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Characteristics of Pharmacist's interventions triggered by prescribing errors related to computerized physician order entry in French hospitals: a cross-sectional observational study

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Abstract

Objectives

Computerized physician order entry (CPOE) systems facilitate the review of medication orders by pharmacists. Reports have emerged that show conception flaws or the misuse of CPOE systems generate prescribing errors. We aimed to characterize pharmacist interventions (PIs) triggered by prescribing errors identified as system-related errors (SREs) in French hospitals.

Design

This was a cross-sectional observational study based on PIs prospectively documented in the Act-IP© observatory database from January 2014 to December 2018.

Setting

PISREs from 319 French computerized healthcare facilities were analyzed.

Participants

Among the 319 French hospitals, 232 (72.7%), involving 652 (51%) pharmacists, performed SRE interventions.

Results

Among the 331,678 PIs recorded, 27,058 were qualified as due to SREs (8.2%). The main drug-related problems associated with PISREs were supratherapeutic (27.5%) and subtherapeutic dosage (17.2%), non-conformity with guidelines/contraindications (22.4%), and improper administration (17.9%). The PI prescriber acceptation rate was 78.9% for SREs versus 67.6% for other types of errors. Concerning the certification status of CPOE systems, the PISRE ratio was 9.4% for non-certified systems versus 5.5% for certified systems. The PISRE ratio for senior pharmacists was 9.2% and that for pharmacy residents 5.4%. Concerning prescriptions made by graduate prescribers and those made by residents, the PISRE ratio was 8.4 % and 7.8%, respectively.

Conclusion

Computer-related prescribing errors are common. The PI acceptance rate by prescribers was higher than that observed for PIs that were not CPOE related. This suggests that physicians consider the potential clinical consequences of SREs for patients to be more frequently serious than interventions unrelated to CPOE. CPOE medication review requires continual pharmacist diligence to catch these errors. The significantly lower PISRE ratio for certified software should prompt patient safety agencies to undertake studies to identify the safest software and discard software that is potentially dangerous.

Article Summary

Strengths and limitations of this study

- This study provides an overview of prescribing issues related to the use of CPOE systems at the national level.
- Beyond this large register of prescribing problems related to CPOE use, this is the first study to evaluate pharmacist interventions in daily practice for such a large sample of interventions, pharmacists, and hospitals.
- This study focuses on declarative data based on interventions performed by hospital pharmacists.
- These pharmacist interventions highlight prescription problems, but they are not exhaustive.

1. Introduction

Every day, numerous hospitalized patients are subject to drug-related problems (DRPs), resulting in suboptimal therapy, suffering, and decreased quality of life, as well as high healthcare costs for society [1, 2]. Computerized physician order entry (CPOE) systems, along with clinical decision support systems, improve the safety, quality, and value of patient care [3]. According to a meta-analysis, CPOE systems have reduced hospital medication errors by approximately 12.5% [10.6-14.4%][4]. However, CPOE systems also have the potential to introduce or contribute to errors. Indeed, new mechanisms that lead to prescription errors have been identified with CPOE: wrong patient selection, failure to report drug allergies, incorrect entry or wrong selection of medication, dose, route, or time of administration, and confusing free-text comments [5-10].

In France, as in other countries, various incentives and requirements have been put in place to encourage computerized drug prescribing, such as France's "Digital Hospital" program [11]. Since the 2000s, prescribing errors associated with the use of CPOE have been slowly coming to light as healthcare has become increasingly computerized [9]. Compared to handwritten prescriptions, the analysis of electronic prescriptions requires a particular effort on the part of pharmacists and other health professionals to detect errors [9]. System-related errors (SREs) are defined as those in which the electronic prescribing system functionality or design contributed to the error, with little possibility that another cause, such as lack of knowledge, produced the error. For example, an order for an inappropriate drug located on a drop-down menu next to a likely drug selection is a system-related error [12].

A pharmacist intervention (PI) due to a SRE is defined as any PI resulting from the identification of a prescribing error by a pharmacist that would probably not have occurred in the context of a handwritten prescription and of which at least one cause is related to the use of a computer (software system configuration issue, software functionality issue, or software misuse) [13-16].

Most studies concerning PIs triggered by system-related prescribing errors were conducted within a single hospital [17-19]. As a result, it is not possible to assess the extent of prescribing errors related to electronic systems or draw conclusions about subsequent PIs at a national level.

In 2003, the French Society of Clinical Pharmacy (SFPC) developed and validated a tool for classifying and documenting clinical PIs [20]. This tool allows the reporting of DRPs and PIs performed during the daily review of medication orders [24]. In 2006, a website, Act-IP©, was created with the objectives to (a) create a documentation system that is freely accessible to any pharmacist, through the French Society of Clinical Pharmacy Web site (http://www.actip.sfpc.eu/actip/index/ficheip/) and (b) pool the data recorded by all pharmacists to conduct epidemiological studies concerning DRPs detected by pharmacists [21]. The pooling of PIs constitutes an observatory of clinical pharmacy practices, called the "Act-IP© Observatory".

The aim of this study was to characterize PIs triggered due to SREs in French hospitals between 2014 and 2018. Our secondary objective was to determine the physician acceptance rate and its frequency according to the certification status (certified versus non-certified) of the CPOE systems.

2. Methods

2.1. Study design

This was a cross-sectional observational study using PIs prospectively documented in the Act-IP© observatory over a five-year period from January 1, 2014 to December 31, 2018. The main outcome was a PI due to a SRE (PISRE) reported by French hospital pharmacists on the Act-IP© observatory. Ethical approval for the study was obtained on February 19, 2020 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891).

2.2. Data sources

The data comes from the Act-IP© Observatory. Based on the SFPC criteria, using the report form developed and validated for routine documentation of the PIs, Act-IP© users completed the online report form notifying the date, type of DRP, PI, type of drug involved (according to the ATC (Anatomical Therapeutic Chemical) classification), acceptance of the intervention by the prescriber, and free-text details of the context. Ten categories were determined for DRPs and seven for PIs (Appendix 1). A PI was considered to be "accepted" if the physician took it into account and modified the prescription as suggested by the pharmacist or "refused" if the prescription remained unchanged, including cases of

expressed refusal by the prescriber. If acceptance of the intervention was impossible to ascertain (i.e. discharged patients or those transferred to another ward before acceptance), the PI was noted as "not assessable". The pharmacist's academic background, hospital characteristics, and software used were documented online by the pharmacist when he/she registered onto the Act-IP© website. Since July 2013, pharmacists have been able to indicate whether the DRP was "related to the electronic system" or not for each registered PI. For the purpose of this study, DRPs identified as "related to the electronic system" were considered to be PISREs.

French law made the certification of CPOE systems mandatory on December 29, 2011. However, two decrees abolished this obligation in 2017. Certification is now based on the sole initiative of the software developer. Forty-eight hospital CPOE software packages are currently certified by the agency for patient safety [Haute Autorité de Santé (HAS)] [22]. For our analysis, PIRSEs were classified according to the HAS status of the CPOE system (certified versus not certified).

2.3. Analysis

The PISRE ratio was estimated relative to the total number of PIs. Proportions were compared using the chi-square test. PISREs coded as "refused" or "not assessable" were combined and compared to the accepted PISREs. Probability values < 0.001 were considered to be statistically significant. Statistical analyses were performed using Stata 13 (Stata Corporation, College Station, Texas, USA). Several qualitative examples are given to illustrate PISREs.

4. Results

From January 2014 to December 2018, 331,678 PIs were entered into the Act-IP© observatory. Among them, 27,058 (8.2%) were indicated to be system-related prescribing errors (Figure 1).

Over the study period, 1,219 pharmacists from 319 hospitals recorded PIs in the Act-IP© observatory database. The geographical location of the hospitals involved is shown in Figure 2. Among them, 232 (72.7%), involving 652 (51%) pharmacists, performed SRE interventions. Among the 319 hospitals, 87 (27.3%) did not qualify any PIs as being due to a SRE. PIs come from 82 software involving 19 certified systems.

The characteristics of the PISREs are summarized in Table 1. The most commonly identified type of DRP was "supratherapeutic dosage", followed by "non-conformity with guidelines/contraindications" and "improper administration". Among the 27,058 PISREs, 78.9% (n = 21,356) were accepted. The PISRE ratio was 9.4% for non-certified systems versus 5.5% for certified systems (p-value < 0.001). Table 2 presents examples of drug-related problems classified as being triggered by prescribing errors due to the CPOE system.

5. Discussion

This study provides an overview of prescription problems related to CPOE system used in French hospitals. It provides insights into the main situations and medications involved in computer-related prescribing problems detected by pharmacists by providing a broad description of PIs performed during the daily review of routine medication orders. One strength of this study is that it is based on a large number of hospitals scattered throughout France, as no prior study of such extent evaluating PIs in daily practice has been published.

5.1. PISRE rate

Our PISRE rate (8.2%) is within the range reported by Korb-Savoldelli et al. [19]. They analyzed peer-reviewed studies (n = 14) that quantitatively reported medication-prescription errors related to CPOE. The prevalence of CPOE system-related medication errors relative to all prescription medication errors ranged from 6.1 to 77.7% (median = 26.1% [IQR:17.6–42,1]) and was less than 6.3% relative to the number of prescriptions reviewed. Ours is the first large-scale descriptive study using an observatory hospital pharmacy practice database to study computer-related prescribing errors.

5.2. DRPs induced by CPOE

The main category of DRPs identified as PISREs were supratherapeutic (27.5%, 7,436) and subtherapeutic dosage (17.2%, 4,646), non-conformity to guidelines/hospitals' drug formularies (22.4%, 6,069) (i.e. medication selection non-compliant with the hospital drug formulary), and improper administration (17.9%, 4,838) (i.e. incorrect or no formulation, wrong timing). According to Korb-Savoldelli et al., all studies reported "wrong dose" and "wrong drug" errors [19], with the "wrong dose"

error being that most frequently reported (from 7 to 67.4%, median = 31.5% [IQR:20.5–44.5]). Many of the prescription errors due to CPOE systems can have serious consequences for patients, depending on the clinical circumstances. Although some of are unlikely to occur (e.g. IV ketoprofen 150 ampoules/day instead of 150 mg/d), they nevertheless illustrate flaws in certain CPOE systems [23]. However, our data do not allow the discrimination between software errors, connection problems, and human error.

5.3. CPOE systems

The proportion of PIs triggered by software-related prescription errors was higher for non-certified (9.4%) than certified software (5.5%). In France, certification tests produced by the HAS are intended to technically assess the functionality of the software in various situations, as the CPOE evaluation methodology simulates various clinical scenarios [24]. French regulations do not require CPOE developers to carry out usability studies before the systems are marketed. Nevertheless, despite the limitations of this type of certification criteria, which have already been highlighted [25], our results show that prescribing with CPOE-certified systems results in fewer prescription errors than prescribing with non-certified software. These results are consistent with those of other studies, i.e. all software is not equal and some is safer than others [26-28].

5.4. Prescribers

The PISRE ratio was higher for prescriptions made by graduate prescribers (8.4%) than medical residents (7.8%) (p-value < 0.001). This finding is, at first glance, counterintuitive, as one would expect that a prescriber who has been practicing for several years in the same health facility would make fewer CPOE-related prescription errors with the software than a resident who has only been using the software for a few months. Observational studies show that medical residents make most prescriptions and transcribe them to the software prescription instructions of senior prescribers during the medical examination [29]. It is thus possible that, in some hospitals, senior physicians are only occasional users of the prescription software. According to Nerich et al., the occasional use of software (< 1 prescription per day) is a risk factor for prescription error (OR = 3.85, 95% CI [2.08-7.14]) [30]. Tolley described how a junior doctor remarked that there was no one he could ask for help with using the ePrescribing system, as he was “the most experienced person on this floor with regards to the ePrescribing system”.

She also described how one consultant admitted she had not "learnt how to prescribe properly" because she did not "use the system often enough and regularly enough to know the quirks and tweaks". This consultant relied on her junior staff to prescribe on the system [31].

5.5. Act-IP© Pharmacist' users

The PISRE ratio for senior pharmacists (9.2%) was higher than that of pharmacy residents (5.4%). This is consistent with the results of a study performed in a UK teaching hospital showing that the likelihood of senior pharmacists identifying errors was greater than that of junior pharmacists [32] and in accordance with our expectations. A study concerning French pharmacy students showed that they trust the contribution of computerization to healthcare without critical analysis. This results in overconfidence in the computer tool, perceived to be reliable, and makes users less willing to search for the errors produced by this tool [33]. They are therefore not aware that the review of computerized prescription orders requires additional effort to identify prescription errors. This is the consequence of the lack of teaching/training about this subject in French pharmacy schools. This situation contrasts strikingly with the content of the curricula taught in the United Kingdom and USA, for example [34,35].

5.6. Prescriber Acceptance rate

The rate of acceptance of PISREs by prescribers was 78.9% versus 67.6% for other PIs. This suggests that prescribers recognize the relevance of such interventions due to the potential clinical consequences of such prescription errors. This rate varies from 65.9 to 92% in studies of drug errors induced by computerized prescription [10, 14], suggesting that physicians consider the potential clinical consequences of SRE to patients to be more frequently serious than interventions unrelated to CPOE. In light of our findings, a CPOE-related prescription error is a factor that favors acceptance of the PI. These points warrant further studies.

5.7. Limits

Our study had several limitations. First, it focused on declarative data based on interventions performed by hospital pharmacists. These PIs highlight prescription problems, but are not exhaustive. However, the large sample size probably provides a relatively precise vision of the problem at the national level.

Second, several pharmacists analyzing the same drug prescriptions may not all track down the same problems. For example, the mean percentage of detected prescribing errors was 59% in a study involving 57 hospital pharmacies, with a broad range of 7 to 88% between pharmacies [36]. In the absence of specific studies to determine the performance of pharmacists in detecting prescription errors induced by CPOE-system flaws and misuse, we are reduced to simply assuming that such variation may be observed. In addition, there are various definitions of PISREs in the literature [13-16]. This suggests that there is a certain level of subjectivity when a pharmacist characterizes a PI as being related to a computer-generated prescription. Among hospitals that entered the PIs on Act-IP©, 87 never qualified a PI as being a SRE. There are two possible explanations for this observation. The first, and relatively unlikely, is that the software is near perfect and that there was no misuse by prescribers. For example, the absence of PISREs for these hospitals could result from the absence of computer-related errors due to the use of high-performance software and/or appropriately trained prescribers. The second possibility is that pharmacists do not establish a link between certain prescription errors and misuse of the prescription software and/or its design flaws. Conversely, a high rate of PISREs for a given hospital may result from software conception flaws and/or misuse of the software by prescribers and pharmacists who are very aware of the role of CPOE-systems in generating prescription errors. Regardless of the considered scenario, it is important to remember that differences in PISRE rates may also be due to the quality of the training provided. Studies have shown that insufficient training on an ePrescribing system can contribute to errors [37, 38]. Tolley illustrated how pharmacists did not receive any formal training about the system after starting at a hospital trust and observed that no formal training was offered when pharmacists changed roles. It has been shown that training plays a role in the users' experience but there is a lack of published research in this area [31]. Thus, further research is warranted to lift the veil on these unknowns.

Our results highlight that prescribing problems related to computer software are common in France. This is a concern that affects most (if not all) CPOE systems currently being used and therefore all hospitals, to varying degrees. Identifying the most dangerous software appears to be a priority to improve the quality and safety of patient care.

6. Conclusion

Computer-related prescribing errors are common, with wrong dose being the most frequent type of error. Such errors concern all drug classes and have potentially serious adverse clinical consequences if they are not intercepted by pharmacists when performing their daily medication review. The message appears to be well received by prescribers who agree to change their prescription more frequently than for PIs not related to CPOE use. CPOE medication review requires additional pharmacist diligence to catch such errors. As the PISRE ratio is significantly lower for certified software, patient safety agencies should undertake studies to identify the safest software so as to discard software that is potentially dangerous.

Author contributions

Manon Videau and Bruno Charpiat designed the study, performed the statistical analyses, interpreted the results, and wrote the first version of the manuscript. Céline Vermorel contributed to the design of the study, performed the statistical analyses, and revised the manuscript. Jean-Luc Bosson contributed to the design of the study and revised the manuscript. Ornella Conort contributed substantially to the interpretation of the data and contributed to the revision of the manuscript. Pierrick Bedouch designed the study, performed the statistical analyses, interpreted the results, and revised the manuscript.

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Statement on conflicts of interest

The authors declare that they have no conflicts of interest.

Patient consent for publication

Not required

Ethical approval

Ethical approval for the study was obtained on February 19, 2020 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891).

Summary table

Table 1. Characteristics of Act-IP© observatory PISREs and PIs between 2014 to 2018.

Table 2. Examples of PISREs and drug-by-drug related problems (N = 27,822).

Summary Figures

Figure 1. Flowchart, PISRE selection in Act-IP© observatory (extraction on 11th February 2019)

Figure 2. Geographical location of French hospitals that entered data into the Act-IP © observatory between 2014 and 2018

Table 1. Characteristics of all Act-IP© observatory PISREs and PIs between 2014 to 2018.

Characteristics	PISRE (N = 27,058)	PI total (N = 331,678)	ratio	
	n	n	%	p-value
Drug related problem				
Supratherapeutic dosage	7,436	72,912	10.2	
Non-conformity with guidelines/hospital formulary	6,069	86,072	7.1	
Improper administration	4,838	49,184	9.8	
Subtherapeutic dosage	4,646	29,105	16.0	
Untreated indication	2,366	30,138	7.9	
Drug without indication	1,302	27,690	4.7	
Drug interaction	161	18,267	0.9	
Drug monitoring	111	10,303	1.1	
Adverse drug reaction	65	5,854	1.1	
Failure to receive drug	64	2,153	3.0	
Type of intervention				
Dose adjustment	7,447	89,390	8.3	
Drug switch	6,649	85,033	7.8	
Drug discontinuation	5,220	62,715	8.3	
Optimization of administration	4,123	32,558	12.7	
Addition of new drug	3,228	34,198	9.4	
Change of administration route	213	6,978	3.1	
Drug monitoring	178	20,806	0.9	
Prescriber Acceptance				
Interventions accepted	21,356	227,223	9.4	< 0.001*

Interventions not accepted	3,068	51,957	5.9	
Not assessable	2,634	52,498	5.0	
Prescriber's status				
Senior	15,152	180,863	8.4	< 0.001
Resident	11,765	150,136	7.8	
Midwife**	141	679	20.8	
Pharmacist's status				
Senior	21,271	231,519	9.2	< 0.001
Resident	4,640	86,728	5.4	
Not assessable**	1,147	13,431	8.5	
CPOE system status				
Not certified	21,385	226,878	9.4	< 0.001
Certified	5,549	101,516	5.5	
Not assessable**	124	3,284	3.8	
Total	27,058	331,678	8.2	

PI: pharmacist's intervention, PISRE: pharmacist's intervention identified as due to a system-related error, CPOE: computerized prescriber order entry

**Not accepted and not assessable interventions have been regrouped for chi-square test; **excluded from the chi-square analysis*

Table 2. Examples of PISRE and drug by drug-related problems (N = 27,822)

Drug-related problem	Number of drugs involved – n (%)	Most frequent drug (generic name) (n)	Examples
Supratherapeutic dosage	7,571 (27.2)	Paracetamol (1,043), tramadol (223), pantoprazole (212), enoxaparin (204)	"Duplicate prescription: 1 in predefined protocol and 1 outside predefined protocol = 8 g of paracetamol per day"
Non-conformity to guidelines/contra-indication	6,212 (22.3)	Alfuzosin (515), dutasteride (493), silodosin (469), paracetamol (460), tamsulosin (373)	"prescription of dutasteride, which is not in the hospital drug formulary, with a risk of treatment omission"
Improper administration	4,972 (17.9)	Paracetamol (277), levothyroxine (130), pregabalin (130), methylprednisolone (124)	"selection of IV terbutaline for administration by aerosol"
Subtherapeutic dosage	4,738 (17.0)	Enoxaparin (965), heparin (450), tinzaparin (186), paracetamol (140), macrogol (105),	"Enoxaparin 4000 UI/0.4 ml prescription: 1 IU instead of 1 syringe"
Untreated indication	2,441 (8.8)	acetylsalicylic acid (82), pregabalin (80), paracetamol (74), tinzaparin (69), bisoprolol (69), enoxaparin (68),	"prescription of pregabalin not renewed (hospital stay longer than the duration of the prescription)"

Drug without indication	1,340 (4.8)	Pantoprazole (66), amoxicillin and beta-lactamase inhibitor (44), cholecalciferol (40), ceftriaxone (34), enoxaparin (30)	"duplicate prescription of pantoprazole per os and IV by two prescribers"
Drug interaction	262 (0.9)	Amiodarone (27), fluindione (9), levothyroxine (9)	"cordarone and escitalopram combination contra-indicated: risk of "torsade de pointes" not modified during drug interaction alert with Clinical Decision Support System (CDSS)"
Drug monitoring	124 (0.4)	Fluindione (25), polystyrene sulfonate (8), paracetamol (4)	
Adverse drug reaction	70 (0.3)	Polystyrene sulfonate (11), furosemide (6), atorvastatin (4), tramadol (3), macrogol (3)	"increased risk of adverse reactions by the combination of atorvastatin and fenofibrate"
Failure to receive drug	92 (0.3)	Esomeprazole (3), cholecalciferol (3), acetylsalicylic acid (3), furosemide (3)	"Prescription of furosemide not appearing on the nursing plan"

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Figure 1. Flowchart, PISRE selection in Act-IP© observatory (extraction on 11th February 2019)

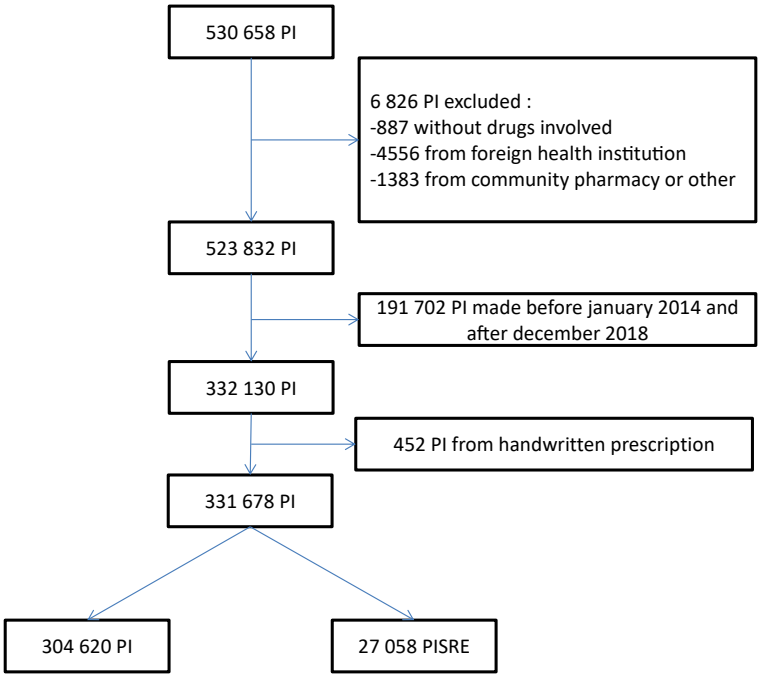
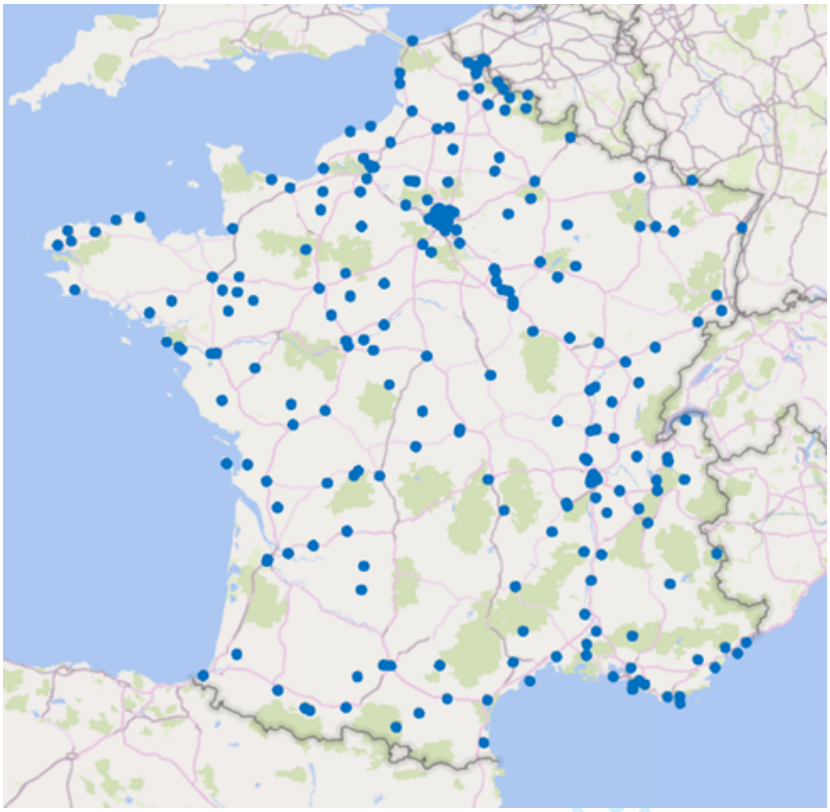


Figure 2. Geographical location of French hospitals that entered data into the Act-IP © observatory between 2014 and 2018



Appendix 1. The Pharmacist intervention form

PHARMACIST INTERVENTION FORM

DATE: / / **INTERVENTION N°:** **CENTER N°:**

PATIENT:

Last name:
First name:

Age: years / Weight: Kg
Sex: ❒ M ❒ F

Hospital ward:
❒ Psychiatry
❒ Acute care
❒ Long term care
❒ Rehabilitation ward

DRUG NAME (INN):

1- DRUG RELATED PROBLEM (1 choice):
1 ❒ Non conformity to guidelines or contra-indication
2 ❒ Untreated indication
3 ❒ Subtherapeutic dosage
4 ❒ Supratherapeutic dosage
5 ❒ Drug without indication
6 ❒ Drug interaction
- ❍ To be taken into account
- ❍ Use with caution
- ❍ Combination to be avoided
- ❍ Combination contra-indicated
- ❍ Documented but not in VIDAL®

7 ❒ Adverse drug reaction
8 ❒ Improper administration
9 ❒ Failure to receive drug
10 ❒ Drug monitoring

3- DRUG CLASSIFICATION (ATC):
❒ A Alimentary tract & metabolism
❒ B Blood & blood forming organs
❒ C Cardiovascular system
❒ D Dermatological
❒ G Genito urinary system & sex hormones
❒ H Systemic hormonal preparations
❒ J Anti-infective for systemic use
❒ L Anti-neoplastic & immunomodulating agents
❒ M Musculo-skeletal system
❒ N Nervous system
❒ P Antiparasitic products
❒ R Respiratory system
❒ S Sensory organs
❒ V Various

2- INTERVENTION (1 choice):
1 ❒ Addition of a new drug
2 ❒ Drug discontinuation
3 ❒ Drug switch
4 ❒ Change of administration route
5 ❒ Drug monitoring
6 ❒ Administration modalities optimisation
7 ❒ Dose adjustment

4- INTERVENTION FOLLOW-UP:
❒ Accepted
❒ Non accepted
❒ Non assessable

DETAILS ⇒If necessary, give details on any aspects of the detected DRP and describe the intervention. precisely

Context

Problem

Intervention

BMJ Open

Characteristics of Pharmacist's interventions triggered by prescribing errors related to computerized physician order entry in French hospitals: a cross-sectional observational study

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Characteristics of Pharmacist's interventions triggered by prescribing errors related to computerized physician order entry in French hospitals: a cross-sectional observational study

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Abstract: 305/300 words

Main text: 2785/4000 words

Abstract

Objectives

Computerized physician order entry (CPOE) systems facilitate the review of medication orders by pharmacists. Reports have emerged that show conception flaws or the misuse of CPOE systems generate prescribing errors. We aimed to characterize pharmacist interventions (PIs) triggered by prescribing errors identified as system-related errors (SREs) in French hospitals.

Design

This was a cross-sectional observational study based on PIs prospectively documented in the Act-IP© observatory database from January 2014 to December 2018.

Setting

PISREs from 319 French computerized healthcare facilities were analyzed.

Participants

Among the 319 French hospitals, 232 (72.7%) performed SRE interventions, involving 652 (51%) pharmacists.

Results

Among the 331,678 PIs recorded, 27,058 were qualified as due to SREs (8.2%). The main drug-related problems associated with PISREs were supratherapeutic (27.5%) and subtherapeutic dosage (17.2%), non-conformity with guidelines/contraindications (22.4%), and improper administration (17.9%). The PI prescriber acceptation rate was 78.9% for SREs versus 67.6% for other types of errors. The PISRE ratio was estimated relative to the total number of PIs. Concerning the certification status of CPOE systems, the PISRE ratio was 9.4% for non-certified systems versus 5.5% for certified systems (p-value<0.001). The PISRE ratio for senior pharmacists was 9.2% and that for pharmacy residents 5.4% (p-value<0.001). Concerning prescriptions made by graduate prescribers and those made by residents, the PISRE ratio was 8.4 % and 7.8%, respectively (p-value<0.001).

Conclusion

Computer-related prescribing errors are common. The PI acceptance rate by prescribers was higher than that observed for PIs that were not CPOE related. This suggests that physicians consider the potential clinical consequences of SREs for patients to be more frequently serious than interventions unrelated to CPOE. CPOE medication review requires continual pharmacist diligence to catch these errors. The significantly lower PISRE ratio for certified software should prompt patient safety agencies to undertake studies to identify the safest software and discard software that is potentially dangerous.

Article Summary

Strengths and limitations of this study

- This study provides an overview of prescribing issues related to the use of CPOE systems at the national level.
- Beyond this large register of prescribing problems related to CPOE use, this is the first study to evaluate pharmacist interventions in daily practice for such a large sample of interventions, pharmacists, and hospitals.
- This study focuses on declarative data based on interventions performed by hospital pharmacists.
- These pharmacist interventions highlight prescription problems, but they are not exhaustive.

1. Introduction

Every day, numerous hospitalized patients are subject to drug-related problems (DRPs), resulting in suboptimal therapy, suffering, and decreased quality of life, as well as high healthcare costs for society [1, 2]. Computerized physician order entry (CPOE) systems, along with clinical decision support systems, improve the safety, quality, and value of patient care [3]. According to a meta-analysis, CPOE systems have reduced hospital medication errors by approximately 12.5% IC95% [10.6-14.4%] [4]. However, CPOE systems also have the potential to introduce or contribute to errors. Indeed, new mechanisms that lead to prescription errors have been identified with CPOE: wrong patient selection, failure to report drug allergies, incorrect entry or wrong selection of medication, dose, route, or time of administration, and confusing free-text comments [5-10].

In France, as in other countries, various incentives and requirements have been put in place to encourage computerized drug prescribing, such as France's "Digital Hospital" program [11]. Since the 2000s, prescribing errors associated with the use of CPOE have been slowly coming to light as healthcare has become increasingly computerized [9]. Compared to handwritten prescriptions, the analysis of electronic prescriptions requires a particular effort on the part of pharmacists and other health professionals to detect errors [9]. System-related errors (SREs) are defined as those in which the electronic prescribing system functionality or design contributed to the error, with little possibility that another cause, such as lack of knowledge, produced the error. For example, an order for an inappropriate drug located on a drop-down menu next to a likely drug selection is a system-related error [12].

A pharmacist intervention (PI) due to a SRE is defined as any PI resulting from the identification of a prescribing error by a pharmacist that would probably not have occurred in the context of a handwritten prescription and of which at least one cause is related to the use of a computer (software system configuration issue, software functionality issue, or software misuse) [13-16].

Most studies concerning PIs triggered by system-related prescribing errors were conducted within a single hospital [17-19]. As a result, it is not possible to assess the extent of prescribing errors related to electronic systems or draw conclusions about subsequent PIs at a national level.

In 2003, the French Society of Clinical Pharmacy (SFPC) developed and validated a tool for classifying and documenting clinical PIs [20]. This tool allows the reporting of DRPs and PIs performed during the daily review of medication orders [21]. In 2006, a website, Act-IP©, was created with the objectives to (a) create a documentation system that is freely accessible to any pharmacist, through the French Society of Clinical Pharmacy Web site (http://www.actip.sfpc.eu/actip/index/ficheip/) and (b) pool the data recorded by all pharmacists to conduct epidemiological studies concerning DRPs detected by pharmacists [22]. The data recording is on a voluntary basis. The pooling of PIs constitutes an observatory of clinical pharmacy practices, called the "Act-IP© Observatory".

The aim of this study was to characterize PIs triggered due to SREs in French hospitals between 2014 and 2018. Our secondary objective was to determine the physician acceptance rate and its frequency according to the certification status (certified versus non-certified) of the CPOE systems.

2. Methods

2.1. Study design

This was a cross-sectional observational study using PIs prospectively documented in the Act-IP© observatory over a five-year period from January 1, 2014 to December 31, 2018. The main outcome was a PI due to a SRE (PISRE) reported by French hospital pharmacists on the Act-IP© observatory. Ethical approval for the study was obtained on February 19, 2020 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891).

2.2. Data sources

The data comes from the Act-IP© Observatory. Based on the SFPC criteria, using the report form developed and validated for routine documentation of the PIs, Act-IP© users completed the online report form notifying the date, type of DRP, PI, type of drug involved (according to the ATC (Anatomical Therapeutic Chemical) classification), acceptance of the intervention by the prescriber, and free-text details of the context. Ten categories were determined for DRPs and seven for PIs (Appendix 1). A PI was considered to be "accepted" if the physician took it into account and modified the prescription as suggested by the pharmacist or "refused" if the prescription remained unchanged, including cases of

expressed refusal by the prescriber. If acceptance of the intervention was impossible to ascertain (i.e. discharged patients or those transferred to another ward before acceptance), the PI was noted as "not assessable". The pharmacist's academic background, hospital characteristics, and software used were documented online by the pharmacist when he/she registered onto the Act-IP© website. To be registered onto the Act-IP© website, pharmacists had prior to accept terms and conditions and allowed the use of their data for analysis. Since July 2013, pharmacists have been able to indicate whether the DRP was "related to the electronic system" or not for each registered PI. For the purpose of this study, DRPs identified as "related to the electronic system" were considered to be PISREs.

French law made the certification of CPOE systems mandatory on December 29, 2011. However, two decrees abolished this obligation in 2017. Certification is now based on the sole initiative of the software developer. Forty-eight hospital CPOE software packages are currently certified by the agency for patient safety [Haute Autorité de Santé (HAS)] [23]. For our analysis, PIRSEs were classified according to the HAS status of the CPOE system (certified versus not certified).

2.3. Analysis

The PISRE ratio was estimated relative to the total number of PIs. Proportions were compared using the chi-square test. PISREs coded as "refused" or "not assessable" were combined and compared to the accepted PISREs. Probability values < 0.001 were considered to be statistically significant. Statistical analyses were performed using Stata 13 (Stata Corporation, College Station, Texas, USA). Several qualitative examples are given to illustrate PISREs.

4. Results

From January 2014 to December 2018, 331,678 PIs were entered into the Act-IP© observatory. Among them, 27,058 (8.2%) were indicated to be system-related prescribing errors (Figure 1).

Over the study period, 1,219 pharmacists from 319 hospitals recorded PIs in the Act-IP© observatory database. The geographical location of the hospitals involved is shown in Figure 2. Among them, 232 (72.7%), involving 652 (51%) pharmacists, performed SRE interventions. Among the 319 hospitals, 87

(27.3%) did not qualify any PIs as being due to a SRE. PIs come from 82 software involving 19 certified systems.

The characteristics of the PISREs are summarized in Table 1. The most commonly identified type of DRP was “supratherapeutic dosage”, followed by “non-conformity with guidelines/contraindications” and “improper administration”. Among the 27,058 PISREs, 78.9% (n = 21,356) were accepted. The PISRE ratio was 9.4% for non-certified systems versus 5.5% for certified systems (p-value < 0.001). Appendix 2 presents examples of drug-related problems classified as being triggered by prescribing errors due to the CPOE system. For example: Prescription errors can be the same whether they are handwritten prescriptions or computer-assisted prescriptions. Indeed, the combination of amiodarone and escitalopram can appear on handwritten prescription because of prescriber’s lack of knowledge. With CPOE, Clinical Decision Support System (CDSS) tool can alert on drug-drug interaction. However, high frequency of alerts and dozens of daily interruptions for clinicians are responsible of "alert fatigue" and practitioners override alerts [24]. We can also find duplicate orders, meaning the same drug is prescribed twice. With predefined order set, it is common to have 8 grams of paracetamol per day prescribed. Duplication errors are partially explained by the fact that many screens are required to view patient medications, making intrinsically difficult to spot duplicates [25].

5. Discussion

This study provides an overview of prescription problems related to CPOE systems used in French hospitals. It provides insights into the main situations and medications involved in computer-related prescribing problems detected by pharmacists by providing a broad description of PIs performed during the daily review of routine medication orders. Thus one strength of this study is that it is based on a large number of hospitals scattered throughout France, as no prior study of such extent evaluating PIs in daily practice has been published.

5.1. PISRE rate

Our PISRE rate (8.2%) is within the range reported by Korb-Savoldelli et al. [19]. They analyzed peer-reviewed studies (n = 14) that quantitatively reported medication-prescription errors related to CPOE.

The prevalence of CPOE system-related medication errors relative to all prescription medication errors ranged from 6.1 to 77.7% (median = 26.1% [IQR:17.6–42,1]) and was less than 6.3% relative to the number of prescriptions reviewed. Ours is the first large-scale descriptive study using an observatory hospital pharmacy practice database to study computer-related prescribing errors.

5.2. DRPs induced by CPOE

The main category of DRPs identified as PISREs were supratherapeutic (27.5%, 7,436) and subtherapeutic dosage (17.2%, 4,646), non-conformity to guidelines/hospitals' drug formularies (22.4%, 6,069) (i.e. medication selection non-compliant with the hospital drug formulary), and improper administration (17.9%, 4,838) (i.e. incorrect or no formulation, wrong timing). According to Korb-Savoldelli et al., all studies reported "wrong dose" and "wrong drug" errors [19], with the "wrong dose" error being that most frequently reported (from 7 to 67.4%, median = 31.5% [IQR:20.5–44.5]). Many of the prescription errors due to CPOE systems can have serious consequences for patients, depending on the clinical circumstances. Although some of are unlikely to occur (e.g. IV ketoprofen 150 ampoules/day instead of 150 mg/d), they nevertheless illustrate flaws in certain CPOE systems [26]. However, our data do not allow the discrimination between software errors, connection problems, and human error.

5.3. CPOE systems

The proportion of PIs triggered by software-related prescription errors was higher for non-certified (9.4%) than certified software (5.5%). In France, certification tests produced by the HAS are intended to technically assess the functionality of the software in various situations, as the CPOE evaluation methodology simulates various clinical scenarios [27]. French regulations do not require CPOE developers to carry out usability studies before the systems are marketed. Nevertheless, despite the limitations of this type of certification criteria, which have already been highlighted [28], our results show that prescribing with CPOE-certified systems results in fewer prescription errors than prescribing with non-certified software. These results are consistent with those of other studies, i.e. all software is not equal and some is safer than others [29-31].

5.4. Prescribers

The PISRE ratio was higher for prescriptions made by graduate prescribers (8.4%) than medical residents (7.8%) (p-value < 0.001). This finding is, at first glance, counterintuitive, as one would expect that a prescriber who has been practicing for several years in the same health facility would make fewer CPOE-related prescription errors with the software than a resident who has only been using the software for a few months. Observational studies show that medical residents make most prescriptions and transcribe them to the software prescription instructions of senior prescribers during the medical examination [32]. It is thus possible that, in some hospitals, senior physicians are only occasional users of the prescription software. According to Nerich et al., the occasional use of software (< 1 prescription per day) is a risk factor for prescription error (OR = 3.85, 95% CI [2.08-7.14]) [33]. Tolley described how a junior doctor remarked that there was no one he could ask for help with using the ePrescribing system, as he was "the most experienced person on this floor with regards to the ePrescribing system". She also described how one consultant admitted she had not "learnt how to prescribe properly" because she did not "use the system often enough and regularly enough to know the quirks and tweaks". This consultant relied on her junior staff to prescribe on the system [34].

5.5. Act-IP© Pharmacist' users

The PISRE ratio for senior pharmacists (9.2%) was higher than that of pharmacy residents (5.4%). This is consistent with the results of a study performed in a UK teaching hospital showing that the likelihood of senior pharmacists identifying errors was greater than that of junior pharmacists [35] and in accordance with our expectations. A study concerning French pharmacy students showed that they trust the contribution of computerization to healthcare without critical analysis. This results in overconfidence in the computer tool, perceived to be reliable, and makes users less willing to search for the errors produced by this tool [36]. They are therefore not aware that the review of computerized prescription orders requires additional effort to identify prescription errors. This is the consequence of the lack of teaching/training about this subject in French pharmacy schools. This situation contrasts strikingly with the content of the curricula taught in the United Kingdom and USA, for example [37,38].

5.6. Prescriber Acceptance rate

The rate of acceptance of PISREs by prescribers was 78.9% versus 67.6% for other PIs. This suggests that prescribers recognize the relevance of such interventions due to the potential clinical consequences of such prescription errors. This rate varies from 65.9 to 92% in studies of drug errors induced by computerized prescription [10, 14], suggesting that physicians consider the potential clinical consequences of SRE to patients to be more frequently serious than interventions unrelated to CPOE. In light of our findings, a CPOE-related prescription error is a factor that favors acceptance of the PI. These points warrant further studies.

5.7. Limits

Our study had several limitations. First, it focused on declarative data based on interventions performed by hospital pharmacists. These data are prospectively enter by pharmacists. There for, these PIs highlight prescription problems, but are not exhaustive. However, as illustrated by publications related to other databases on information technology incidents, despite their limitations, voluntary reports are useful to examinate the nature of information technology events [39,40]. And the large sample size probably provides a relatively precise vision of the problem at the national level. Second, several pharmacists analyzing the same drug prescriptions may not all track down the same problems. For example, the mean percentage of detected prescribing errors was 59% in a study involving 57 hospital pharmacies, with a broad range of 7 to 88% between pharmacies [41]. In the absence of specific studies to determine the performance of pharmacists in detecting prescription errors induced by CPOE-system flaws and misuse, we are reduced to simply assuming that such variation may be observed. In addition, there are various definitions of PISREs in the literature [13-16]. This suggests that there is a certain level of subjectivity when a pharmacist characterizes a PI as being related to a computer-generated prescription. Among hospitals that entered the PIs on Act-IP©, 87 never qualified a PI as being a SRE. There are two possible explanations for this observation. The first, and relatively unlikely, is that the software is near perfect and that there was no misuse by prescribers. For example, the absence of PISREs for these hospitals could result from the absence of computer-related errors due to the use of high-performance software and/or appropriately trained prescribers. The second possibility is that pharmacists do not establish a link between certain prescription errors and misuse of the prescription software and/or its design flaws.

Conversely, a high rate of PISREs for a given hospital may result from software conception flaws and/or misuse of the software by prescribers and pharmacists who are very aware of the role of CPOE-systems in generating prescription errors. Regardless of the considered scenario, it is important to remember that differences in PISRE rates may also be due to the quality of the training provided. Studies have shown that insufficient training on an ePrescribing system can contribute to errors [42,43]. Tolley illustrated how pharmacists did not receive any formal training about the system after starting at a hospital trust and observed that no formal training was offered when pharmacists changed roles. It has been shown that training plays a role in the users' experience but there is a lack of published research in this area [34]. Thus, further research is warranted to lift the veil on these unknowns.

Our results highlight that prescribing problems related to computer software are common in France. This is a concern that affects most (if not all) CPOE systems currently being used and therefore all hospitals, to varying degrees. Identifying the most dangerous software appears to be a priority to improve the quality and safety of patient care.

6. Conclusion

Computer-related prescribing errors are common, with wrong dose being the most frequent type of error. Such errors concern all drug classes and have potentially serious adverse clinical consequences if they are not intercepted by pharmacists when performing their daily medication review. The message appears to be well received by prescribers who agree to change their prescription more frequently than for PIs not related to CPOE use. CPOE medication review requires additional pharmacist diligence to catch such errors. As the PISRE ratio is significantly lower for certified software, patient safety agencies should undertake studies to identify the safest software so as to discard software that is potentially dangerous.

Author contributions

Manon Videau and Bruno Charpiat designed the study, performed the statistical analyses, interpreted the results, and wrote the first version of the manuscript. Céline Vermorel contributed to the design of the study, performed the statistical analyses, and revised the manuscript. Jean-Luc Bosson contributed to the design of the study and revised the manuscript. Ornella Conort contributed substantially to the interpretation of the data and contributed to the revision of the manuscript. Pierrick Bedouch designed the study, performed the statistical analyses, interpreted the results, and revised the manuscript.

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Statement on conflicts of interest

The authors declare that they have no conflicts of interest.

Patient consent for publication

Not required

Ethical approval

Ethical approval for the study was obtained on February 19, 2020 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891).

Data availability

Deidentified participant data are available upon reasonable request to Act-IP© Administrator (email address: actip@sfpc.eu).

Summary table

Table 1. Characteristics of Act-IP© observatory PISREs and PIs between 2014 to 2018.

Summary Figures

Figure 1. Flowchart, PISRE selection in Act-IP© observatory (extraction on 11th February 2019)

Figure 2. Geographical location of French hospitals that entered data into the Act-IP © observatory between 2014 and 2018

Table 1. Characteristics of all Act-IP© observatory PISREs and PIs between 2014 to 2018.

Characteristics	PISRE (N = 27,058)	PI total (N = 331,678)	ratio	
	n	n	%	p-value
Drug related problem				
Supratherapeutic dosage	7,436	72,912	10.2	
Non-conformity with guidelines/hospital formulary	6,069	86,072	7.1	
Improper administration	4,838	49,184	9.8	
Subtherapeutic dosage	4,646	29,105	16.0	
Untreated indication	2,366	30,138	7.9	
Drug without indication	1,302	27,690	4.7	
Drug interaction	161	18,267	0.9	
Drug monitoring	111	10,303	1.1	
Adverse drug reaction	65	5,854	1.1	
Failure to receive drug	64	2,153	3.0	
Type of intervention				
Dose adjustment	7,447	89,390	8.3	
Drug switch	6,649	85,033	7.8	
Drug discontinuation	5,220	62,715	8.3	
Optimization of administration	4,123	32,558	12.7	
Addition of new drug	3,228	34,198	9.4	
Change of administration route	213	6,978	3.1	
Drug monitoring	178	20,806	0.9	
Prescriber Acceptance				
Interventions accepted	21,356	227,223	9.4	< 0.001*

Interventions not accepted	3,068	51,957	5.9	
Not assessable	2,634	52,498	5.0	
Prescriber's status				
Senior	15,152	180,863	8.4	< 0.001
Resident	11,765	150,136	7.8	
Midwife**	141	679	20.8	
Pharmacist's status				
Senior	21,271	231,519	9.2	< 0.001
Resident	4,640	86,728	5.4	
Not assessable**	1,147	13,431	8.5	
CPOE system status				
Not certified	21,385	226,878	9.4	< 0.001
Certified	5,549	101,516	5.5	
Not assessable**	124	3,284	3.8	
Total	27,058	331,678	8.2	

PI: pharmacist's intervention, PISRE: pharmacist's intervention identified as due to a system-related error, ratio = PISRE / PI Total, CPOE: computerized prescriber order entry

**Not accepted and not assessable interventions have been regrouped for chi-square test; **excluded from the chi-square analysis*

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Main Document
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1 – Title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6 – lines 35-37
Methods			
Study design	4	Present key elements of study design early in the paper	Page 6 – lines 40-42
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 6 – lines 46-50
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Pages 6 – lines 46-50
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 5 – lines 20-23 Page 6 – lines 41-42 Page 6-7 – lines 50 - 65
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6 – lines 46 – 52 Page 7 – lines 53- 65
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	Figure 1 Page 7 – lines 73-74
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7 – lines 61-71
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7 – lines 66 - 71
		(*b*) Describe any methods used to examine subgroups and interactions	Page 7 – lines 66 - 71
		(*c*) Explain how missing data were addressed	Figure 1
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed	Figure 1

		eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Figure 2
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1 Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	Page 7 - 8 – line 75 - 88
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 1 Page 7 - 8 – line 73 - 83
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 8_9 – lines 95-108
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 11 - 12 – lines 164- 192
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 9-11 – lines 103-163
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 11 - 12 – lines 170- 196
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 14 – lines 270-275

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Figure 1. Flowchart, pharmacist interventions system-related errors (PISRE) selection in Act-IP© observatory (extraction on 11th February 2019)

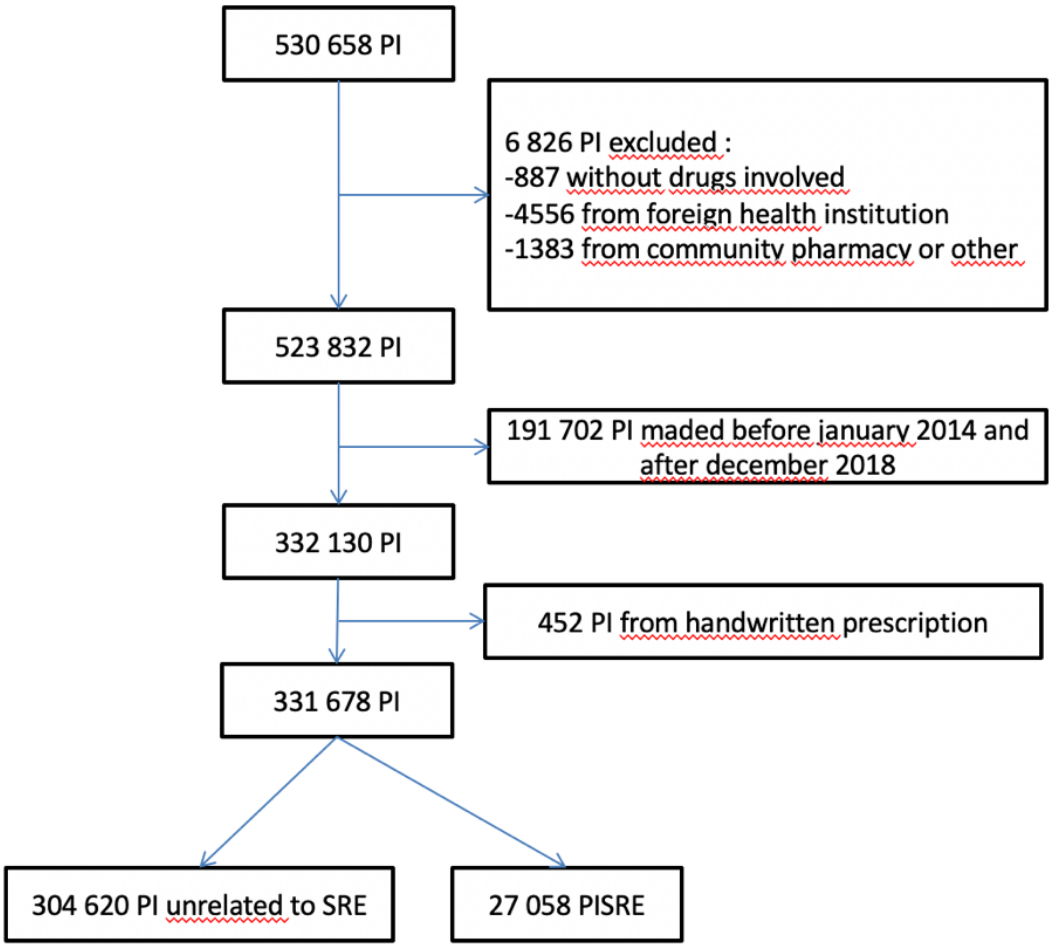
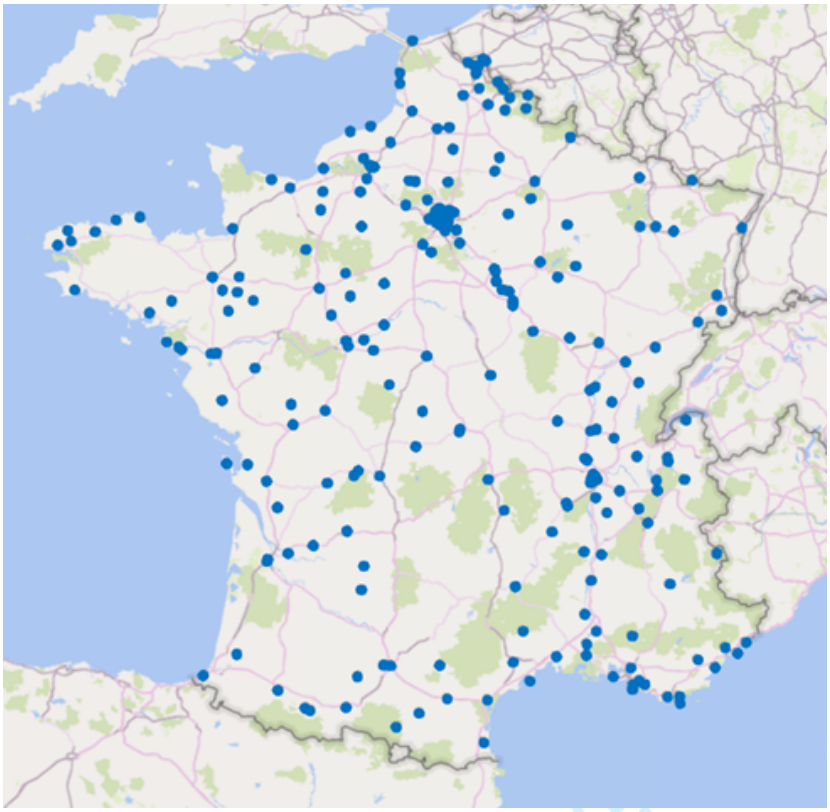


Figure 2. Geographical location of French hospitals that entered data into the Act-IP © observatory between 2014 and 2018



Appendix 1. The Pharmacist intervention form

PHARMACIST INTERVENTION FORM

DATE: / / **INTERVENTION N°:** **CENTER N°:**

PATIENT:

Last name:
First name:

Age: years / Weight: Kg
Sex: ❒ M ❒ F

Hospital ward:
❒ Psychiatry
❒ Acute care
❒ Long term care
❒ Rehabilitation ward

DRUG NAME (INN):

1- DRUG RELATED PROBLEM (1 choice):
1 ❒ Non conformity to guidelines or contra-indication
2 ❒ Untreated indication
3 ❒ Subtherapeutic dosage
4 ❒ Supratherapeutic dosage
5 ❒ Drug without indication
6 ❒ Drug interaction
- ❍ To be taken into account
- ❍ Use with caution
- ❍ Combination to be avoided
- ❍ Combination contra-indicated
- ❍ Documented but not in VIDAL®

7 ❒ Adverse drug reaction
8 ❒ Improper administration
9 ❒ Failure to receive drug
10 ❒ Drug monitoring

3- DRUG CLASSIFICATION (ATC):
❒ A Alimentary tract & metabolism
❒ B Blood & blood forming organs
❒ C Cardiovascular system
❒ D Dermatological
❒ G Genito urinary system & sex hormones
❒ H Systemic hormonal preparations
❒ J Anti-infective for systemic use
❒ L Anti-neoplastic & immunomodulating agents
❒ M Musculo-skeletal system
❒ N Nervous system
❒ P Antiparasitic products
❒ R Respiratory system
❒ S Sensory organs
❒ V Various

2- INTERVENTION (1 choice):
1 ❒ Addition of a new drug
2 ❒ Drug discontinuation
3 ❒ Drug switch
4 ❒ Change of administration route
5 ❒ Drug monitoring
6 ❒ Administration modalities optimisation
7 ❒ Dose adjustment

4- INTERVENTION FOLLOW-UP:
❒ Accepted
❒ Non accepted
❒ Non assessable

DETAILS ⇒If necessary, give details on any aspects of the detected DRP and describe the intervention. precisely

Context

Problem

Intervention

Appendix 2. Examples of PISRE and drug by drug-related problems (N = 27,822)

Drug-related problem	Number of drugs involved – n (%)	Most frequent drug (**international nonproprietary names)** (n)	Examples
Supratherapeutic dosage	7,571 (27.2)	Paracetamol (1,043), tramadol (223), pantoprazole (212), enoxaparin (204)	"Duplicate prescription: 1 in predefined protocol and 1 outside predefined protocol = 8 g of paracetamol per day"
Non-conformity to guidelines/contra-indication	6,212 (22.3)	Alfuzosin (515), dutasteride (493), silodosin (469), paracetamol (460), tamsulosin (373)	"prescription of dutasteride, which is not in the hospital drug formulary, with a risk of treatment omission"
Improper administration	4,972 (17.9)	Paracetamol (277), levothyroxine (130), pregabalin (130), methylprednisolone (124)	"selection of IV terbutaline for administration by aerosol"
Subtherapeutic dosage	4,738 (17.0)	Enoxaparin (965), heparin (450), tinzaparin (186), paracetamol (140), macrogol (105),	"Enoxaparin 4000 UI/0.4 ml prescription: 1 IU instead of 1 syringe"
Untreated indication	2,441 (8.8)	acetylsalicylic acid (82), pregabalin (80), paracetamol (74), tinzaparin (69), bisoprolol (69), enoxaparin (68),	"prescription of pregabalin not renewed (hospital stay longer than the duration of the prescription)"

Drug without indication	1,340 (4.8)	Pantoprazole (66), amoxicillin and beta-lactamase inhibitor (44), cholecalciferol (40), ceftriaxone (34), enoxaparin (30)	"duplicate prescription of pantoprazole per os and IV by two prescribers"
Drug interaction	262 (0.9)	Amiodarone (27), fluindione (9), levothyroxine (9)	"cordarone and escitalopram combination contra-indicated: risk of "torsade de pointes" not modified during drug interaction alert with Clinical Decision Support System (CDSS)"
Drug monitoring	124 (0.4)	Fluindione (25), polystyrene sulfonate (8), paracetamol (4)	
Adverse drug reaction	70 (0.3)	Polystyrene sulfonate (11), furosemide (6), atorvastatin (4), tramadol (3), macrogol (3)	"increased risk of adverse reactions by the combination of atorvastatin and fenofibrate"
Failure to receive drug	92 (0.3)	Esomeprazole (3), cholecalciferol (3), acetylsalicylic acid (3), furosemide (3)	"Prescription of furosemide not appearing on the nursing plan"

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Characteristics of Pharmacist's interventions triggered by prescribing errors related to computerized physician order entry in French hospitals: a cross-sectional observational study

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Abstract: 305/300 words

Main text: 3125/4000 words

Abstract

Objectives

Computerized physician order entry (CPOE) systems facilitate the review of medication orders by pharmacists. Reports have emerged that show conception flaws or the misuse of CPOE systems generate prescribing errors. We aimed to characterize pharmacist interventions (PIs) triggered by prescribing errors identified as system-related errors (SREs) in French hospitals.

Design

This was a cross-sectional observational study based on PIs prospectively documented in the Act-IP© observatory database from January 2014 to December 2018.

Setting

PISREs from 319 French computerized healthcare facilities were analyzed.

Participants

Among the 319 French hospitals, 232 (72.7%) performed SRE interventions, involving 652 (51%) pharmacists.

Results

Among the 331,678 PIs recorded, 27,058 were qualified as due to SREs (8.2%). The main drug-related problems associated with PISREs were supratherapeutic (27.5%) and subtherapeutic dosage (17.2%), non-conformity with guidelines/contraindications (22.4%), and improper administration (17.9%). The PI prescriber acceptation rate was 78.9% for SREs versus 67.6% for other types of errors. The PISRE ratio was estimated relative to the total number of PIs. Concerning the certification status of CPOE systems, the PISRE ratio was 9.4% for non-certified systems versus 5.5% for certified systems (p-value<0.001). The PISRE ratio for senior pharmacists was 9.2% and that for pharmacy residents 5.4% (p-value<0.001). Concerning prescriptions made by graduate prescribers and those made by residents, the PISRE ratio was 8.4 % and 7.8%, respectively (p-value<0.001).

Conclusion

Computer-related prescribing errors are common. The PI acceptance rate by prescribers was higher than that observed for PIs that were not CPOE related. This suggests that physicians consider the potential clinical consequences of SREs for patients to be more frequently serious than interventions unrelated to CPOE. CPOE medication review requires continual pharmacist diligence to catch these errors. The significantly lower PISRE ratio for certified software should prompt patient safety agencies to undertake studies to identify the safest software and discard software that is potentially dangerous.

Article Summary

Strengths and limitations of this study

- This study provides an overview of prescribing issues related to the use of CPOE systems at the national level.
- Beyond this large register of prescribing problems related to CPOE use, this is the first study to evaluate pharmacist interventions in daily practice for such a large sample of interventions, pharmacists, and hospitals.
- This study focuses on declarative data based on interventions performed by hospital pharmacists.
- These pharmacist interventions highlight prescription problems, but they are not exhaustive.

1. Introduction

Every day, numerous hospitalized patients are subject to drug-related problems (DRPs), resulting in suboptimal therapy, suffering, and decreased quality of life, as well as high healthcare costs for society [1, 2]. Computerized physician order entry (CPOE) systems, along with clinical decision support systems, improve the safety, quality, and value of patient care [3]. According to a meta-analysis, CPOE systems have reduced hospital medication errors by approximately 12.5% IC95% [10.6-14.4%] [4]. However, CPOE systems also have the potential to introduce or contribute to errors. Indeed, new mechanisms that lead to prescription errors have been identified with CPOE: wrong patient selection, failure to report drug allergies, incorrect entry or wrong selection of medication, dose, route, or time of administration, and confusing free-text comments [5-10].

In France, as in other countries, various incentives and requirements have been put in place to encourage computerized drug prescribing, such as France's "Digital Hospital" program [11]. Since the 2000s, prescribing errors associated with the use of CPOE have been slowly coming to light as healthcare has become increasingly computerized [9]. Compared to handwritten prescriptions, the analysis of electronic prescriptions requires a particular effort on the part of pharmacists and other health professionals to detect errors [9]. System-related errors (SREs) are defined as those in which the electronic prescribing system functionality or design contributed to the error, with little possibility that another cause, such as lack of knowledge, produced the error. For example, an order for an inappropriate drug located on a drop-down menu next to a likely drug selection is a system-related error [12].

A pharmacist intervention (PI) due to a SRE is defined as any PI resulting from the identification of a prescribing error by a pharmacist that would probably not have occurred in the context of a handwritten prescription and of which at least one cause is related to the use of a computer (software system configuration issue, software functionality issue, or software misuse) [13-16].

Most studies concerning PIs triggered by system-related prescribing errors were conducted within a single hospital [17-19]. As a result, it is not possible to assess the extent of prescribing errors related to electronic systems or draw conclusions about subsequent PIs at a national level.

In 2003, the French Society of Clinical Pharmacy (SFPC) developed and validated a tool for classifying and documenting clinical PIs [20]. This tool allows the reporting of DRPs and PIs performed during the daily review of medication orders [21]. In 2006, a website, Act-IP©, was created with the objectives to (a) create a documentation system that is freely accessible to any pharmacist, through the French Society of Clinical Pharmacy Web site (http://www.actip.sfpc.eu/actip/index/ficheip/) and (b) pool the data recorded by all pharmacists to conduct epidemiological studies concerning DRPs detected by pharmacists [22]. The data recording is on a voluntary basis. The pooling of PIs constitutes an observatory of clinical pharmacy practices, called the "Act-IP© Observatory".

The aim of this study was to characterize PIs triggered due to SREs in French hospitals between 2014 and 2018. Our secondary objective was to determine the physician acceptance rate and its frequency according to the certification status (certified versus non-certified) of the CPOE systems.

2. Methods

2.1. Study design

This was a cross-sectional observational study using PIs prospectively documented in the Act-IP© observatory over a five-year period from January 1, 2014 to December 31, 2018. The main outcome was a PI due to a SRE (PISRE) reported by French hospital pharmacists on the Act-IP© observatory. Ethical approval for the study was obtained on February 19, 2020 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891).

2.2. Data sources

The data comes from PIs registered in the Act-IP© Observatory from January 2014 to December 2018. Based on the SFPC criteria, using the report form developed and validated for routine documentation of the PIs, Act-IP© users completed the online report form notifying the date, type of DRP, PI, type of drug involved (according to the ATC (Anatomical Therapeutic Chemical) classification), acceptance of the intervention by the prescriber, and free-text details of the context. Ten categories were determined for DRPs and seven for PIs (Appendix 1). A PI was considered to be "accepted" if the physician took it into account and modified the prescription as suggested by the pharmacist or "refused" if the prescription

remained unchanged, including cases of expressed refusal by the prescriber. If acceptance of the intervention was impossible to ascertain (i.e. discharged patients or those transferred to another ward before acceptance), the PI was noted as "not assessable". The pharmacist's academic background, hospital characteristics, and software used were documented online by the pharmacist when he/she registered onto the Act-IP© website. To be registered onto the Act-IP© website, pharmacists had prior to accept terms and conditions and allowed the use of their data for analysis. Since July 2013, pharmacists have been able to indicate whether the DRP was "related to the electronic system" or not for each registered PI. For the purpose of this study, PISREs were DRPs rated by each pharmacist as "related to the electronic system" in the Act-IP© website.

The reliability of the classification of the type of drug therapy problem and intervention according to the SFPC classification was determined in a previous study by assessing the degree of agreement between 12 pharmacists using the kappa concordance coefficient (kappa=0.76 for drug problems and kappa=0.89 for drug interventions) [20]. Database quality controls were performed by an independent pharmacist to ensure that data coding and entry errors were minimal [22].

French law made the certification of CPOE systems mandatory on December 29, 2011. However, two decrees abolished this obligation in 2017. Certification is now based on the sole initiative of the software developer. Forty-eight hospital CPOE software packages are currently certified by the agency for patient safety [Haute Autorité de Santé (HAS)] [23]. For our analysis, PISREs were classified according to the HAS status of the CPOE system (certified versus not certified).

2.3. Analysis

The PISRE ratio was estimated relative to the total number of PIs. Proportions were compared using the chi-square test. PISREs coded as "refused" or "not assessable" were combined and compared to the accepted PISREs. Probability values < 0.001 were considered to be statistically significant. Statistical analyses were performed using Stata 13 (Stata Corporation, College Station, Texas, USA). Several qualitative examples are given to illustrate PISREs.

2.4. Study participants and public involvement

This research was done without study participant involvement. Patients and/or the public were not involved in the design, or conduct, or dissemination plans of this research.

4. Results

From January 2014 to December 2018, 331,678 PIs were entered into the Act-IP© observatory. Among them, 27,058 (8.2%) were indicated to be system-related prescribing errors (Figure 1).

Over the study period, 1,219 pharmacists from 319 hospitals recorded PIs in the Act-IP© observatory database. The geographical location of the hospitals involved is shown in Figure 2. Among them, 232 (72.7%), involving 652 (51%) pharmacists, performed SRE interventions. Among the 319 hospitals, 87 (27.3%) did not qualify any PIs as being due to a SRE. PIs come from 82 software involving 19 certified systems.

The characteristics of the PISREs are summarized in Table 1. The most commonly identified type of DRP was “supratherapeutic dosage”, followed by “non-conformity with guidelines/contraindications” and “improper administration”. Among the 27,058 PISREs, 78.9% (n = 21,356) were accepted. The PISRE ratio was 9.4% for non-certified systems versus 5.5% for certified systems (p-value < 0.001). Appendix 2 presents examples of drug-related problems classified as being triggered by prescribing errors due to the CPOE system. For example: Prescription errors can be the same whether they are handwritten prescriptions or computer-assisted prescriptions. Indeed, the combination of amiodarone and escitalopram can appear on handwritten prescription because of prescriber’s lack of knowledge. With CPOE, Clinical Decision Support System (CDSS) tool can alert on drug-drug interaction. However, high frequency of alerts and dozens of daily interruptions for clinicians are responsible of "alert fatigue" and practitioners override alerts [24]. We can also find duplicate orders, meaning the same drug is prescribed twice. With predefined order set, it is common to have 8 grams of paracetamol per day prescribed. Duplication errors are partially explained by the fact that many screens are required to view patient medications, making intrinsically difficult to spot duplicates [25].

5. Discussion

This study provides an overview of prescription problems related to CPOE systems used in French hospitals. It provides insights into the main situations and medications involved in computer-related prescribing problems detected by pharmacists by providing a broad description of PIs performed during the daily review of routine medication orders. Thus one strength of this study is that it is based on a large number of hospitals scattered throughout France, as no prior study of such extent evaluating PIs in daily practice has been published.

5.1. PISRE rate

Our PISRE rate (8.2%) is within the range reported by Korb-Savoldelli et al. [19]. They analyzed peer-reviewed studies (n = 14) that quantitatively reported medication-prescription errors related to CPOE. The prevalence of CPOE system-related medication errors relative to all prescription medication errors ranged from 6.1 to 77.7% (median = 26.1% [IQR:17.6–42,1]) and was less than 6.3% relative to the number of prescriptions reviewed. Ours is the first large-scale descriptive study using an observatory hospital pharmacy practice database to study computer-related prescribing errors.

5.2. DRPs induced by CPOE

The main category of DRPs identified as PISREs were supratherapeutic (27.5%, 7,436) and subtherapeutic dosage (17.2%, 4,646), non-conformity to guidelines/hospitals' drug formularies (22.4%, 6,069) (i.e. medication selection non-compliant with the hospital drug formulary), and improper administration (17.9%, 4,838) (i.e. incorrect or no formulation, wrong timing). According to Korb-Savoldelli et al., all studies reported “wrong dose” and “wrong drug” errors [19], with the “wrong dose” error being that most frequently reported (from 7 to 67.4%, median = 31.5% [IQR:20.5–44.5]). Many of the prescription errors due to CPOE systems can have serious consequences for patients, depending on the clinical circumstances. Although some of are unlikely to occur (e.g. IV ketoprofen 150 ampoules/day instead of 150 mg/d), they nevertheless illustrate flaws in certain CPOE systems [26]. However, our data do not allow the discrimination between software errors, connection problems, and human error.

5.3. CPOE systems

The proportion of PIs triggered by software-related prescription errors was higher for non-certified (9.4%) than certified software (5.5%). In France, certification tests produced by the HAS are intended to technically assess the functionality of the software in various situations, as the CPOE evaluation methodology simulates various clinical scenarios [27]. French regulations do not require CPOE developers to carry out usability studies before the systems are marketed. Nevertheless, despite the limitations of this type of certification criteria, which have already been highlighted [28], our results show that prescribing with CPOE-certified systems results in fewer prescription errors than prescribing with non-certified software. These results are consistent with those of other studies, i.e. all software is not equal and some is safer than others [29-31].

5.4. Prescribers

The PISRE ratio was higher for prescriptions made by graduate prescribers (8.4%) than medical residents (7.8%) (p-value < 0.001). This finding is, at first glance, counterintuitive, as one would expect that a prescriber who has been practicing for several years in the same health facility would make fewer CPOE-related prescription errors with the software than a resident who has only been using the software for a few months. Observational studies show that medical residents make most prescriptions and transcribe them to the software prescription instructions of senior prescribers during the medical examination [32]. It is thus possible that, in some hospitals, senior physicians are only occasional users of the prescription software. According to Nerich et al., the occasional use of software (< 1 prescription per day) is a risk factor for prescription error (OR = 3.85, 95% CI [2.08-7.14]) [33]. Tolley described how a junior doctor remarked that there was no one he could ask for help with using the ePrescribing system, as he was “the most experienced person on this floor with regards to the ePrescribing system”. She also described how one consultant admitted she had not “learnt how to prescribe properly” because she did not “use the system often enough and regularly enough to know the quirks and tweaks”. This consultant relied on her junior staff to prescribe on the system [34].

5.5. Act-IP© Pharmacist’ users

The PISRE ratio for senior pharmacists (9.2%) was higher than that of pharmacy residents (5.4%). This is consistent with the results of a study performed in a UK teaching hospital showing that the likelihood

of senior pharmacists identifying errors was greater than that of junior pharmacists [35] and in accordance with our expectations. A study concerning French pharmacy students showed that they trust the contribution of computerization to healthcare without critical analysis. This results in overconfidence in the computer tool, perceived to be reliable, and makes users less willing to search for the errors produced by this tool [36]. They are therefore not aware that the review of computerized prescription orders requires additional effort to identify prescription errors. This is the consequence of the lack of teaching/training about this subject in French pharmacy schools. This situation contrasts strikingly with the content of the curricula taught in the United Kingdom and USA, for example [37,38].

5.6. Prescriber Acceptance rate

The rate of acceptance of PISREs by prescribers was 78.9% versus 67.6% for other PIs. This suggests that prescribers recognize the relevance of such interventions due to the potential clinical consequences of such prescription errors. This rate varies from 65.9 to 92% in studies of drug errors induced by computerized prescription [10, 14], suggesting that physicians consider the potential clinical consequences of SRE to patients to be more frequently serious than interventions unrelated to CPOE. In light of our findings, a CPOE-related prescription error is a factor that favors acceptance of the PI. These points warrant further studies.

5.7. Limits

Our study had several limitations. First, our work is based on declarative data. These interventions are performed by hospital pharmacist and entered on Act-IP © website on a voluntary basis. There for, these PIs highlight prescription problems, but are not exhaustive. Moreover, our team annually analyzes the quantitative and qualitative evolution of the data recorded on the Act-IP © website (unpublished data). We observed that data entry can be irregular or performed with a delay. Indeed, data can be conditioned by pharmacist workload. For example, many pharmacists record prospectively their data on paper on a daily basis and thereafter register them by series on Act-IP©. Data entry can also be total on a given period and can stop during a change of assignment. We consider that these elements have consequences on the quantity of recorded data but not on their quality. However, as illustrated by publications related to other databases on information technology incidents, despite their limitations, studies based on

voluntary reports remain relevant to examine the nature of technology safety problems [39,40]. Moreover, the large sample size probably provides a relatively precise vision of the problem at the national level. Second, several pharmacists analyzing the same drug prescriptions may not all track down the same problems. One of major determinant of a PI is the knowledge of the pharmacist who analyzes the prescription. It is this knowledge that enables him to detect a problem. Thus, a PI that is considered as necessary and is not performed means that it is not recorded and will be absent from the database. This happens when a doctor routinely makes a certain type of prescribing error and the pharmacist fails to detect it [41]. It has been shown that, if several pharmacists analyze the same drug prescriptions, they don't all track down the same problems. In a study involving 57 hospital pharmacies, the mean percentage of detected prescribing errors was 59%, with a broad range of 7–88% between pharmacies [42]. In the absence of specific studies to determine the performance of pharmacists in detecting prescription errors induced by CPOE-system flaws and misuse, we are reduced to simply assuming that such variation may be observed. In addition, there are various definitions of PISREs in the literature [13-16]. This suggests that there is a certain level of subjectivity when a pharmacist characterizes a PI as being related to a computer-generated prescription. Among hospitals that entered the PIs on Act-IP©, 87 never qualified a PI as being a SRE. There are two possible explanations for this observation. The first, and relatively unlikely, is that the software is near perfect and that there was no misuse by prescribers. For example, the absence of PISREs for these hospitals could result from the absence of computer-related errors due to the use of high-performance software and/or appropriately trained prescribers. The second possibility is that pharmacists do not establish a link between certain prescription errors and misuse of the prescription software and/or its design flaws. Conversely, a high rate of PISREs for a given hospital may result from software conception flaws and/or misuse of the software by prescribers and pharmacists who are very aware of the role of CPOE-systems in generating prescription errors. Regardless of the considered scenario, it is important to remember that differences in PISRE rates may also be due to the quality of the training provided. Studies have shown that insufficient training on an ePrescribing system can contribute to errors [43,44]. Tolley illustrated how pharmacists did not receive any formal training about the system after starting at a hospital trust and observed that no formal training was offered when pharmacists changed roles. It has been shown that

training plays a role in the users' experience but there is a lack of published research in this area [34]. Thus, further research is warranted to lift the veil on these unknowns.

Our results highlight that prescribing problems related to computer software are common in France. This is a concern that affects most (if not all) CPOE systems currently being used and therefore all hospitals, to varying degrees. Identifying the most dangerous software appears to be a priority to improve the quality and safety of patient care.

6. Conclusion

Computer-related prescribing errors are common, with wrong dose being the most frequent type of error. Such errors concern all drug classes and have potentially serious adverse clinical consequences if they are not intercepted by pharmacists when performing their daily medication review. The message appears to be well received by prescribers who agree to change their prescription more frequently than for PIs not related to CPOE use. CPOE medication review requires additional pharmacist diligence to catch such errors. As the PISRE ratio is significantly lower for certified software, patient safety agencies should undertake studies to identify the safest software so as to discard software that is potentially dangerous.

Author contributions

Manon Videau and Bruno Charpiat designed the study, performed the statistical analyses, interpreted the results, and wrote the first version of the manuscript. Céline Vermorel contributed to the design of the study, performed the statistical analyses, and revised the manuscript. Jean-Luc Bosson contributed to the design of the study and revised the manuscript. Ornella Conort contributed substantially to the interpretation of the data and contributed to the revision of the manuscript. Pierrick Bedouch designed the study, performed the statistical analyses, interpreted the results, and revised the manuscript.

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Statement on conflicts of interest

The authors declare that they have no conflicts of interest.

Patient consent for publication

Not required

Ethical approval

Ethical approval for the study was obtained on February 19, 2020 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891).

Data availability

Deidentified participant data are available upon reasonable request to Act-IP© Administrator (email address: actip@sfpc.eu).

Summary table

Table 1. Characteristics of Act-IP© observatory PISREs and PIs between 2014 to 2018.

Summary Figures

Figure 1. Flowchart, PISRE selection in Act-IP© observatory (extraction on 11th February 2019)

Figure 2. Geographical location of French hospitals that entered data into the Act-IP © observatory between 2014 and 2018

Table 1. Characteristics of all Act-IP© observatory PISREs and PIs between 2014 to 2018.

Characteristics	PISRE (N = 27,058)	PI total (N = 331,678)	ratio	
	n	n	%	p-value
Drug related problem				
Supratherapeutic dosage	7,436	72,912	10.2	< 0.001
Non-conformity with guidelines/hospital formulary	6,069	86,072	7.1	-
Improper administration	4,838	49,184	9.8	< 0.001
Subtherapeutic dosage	4,646	29,105	16.0	< 0.001
Untreated indication	2,366	30,138	7.9	< 0.001
Drug without indication	1,302	27,690	4.7	< 0.001
Drug interaction	161	18,267	0.9	< 0.001
Drug monitoring	111	10,303	1.1	< 0.001
Adverse drug reaction	65	5,854	1.1	< 0.001
Failure to receive drug	64	2,153	3.0	< 0.001
Type of intervention				
Dose adjustment	7,447	89,390	8.3	-
Drug switch	6,649	85,033	7.8	< 0.001
Drug discontinuation	5,220	62,715	8.3	< 0.001
Optimization of administration	4,123	32,558	12.7	< 0.001
Addition of new drug	3,228	34,198	9.4	< 0.001
Change of administration route	213	6,978	3.1	< 0.001
Drug monitoring	178	20,806	0.9	< 0.001
Prescriber Acceptance				
Interventions accepted	21,356	227,223	9.4	< 0.001*

Interventions not accepted	3,068	51,957	5.9	
Not assessable	2,634	52,498	5.0	
Prescriber's status				
Senior	15,152	180,863	8.4	< 0.001
Resident	11,765	150,136	7.8	
Midwife**	141	679	20.8	
Pharmacist's status				
Senior	21,271	231,519	9.2	< 0.001
Resident	4,640	86,728	5.4	
Not assessable**	1,147	13,431	8.5	
CPOE system status				
Not certified	21,385	226,878	9.4	< 0.001
Certified	5,549	101,516	5.5	
Not assessable**	124	3,284	3.8	
Total	27,058	331,678	8.2	

PI: pharmacist's intervention, PISRE: pharmacist's intervention identified as due to a system-related error, ratio = PISRE / PI Total, CPOE: computerized prescriber order entry

**Not accepted and not assessable interventions have been regrouped for chi-square test; **excluded from the chi-square analysis*

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Figure 1. Flowchart, pharmacist interventions system-related errors (PISRE) selection in Act-IP© observatory (extraction on 11th February 2019)

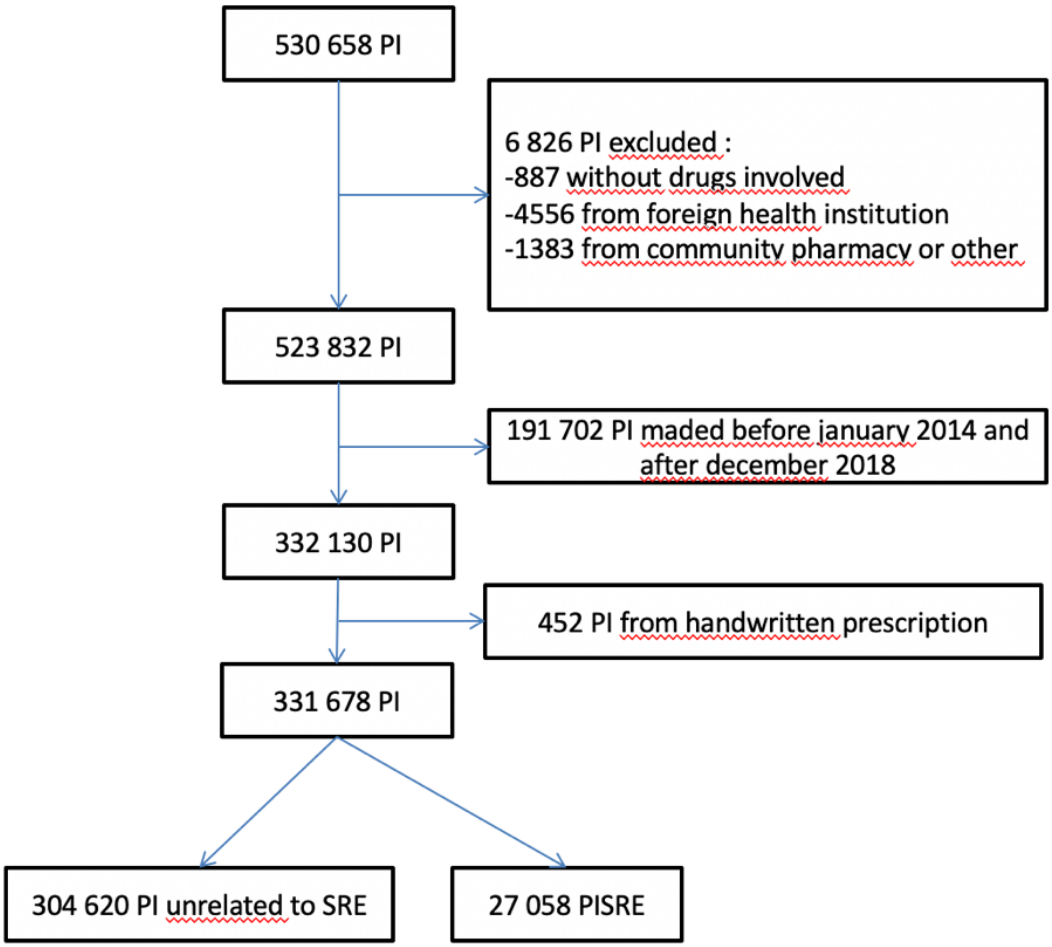
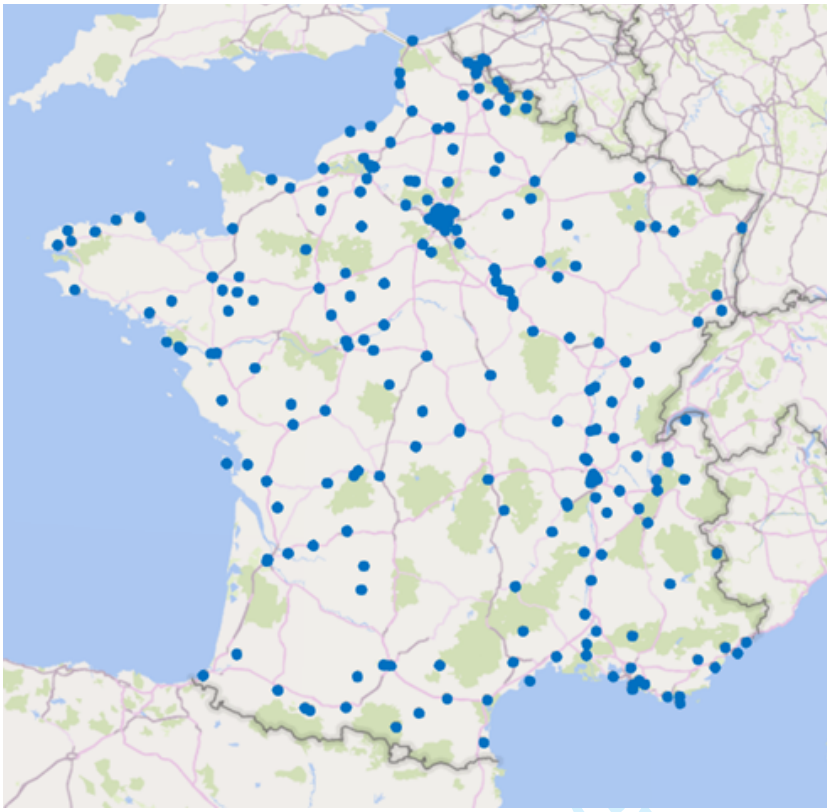


Figure 2. Geographical location of French hospitals that entered data into the Act-IP © observatory between 2014 and 2018



Appendix 1. The Pharmacist intervention form

PHARMACIST INTERVENTION FORM

DATE: / / **INTERVENTION N°:** **CENTER N°:**

PATIENT:

Last name:
First name:

Age: years / Weight: Kg
Sex: ❒ M ❒ F

Hospital ward:
❒ Psychiatry
❒ Acute care
❒ Long term care
❒ Rehabilitation ward

DRUG NAME (INN):

1- DRUG RELATED PROBLEM (1 choice):
1 ❒ Non conformity to guidelines or contra-indication
2 ❒ Untreated indication
3 ❒ Subtherapeutic dosage
4 ❒ Supratherapeutic dosage
5 ❒ Drug without indication
6 ❒ Drug interaction
- ❍ To be taken into account
- ❍ Use with caution
- ❍ Combination to be avoided
- ❍ Combination contra-indicated
- ❍ Documented but not in VIDAL®

7 ❒ Adverse drug reaction
8 ❒ Improper administration
9 ❒ Failure to receive drug
10 ❒ Drug monitoring

3- DRUG CLASSIFICATION (ATC):
❒ A Alimentary tract & metabolism
❒ B Blood & blood forming organs
❒ C Cardiovascular system
❒ D Dermatological
❒ G Genito urinary system & sex hormones
❒ H Systemic hormonal preparations
❒ J Anti-infective for systemic use
❒ L Anti-neoplastic & immunomodulating agents
❒ M Musculo-skeletal system
❒ N Nervous system
❒ P Antiparasitic products
❒ R Respiratory system
❒ S Sensory organs
❒ V Various

2- INTERVENTION (1 choice):
1 ❒ Addition of a new drug
2 ❒ Drug discontinuation
3 ❒ Drug switch
4 ❒ Change of administration route
5 ❒ Drug monitoring
6 ❒ Administration modalities optimisation
7 ❒ Dose adjustment

4- INTERVENTION FOLLOW-UP:
❒ Accepted
❒ Non accepted
❒ Non assessable

DETAILS ⇒If necessary, give details on any aspects of the detected DRP and describe the intervention. precisely

Context

Problem

Intervention

Appendix 2. Examples of PISRE and drug by drug-related problems (N = 27,822)

Drug-related problem	Number of drugs involved – n (%)	Most frequent drug (**international nonproprietary names)** (n)	Examples
Supratherapeutic dosage	7,571 (27.2)	Paracetamol (1,043), tramadol (223), pantoprazole (212), enoxaparin (204)	"Duplicate prescription: 1 in predefined protocol and 1 outside predefined protocol = 8 g of paracetamol per day"
Non-conformity to guidelines/contra-indication	6,212 (22.3)	Alfuzosin (515), dutasteride (493), silodosin (469), paracetamol (460), tamsulosin (373)	"prescription of dutasteride, which is not in the hospital drug formulary, with a risk of treatment omission"
Improper administration	4,972 (17.9)	Paracetamol (277), levothyroxine (130), pregabalin (130), methylprednisolone (124)	"selection of IV terbutaline for administration by aerosol"
Subtherapeutic dosage	4,738 (17.0)	Enoxaparin (965), heparin (450), tinzaparin (186), paracetamol (140), macrogol (105),	"Enoxaparin 4000 UI/0.4 ml prescription: 1 IU instead of 1 syringe"
Untreated indication	2,441 (8.8)	acetylsalicylic acid (82), pregabalin (80), paracetamol (74), tinzaparin (69), bisoprolol (69), enoxaparin (68),	"prescription of pregabalin not renewed (hospital stay longer than the duration of the prescription)"

Drug without indication	1,340 (4.8)	Pantoprazole (66), amoxicillin and beta-lactamase inhibitor (44), cholecalciferol (40), ceftriaxone (34), enoxaparin (30)	"duplicate prescription of pantoprazole per os and IV by two prescribers"
Drug interaction	262 (0.9)	Amiodarone (27), fluindione (9), levothyroxine (9)	"cordarone and escitalopram combination contra-indicated: risk of "torsade de pointes" not modified during drug interaction alert with Clinical Decision Support System (CDSS)"
Drug monitoring	124 (0.4)	Fluindione (25), polystyrene sulfonate (8), paracetamol (4)	
Adverse drug reaction	70 (0.3)	Polystyrene sulfonate (11), furosemide (6), atorvastatin (4), tramadol (3), macrogol (3)	"increased risk of adverse reactions by the combination of atorvastatin and fenofibrate"
Failure to receive drug	92 (0.3)	Esomeprazole (3), cholecalciferol (3), acetylsalicylic acid (3), furosemide (3)	"Prescription of furosemide not appearing on the nursing plan"

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Main Document
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1 – Title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6 – lines 35-37
Methods			
Study design	4	Present key elements of study design early in the paper	Page 6 – lines 40-42
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 6 – lines 46-50
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Pages 6 – lines 46-50
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 5 – lines 20-23 Page 6 – lines 41-42 Page 6-7 – lines 50 - 65
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6 – lines 46 – 52 Page 7 – lines 53- 65
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	Figure 1 Page 7 – lines 73-74
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7 – lines 61-71
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7 – lines 66 - 71
		(*b*) Describe any methods used to examine subgroups and interactions	Page 7 – lines 66 - 71
		(*c*) Explain how missing data were addressed	Figure 1
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed	Figure 1

		eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Figure 2
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1 Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	Page 7 - 8 – line 75 - 88
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 1 Page 7 - 8 – line 73 - 83
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 8_9 – lines 95-108
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 11 - 12 – lines 164- 192
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 9-11 – lines 103-163
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 11 - 12 – lines 170- 196
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 14 – lines 270-275

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.