Example 2: Adverse drug events detection and prevention by artificial intelligence

Data collection:

- Denain General Hospital (Fr)
- Region Hovedstaden Hospitals (Dk)

Research Project:

- PSIP european project
- Funded by the European Research Council
- Coordinator: Pr Régis Beuscart

Data analysis & software design:

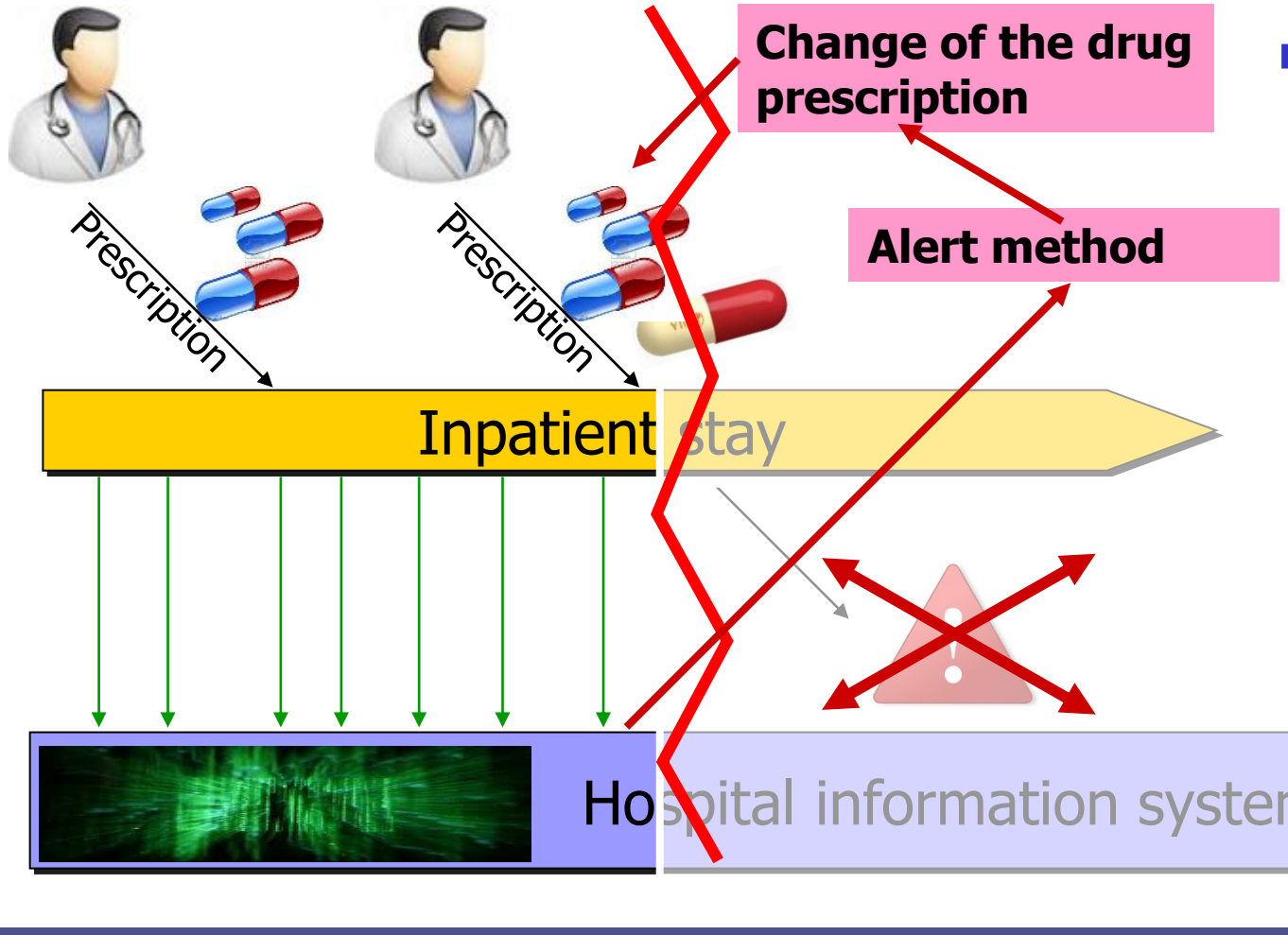
- E Chazard

Adverse drug events

Adverse drug events

- ADEs = Adverse Drug Events
- Several definitions. Institute of Medicine (2007):
  - “An injury resulting from the use of a drug”
  - “An injury due to medication management rather than the underlying condition of the patient”
- Epidemiological data:
  - 98,000 deaths per year in the US
  - An ADE would occur in 5-9% of inpatient stays
- Two fields of research:
  - Prospective ADE prevention
  - Retrospective ADE detection

Prospective prevention of ADEs



- Alert generation, before the ADE occurs, in order to prevent it.

Adverse drug events prevention by CDSS based on level 1 artificial intelligence

Definitions

- CPOE:
  - computerized physician order entry
  - process of electronic entry of medical practitioner instructions for the treatment of (hospitalized) patients
- CDSS:
  - Clinical decision support system
  - Health information technology system that is designed to provide physicians and other health professionals with clinical decision support
  - Often based on level 1 artificial intelligence (rules)
- CPOE + CDSS = the “obvious” solution for adverse drug events prevention?

CDSS & CPOE: Over-alerting, alerte-fatigue => poor clinical efficiency!

- **Over-alerting**: too numerous and inappropriate alerts
- Alerts interrupt the clinicians' workflow and induce **alert-fatigue**
  - Too many alerts
  - => time and mental energy consumption
  - => a mental state whereby users start ignoring critical alerts along with those that may be clinically insignificant
- May prevent CDSS from improving patient safety
- Alert override:
  - **up to 96% of alerts** are overridden by prescribers
  - But alert override is **often inappropriate**, and is sometimes followed by actual ADEs

What solutions have been implemented for over-alerting reduction?

- Support the medical management of the alert
  - Possible, but disappointing evaluation results [Dukes 2011, Dukes 2013]
- Expert filtering or tiering of the alerts, based on relevance
  - possible & efficient [Shah 2005, Van der Sijs 2008, Paterno 2009, Phansalkar 2013]
- Automated filtering or tiering of the alerts
  - Based on override statistics [Lee 2010]: less override but… is override decision reliable? [Slight 2013, Nanji 2014]
  - Based on outcome probability [Chazard 2009, Koutkias 2010, Chazard 2012]… proposed here

Criteria for assessing high-priority DDIs for clinical decision support in EHRs

Phansalkar S - ***BMC med inf & decision making 2013***

27 important criteria for choosing interactions to include for CDS in an EHR:

- **Severity of interaction:** Clinical Importance, likelihood of Mortality, of Morbidity, of Intervention
- **Probability of interaction:** Likelihood of the Adverse Reaction, timing of Administration, pharmacokinetic properties, Dose and Duration, Route, Sequence, Monitoring, Therapeutic window, Combination of drugs
- **Clinical implications:** Management burden, Monitoring planned for the interaction, Awareness of the intervention
- **Patient characteristics:** Alcohol, diet, smoking, drug use, Age, Gender, Concurrent diseases, Other active medications
- **Evidence supporting interaction:** Quantity of evidence, Quality of evidence, Biological plausibility

- Similar conclusions in reviews or studies for overalerting reduction:

[Van der Sijs 2006]
[Kuperman 2007]
[Smithburger 2011]
[Riedman 2011]
[Ammenwerth 2011]
[ung 2013]

Statistics-based contextualization of alerts (3)

Data-mining based segmentation of alert rules (8)

Retrospective ADE detection: a prerequisite for ADE prevention!

Idea driven by

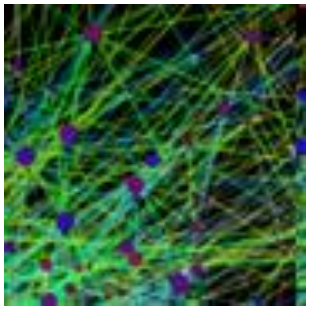
Pr Regis Beuscart, head of the PSIP Project

Funded by the European Research Council, 7th framework program (agreement N°216130)

Which methods for retrospective ADE detection ?

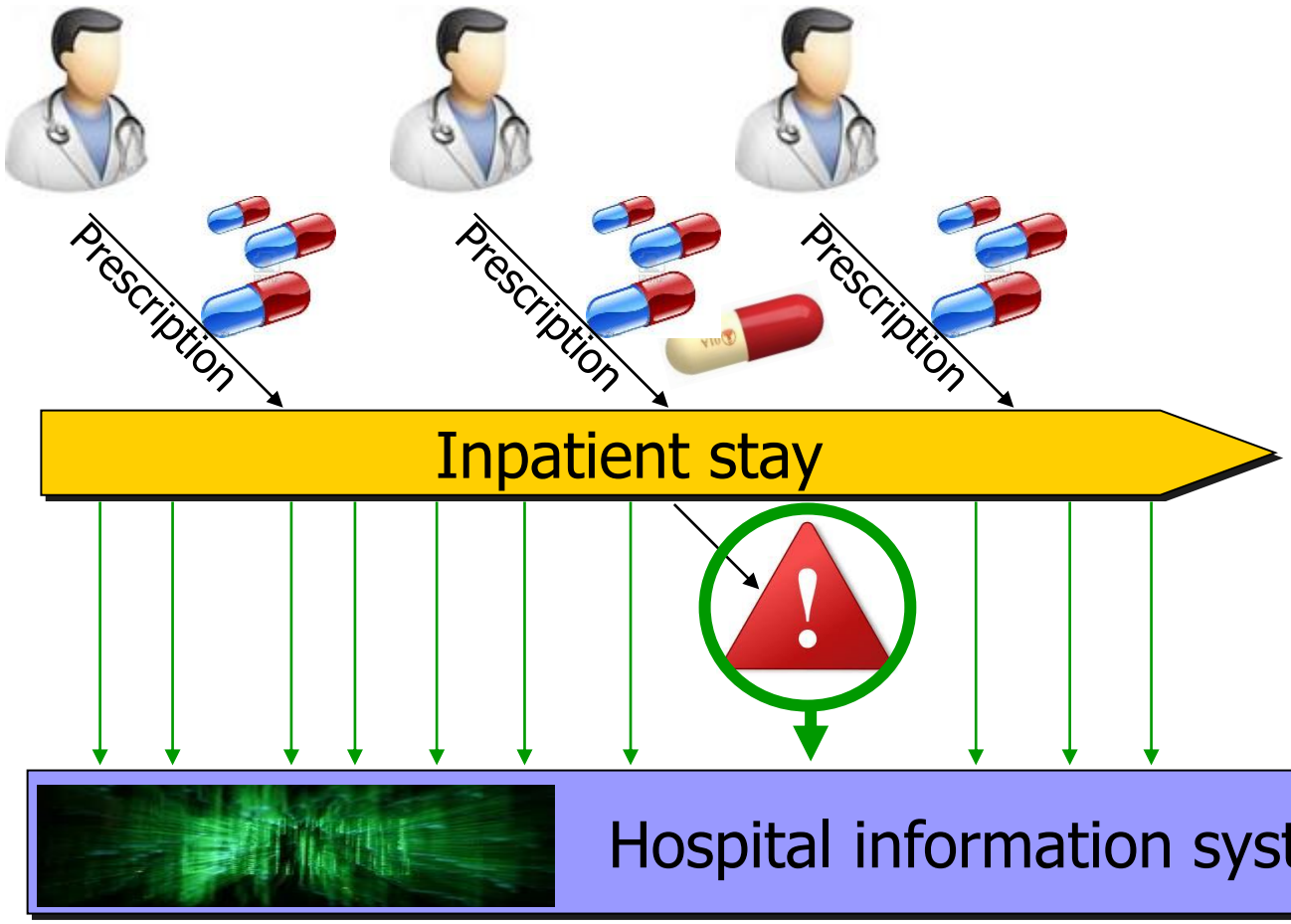
- Reporting systems:
  - Based on spontaneous case reports
  - Mandatory, but underreporting bias: less than 5% cases are declared!

- Expert-operated chart reviews
  - Reference method, expert validation
  - Time consuming: 30 min per case, and some ADEs are very rare…



- Objective: using data reuse & data mining to:
  - Automatically identify past ADE cases
  - Generate ADE detection rules
  - Computing probabilities of occurrence

Retrospective detection of ADEs



- Retrospective identification of past ADEs, although no explicit signal exists in the data

Administrative data

88 years old woman

Diagnoses

I10	Arterial hypertension
Z8671	Personal history of myocardial ischemia
I620	Non-traumatic subdural hemorrhage

Medical procedures

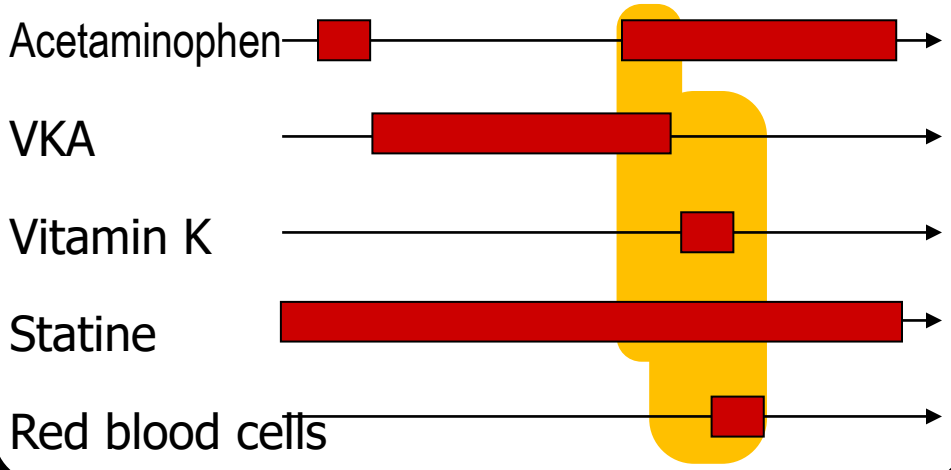
ABJA002	Drainage of an acute subdural hemorrhage, by craniotomy
FELF001	Transfusion

Free-text reports

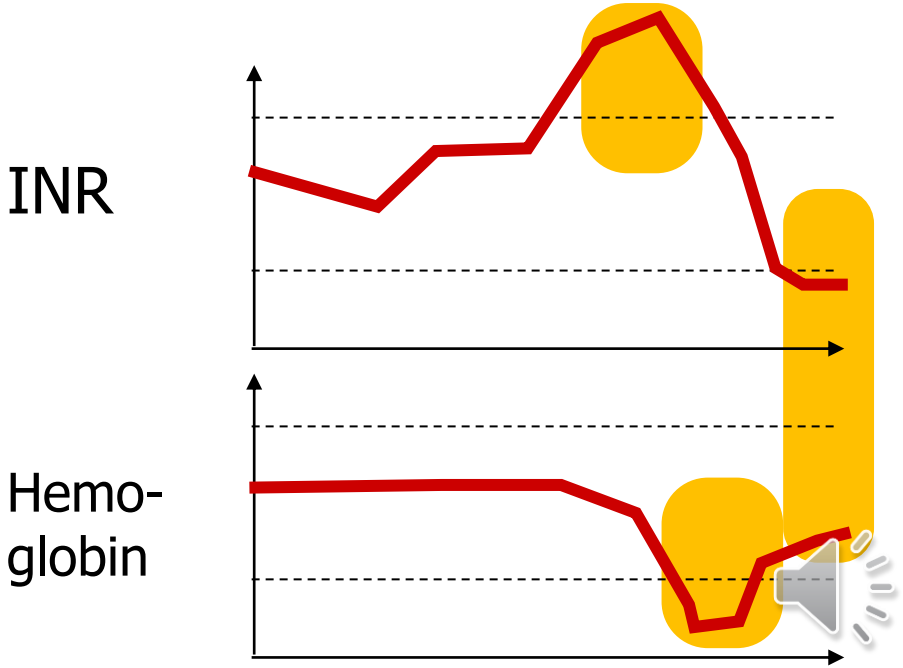
Discharge letter

Surgical report

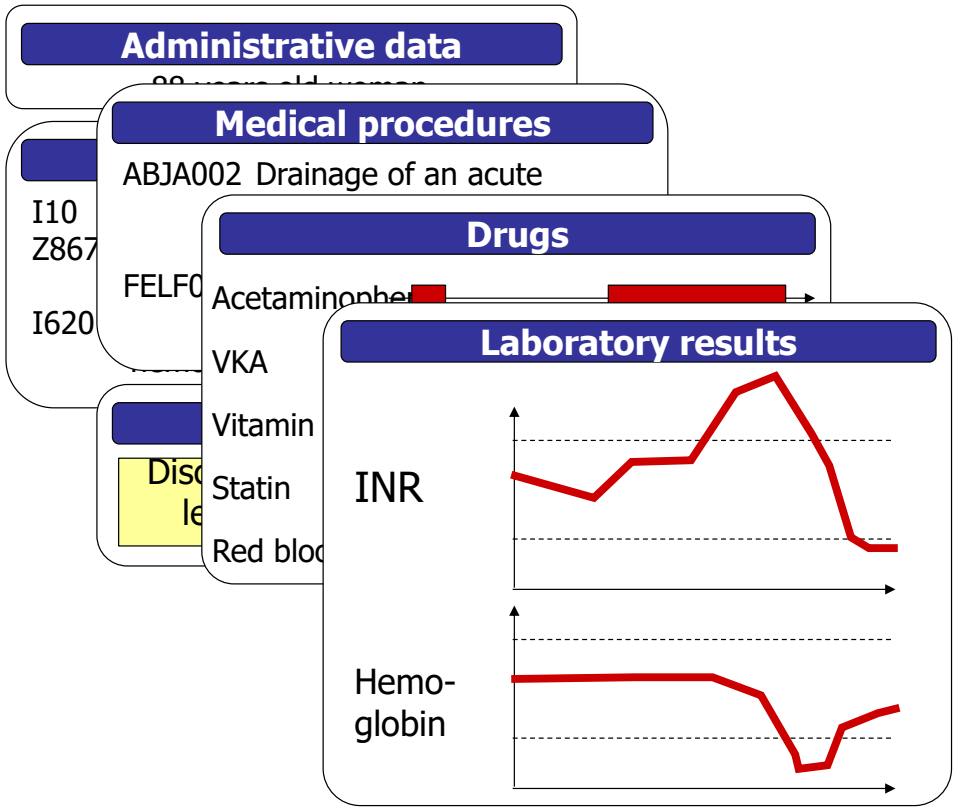
Drugs

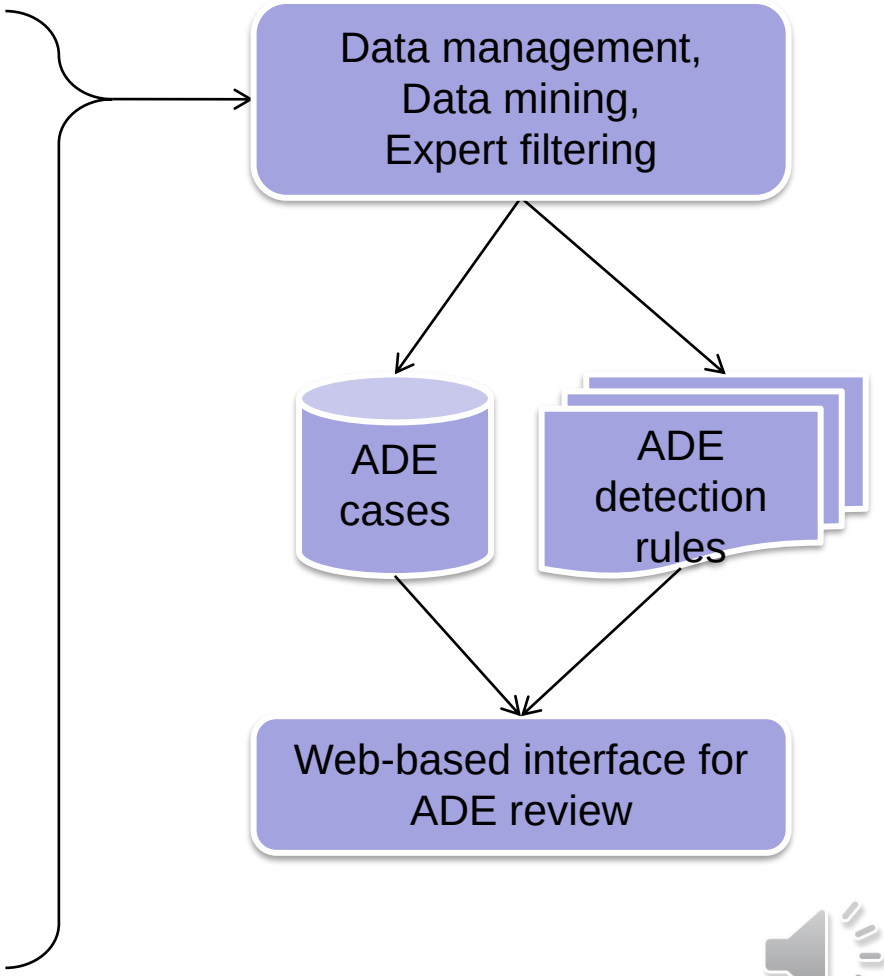


Laboratory results

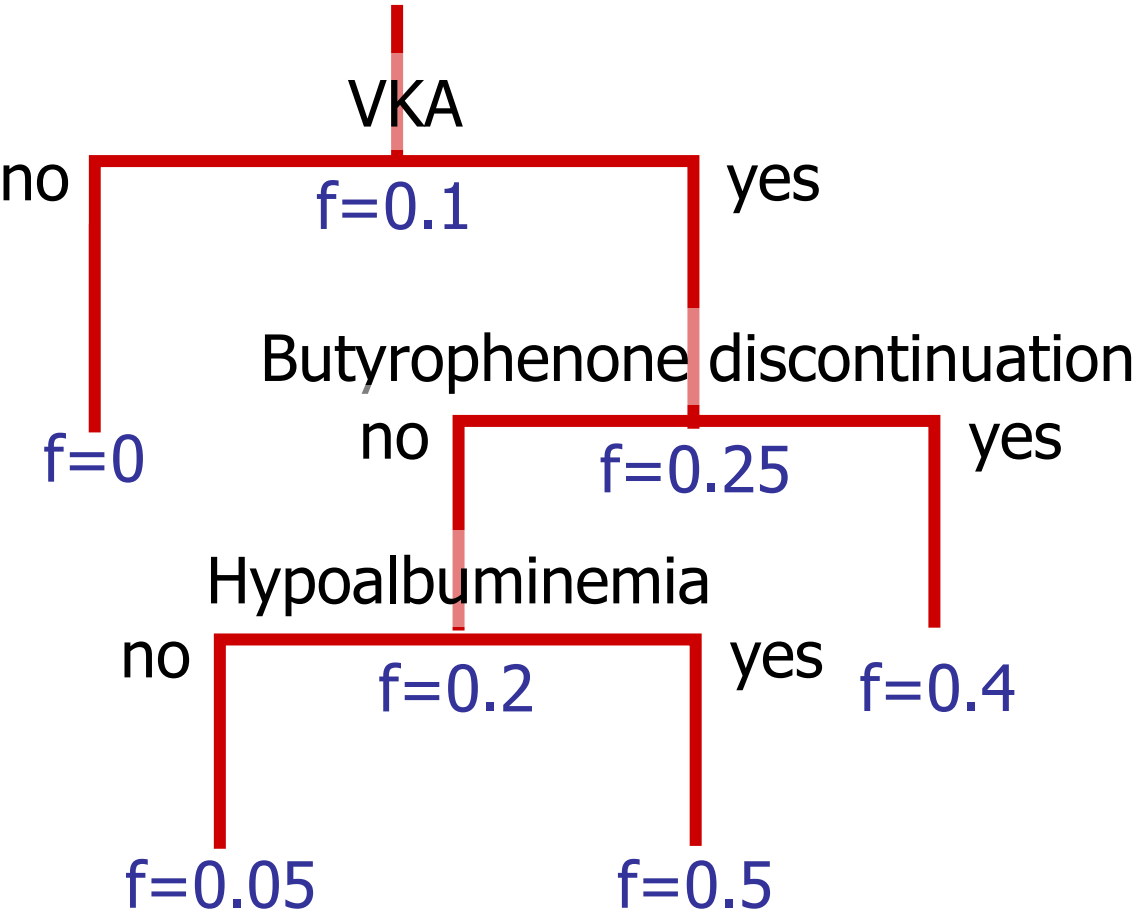


Available data: ~175,000 inpatient stays from 6 hospitals (F, Dk, Bu)



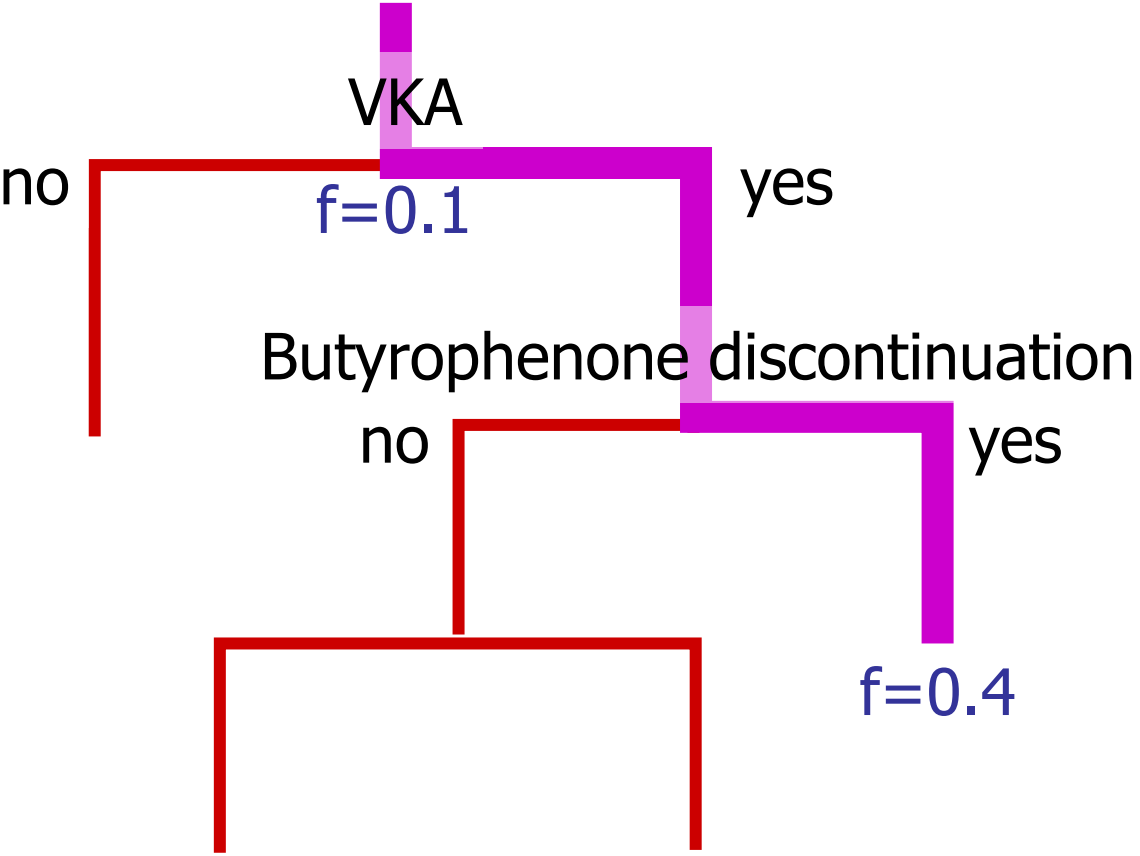


Artificial intelligence
Example of decision tree



- VKA= vitamin K antagonists (anticoagulant)
- INR= international normalized ratio. Evaluates VKA activity
- INR>5 => risk of hemorrhage
- The tree attempts to explain INR>5

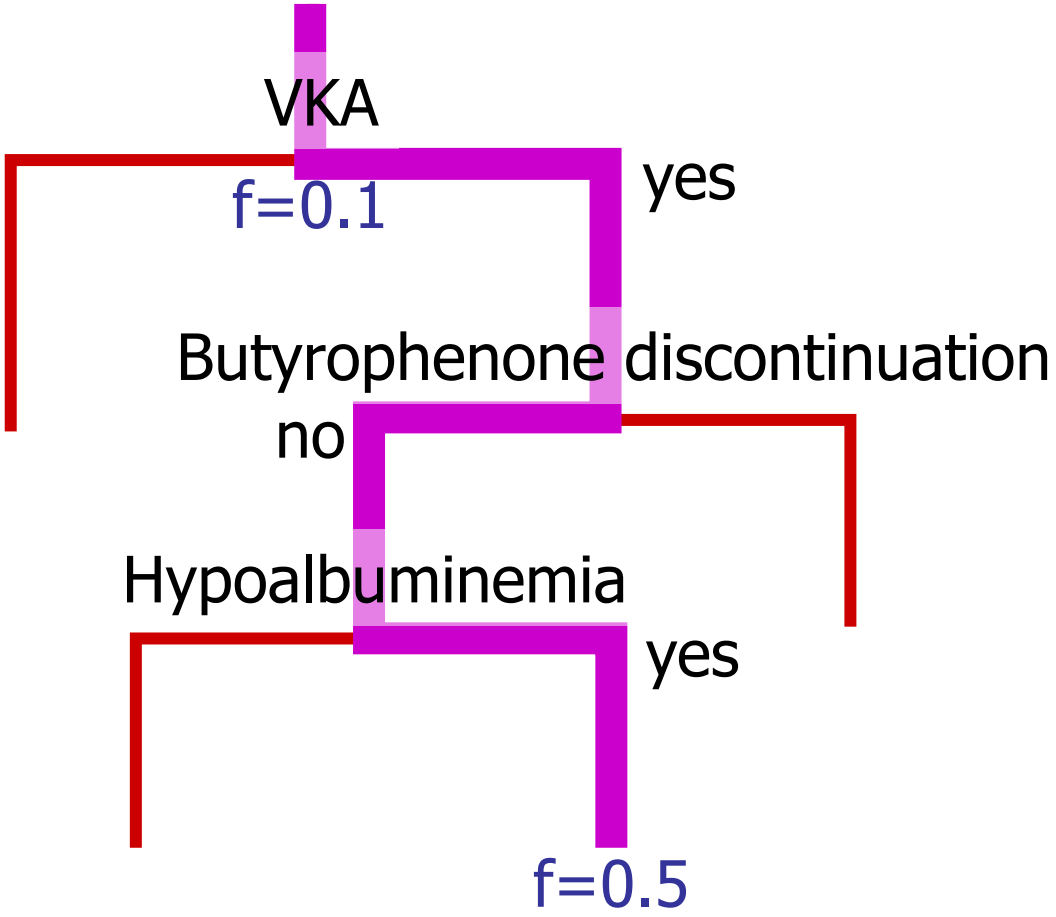
Artificial intelligence
Example of decision tree



Rule #1 (4th leaf):

VKA
& butyrophenone discontinuation
→ P=0.4

Artificial intelligence
Example of decision tree



Rule #2 (3rd leaf):

VKA
& no
butyrophenone
discontinuation
& hypoalbuminemia
→ P=0.5

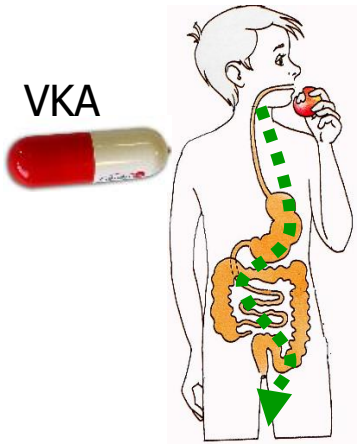
Validation of retrospective ADE detection

I. Validation of each rule, on a bibliographic point of view

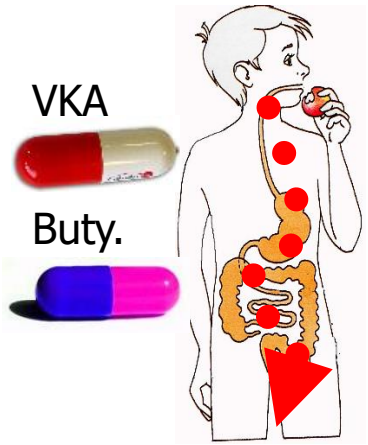
II. Validation of the tool, on a statistical point of view

Artificial intelligence
Expert validation of rules

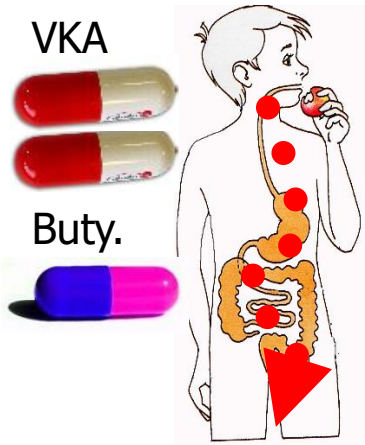
Butyrophenone:
neuroleptic drugs, may accelerate the intestinal transit



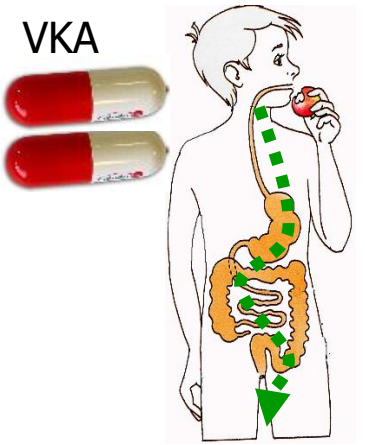
Step 1: normal VKA intake



Step 2: butyrophenone => transit acceleration => too low INR



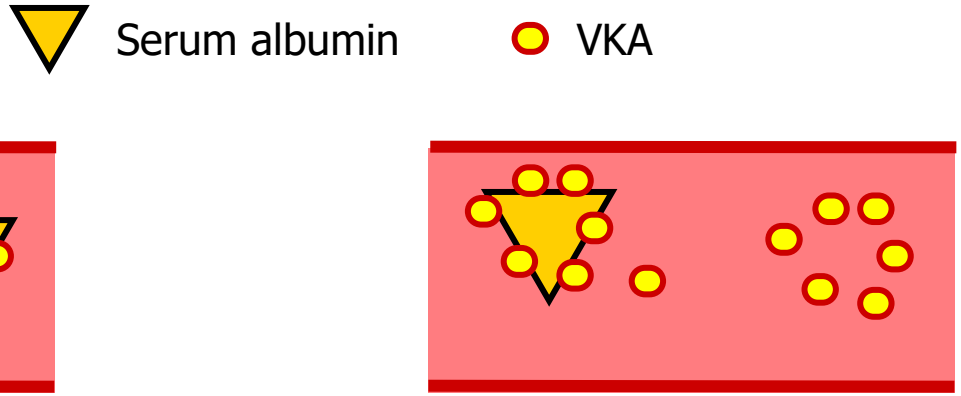
Step 3: increased intake of VKA => normal INR



Step 4: buty. discontinuation => normal transit => too high INR

Artificial intelligence
Expert validation of rules

Albumine = plasmatic protein to which VKA bind. Only the non-bound part is biologically active.



Normal state:
99% of the VKA bind to albumin.
Only 1% of VKA are biologically active.
The intake is based on it.

Hypoalbuminemia:
decrease of the bound fraction,
increase of the non-bound fraction
=> too high INR (with constant intake)

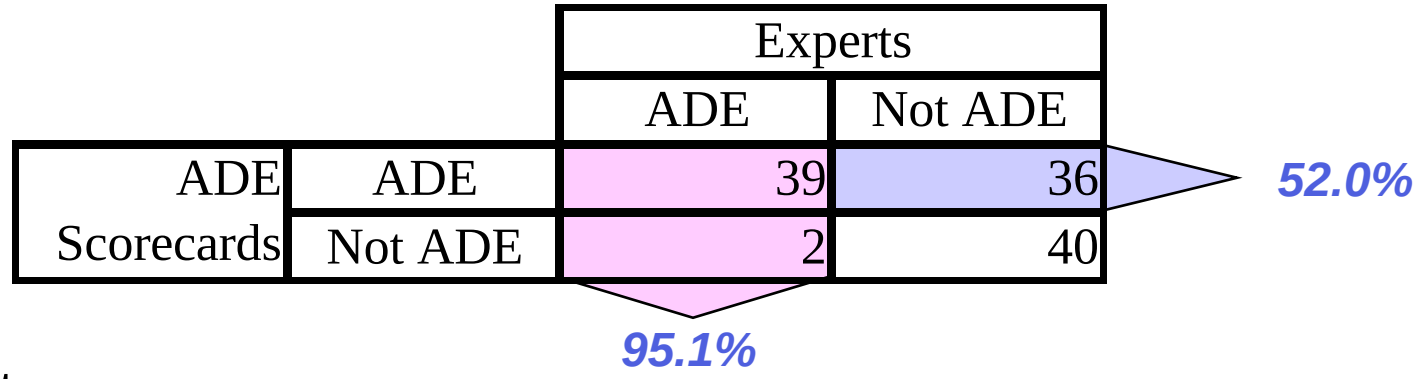
=> Need for validation, explanations, reorganization!

Overview of ADE detection rules

Kind of Outcome	# Rules
Coagulation disorders	
Hemorrhage (detected by the administration of haemostatic)	7
Heparin overdose (activated partial thromboplastin time>1.23)	5
VKA overdose (INR>4.9 or administration of vitamin K)	59
Thrombopenia (count<75,000)	24
Other coagulation disorders	23
Ionic and renal disorders	
Hyperkalemia (K^+>5.3 mmol/l)	63
Renal failure (creatinine>135 µmol/l or urea>8 mmol/l)	8
Other ionic disorders	4
Miscellaneous	
Anemia (Hb<10g/dl)	2
Bacterial infection (detected by the administration of antibiotic)	4
Diarrhea (detected by the administration of an anti-diarrheal)	2
Fungal infection (detected by the administration of an antifungal)	10
Hepatic cholestasis (alk. Phos.>240 UI/l or bilirubins>22 µmol/l)	3
Hepatic cytolysis (ala. trans.>110 UI/l or asp. trans.>110 UI/l)	4
Hypereosinophilia (eosinophilocytes>10^9/l)	4
High level of pancreatic enzymes (amylase>90 UI/l or lipase>90 UI/l)	7
Neutropenia (count<1,500/mm^3)	2
Others	5
Total	***236***

Evaluation of the ADE retrospective detection

- Complete 2010 year of one hospital
  - Number of stays : 14,747
  - Number of hyperkalemia cases : 117 (7.93‰) → exhaustive review



- Result
  - Precision 39/75= 52.0%
  - Recall 39/41= 95.1%
  - Harmonic mean 67.2%
  - Number of reported cases 0/41= 0%

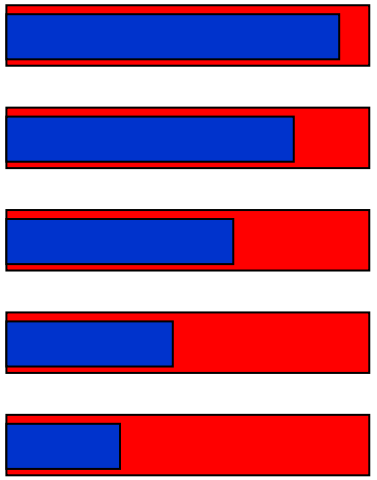
Ability of the rules to retrospectively detect actual ADEs

- Expert-operated case review

	Validated cases / reviewed cases	Precision *[95% confidence interval]*
Hyperkalemia *(K+>5.3mmol/l)*	54 / 101	53.5% *[43.7;63.2]*
VKA overdose *(INR>4.9)*	5 / 9	55.6% *[23.1;88.0]*
Renal failure *(creat.>135 µmol/l or urea>16.6 mmol/l)*	35 / 75	46.7% *[35.4;58.0]*
Other outcomes	14 / 53	26.4% *[14.5;38.3]*
TOTAL	**108 / 238**	**45.4% *[39.1;51.7]***

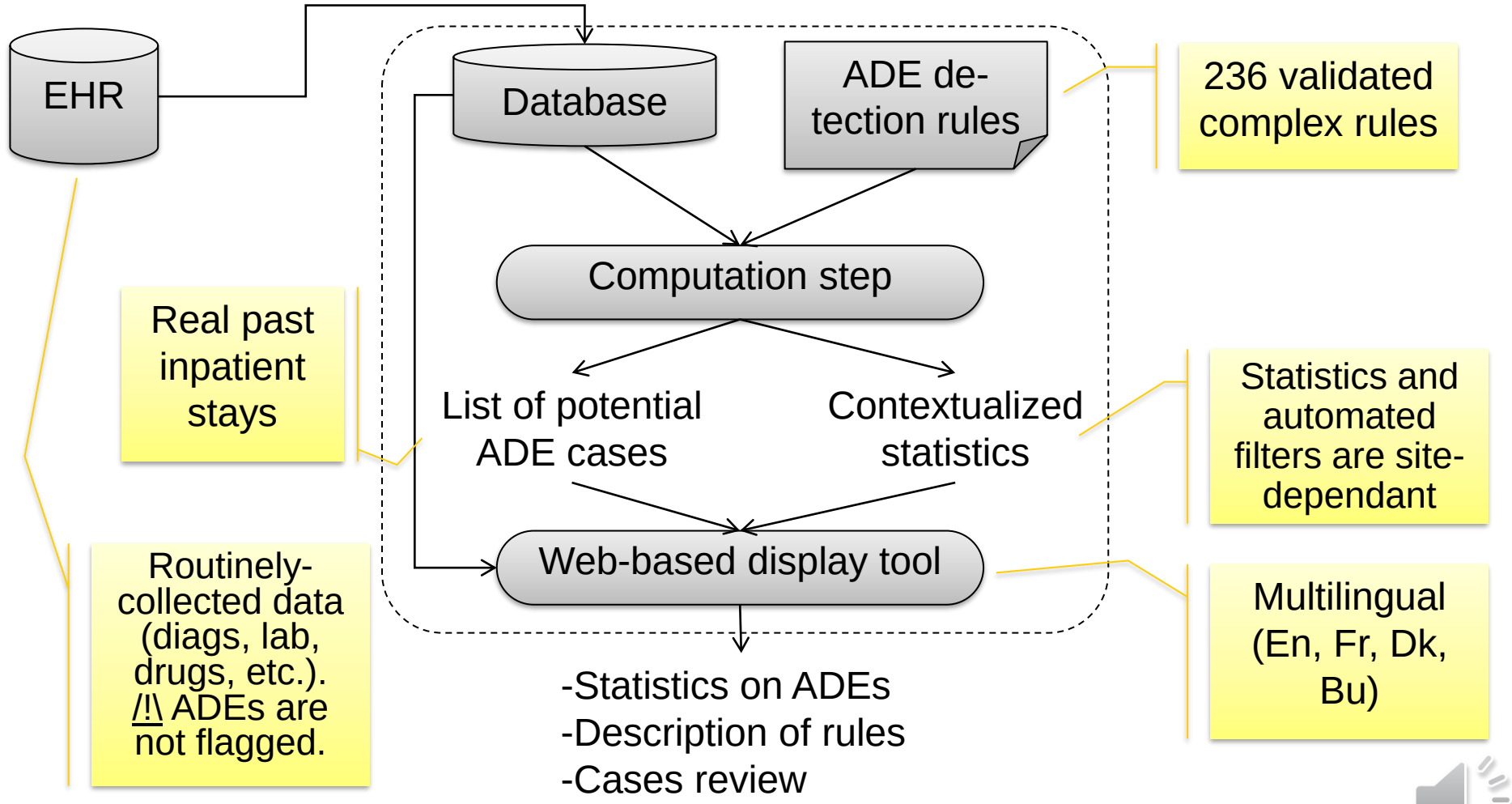
How to evaluate an ADE detection rule?

- Evaluation of the accuracy of:
  - *thiazide diuretic & renal failure → hyperkalemia*
  - Which means: if the 3 conditions are present, then this is an ADE
- Several evaluations:
  1. The 2 causes are present, the outcome is present, and time consistent
  2. The 2 causes may explain the outcome
  3. The 2 causes are the main causes of the outcome
  4. There is a medication error
  5. There is a preventable medication error
- And: usability, acceptability, human factors ?



The ADE Scorecards, a web-based tool for ADE detection and visualization

The “ADE Scorecards”, a tool for automated ADE detection in EHR



PSIP - Scorecards Connection Page - Mozilla Firefox

Fichier Édition Affichage Historique Marque-pages Outils ?

http://expert-explorer.eu/scorecards/

faculté de médecine lille

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Scorecards / Tableaux de Bord

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Department / Service

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Edit detailed statistics

Analysis period

jan-nov 2010

Detected effects

Select all | Deselect all

- anemia (Hb<10g/dl) (34)
- biological pancreatitis (amylase>90 UI/l or lipase>90 UI/l) (6)
- fungal infection (detected by prescription of a systemic antifungal) (21)
- hemorrhage (detected by a prescription of hemostatic) (27)
- hepatic cytolysis (alanine transa.>110 or aspartate transa.>110) (15)
- high a CPK rate (CPK>195 UI/l) (5)
- hyperkalemia (K+>5.3) (99)
- hyponatremia (Na+<130) (5)
- mycosis (detected by the prescription of local antifungal) (1)
- neutropenia (count<1500/mm3) (2)
- renal failure (creat.>135 micromol/L or urea>16.6 mmol/L) (111)
- thrombopenia (count<75,000) (1)
- too high INR>4.9) (6)

Generate Scorecards

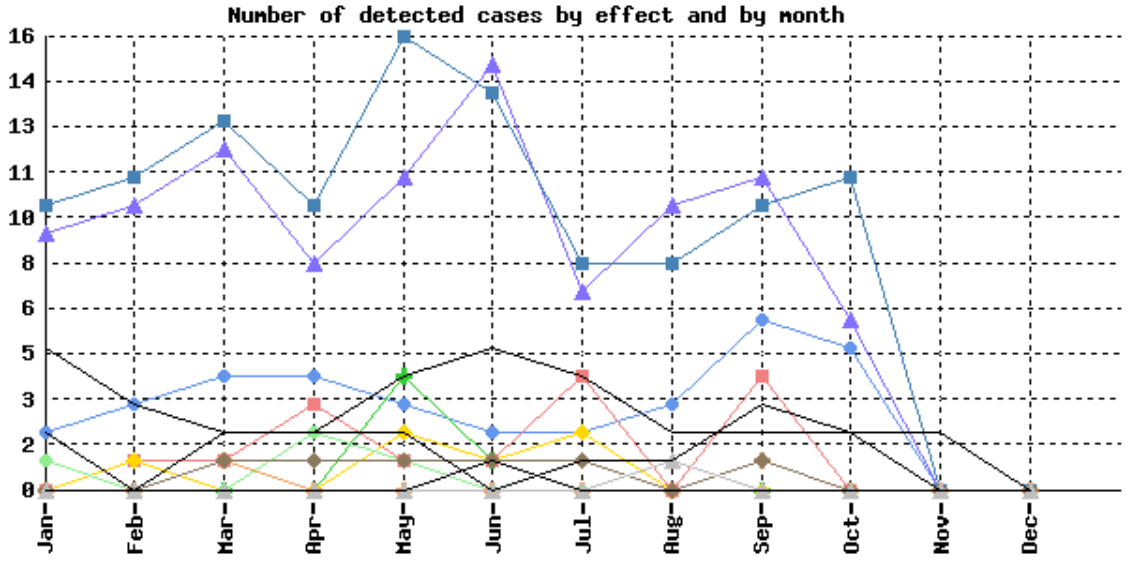
Synthesis

Number of stays with adverse events

Deselect all / Select all	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Anemia (Hb<10g/dl)	2	3	4	4	3	2	2	3	6	5	0	
Biological pancreatitis (amylase>90 UI/l or lipase>90 UI/l)	0	0	1	1	1	1	1	0	1	0	0	
Fungal infection (detected by prescription of a systemic antifungal)	5	3	2	2	2	0	1	1	3	2	0	

Number of stays with adverse events

	Deselect all / Select all	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
☑	Anemia (Hb<10g/dl)	2	3	4	4	3	2	2	3	6	5	0	
☑	Biological pancreatitis (amylase>90 UI/l or lipase>90 UI/l)	0	0	1	1	1	1	1	0	1	0	0	
☑	Fungal infection (detected by prescription of a systemic antifungal)	5	3	2	2	2	0	1	1	3	2	0	
☑	Hemorrhage (detected by a prescription of hemostatic)	2	0	2	2	4	5	4	2	2	2	2	
☑	Hepatic cytolysis (alanine transa.>110 or aspartate transa.>110)	0	1	1	3	1	1	4	0	4	0	0	
☑	High a CPK rate (CPK>195 UI/l)	0	0	0	0	4	1	0	0	0	0	0	
☑	Hyperkalemia (K+>5.3)	9	10	12	8	11	15	7	10	11	6	0	
☑	Hyponatremia (Na+<130)	1	0	0	2	1	0	0	0	1	0	0	
☑	Mycosis (detected by the prescription of local antifungal)	0	0	0	0	0	1	0	0	0	0	0	
☑	Neutropenia (count<1500/mm3)	0	0	1	0	0	0	0	0	1	0	0	
☑	Renal failure (creat.>135 micromol/L or urea>16.6 mmol/L)	10	11	13	10	16	14	8	8	10	11	0	
☑	Thrombopenia (count<75,000)	0	0	0	0	0	0	0	1	0	0	0	
☑	Too high INR>4.9)	0	1	0	0	2	1	2	0	0	0	0	



Hyperkalemia (K+>5.3)

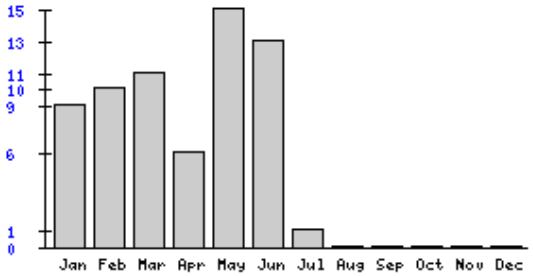
Characteristics of identified stays, all the rules together

Data from the coded diagnostics

Effective	65
Average age	75
Men - Women	42% - 58%
Deaths	15%

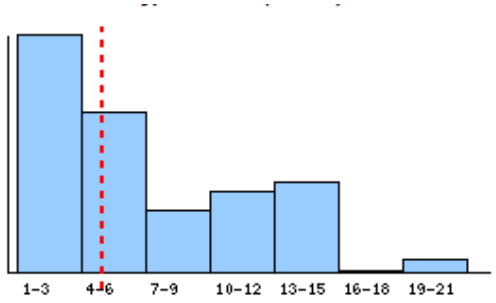
Cancers	25%
Cardiomyopathies	60%
Renal insufficiency	20%
Hepatic insufficiency	8%
Respiratory insufficiency	31%
Alcoholism	6%

Number of cases per month



Adverse events occurred under the above conditions.

Histogram of appearance delay



Conditions leading to Hyperkalemia (K+>5.3)	Number of cases confidence ; median delay
(1) HMWH can induce hyperkaliemia, specially with renal insufficiency.	5

Conditions leading to Hyperkalemia (K+>5.3)	Number of cases confidence ; median delay
(1) **LMWH can induce hyperkaliemia, specially with renal insufficiency.**	2
Renal failure & Low weight heparin & Age < 70	17% ; 4.5j
(2) **HMWH can induce hyperkaliemia, specially with ACE inhibitors and renal insufficiency.**	2
Renal failure & High weight heparin & Angiotensin conversion enzyme inhibitor	13% ; 2j
(3) **The suspension of some laxatives may reveal hyperkalemia.**	1
Renal failure & Suspension of other laxative & Hepatic cholestasis	34% ; 2j
(4) **The suspension of propulsive laxative may reveal hyperkalemia.**	1
Renal failure & Propulsive laxative	34% ; 2j
(5) **Angiotensin-converting enzyme and sartans may cause hyperkalemia.**	3
Renal failure & Angiotensin conversion enzyme inhibitor & Opioïd	11% ; 2j
(6) **The suspension of potassium lowering diuretic may reveal hyperkalemia.**	6
Renal failure & Suspension of potassium lowering diuretic & NO Thrombin inhibitor	11% ; 3j
(7) **The suspension of aminoglycoside may reveal hyperkalemia.**	1
Renal failure & Suspension of aminoglycoside	17% ; 15j
(8) **Prescription of nonsteroidal anti-inflammatory drugs may cause hyperkalemia.**	1
Renal failure & NSAI & NO Potassium sparing diuretic	50% ; 1j
GLOBAL	***65***

Confidence (a%): percentage of stays for which the effect occurs among the stays meeting the conditions.
Median delay: from the moment when all conditions of the rule are met, period from which over 50% of effects will be appeared.

Details of rules

[1] HMWH can induce hyperkaliemia, specially with renal insufficiency.

Details of rules

[1] HMWH can induce hyperkaliemia, specially with renal insufficiency.

Renal failure & **High weight heparin** → Hyperkalemia (K+>5.3)

Somes aldosteronism or metabolic acidosis cases have been described with heparins. The risk is increased in case of a kidney insufficiency.
Ref. : Martindale -The complete drug reference- 34ème ed, The Pharmaceutical Press, London 2005 : 927-31.

In case of a high molecular weight heparin treatment, the dosage has to be adapted and the clinical and biological monitoring have to be increased.

TOP

[2] HMWH can induce hyperkaliemia, specially with diabetic patients and renal insufficiency.

Renal failure & **High weight heparin** & **Diabetes** → Hyperkalemia (K+>5.3)

Somes aldosteronism or metabolic acidosis cases have been described with heparins. The risk is increased in case of diabetes and renal insufficiency.
Ref. : Martindale -The complete drug reference- 34ème ed, The Pharmaceutical Press, London 2005 : 927-31.

In case of an high molecular weight heparin treatment, the dosage has to be adapted and the clinical and biological monitoring have to be increased.

TOP

[3] HMWH can induce hyperkaliemia, specially with ACE inhibitors and renal insufficiency.

Renal failure & **High weight heparin** & **Angiotensin conversion enzyme inhibitor** → Hyperkalemia (K+>5.3)

Somes aldosteronism or metabolic acidosis cases have been described with heparins. The risk is increased in case of an angiotensin-converting enzyme inhibitor treatment and renal insufficiency.

Conditions leading to Hyperkalemia (K+>5.3)	Number of cases confidence ; median delay
(1) **LMWH can induce hyperkaliemia, specially with renal insufficiency.**	2
Renal failure & Low weight heparin & Age < 70	17% ; 4.5j
(2) **HMWH can induce hyperkaliemia, specially with ACE inhibitors and renal insufficiency.**	2
Renal failure & High weight heparin & Angiotensin conversion enzyme inhibitor	13% ; 2j
(3) **The suspension of some laxatives may reveal hyperkalemia**	1
Renal failure & Suspension of other laxative & Hep	
(4) **The suspension of propulsive laxativ**	
Renal failure & Propulsive laxative	
(5) **Angiotensin-converting enzyme and s hyperkalemia.**	
Renal failure & Angiotensin conversion enzyme in	
(6) **The suspension of potassium loweri hyperkalemia.**	
Renal failure & Suspension of potassium lowering	
(7) **The suspension of aminoglycoside m**	
Renal failure & Suspension of aminoglycoside	
(8) **Prescription of nonsteroidal anti-infla hyperkalemia.**	
Renal failure & NSAI & NO Potassium sparing diu	
GLOBAL	***65***

Angiotensin-converting enzyme and sartans may cause hyperkalemia.

July 2010 (0 cases):

June 2010 (1 cases):

- View Stay details

May 2010 (2 cases):

- View Stay details

Close

Confidence (a%): percentage of stays for which the effect occurs among the stays meeting the conditions.
Median delay: from the moment when all conditions of the rule are met, period from which over 50% of effects will be appeared.

Details of rules

[1] HMWH can induce hyperkaliemia, specially with renal insufficiency.

Back to the stay | More information | Rule info

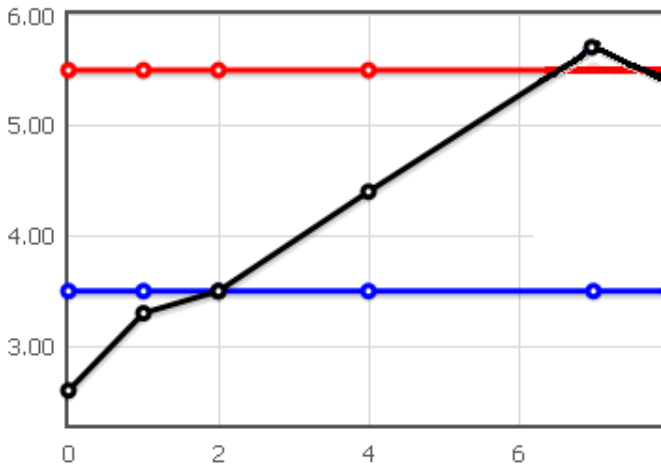
PSIP

ATC	Drug name	0 5 10
	1000 ml POLYIONIQUE G5 + POTASSIUM CHL A + SPASFON SOL INJ	
A02BC02	INIPOMP 20 MG, CPR (VOIR INEXIUM 20)	
A06AD15	FORLAX 10G PDR ORALE SACHET PR SOL BUV	
A07DA03	IMODIUM 2MG GELULE VERT FONCE ET VERT CLAIR	
A07XA04	TIORFAN 100MG GELULE BLEU CLAIR ET BLEU FONCE	
A10AB05	NOVOMIX 30 FLEXPEN 100 U/ML, SUSP INJ, STYLO 3 ML	
A12BA01	KALEORID 1000MG LP CPR ENR	
B01AC06	KARDEGIC 75 MG, PDR PR SOL BUV, SACHET	
C01DX12	CORVASAL 4MG CPR SECABLE BLANC	
C07AB03	ATENOLOL 50 MG ARROW, CPR	
C09BA04	PRETERAX, CPR	
C10AA03	ELISOR 20MG CPR SECABLE = PRAVASTATINE 20 MG SANDOZ	
J01DA23	OROKEN 200MG CPR PELLICULE (PRESCRIPTION PAPIER OBLIGATOIRE ANTIBIO)	
N06DX02	TANAKAN 40MG CPR ENR BRUN ROUGE	
V03AE01	KAYEXALATE 454G PDR PR SUSP BUV/RECT	

Show all | Hide all

- [ ] 100 % FORMULE
- [ ] BT.
- [ ] CCMH
- [ ] CL1
- [ ] CREAT.
- [ ] CRP
- [ ] GB
- [ ] GGT.
- [ ] GR(Millions/ml
- [ ] HB
- [ ] HT
- [ ] INR
- [x] K1
- [ ] L%
- [ ] MONOCYTES%
- [ ] MYELOCYTES%
- [ ] NA1
- [ ] PB%
- [ ] PE%
- [ ] PHAL.
- [ ] PLAQ.
- [ ] PN%
- [ ] PROTIDES TOTAU
- [ ] Proteinurie
- [ ] RA.
- [ ] TCA
- [ ] TCA patient
- [ ] TCAr
- [ ] TCMH
- [ ] TGO.
- [ ] TGP.
- [ ] TP.
- [ ] UREE SG
- [ ] VGM
- [ ] Glycosurie
- [ ] Ly
- [ ] Mo
- [ ] Mye
- [ ] Pb
- [ ] Pe
- [ ] Pn

K1



Back to the stay | More information | Rule info

PSIP

ATC	Drug name	0 5 10
	1000 ml POLYIONIQUE G5 + POTASSIUM CHL A + SPASFON SOL INJ	
A02BC02	INIPOMP 20 MG, CPR (VOIR INEXIUM 20)	
A06AD15		
A07DA03		
A07XA04		
A10AB05		
A12BA01		
B01AC06		
C01DX12		
C07AB03		
C09BA04		
C10AA03		
J01DA23	OROKEN 200MG CPR PELLICULE (PRESCRIPTION PAPIER OBLIGATOIRE ANTIBIO)	
N06DX02	TANAKAN 40MG CPR ENR BRUN ROUGE	
V03AE01	KAYEXALATE 454G PDR PR SUSP BUV/RECT	

Stay info - Mozilla Firefox

http://www.expert-explorer.eu/stay_frames_info_rule.php?h[redacted]effect_scor

Rule info

hyperkalemia (K+>5.3)
HMG CoA reductase inhibitor & **NO** hypoalbuminemia & inflammation → hyperkalemia (K+>5.3)
NO renal failure & beta blocker → hyperkalemia (K+>5.3)
NO renal failure & angiotensin conversion enzyme inhibitor → hyperkalemia (K+>5.3)
NO renal failure & potassium → hyperkalemia (K+>5.3)

Terminé

Show all | Hide all

- [ ] 100 % FORMULE
- [ ] BT.
- [ ] CCMH
- [ ] CL1
- [ ] CREAT.
- [ ] CRP
- [ ] GB
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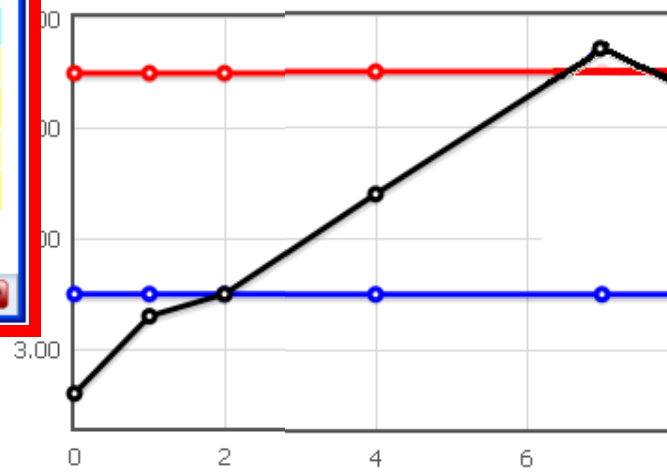

Back to the stay | More information | Rule info

PSIP

ATC		10
	1000 ml POLYIONIQUE (SPASFON SOL INJ	
A02BC02	INIPOMP 20 MG, CPR (	
A06AD15	FORLAX 10G PDR ORAL	■
A07DA03	IMODIUM 2MG GELULE	
A07XA04	TIORFAN 100MG GELUL	
A10AB05	NOVOMIX 30 FLEXPEN	☑
A12BA01	KALEORID 1000MG LP	
B01AC06	KARDEGIC 75 MG, PDR	■
C01DX12	CORVASAL 4MG CPR S	☑
C07AB03	ATENOLOL 50 MG ARR	■
C09BA04	PRETERAX, CPR	■
C10AA03	ELISOR 20MG CPR SE SANDOZ	
J01DA23	OROKEN 200MG CPR P PAPIER OBLIGATOIRE A	☑
N06DX02	TANAKAN 40MG CPR EN	☑
V03AE01	KAYEXALATE 454G PDR PR SUSP BUV/RECT	■

Stay info - Mozilla Firefox

http://www.expert-explorer.eu/stay_frames_info.

More information

Stay	
Age	83
Gender	female
Death	no
Length of stay	9 days

ICD10 Diagnoses
E119 - D.N.I.D., SANS COMPLIC.
I251 - CARDIOPATHIE ARTERIOSCLEREUSE
I10 - HYPERTENSION ESSENTIELLE
E8760 -
N300 - CYSTITE AIG.
B961 - KLEBSIELLA PNEUMONIAE, CAUSE DE MAL. CLASSEES DANS D'AUTRES CHAP.

Terminé

Show all | Hide all

- [ ] 100 % FORMULE
- [ ] BT.
- [ ] CCMH
- [ ] CL1
- [ ] CREAT.
- [ ] CRP
- [ ] GB
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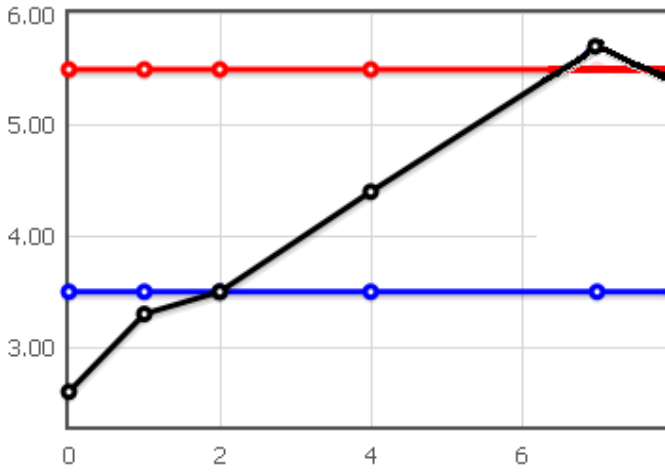
K1



Back to the stay | More information | Rule info

PSIP

ATC	
	1000 SPAS
A02BC02	INIPC
A06AD15	FORL
A07DA03	IMOD
A07XA04	TIOR
A10AB05	NOVO
A12BA01	KALE
B01AC06	KARD
C01DX12	CORV
C07AB03	ATEN
C09BA04	PRET
C10AA03	ELISO SAND
J01DA23	OROI PAPI
N06DX02	TANA
V03AE01	KAYE

Show all | Hide all

100 % FORMULE | INR | K1 | PROTIDES | VGM | TOTAU | Proteinurie | Glycosurie | RA. | Ly | TCA | Mo | TCA patient | Mye | TCAr | Pb | TCMH | Pe | TGO. | Pn | TGP. | TP. | UREE SG

ES%

TES%

Sans titre - Bloc-notes

Fichier Edition Format Affichage ?

cher confrere,

nous laissons sortir ce jour, @ @ @ @, nee le @/@/@, @ @ @ @ @ @ @, hospitalisee dans notre service du @/@/@ au @/@/@ pour diarrhees et vomissements.

antecedents

sur le plan chirurgical
-appendicectomie
-cholecystectomie
-prothese totale de hanche gauche sur coxarthrose
-prolapsus en @ avec pose de pessaire
-hysterectomie

sur le plan medical
-dnid insulino-requerant
-rgo
-hta
-dyslipidemie
-cardiopathie ischemique
-hernie discale avec cruralgie.

histoire de la maladie
la patiente a ete adressee aux urgences du centre @ de @ pour intolerance alimentaire dans un contexte de diarrhees, vomissements et febricule a 38° evoluant depuis le @/@/@.

examen clinique
a son arrivee dans le service, la patiente presentait un etat general relativement conserve avec cependant une asthenie evoluant de facon chronique, elle presentait egalement une douleur lombaire chronique.
il n'existait pas d'amaigrissement recent. la patiente etait apyretique.

sur le plan cardiovasculaire, les constantes etaient bonnes avec une tension arterielle a 10/@ et une frequence cardiaque a 95. il n'existait pas de signe fonctionnel cardiaque. a l'examen, on ne notait aucun signe d'insuffisance cardiaque droite ou gauche.
l'auscultation etait sans particularite avec des bruits du coeur reguliers, absence de souffle cardiaque ou vasculaire.

sur le plan respiratoire, saturation a 95% en air ambiant, la patiente ne se plaignait d'aucun signe fonctionnel respiratoire. l'auscultation etait sans particularite, les murmures vesiculaires etaient bilateraux et symetriques sans bruit surajoute.

What did we learn about ADEs with the ADE Scorecards?

Installed in 5 hospitals (2 Danish, 2 French and 1 Bulgarian)

Routinely used by the physicians and pharmacists of a French general hospital during three years

Statistics about ADEs

	Nb of cases of outcome *	Nb of cases occurring during the stay	Nb of potential ADEs (automated detection)	Nb of confirmed ADEs (expert review)**
Hyperkalemia	1301 *2.67%*	703 *2.84%*	507 *2.05%*	271 *1.1%*
Renal failure	2293 *4.7%*	728 *2.94%*	404 *1.63%*	189 *0.76%*
VKA overdose	625 *1.28%*	321 *1.3%*	246 *0.99%*	137 *0.55%*
Other kinds of outcomes	13936 *28.56%*	7171 *28.97%*	1438 *5.81%*	380 *1.53%*
Total	**14454 (29.62%)**	**7624 (30.8%)**	**2196 (8.87%)**	**997 (4.03%)**

**: the number of events is reported to the total number of stays, but next numbers are related to inpatient stays lasting at least 2 days*

***: extrapolated from a sample*

Location	Hyperkalemia	Renal failure	VKA overdose	Other kinds of outcomes	Total
All Hospitals	1.67%	1.62%	0.77%	4.18%	7.23%

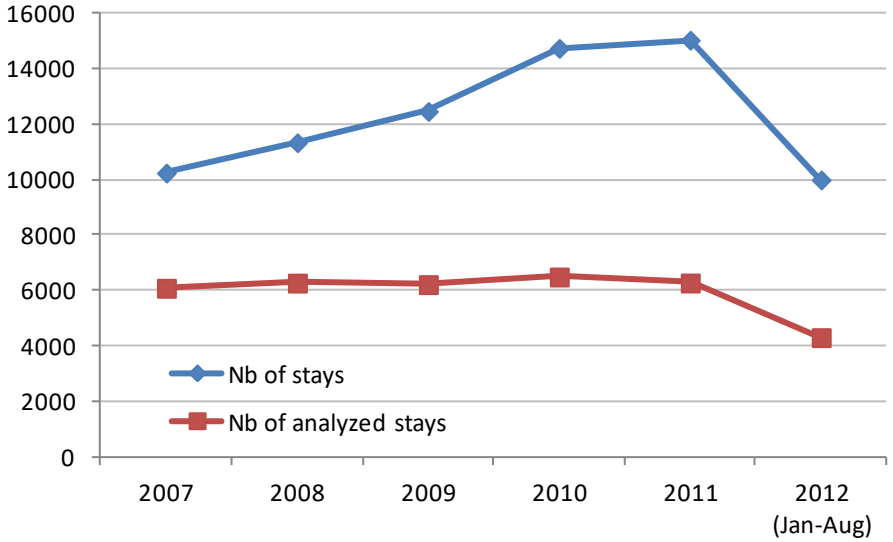
Hospital	Hyperkalemia	Renal failure	VKA overdose	Other kinds of outcomes	Total
Hospital 1 (Dk)	0.47%	0.97%	0.10%	5.86%	6.78%
Hospital 2 (Fr)	3.05%	1.53%	0.76%	0.76%	4.58%
Hospital 3 (Dk)	0.88%	0.61%	0.00%	4.02%	5.07%
Hospital 4 (Fr)	10.57%	2.94%	0.00%	8.22%	18.20%
Hospital 5 (Bu)	0.05%	0.02%	0.00%	0.14%	0.19%
Hospital 6 (Fr)	1.67%	1.62%	0.77%	4.18%	7.23%

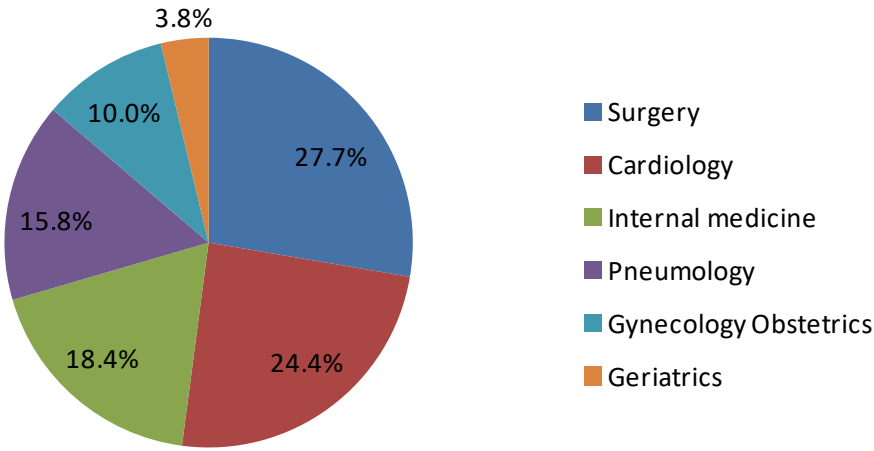
Department of Hosp 6	Hyperkalemia	Renal failure	VKA overdose	Other kinds of outcomes	Total
Surgery	0.89%	0.48%	0.14%	3.09%	4.12%
Geriactrics	3.41%	3.41%	0.00%	5.40%	10.51%
Gyneco obst.	0.00%	0.00%	0.00%	0.41%	0.41%
Cardiology	2.65%	2.79%	1.36%	4.23%	9.89%
Internal medicine	2.67%	2.58%	1.62%	10.22%	14.61%
Pneumology	2.77%	2.66%	2.11%	6.21%	11.86%

Department of Hosp 1	Hyperkalemia	Renal failure	VKA overdose	Other kinds of outcomes	Total
Neurology	1.09%	2.46%	0.82%	6.83%	9.84%
Cardio/endoc.	1.17%	2.09%	0.31%	6.28%	8.38%
Geriatrics	1.02%	2.24%	0.20%	17.48%	18.70%
Gynecology	0.00%	0.00%	0.00%	0.00%	0.00%
Intensive care	0.28%	1.40%	0.00%	11.76%	13.17%
Internal Med.	0.73%	1.52%	0.00%	10.46%	11.92%
Obstretrics	0.00%	0.00%	0.00%	1.47%	1.47%
Orthopedic	0.18%	0.80%	0.00%	8.57%	9.10%
Rheumatology	1.12%	1.57%	0.22%	18.61%	20.18%
Urology	0.36%	0.72%	0.09%	4.43%	5.15%

Characteristics of the patients (n=73,836 inpatient stays)

Parameter	Overall	Cardiology	Gyn. Obs.	p value (all)
Age (years)	60.2	67.6	28	*p<0.001*
Length of stay (days)	8.01	8.19	11.6	*p<0.001*
Proportion of men	40.80%	42.80%	0.00%	*p<0.001*



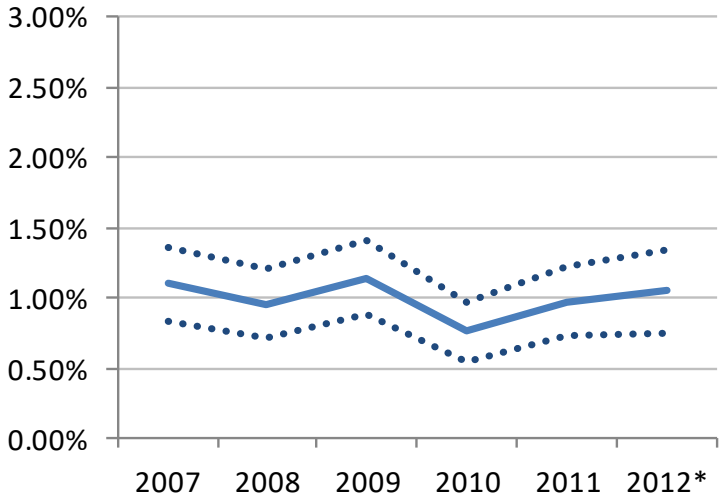


Potential ADE cases with INR increase (INR≥5)

due to vitamin K antagonist overdose or interaction may induce a severe hemorrhage

- Estimated proportion:

0.99% [0.89%;1.09%]



- Interesting data:

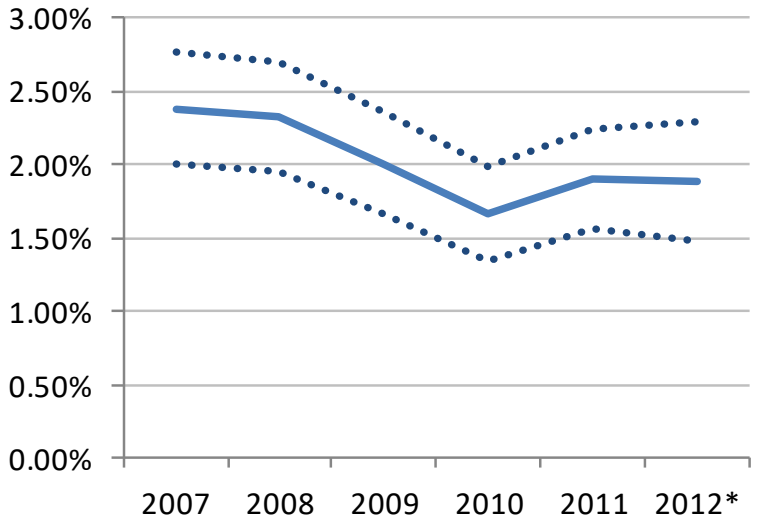
Parameter	Overall	Cardiology	Gyn. Obs.	p val (all)
VKA	8.34%	15.50%	0.00%	*p<0.001*
Chr. hepatic insuf.	4.90%	13.70%	0.04%	*p<0.001*
INR increase (all)	2.46%			
Potential ADE	0.99%	1.36%	0.00%	*p<0.001*

Potential ADE cases with hyperkalemia (K^+>5.5mmol/l)

may induce lethal cardiac rhythm troubles

- Estimated proportion:

2.03% [1.89%;2.18%]



- Interesting data:

Parameter	Overall	Cardiology	Gyn. Obs.	p val (all)
Diuretics	23.30%	41.10%	0.00%	*p<0.001*
Chr. renal insuf.	2.02%	3.04%	0.04%	*p<0.001*
Hyperkalemia (all)	5.43%			
Potential ADE	2.03%	2.65%	0.00%	*p<0.001*

For each ADE detection rule, contextualized statistics are computed in each setting

Rule: vitamin K antagonist & amoxicilline&clav.ac. & age ≥ 70 ⟶ appearance of high INR (INR≥5)

Department	Confidence (PPV)	Support (frequency)	Median delay	Relative risk	Fisher's test P value
X all departments	10/57=**17.5%**	10/5322=**1.9‰**	6.5j	13.38	0
X medicine B	3/17=**17.7%**	3/966=**3.1‰**	3j	9.31	0.005
X pneumology	5/28=**17.9%**	5/818=**6.1‰**	11j	6.41	0.0016
Y all departments	1/10=**10%**	1/11923=**0.1‰**	6j	33.09	0.0306
Y apoplexy	*No stay matches the conditions*				
Y cardio & endocrinology	1/2=**50%**	1/1967=**0.5‰**	6j	51.71	0.0202
Y geriatrics	0/2=**0%**	0/493=**0‰**		0	1
Y gynecology	*No stay matches the conditions*				
Y intensive care unit	*No stay matches the conditions*				
Y internal medicine	0/5=**0%**	0/1514=**0‰**		0	1
Y obstetrics	*No stay matches the conditions*				
Y orthopedics	*No stay matches the conditions*				
Y rheumatology	*No stay matches the conditions*				
Y urology	*No stay matches the conditions*				
Z all departments	0/1=**0%**	0/1022=**0‰**		0	1
W all departments	0/8=**0%**	0/7685=**0‰**		0	1

Department	Confidence (PPV)	Support (frequency)	Median delay	Relative risk	Fisher's test P value
X all dpts	10/57=**17.5%**	10/5322=**1.9‰**	6.5j	13.38	0

Comment:

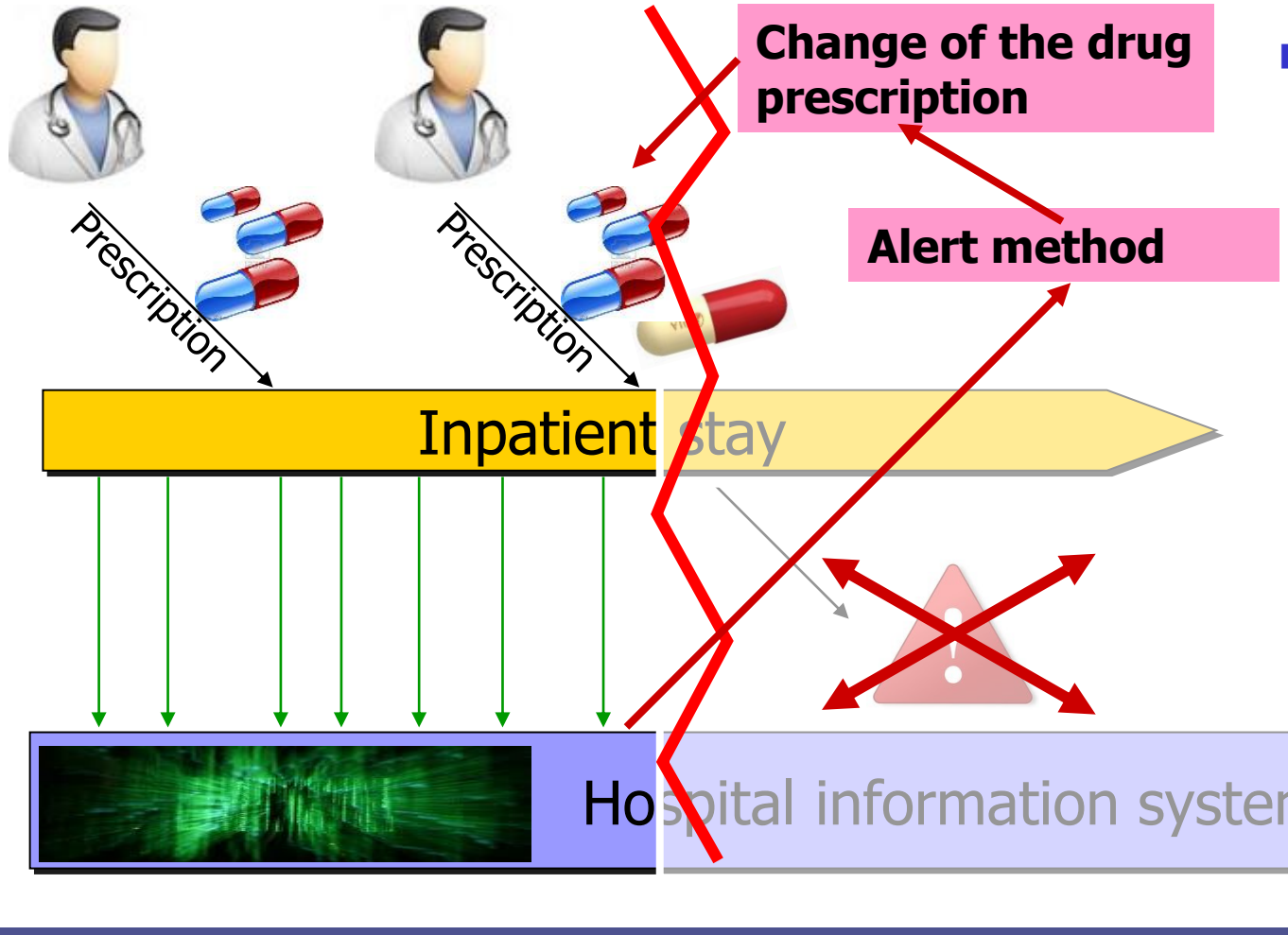
- *Les pénicillines augmentent le risque hémorragique sous AVK.*
- *Une augmentation de l'activité des anti-vitamine K peut être observée chez les patients traités par pénicillines. Le risque hémorragique est accru*
  Ref : thésaurus IAM-AFSSAPS juin 2009.
- *En cas de prise de pénicillines, la posologie des AVK sera adaptée et la surveillance clinique et biologique accrue.*

Toward an ADE prevention by CDSS based on level 2 artificial intelligence

Level 2 AI: the failure of fully-automated machine learning

- Supervised data mining:
  - Good predictive power
  - Enables to filter, reorganize and explain knowledge
- “Black boxes”, such as deep learning
  - Better predictive power
  - Does not enable to manage knowledge!
- However, some other steps are from far more crucial: feature extraction

Prospective prevention of ADEs



- Alert generation, before the ADE occurs, in order to prevent it.

Prospective prevention of ADEs
Our contextualized approach

- E.g. VKA & PPI → risk of hemorrhage
- Usual implementation of alerts:

Medical unit A	Medical unit B	Medical unit C
VKA & PPI → interruptive **alert**		

- PSIP's contextualized implementation of alerts:

Medical unit A	Medical unit B	Medical unit C
Empirical probability=10% VKA&PPI→ **interruptive alert**	Empirical probability=0.01% VKA&PPI→ *silent or non-interruptive alert*	Unseen circumstances VKA&PPI→ **interruptive alert**

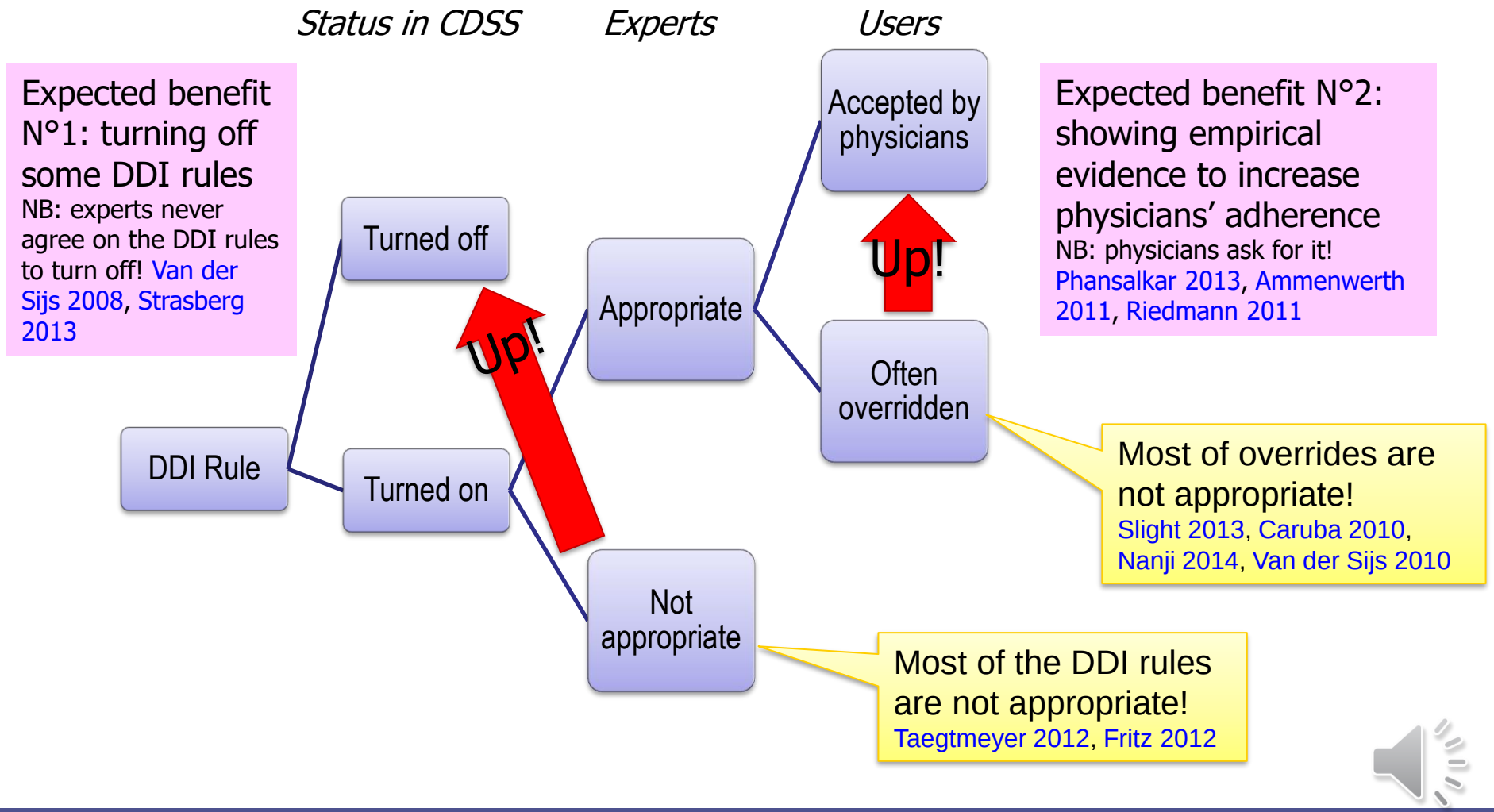
- … and "personalized medicine"!

Unless age>70

Prospective prevention of ADEs
The PSIP approach

- Implementation of 3 CDSS:
  - The IBM prototype
  - The Medasys prototype
  - The PSIP prescription simulation
- Major characteristics:
  - Filtering of alerts, based on contextualized statistics
    ➔ less alerts, more accurate
  - More complex rules (statistical segmentation)
    ➔ more accurate evaluation of the probabilities
  - Innovative alert methods:
    - less interruptive
    - Showing actual pas ADE cases => more acceptable

Benefits expected from the computation of empirical risk



What is the empirical risk of a drug administration?

Quantitative studies in CDSS evaluation

Conditions are present

Alert is sent

Alert is overridden

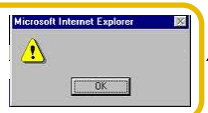
Sentinel trigger

Clinical damage

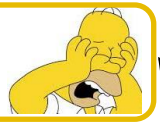
Late trigger

- VKA & haloperidol discont.

- Risk of hemorrhage



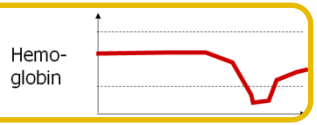
- It won't happen



- INR increase
- "Near miss"

- Hemorrhage

- Anemia



Alert accuracy (Se, Sp) by chart review

Override accuracy by chart review

Quantitative studies in CDSS evaluation – our approach

Conditions are present

Alert is sent

Alert is overridden

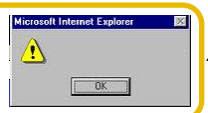
Sentinel trigger

Clinical damage

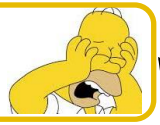
Late trigger

- VKA & haloperidol discont.

- Risk of hemorrhage



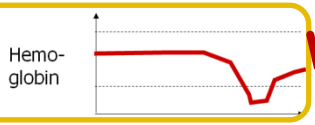
- It won't happen



- INR increase
- "Near miss"

- Hemorrhage

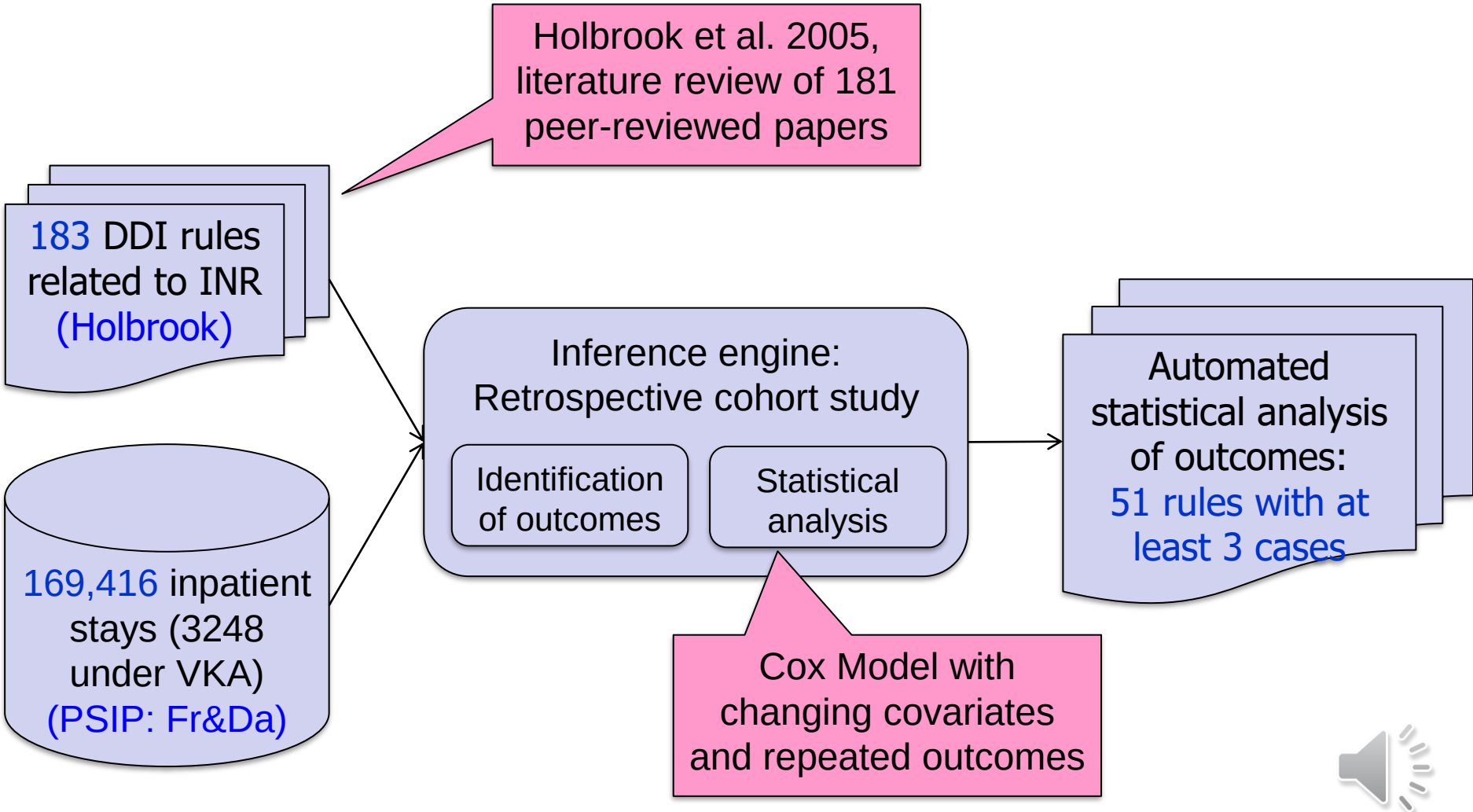
- Anemia



Alert accuracy (Se, Sp) by chart review

Override accuracy by chart review

Automated computation of the probability of outcome for each DDI rule



Results for INR ≥ 5

Drugs with Hazard ratio significantly ≠ 1:

- Fenofibrate
  HR=3.09
  [1.34; 7.13]
- Methylprednisolone
  HR=3.02
  [1.37; 6.68]
- Simvastatin
  HR=2.52
  [1.36; 4.67]
- Ofloxacin
  HR=0
  n=123

Drug category	Drug interacting with VKA	Outcome	Number	HR	p value
Analgesics and antipyretics	Etodolac	INR≤1.5	3	0	0.72
	Paracetamol (acetaminophen)	INR≥5	958	0.94	0.8
	Tramadol	INR≥5	431	0.65	0.22
Antibiotics	Amoxicillin	INR≥5	781	1.12	0.65
	Amoxicillin and enzyme inhibitor	INR≥5	666	1.24	0.4
	Ciprofloxacin	INR≥5	124	1.14	0.83
	Clarithromycin	INR≥5	29	0.96	0.97
	Cloxacillin	INR≤1.5	14	0	0.17
	Dicloxacillin	INR≤1.5	24	4.58	0.04 ***
	Erythromycin	INR≥5	5	8.43	0.13
	Levofloxacin	INR≥5	44	2.04	0.37
	Metronidazole	INR≥5	83	2.06	0.21
	Norfloxacin	INR≥5	18	0	0.31
	Ofloxacin	INR≥5	123	0	0.009 ***
	Rifampicin	INR≤1.5	30	0.55	0.51
	Teicoplanin	INR≤1.5	30	0.89	0.91
	Tetracycline	INR≥5	7	0	0.56
	Tranexamic acid	INR≥5	14	0	0.51
	Trimethoprim sulfamethoxazole	INR≥5	31	0	0.18
Cardiovascular & anti-hypertensive drugs	Amiodarone	INR≥5	670	0.94	0.81
	Candesartan	INR≤1.5	164	1.24	0.57
	Diltiazem	INR≥5	173	1.23	0.63
	Disopyramide	INR≥5	5	0	0.85
	Furosemide	INR≤1.5	1551	0.89	0.45
	Propafenone	INR≥5	4	0	0.75
	Propranolol	INR≥5	41	0	0.26
	Telmisartan	INR≤1.5	15	1.22	0.85
Central nervous system drugs	Barbiturates	INR≤1.5	15	1.63	0.53
	Carbamazepine	INR≤1.5	13	1.78	0.46
	Chlordiazepoxide	INR≤1.5	5	0	0.88
	Citalopram	INR≥5	79	0.95	0.93
	Fluoxetine	INR≥5	26	1.63	0.65
	Quetiapine	INR≥5	5	5.63	0.18
	Ropinirole	INR≥5	3	0	0.67
	Sertraline	INR≥5	21	1.85	0.58
Drugs acting on hemostasis	Acetylsalycilic acid	INR≥5	683	1.04	0.87
	Heparin (unfractionated)	INR≥5	294	0.61	0.15
Drugs for acid-related disorders	Omeprazole	INR≥5	130	0.32	0.17
	Sucralfate	INR≤1.5	11	9	0.005 ***

Results for INR ≤ 1.5

Drugs with Hazard ratio significantly ≠ 1:

- Dicloxacillin
  HR=4.58
  [1.81; 11.56]
- Sucralfate
  HR=9
  [3.13; 25.88]

Drug category	Drug interacting with VKA	Number	HR	p value
Analgesics and antipyretics	Etodolac	3	0	0.72
Antibiotics	Cloxacillin	14	0	0.17
	Dicloxacillin	24	4.58	0.04 ***
	Rifampicin	30	0.55	0.51
	Teicoplanin	30	0.89	0.91
Cardiovascular & anti-hypertensive drugs	Candesartan	164	1.24	0.57
	Furosemide	1551	0.89	0.45
	Telmisartan	15	1.22	0.85
Central nervous system drugs	Barbiturates	15	1.63	0.53
	Carbamazepine	13	1.78	0.46
	Chlordiazepoxide	5	0	0.88
Other drugs	Azathioprine	15	0	0.26
	Bosentan	5	0	0.49
	Chelation therapy	5	0	0.57
	Mesalazine (5-ASA)	10	0	0.31
	Sucralfate	11	9	0.005 ***
	Sulfasalazine	8	3.23	0.33

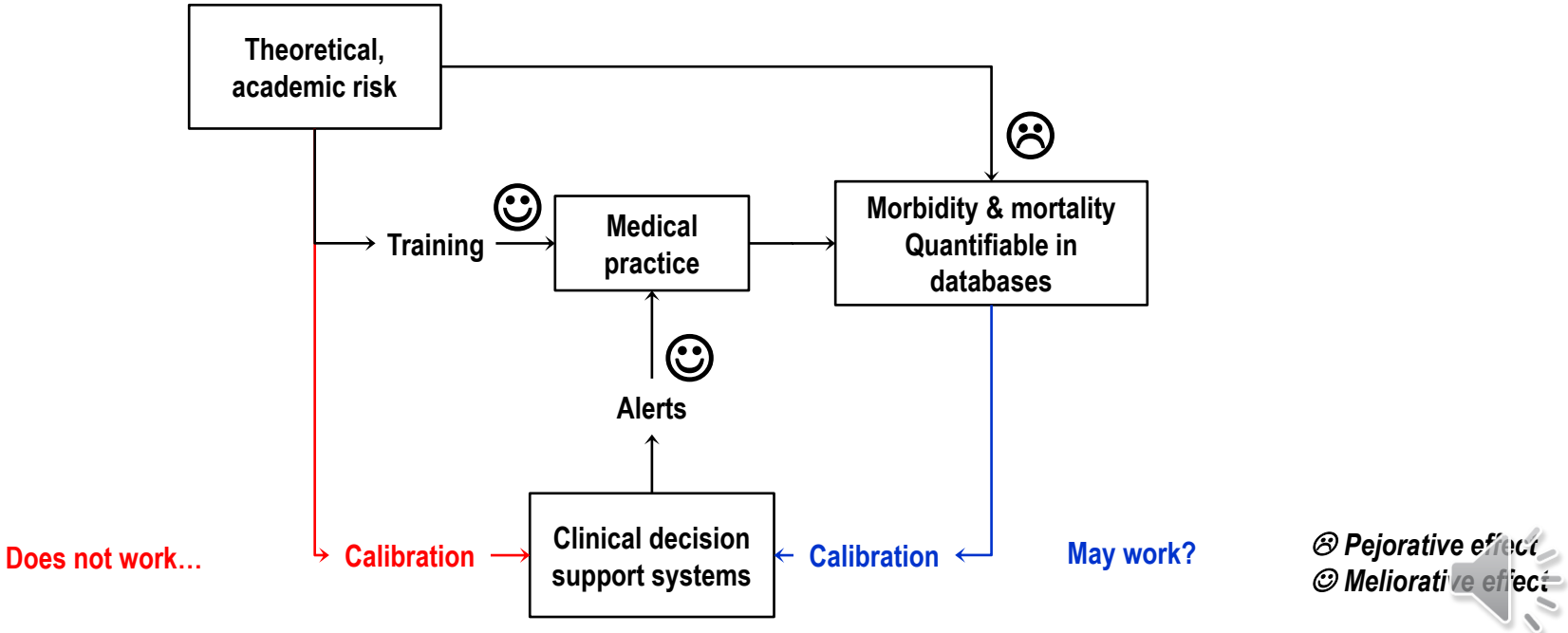
Apparent discrepancy between our results and the literature

Outcome	Drug	Causation (review from [37])	Severity (review from [37])
	Fenofibrate (HR>1)	Highly probable	Moderate
	Methylprednisolone (HR>1)	Highly improbable	Major
	Simvastatin (HR>1)	Probable	Minor
INR≥5	Ofloxacin (with HR<1)	Possible	Major
	85 other drugs (HR not different from 1)	*highly improbable: 9% possible: 32% probable: 30% highly probable: 29%*	*nonclinical: 50% minor: 4% moderate: 33% major: 13%*
	Sucralfate (HR>1)	Highly probable	Non clinical
	Dicloxacillin (HR>1)	Probable	Moderate
INR≤1.5	*31 other drugs (HR not different from 1)*	*highly improbable: 14% possible: 14% probable: 29% highly probable: 43%*	*nonclinical: 46% minor: 7% moderate: 36% major: 11%*

=> Empirical probabilities take into account the knowledge and monitoring of the physician, not only theoretical knowledge!

Toward a new paradigm for ADE prevention?

- Mixed results of ADE prevention by alert systems:
  - Over-alerting, poor positive predictive value
  - Alert fatigue, poor alert acceptation, even when appropriate
  - Poor clinical impact (except dose computation in pediatrics)
- Hypothesis: let's calibrate CDSS on the empirical risk, and not the theoretical risk!



We also learnt: finally, artificial intelligence should integrate the human workflow

Clinical evaluation of the ADE Scorecards

- Initial design:

Pharmacist

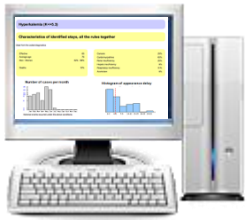
Prescription analyses

Weekly meetings

Good accuracy
0%,
%)

User-centered design, good evaluation (questionnaire)

ADE Scorecards



Regular spontaneous use of the soft

Physicians

Improvement of the drug management

Decrease of morbidity

Professional in charge of quality of care

Patient records screening

Morbidity and mortality reviews

Clinical evaluation of the ADE Scorecards

- support to a global quality improvement approach:

Pharmacist

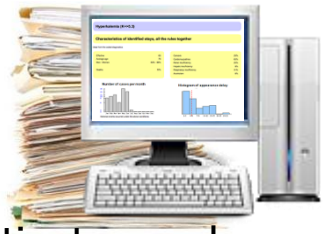
Prescription analyses

•Faster preparation
•Real local cases (not perceived as theoretical)

Faster preparation for drug-related morbidity

Weekly meetings

Professional in charge of quality of care



Patient records screening

Morbidity and mortality reviews

Physicians

Improvement of the drug management?

Decrease of morbidity?

More generally speaking

- Digitization (1990-2015):
  - Notably driven by the problem of the cost of labor. Example of France:
    - Cost of labor = net salary * 1.85
    - 35 hours per week
    - Increase of support services *vs* business units
  - Perverse effects:
    - A part of the population becomes unemployable…
    - Work transfer from poorly qualified people to managers
    - And then, managers work below their qualification level
- A “good” artificial intelligence:
  - May respect the human workflow
  - May help transferring tasks to less qualified people
  - Based on current scientific knowledge, requires human validation

Thank you for your attention!

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