an alternative to Warfarin/Coumadin.

There are actually several new oral anticoagulant coming out. The first is Xarelto (Rivaroxaban) by Ortho-McNeill. This medical will probably hit the market early next year. It will be aimed at knee/hip replacement patients.

The next medication is Dabigatran by Boehringer-Ingelheim. It is a little further behind in testing (here in the U.S.) then Rivaroxaban. When marketed (probably 2 years from now) it will be aimed at Atrial Fib patients.

The third is Apixaban. It is still undergoing testing and will probably be 3 years down the line.

All serious reports  
Primary country source: US, GB, CH, JP

## Started by

Decided I had better put the name of the research drug on the thread.  
Have any of you participated in this study?  
My husband is on phase III and I'm just hoping and praying this is taking care of his clot, which was behind his injured knee.  
I sure hope it works, because he cannot have knee surgery until the three months is up on this study drug.

5369

## Re:

Reply #1 by

There are several new breeds of oral anticoagulant medications undergoing Phase III Trials. These new oral anticoagulants are aimed at alternative replacements for coumadin/warfarin. From studies, there appears to be less side affects associated with these new oral anticoagulants. Example, no monthly INR checks, less chance of bleeding complications as opposed to coumadin, more stable INR.

Rivaroxaban is a product produced by Bayer Pharmaceuticals. The other contenders are:

Apixaban - A collaborative effort between Britol-Meyers Squibb and Pfizer Pharmaceuticals.

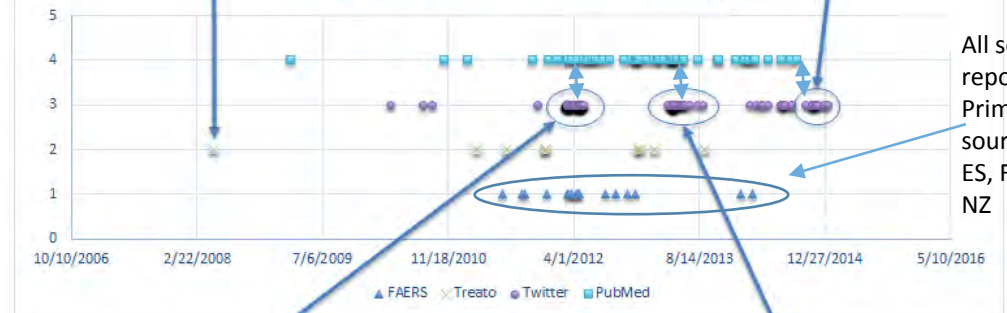
Pradaxa® (dabigatran etexilate) a product by Boehringer-Ingelheim Pharmaceuticals.

Again, each of these products are aimed as an alternative to Coumadin/Warfarin and probably won't be available on the market until 2010 (approximately). All the products are doing extremely well in their Phase trialing testing. Me personally, I will remain a coumadin user only because Coumadin has been on the market for many of years and the known side affects are published. The long-term side affects of all the new oral anticoagulants will not be known for many years. Despite Coumadin's bad reputation, it is still one of the safest long term medications on the market. Some patients do experience problems taking Coumadin; I'm lucky not to be one of them. For these particular patients, the new oral anticoagulants may just be the answer they are looking for.

## Patient concern/anticipation

Ischemic Stroke and Intracranial Hemorrhage With Aspirin, Dabigatran, and Warfarin... [goo.gl/lb/w0V0W5](#) #health

## Dabigatran and Cerebral Haemorrhage



All serious reports  
Primary country source: US, GB, ES, FR, AU, MX, NZ

Irreversible catastrophic **brain hemorrhage** after minor injury in a patient on **dabigatran** [dvr.it/1HL4XZ](#)

Two new papers on **dabigatran** etexilate (Pradaxa) and **intracranial hemorrhage** The Journal of Neurosurgery Publish... [bit.ly/ZV6LFz](#)

# Case Study: New Oral Anticoagulants & Risk of Cerebral Hemorrhage

- In RECORD2, extended-duration rivaroxaban (35+/-4 days) demonstrated a 79% RRR in total VTE and a similar rate of major bleeding in patients undergoing THR surgery compared to patients dosed with short-duration therapy with enoxaparin (10-14 days) followed by placebo.

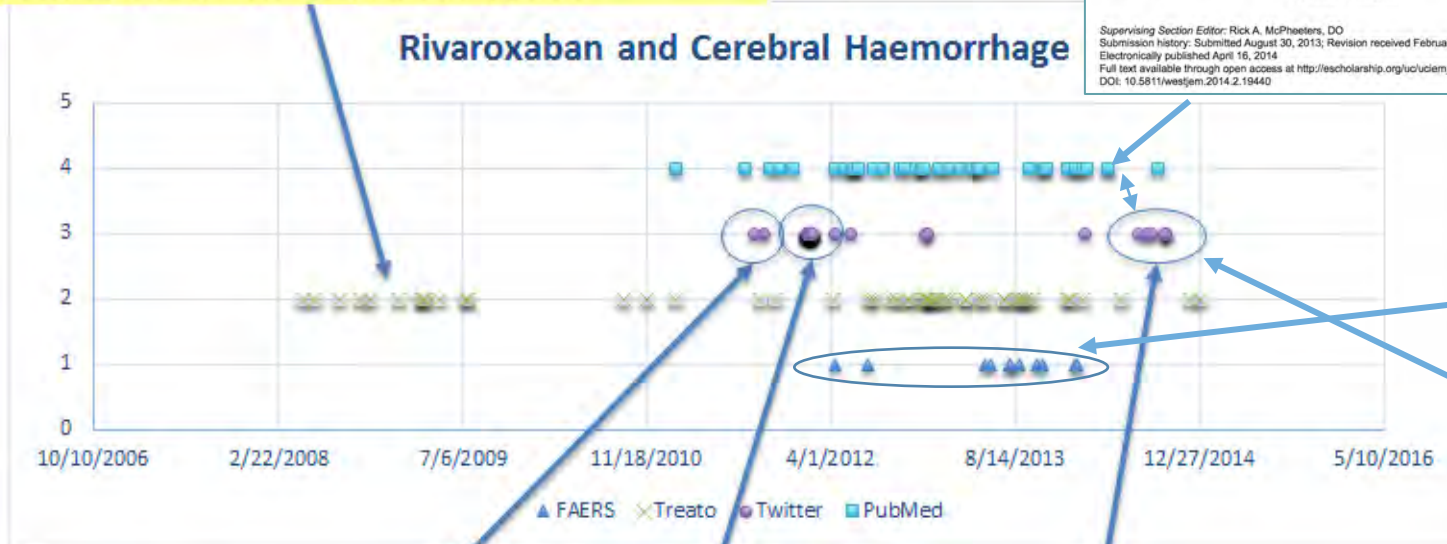
**CASE REPORT**

**A Case of Rivaroxaban Associated Intracranial Hemorrhage**

Jean Chin-Yu Lo, MD\*  
Roy R. Gerona, PhD†

\*Loma Linda University, Department of Emergency Medicine, Loma Linda, California  
†University of California San Francisco, Department of Laboratory Medicine, San Francisco, California

Supervising Section Editor: Rick A. McPheeters, DO  
Submission history: Submitted August 30, 2013; Revision received February 10, 2014; Accepted February 14, 2014  
Electronically published April 16, 2014  
Full text available through open access at [http://escholarship.org/uc/uciem\\_westjem](http://escholarship.org/uc/uciem_westjem)  
DOI: 10.5811/westjem.2014.2.19440



All serious reports  
Primary country source:  
US, GB, JP, TR, DE, LU, AU

How I treat target-specific oral anticoagulant-associated bleeding  
[feedly.com/k/1mwTTkz](http://feedly.com/k/1mwTTkz)

@harisrahman dr haris - this from blood journal right?

@dytia\_aurinh Yup! I ten read it at the office :)

@harisrahman difficult to read on mobile \*had few case of rivaroxaban intracranial bleeding esp in geri - so interested to read the paper

*Patient - Healthcare professional discussion*

Rivaroxaban has less risk of brain bleeding in patients at high risk for stroke  
[divr.it/18kV8y](http://divr.it/18kV8y)

Rivaroxaban (Xarelto) is alternative to warfarin for atrial fibrillation. Does not require INR and less intracranial bleeding.

the first case report documenting intracranial hemorrhage associated with rivaroxaban  
[ncbi.nlm.nih.gov/pmc/articles/P...](http://ncbi.nlm.nih.gov/pmc/articles/P...)





## Case Study: Summary of Findings

### ▪ Twitter:

- **Too much “noise”** (promotional material / advertisements also identified): **no surprise!**
- **Complexity** in the analysis (posts may embody Web links & images - many duplicates)
- The majority of messages referred to **scientific publications** (close to PubMed entries)
- Limited **personal opinions / experiences** of **potential patients**, but discussions among patients and healthcare professionals concerning the anticipated alternative therapeutic option

### ▪ PubMed:

- **MeSH indexing** can increase the relevance of the results (time constraint!)
- Both **case reports & review/opinion papers** retrieved

### ▪ FAERS:

- **Significant difference** in the number of reports obtained between **exact and broad searches**
- Serious events reported from various countries





## Concluding Remarks

- **Proof-of-concept** development for systematic access to diverse public data sources for pharmacovigilance
- Case study indicated
  - the **kind of data** that are available in each source
  - the **necessity to contextualize queries** according to the data source used
- The **joint visualization** of data across a **common timeline** was proven very helpful for drug safety experts (rigorous visual inspection, evolution of data across time, potential associations in the production of data from diverse sources)
- **Further analysis** underway with **additional case studies**



## Acknowledgement

Vassilis Koutkias received funding from a Marie Curie Intra European Fellowship within the 7th European Community Framework Programme FP7/2007-2013 under REA grant agreement n° 330422 – the SAFER project

Further information: <http://safer-project.eu/>





# Thank you!

## Exploiting Heterogeneous Open Data for Pharmacovigilance

V. Koutkias,<sup>1</sup> A. Lillo-Le Louët,<sup>2</sup> M.-C. Jaulent<sup>1</sup>

Contact: [vasileios.koutkias@inserm.fr](mailto:vasileios.koutkias@inserm.fr)

<sup>1</sup> INSERM, U1142, LIMICS, F-75006, Paris, France; Sorbonne Universités, UPMC Univ Paris 06, UMR\_S 1142, LIMICS, F-75006, Paris, France; Université Paris 13, Sorbonne Paris Cité, LIMICS, (UMR\_S 1142), F-93430, Villetaneuse, France;

<sup>2</sup> Centre Régional de Pharmacovigilance, Hôpital Européen Georges-Pompidou, AP-HP, F-75908, Paris, France

