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## **Clinical Usefulness of Electronic Drug-Drug Interaction Checking in the Care of Cardiovascular Surgery Inpatients**

Taegtmeyer, A B; Kullak-Ublick, G A; Widmer, N; Falk, V; Jetter, A

**Abstract:** Objectives: Drug-related problems (DRPs) are events or circumstances involving drug therapy that actually or potentially interfere with desired health outcomes. This study tested the applicability of clinical decision support software in identifying and managing DRPs among cardiovascular surgery inpatients. Methods: Two clinical pharmacologists attended ward rounds on a low-dependency cardiovascular surgery ward every 2 weeks over a 7-month period. Three hundred and three patients were assessed. On average, patients received 17 scheduled and 'as required' medicines. DRPs were identified 'manually' via assessment of electronic prescription charts and patient records and 'electronically' using clinical decision support software (Pharmavista®). The numbers of alerts for optimizing medication safety generated by the two methods were compared. Results: Manual checking identified 346 DRPs leading to 346 alerts in 201 patients (overall 1.1 alerts/patient). Relevant interactions accounted for 44% of DRPs detected by clinical pharmacologists. Clinical decision support software, which could only report interactions, however, generated 1,370 alerts (average 4.5 alerts/patient). Only 147 (11%) drug-drug interaction alerts were identical to those identified by manual checking; the remaining 89% were considered not clinically relevant. Conclusions: Compared to identification of DRPs by clinical pharmacologists, the clinical decision support software performed poorly due to over-alerting and inability to assess for problems not caused by drug-drug interactions.

DOI: <https://doi.org/10.1159/000343272>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-69594>

Journal Article

Accepted Version

Originally published at:

Taegtmeyer, A B; Kullak-Ublick, G A; Widmer, N; Falk, V; Jetter, A (2012). Clinical Usefulness of Electronic Drug-Drug Interaction Checking in the Care of Cardiovascular Surgery Inpatients. *Cardiology*, 123(4):219-222.

DOI: <https://doi.org/10.1159/000343272>

## **Clinical usefulness of electronic drug-drug interaction checking in the care of cardiovascular surgery inpatients**

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**Short title:** Clinical decision support in cardiovascular surgery

**Word count** (Abstract + text): 1782

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### **Conflict of interest notification**

All authors have no conflicts of interest relevant to the contents of this paper to disclose.

## **Abstract**

*Objectives:* Drug-related problems (DRPs) are events or circumstances involving drug-therapy that actually or potentially interfere with desired health outcomes. The study tested the applicability of clinical decision support software in identifying and managing DRPs among cardiovascular surgery inpatients.

*Methods:* Two clinical pharmacologists attended ward-rounds on a low-dependency cardiovascular surgery ward every two weeks over a seven month period. Three hundred and three patients were assessed. On average, patients received 17 scheduled and `as-required` medicines. DRPs were identified `manually` by assessing electronic prescription charts and patient records and `electronically` using clinical decision support software (Pharmavista®). The number of alerts for optimizing medication-safety generated by the two methods were compared.

*Results:* Manual-checking identified 346 DRPs leading to 346 alerts in 201 patients (overall 1.1 alerts/patient). Relevant interactions accounted for 44% of DRPs detected by clinical pharmacologists. Clinical decision support software, which could only report interactions, however, generated 1370 alerts (average 4.5 alerts/patient). Only 147 (11%) of drug-drug interaction alerts were identical to those identified by manual-checking; the remaining 89% were considered not clinically relevant.

*Conclusions:* Compared to identification of DRPs by clinical pharmacologists, the clinical decision support software performed poorly due to over-alerting and inability to assess for problems not caused by drug-drug interactions.

**Key-words:** medication-safety, interaction checking, clinical decision support system, cardiovascular surgery

## **Introduction**

Computerised physician order entry (CPOE) is becoming more widespread in the care of cardiovascular surgery inpatients. While CPOE is associated with a reduction in drug-prescribing errors [1] – primarily through prevention of misinterpretation of hand-written prescriptions – new problems related to the electronic nature of drug prescribing itself have emerged with time [2]. Furthermore, CPOE cannot prevent drug-related problems (DRPs) which arise for example due to concurrent morbidities, renal or hepatic dysfunction, or drug-drug interactions. Clinical pharmacology and/or clinical pharmacy services can provide valuable input in identifying DRPs and providing suggestions as to how they might be avoided. Such services however are labour-intensive and costly. An alternative is the use of clinical decision support software (CDSS) which can be integrated into the electronic prescribing process. However, the applicability of such a system in the care of cardiovascular surgery inpatients is not known. The purpose of this study was to determine the applicability of a simple computerised decision support system which assessed for drug-drug interactions (the commonest type of CDSS in Europe) in a group of such patients by comparing its performance with that of clinical pharmacologists in identifying DRPs.

## **Methods and Materials**

Ward-rounds of pre- and post-operative cardiovascular surgery patients were attended every second week by two clinical pharmacologists over a seven month period from November 2010 to June 2011. This study period was chosen because the treating surgeons and physicians did not change during this time. The setting was a ward without intensive care or high-dependency beds. All patients were cared for using integrated electronic medical records (with electronic prescribing). An additional feature of the electronic prescription chart was the electronic drug interactions check

CDSS supplied by Pharmavista® (e-mediat AG, Bern, Switzerland) [3]. When requested to do so by the prescriber, this programme assessed potential drug-drug interactions and graded these according to the required intervention (based on the Operational Classification of Drug Interactions by Hansten, Horn and Hazlet [4]). The CDSS did not flag up potential problems automatically. Such alerts are known as `non-interruptive` alerts and differ from `interruptive` alerts which require acknowledgement from the prescriber of the awareness of the DRP usually in the form of a mouse-click. It was not known how often the interactions check software was used by the prescribing surgeons. Other than the voluntary drug interactions check, no electronic clinical decision support (regarding dosing, for example) was embodied in the electronic prescription chart.

Clinical pharmacologists assessed the electronic prescription charts for the presence of drug-related issues. Internet-based databases including Swiss, German and US-American product information, PubMed, the Pharmavista® tool [3] and the Micromedex® Healthcare Series (Thomson Reuters, Greenwood Village, Colorado, USA) [5] were used.

DRPs were defined according to the Pharmaceutical Care Network Europe (PCNE) Classification for Drug-related Problems Version 6.2 (revised 14-01-2010), which defines a drug-related problem as `an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes` [6]. Drug-related issues included all DRPs and instances where specific information regarding drug-therapy (such as the pharmacokinetics of intravenous or orally administered antibiotics) was requested by the treating surgeons. Proposals for optimizing drug safety were then given to the treating surgeons face-to-face on the ward round.

For the purposes of analysis, DRPs were classified according to a simplified PCNE system which defined the drug-related issues as lack of treatment effect (P1 of PCNE version 6.2), adverse drug event (P2) and provision of information. Underlying causes of a lack of treatment effect or an adverse drug event were classified as resulting from an interaction (C1.3), inappropriate dosing (C3), contraindication (C1.1), inappropriate timing of administration (C5.1), inappropriate duplication of therapeutic group or active ingredient (C1.4), unclear prescription (including problems arising from electronic prescribing) (C6.2), need for therapeutic drug monitoring (C3.5), known side effect of drug, failure to correctly document drug allergies and suboptimal choice of drug form (C2.1) or drug (C1.1).

Data are presented as numbers and percentages. The average number of drugs prescribed per patient was determined from a randomly selected subgroup of 30 patients. Similarly, data on the number of drug prescriptions which CDSS was unable to recognize was collected for 7 ward-rounds and used to estimate an overall percentage of drug prescriptions which could not be included in the automated analysis for drug-drug interactions. A positive predictive value calculation was performed using clinical pharmacologists' judgements as the gold standard.

## **Results**

Electronic prescription charts of 303 patients were assessed. On average, each patient had 17 different medications prescribed on a regular and 'as required' basis. Of these prescriptions, approximately 4.5% could not be recognized by CDSS as they had been entered into the electronic drug chart as 'free text' fields.

The types and frequencies of drug-related issues are shown in Table 1. Potential adverse drug events were the most common (72%), followed by potential lack of treatment effect (15%), actual adverse drug events (6%) and provision of information pertaining to drug prescriptions as requested by the treating surgeons (4%). Drug-drug interactions were the underlying cause of 153 DRPs (44% of all DRPs). The five most common drug-drug interactions were paracetamol in combination with an enzyme inducer (such as rifampicin or phenytoin, n = 9), the combination of rifampicin and an opiate analgesic (n = 7), the combination of polyvalent cations with fluoroquinolones (n = 6) or levothyroxine (n = 6), and the combination of amiodarone with statins (n = 5). Formally contraindicated drug-drug combinations were the combination of amiodarone with domperidone, an antiemetic associated with QTc-prolongation (n = 4). These latter cases, however, did not cause any manifest adverse drug events.

CDSS identified 147 of these 153 interactions, in addition to reporting on an additional 1223 interactions which were not judged clinically relevant by the clinical pharmacologists (Figure 1). In addition to this `over-alerting`, whereby only 11% of computer generated alerts were clinically applicable, 61% of all drug-related issues could not be identified by this form of CDSS, therefore representing a simultaneous gross `under-alerting`. The positive predictive value of CDSS for interactions was 0.107 when considering clinical pharmacologists` judgements to be the `gold standard`.

A small but relevant number of DRPs were related to the CPOE system itself (n = 9), as shown in the footnote to the table (Table 1).



## Discussion

While the incidence of DRPs in this group of cardiovascular surgery inpatients was less than that found in other studies of hospitalized patients [7], drug-drug interactions were the underlying cause for the majority of the detected DRPs. This was higher than found in a previous study of medical inpatients at the same hospital (33% [8]) and likely reflects the more frequent use of drugs such as amiodarone and rifampicin in our patient population. While CDSS was able to detect nearly all of the drug-drug interactions seen by clinical pharmacologists, it also generated a large number of over-alerts (89% of CDSS-generated alerts were not judged to be clinically relevant) in addition to being unable to alert on dosing adaptation, drug allergies and other contraindications.

The implications of these findings are three-fold. First, in order to be clinically applicable, CDSS should be optimised to detect all relevant drug-related problems. Such systems are however expensive and still under development. Secondly, we found a failure to detect all clinically relevant drug-drug interactions, despite the large number of alerts generated by CDSS. In this study, reasons why CDSS was unable to identify six relevant drug-drug interactions were inability to recognise drug prescriptions entered as `free text` (and not chosen from drop-down menus) and the exceeding of the CDSS`s computational capacity in one case. These limitations of CDSS should be addressed and eliminated in future software development. Thirdly, the large number of over-alerts seen in this and other studies [9,10] is cause for concern as clinicians are more likely to ignore all alerts when only 1 out of 10 alerts is relevant, thereby deriving no benefit for their patients from the CDSS. In the recent study of CDSS-generated drug-drug interaction alerts by Seidling et al. only 1.4% of non-interruptive alerts were accepted [9]. For `interruptive` alerts the authors identified the frequency of the alert, the quality of the message displayed, the alert

level and the contextual setting (for example inpatients and prescriptions involving drugs with dose-dependent toxicity) as being associated with increased acceptance [9].

The present study has limitations. The judgements of the two clinical pharmacologists were taken as the `gold standard` for the purposes of determining the performance of CDSS in this setting but they may have been incomplete or biased. However, there are no established `gold-standards` in this field. For a simple 10-category system for classifying DRPs, inter-rater agreement was found to be 0.68 [11]. The CDSS system used here is one which is more widespread in Europe than in the United States, where systems capable of alerting on DRPs not solely arising from drug-drug interactions are commonly in place. Whether the findings of our study are more widely applicable to other patient settings, other clinical pharmacology and clinical pharmacist services and other prescribers merits further study.

## **Conclusions**

Taken together, our findings show that drug-drug interaction CDSS in its current form is unlikely to be of assistance to surgeons treating cardiovascular surgery inpatients due to a combination of over-alerting and the high number and complexity of drug-related problems which go beyond drug-drug interactions. Monitoring of the prescribed drug regimen by a clinical pharmacologist remains an important measure towards optimizing medication-safety in cardiovascular surgery patients until both CPOE and CDSS are optimized.

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**Table 1** Drug-related issues (n = 359, of which 346 were drug-related problems) and where applicable, their underlying causes in 303 cardiovascular surgery inpatients

<b>Drug-related issue</b>	<b>Underlying cause</b>	<b>Number (% of total)</b>	<b>Number identified by CDSS (% of all drug-related issues/% of total interactions found by CDSS [n= 1370])</b>
Lack of treatment effect:		0	0
Adverse drug event:	Known side-effect of drug	21 <sup>‡</sup> (5.8)	0
	Interaction	1 (0.3)	1 (0.3/0.1)
Potential lack of treatment effect:	Interaction	44 (12.2)	40 (11.1/2.9)
	Inappropriate dose	9* (2.5)	0
	Time of administration	1 (0.3)	0
Potential adverse drug event:	Known side effect of drug	33 (9.1)	0
	Interaction	104 (29.0)	102 (28.4/7.4)
	Time of administration	5 (1.4)	0
	Drug choice**	17 (4.7)	0
	Inappropriate dose	45 (12.5) †	0

Contraindication	28 (7.8)	4 (1.1/0.3)
Need for therapeutic drug monitoring	3 (0.8)	0
Prescription unclear	11 (3.0)	0
Duplication of therapeutic class	15 (4.2)	0
Documentation of allergies:	7 (1.9) ‡	0
Information given:	15 (4.2)	0

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¥ 2 adverse drug events reported to the authorities (one case of paradoxical reaction to lorazepam and one case of levodopa withdrawal symptoms)

\* 7 due to incorrect prescription of low molecular weight heparin as 1 unit instead of 1 pre-filled syringe – a problem facilitated by the electronic prescribing process.

\*\* 2 due to incorrect prescription of apomorphine instead of morphine for analgesia – a problem facilitated by the electronic prescribing process per se.

† 15 instances where dosing exceeded maximum licensed dose, 5 instances where dose adjustment for intermittent haemodialysis was indicated, remainder due to impaired renal or hepatic function and in response to therapeutic drug monitoring results.

‡ 1 instance where a drug was administered despite the patient having a documented allergy, however no adverse drug event occurred.

**Figure 1** Area proportional Venn diagram of alerts generated by the clinical decision support software (CDSS) and by clinical pharmacologists (CP). Figures are absolute numbers.

