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Title page

The impact of an electronic alert to reduce the risk of co-prescription of low molecular weight heparins and direct oral anticoagulants

Authors

Alison Brown [a]

Gillian Cavell [a]

Nikita Dogra [b]

Cate Whittlesea [b]

a. Pharmacy Department. King's College Hospital, London, England
b. UCL School of Pharmacy, London, England

Key words

Medication Safety

Anticoagulants

Clinical Decision Support Systems

Electronic Prescribing

Alert overriding

Abstract

Objective

To use the electronic prescribing system to identify how prescribers have responded to the duplicate 'Anticoagulant Alert' and the extent to which the system has prevented unintentional prescription of Low Molecular Weight Heparins (LMWHs) to patients prescribed Direct Acting Anticoagulants (DOACs). To determine the clinical appropriateness of the actions taken by the prescriber following the alert override and the impact this has on patient safety.

Material and Methods

A retrospective service evaluation was conducted to determine the impact of a duplicate 'Anticoagulant Alert' on the prevention of prescription of LMWHs to patients already prescribed DOACs at a 950-bed acute teaching hospital in the UK. The number of alert overrides, actions taken by the prescriber following the alert override, and the clinical appropriateness of prescribers' actions over a 15-month period were evaluated.

Results

Of the 894 alerts that triggered over the study period 111 were in response to attempts to prescribe a LMWH to a patient prescribed a DOAC. The alert was overridden in 65 (58.6%) cases but accepted, preventing co-prescription of duplicate anticoagulants, in 46 (41.4%) cases. Overrides were appropriate and justified in 44/65 cases. In 6 cases duplicate anticoagulants were prescribed and administered but without patient harm.

Conclusion

The anticoagulant alert prevented duplicate anticoagulant prescribing for 46 patients reducing the risk of patient harm from duplicate-anticoagulation. The 58.6% of alerts that were overridden were appropriate and justified in the majority of cases. Where duplicate doses were administered, no harm was observed. The electronic alert has improved the safe use of anticoagulants within our organisation.

Introduction

Preventable prescribing errors with potential for patient harm occur across all healthcare systems [1].

Electronic prescribing (EP) systems are increasingly being implemented in UK hospitals [2,3,4]. EP systems aim to improve patient safety by reducing medication errors and adverse drug events, particularly prescribing errors [5,6]. EP systems may incorporate clinical decision support (CDS) to help guide the prescriber to make correct choices of drug, dose and frequency [7]. Electronic CDS has the potential to reduce the numbers of wrong dose errors, duplicate prescriptions, and prescriptions for interacting drugs [6,8]. Additionally, patient specific alerts can highlight known contraindications and side effects. However, the effectiveness of electronic alerts in preventing prescribing errors is unclear as their effectiveness depends on the prescriber's response [9]. Alerts may be appropriately actioned or overridden [2,8,9].

A review of publications describing the overrides of drug safety alerts in computerised prescribing systems identified an override rate of 49-96% for all alert types [7].

More recently, an observation study of medical and non-medical prescribing alert override rates in a UK hospital identified that 69% of 199 alerts were overridden [2]. Similarly, an override rate of 73.3% for patient allergy, drug-drug interaction and duplicate drug alerts was identified in a US hospital [10]

Anticoagulants

Anticoagulants, including vitamin K antagonists, direct thrombin inhibitors, factor Xa inhibitors and heparins, are high risk drugs widely prescribed and administered in primary and secondary care. Their modes of action, and the ways in which they are prescribed, varies.

Until relatively recently warfarin, a vitamin K antagonist, was the most frequently prescribed oral anticoagulant. Because of its mode of action and delayed onset of action, warfarin is prescribed and administered concurrently with a heparin until the patient is therapeutically anticoagulated as measured by the International Normalised Ratio (INR), when the heparin is discontinued. The onset of action of DOACs is faster negating the need for concurrent administration of a heparin. Duplicate administration of a DOAC and a LMWH can result in overanticoagulation and patient harm.

In 2014, NHS England issued a Patient Safety Alert to raise awareness of the potential for patient harm from the use of LMWHs when contraindicated [11]. This was in response to 75 medication incident reports received by the National Reporting and Learning System (NRLS) between January 2012 and March 2014, associated with the use of LMWHs when contraindicated including inappropriately co-prescribed anticoagulants.
DOACs have a relatively low bleeding risk and good overall safety profile. However, unintentional co-prescription of DOACs with other anticoagulants, including LMWHs, can result in active bleeding and serious patient harm. Co-prescription of anticoagulants can occur due to a lack of knowledge of their modes and onsets of action, or lack of recognition that the patient is prescribed an anticoagulant (e.g. due to unfamiliarity with drug names).

The aim of this service evaluation was to determine the extent to which a duplicate 'Anticoagulant Alert' within the EP system has prevented unintentional co-prescription of a LMWH to a patient already prescribed a DOAC. Our objectives were:

- To determine the number of alerts triggered by the attempted co-prescription of DOACs and LMWHs within the electronic prescribing system.
- To determine the number of duplicate prescriptions prevented
- To determine the number of alerts overridden
- To determine the clinical appropriateness of unprevented co-prescription of anticoagulants

Methods

Setting and study design

The study took place in a 950-bed acute teaching hospital in London, UK. The hospital uses an electronic prescribing and medicine administration (EPMA) system with integrated electronic clinical notes and laboratory results systems (Sunrise Allscripts Clinical Manager). The EP module includes a range of specific clinical alerts to highlight high-risk prescribing scenarios. The study was a retrospective service evaluation of the effectiveness of the duplicate anticoagulant alert (anticoagulant MLM). The project met the criteria for a service evaluation. Ethics approval was therefore not required.

The duplicate anticoagulant alert

Our organisation implemented an anticoagulant alert (MLM) within our EPMA system in May 2014. The alert warns the prescriber if they attempt to enter an electronic order for an anticoagulant for a patient already prescribed an anticoagulant. In response, the prescriber has the option to cancel one of the anticoagulant orders, or override the alert and continue

with the duplicate prescription. Since June 2017, the prescriber is unable to complete a duplicate prescription without actively acknowledging an override by explaining their decision in a free text box within the alert. The aim is that unintentional or unconsidered co-prescription of anticoagulants is prevented reducing the risk of patient harm.

The alert, which appears during the prescribing process between the prescription being drafted within the patient record and submitted as a confirmed prescription, provides a summary of the situation highlighting to the prescriber exactly why the alert has been generated. The alert is generated if a patient has an active prescription for a DOAC, including prescriptions where the first dose is scheduled to be administered in the future, and prescriptions where doses are temporarily being withheld, and a prescription for a LMWH is entered.

The alert is given a priority which, in the case of anticoagulant duplication, is 'High'. To acknowledge the alert and proceed the prescriber is required to provide an acknowledgement comment as free text. Until this is completed the prescriber's only option is to 'Go Back' and cancel the prescription for the second anticoagulant, avoiding the potential risks with duplication (Figure 1)

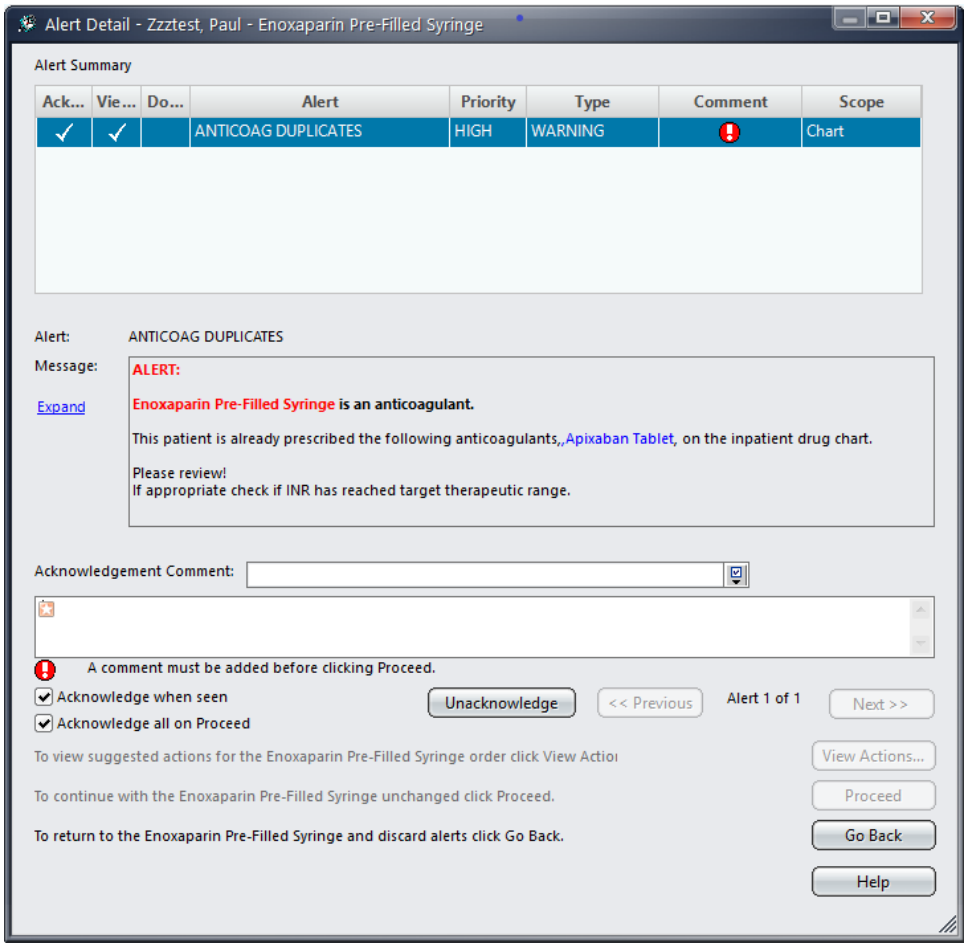

Figure 1 – Image of the Anticoagulant alert highlighting an attempt to prescribe enoxaparin to a patient already prescribed apixaban.

Data collection

Data were collected for anticoagulant alerts generated by the EP system between 26th June 2017 and 8th October 2018 for adult inpatients on wards other than Critical Care Units, where an alternative EPMA system is in use. We specifically focused on the prescription of LMWHs to patients currently prescribed DOACs (Table 1)

Table 1. LMWHs and DOACs investigated

DOAC (1st Drug Prescribed)		LMWH (2nd Drug Prescribed)
Apixaban or Edoxaban or Rivaroxaban or Dabigatran	and	Dalteparin or Enoxaparin

A report, presented as an Excel spreadsheet, was generated from the EPMA system. The report listed all occasions when the alert was triggered in response to an attempt to prescribe any anticoagulant to a patient with an active prescription for an anticoagulant. The report included the date and time the alert was generated, the patient's hospital number, the drug (dose, route and frequency) triggering the alert, anticoagulants discontinued within 15 minutes of the alert being generated and the prescribers' comments to acknowledge the alert override. We assumed that prescriptions cancelled within a 15-minute timeframe were cancelled in direct response to the anticoagulant alert generated to highlight the potential for duplicate anticoagulant prescribing and prompt the prescriber to reconsider their decision to prescribe a LMWH. From this report we identified all alerts generated when a prescriber attempted to prescribe a LMWH to a patient already prescribed a DOAC.

Details of incidents were collated on a piloted data collection tool. Each incident was reviewed to determine:
(1) the number of duplicate prescriptions prevented
(2) the documented reason if the alert was overridden
(3) whether a LMWH was prescribed to be given concurrently with a DOAC
(4) whether the patient was administered a LMWH within a time frame which would result in therapeutic duplication
(5) whether patient harm resulted from therapeutic duplication of the LMWH and DOAC.
Alert acceptance was defined as a change in prescription to stop either the LMWH or DOAC within 15mins of the alert being generated. The order was considered an alert override if the prescriber did not discontinue the prescription for the LMWH or DOAC within 15mins of the alert.

Clinical Appropriateness

A framework to assess the clinical appropriateness of anticoagulant alert overrides was developed by a senior anticoagulation and haematology pharmacist, and a senior medication safety pharmacist, piloted and modified to ensure all scenarios encountered could be assigned within the framework (Figure 2)**.**

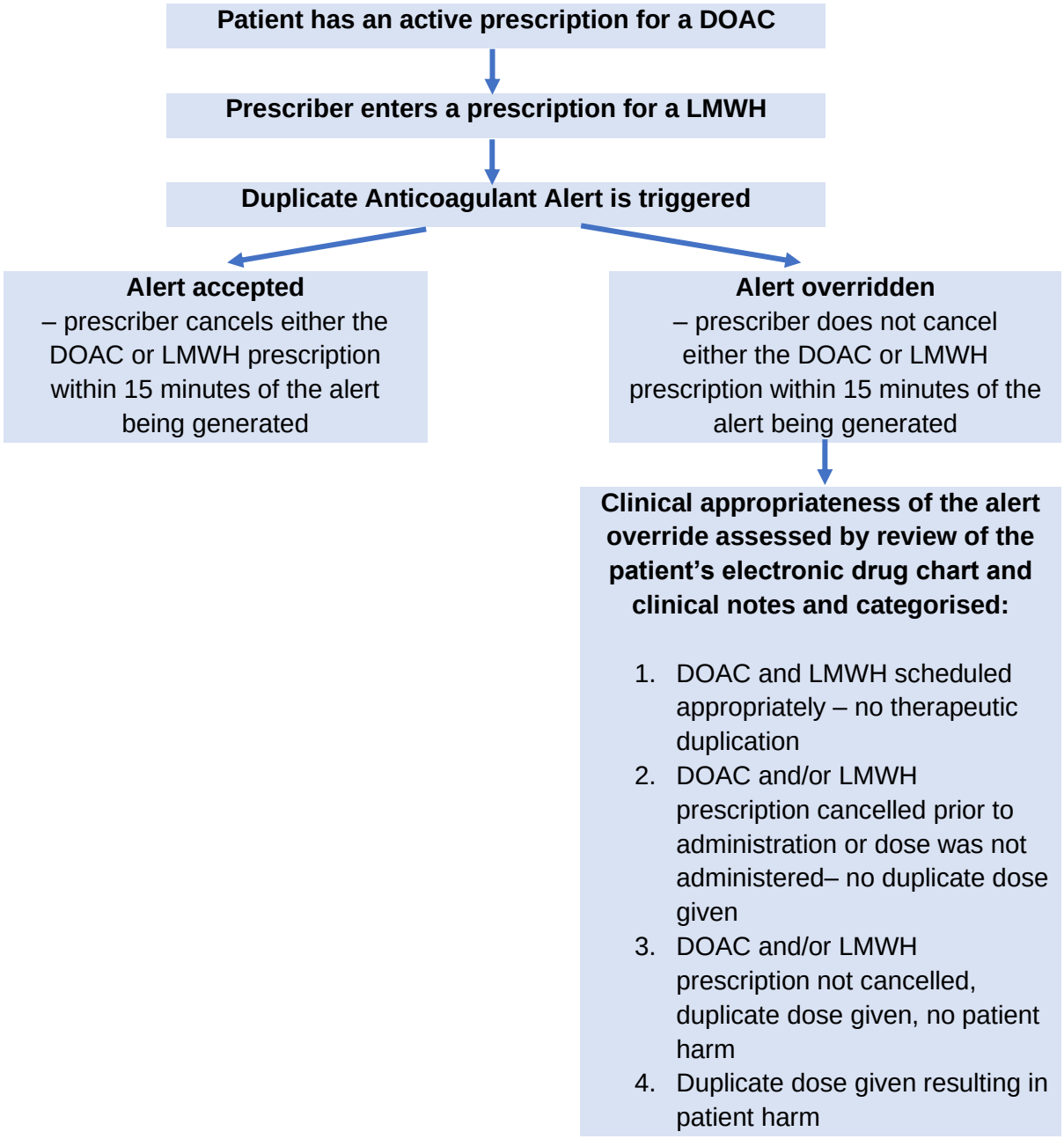

Figure 2

Process of investigation and review of Duplicate Anticoagulant alerts generated in response to prescription of a LMWH to a patient prescribed a DOAC.

In cases where the alert was overridden the patient's electronic patient record, including prescription and medicines administration record were reviewed retrospectively to determine whether duplicate anticoagulant therapy was administered.

Duplicate anticoagulant therapy was defined as a therapeutic overlap of a LMWH and DOAC where the interval between two doses administered was clinically contraindicated. (Table 2)

Table 2. Minimum interval (hrs) between administration of DOAC and LMWH to avoid therapeutic duplication according to their pharmacokinetic profiles

DOAC	**LMWH**	**Minimum time interval (hrs)**
Apixaban	Dalteparin /Enoxaparin	10hrs*
Dabigatran	Dalteparin / Enoxaparin	10hrs*
Rivaroxaban	Dalteparin / Enoxaparin	24hrs
Edoxaban	Dalteparin / Enoxaparin	24hrs

*Doses of dalteparin or enoxaparin should not be given within 12 hours of apixaban or dabigatran administration [11,12]. However due to the scheduling of doses within our EPMA system, designed to coincide with routine drug administration rounds on wards, the interval was modified for this study in conjunction with guidance provided by the senior anticoagulation pharmacist.
If a patient received doses of two anticoagulants within the minimum agreed dosing interval, the EPR was reviewed for signs of patient harm e.g. bruising or bleeding.

Alert overrides were considered appropriate if the prescriber scheduled the LMWH and DOAC administration times appropriately, avoiding therapeutic duplication, for example – if the LMWH enoxaparin was prescribed and scheduled to be administered more than 10 hours after the last dose of apixaban had been administered.
Alert overrides were not appropriate if: (1) the prescriber did not cancel the dose of the LMWH and/or DOAC within 15 minutes of the alert, even if the prescription was subsequently cancelled prior to administration, or the dose was not administered or (2) the prescriber did not cancel the prescription for the DOAC or LMWH prior to administration resulting in the patient receiving doses of two anticoagulants and therapeutic duplication.
The senior anticoagulant pharmacist (AB) determined appropriateness of alert overrides by reviewing prescriber comments within the alert and the patient's EPR.

Outcomes

The primary outcome was the number of duplicate prescriptions for DOACs and LMWHs prevented by the alert. The secondary outcomes were the numbers of alerts overridden, the appropriateness of the alert overrides and the impact of duplicate anticoagulant therapy on the patient.

Data analysis

Numbers of duplicate prescriptions prevented and alert overrides were determined. Clinical appropriateness of the overrides were determined.

Results

Between 26th June 2017 and 8th October 2018, 894 duplicate anticoagulant alerts triggered. Seven hundred and eighty-three alerts were triggered to highlight co-prescription of anticoagulants other than the prescription of a LMWH to a patient prescribed a DOAC. One hundred and eleven alerts followed an attempt to prescribe a LMWH to a patient already prescribed a DOAC (12.4% 111/894) and were included in this reivew.
Of the 111 alerts included, 65 (58.6% 65/111) were overridden (duplicate prescription completed) and 46 (41.4% 46/111) alerts were accepted (duplicate prescription avoided).

The 65 cases where the alert was overridden and the duplicate prescription was completed were evaluated for clinical appropriateness. In 44 of these cases (44/65, 67.7%) anticoagulant doses due after the alert override were scheduled appropriately without therapeutic duplication (Table 2). Fifteen duplicate prescriptions (15/65, 23.1%) were either cancelled prior to administration of the duplicate anticoagulant or the duplicate anticoagulant prescription was identified and no doses were administered concurrently.
DOACs and LMWHs were administered against six prescriptions (6/65, 9.2%) including 3 occasions within 2-3 hours of each other with potential for overanticoagulation. No patient harm was identified from review of the patient's EPR. (Table 3)

Table 3. Duplicate Anticoagulant Alert overrides and outcomes (n=65)

Prescription not completed	Overrides appropriate	Overrides Inappropriate		
No therapeutic duplication (n=90)		Potential for therapeutic duplication (n=21)		
	DOAC and LMWH scheduled appropriately	DOAC and LMWH co-prescribed. One prescription cancelled or dose not administered.	DOAC and LMWH co-prescribed. No prescription cancelled.	DOAC and LMWH co-prescribed. No prescription cancelled.
No duplicate dose prescribed	No duplicate dose administered	No duplicate dose administered	Duplicate dose administered	Duplicate dose administered Patient harm documented
46	44	15	6	0

Discussion

Duplicate prescriptions were prevented following the generation of the alert in 41.4% of cases. Although more than half of the alerts (58.6%) were overridden by the prescriber, subsequent prescriptions were scheduled appropriately to ensure continuity of therapy without therapeutic duplication in the majority of cases. Further interventions, such as highlighting of the issue by clinical pharmacists during prescription screening or by nurses administering medications, prevented administration of doses against duplicate prescriptions not prevented by the alert.

Appropriate alert overrides followed prescription of single *stat.* doses of LMWHs in situations where patients were nil by mouth or unable to swallow, non-availability of the prescribed DOAC on the ward at the time the DOAC dose was due, the withholding of the prescribed DOAC dose prior to a procedure, or prescription of a DOAC scheduled to be started the following day.

Duplicate doses were administered against six prescriptions, representing 5.4% (6/111) of alerts studied. Overall, therefore, after the duplicate anticoagulant alert had triggered,

anticoagulant prescriptions were prescribed and/or scheduled correctly for 81.1% of patients. Administration of a duplicate dose was prevented in a further 15 patients.

A review of the literature describing how prescribers respond to electronic alerts identified that alerts were overridden in 46.2%-96.2% of cases, across all types of alerts [14]. Override rates vary according to the situation the prescriber is being alerted to, the timing of the alert in relation to the prescriber's workflow and the characteristics of the alert itself. Few studies have quantified alert and alert override rates for therapeutic duplication. In UK hospitals, where electronic prescribing with clinical decision support is less well established than in the US, observation studies have identified override rates of 69% for alerts relating to antibiotic review and VTE risk assessment in an adult setting [2], and 89% of prescriptions relating to allergy, drug-drug interactions, drug duplication and therapeutic duplication in paediatrics [15]. 'Override' rates identified in our study (58.6%) compare favourably to these rates.

Our study focused on one specific alert type for a specific prescribing scenario: preventing clinically significant duplicate prescription of anticoagulants from different classes with potential for overanticoagulation and patient harm. One study, which reported alert acceptance and override rates according to alert category, identified acceptance and override rates of 14% and 86% respectively for therapeutic duplication, although the specific drugs involved are not referred to [16]. Therapeutic duplication override rates of 95% were identified in a study in a UK paediatric hospital [15]. It is possible that in our study, the lower override rate (58.6%) we observed was because of the specificity and clinical importance of the therapeutic scenario represented by the alert, although as a result of this specificity the numbers of observations were relatively low.

Reasons for alert overrides in EP systems have been described and include the design and frequency of alerts, clinical relevance, interruptions and timing in relation to workflow and prescriber characteristics [9,17,18].

Ideally alerts should be specific to the situation being highlighted and should change prescribers' behaviours. The design of alerts in CDS systems has been described as 'modal' and 'non-modal'. Non-modal alerts provide information to prescribers but no action is required before a prescription can be completed. Modal alerts provide information and prevent completion of the prescription until the information provided in a dialogue box has been acknowledged. Acknowledgement may be by simply clicking a tick box or it may require a free text entry to explain the rationale behind the prescriber's decision [19]. In both

cases the prescriber is prompted to reconsider their prescribing decision and either cancel the prescription or proceed.
A scenario-based study of junior doctor prescribing demonstrated that a modal e-prescribing alert reduced the number of prescribing errors to a greater extent than non-modal alerts. Prescribers shown modal alerts were 3.6 times less likely to make an error than those shown non-modal alert, and 11 times less likely than if no alert was shown [19].
The duplicate anticoagulant alert described in this study is modal in design.

Reasons for overrides were documented in text for 60 overrides. Overrides by entering spurious text, e.g. single characters, were identified for 5 prescriptions. This compares favourably to one study in which 0% of therapeutic duplication overrides included a reason for the override [15] and confirms the value of the mandatory documentation of alert acknowledgement with written justification for the alert override which is a feature of the anticoagulant alert in our hospital.

Of the 65 overridden alerts subsequent doses of both anticoagulants were scheduled appropriately and therapeutic duplication was avoided in 44 cases, highlighting conscious decision making by the prescriber at the point of completion of the prescription.

Whilst we categorised all situations where a prescription for a LMWH for a patient already prescribed a DOAC was completed as an override, the majority of these (44/65) were appropriate and justified within the acknowledgement section of the alert. The word ‘override’ in this situation may not be the correct terminology. ‘Override’ has negative connotations and suggests a refusal or decision to ignore advice. The aim of the alert is to prompt prescribers to reconsider and justify their decision in the light of potential therapeutic duplication. Subsequent acknowledgement of the alert and an appropriate prescribing decision is confirmation that the alert has achieved its aims. The 44 instances where appropriate action was taken should be categorised differently to inappropriate over-rides or override by-passes. The effectiveness of the alert in preventing therapeutic duplication can therefore be described as 81% (90/111).

A further 15 duplicate prescriptions were either cancelled prior to administration of a duplicate anticoagulant, or an intervention was made which resulted in a scheduled duplicate anticoagulant not being administered. This highlights the important role of checks and clinical decision making by front-line practitioners, including doctors, pharmacists and nurses, on a day-to-day basis as an additional feature of the medicines process to ensure patient safety with high risk drugs.

Despite these system approaches to promote safe anticoagulant use therapeutic duplication did occur and duplicate anticoagulant doses were administered to 6 patients. For these patients there was no evidence of patient harm on retrospective review of the electronic patient record.

One study conducted in a US inpatient setting demonstrated that presenting prescribers with a list of alert override reasons, customised according to the type of alert being generated, increases the appropriateness of override documentation compared to using a non-customised list. Customised lists for overriding alerts for 'Drug Allergy', 'Dose Range' and 'Drug-Drug Interaction' and non-customised lists all included an 'Other' option. However, the 'Other' option was rarely selected when prescribers were documenting reasons for overrides from the customised list of specific options relating to the alert their prescription had triggered [8]. The development of a customised list of reasons to override the duplicate anticoagulant alert in our EPMA system could be considered to reduce the rate of inappropriate overrides and further improve the safe prescribing of anticoagulants.

It was beyond the scope of this study to clinically evaluate the appropriateness of the prescribers' decisions to accept the alert and cancel the prescription for the LMWH they were attempting to prescribe. We assume that these decisions were appropriate and that the prescribers were prompted to identify that the patient they were prescribing for was already receiving an anticoagulant where previously this was either not known to them or had been overlooked, and the LMWH was not indicated. In these cases potentially harmful overanticoagulation was averted for 46 patients.

Limitations

Our study does have limitations. We have evaluated a specific alert which highlights a known high risk prescribing scenario in a single large teaching hospital. The alert has been designed and implemented in-house. The results may not be generalisable to other secondary care settings using different EP systems.

The alert is generated where a prescription for a second anticoagulant is started for a patient with an existing active prescription for another anticoagulant. If prescriptions for two anticoagulants are entered and confirmed at the same time the anticoagulant alert is not generated, and duplicate prescribing could occur in the same way as without the alert, ie. dependent on the prescriber's knowledge and clinical decision making skills at the time. If such errors occur these should be identified and corrected by those processes which prevented the administration of duplicate anticoagulant doses where the alert was inappropriately overridden.

We did not conduct interviews with prescribers to understand their views on the advantages and disadvantages of the alerts. We do not know how prescribers perceive the alerts when they intentionally and appropriately override them or whether they contributed to the prescriber's decision making process at the point of prescribing, particularly the planning and scheduling of intervals between LMWH and DOAC doses.

Conclusion

We describe the beneficial impact of a highly specific, highly clinically relevant alert with high clinical value in the prevention of a nationally agreed risk to patient safety.

The study confirms that there is risk of duplicate anticoagulant prescribing within electronic prescribing systems and that the presence of a modal electronic alert to highlight this potential to prescribers prevents completion of an unintended duplicate prescription.

There is a need to be able to override the alert, enabling appropriate scheduling of transfer of therapy between anticoagulant agents where appropriate. The reasons for inappropriate overrides need to be understood to inform the development of further mechanisms within the prescribing system to highlight unresolved risks.

In the future, a list of standardised, justified reasons to override prescriptions for LMWHs for patients already prescribed a DOAC, based on the reasons observed in this study, could be formalised and included as part of the modal alert within our electronic prescribing system.

Contributors

GC and AB conceived this study and devised the data collection and interpretation methods. ND extracted and analysed the data. AB provided expert clinical supervision. CW provided academic guidance and support. All authors have contributed to the drafting of the manuscript and have seen and approved the final version.

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Declarations of interest

None

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Summary Table

What was already known on this topic

- Alerts generated within clinical decision support systems are frequently overridden.
- Override decisions may not always be clinically justified and may be associated with patient harm
- Override rates may be high where frequent alerts are generated for non-clinically important medication-related problems.

What this study adds to our knowledge

- Electronic prescribing alone does not prevent attempts to prescribe therapeutic duplicates of high risk drugs
- An electronic alert generated to raise awareness of high risk duplicate anticoagulant prescribing prevented completion of prescriptions of LMWHs where patients were already receiving DOACs
- Overrides of an alert to highlight a specific high risk prescribing scenario were appropriate in the majority of cases

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Examples

1. Actions appropriate

1st anticoagulant (DOAC)	Edoxaban
2nd anticoagulant (LMWH)	Enoxaparin 80mg subcutaneously once daily
Override justification	Patient on treatment dose Clexane to anticoagulate in AF. Will start edoxaban from tomorrow. STAT dose of required as per pharmacy
Prescribing outcome	Scheduled appropriately. No duplicate anticoagulation
Patient Outcome	No patient harm. *Omission of anticoagulation between discontinuation of the enoxaparin prescription and the first dose of prescribed edoxaban was prevented.*

2. Actions inappropriate – duplicate anticoagulant prescribed but cancelled prior to administration

1st anticoagulant (DOAC)	Rivaroxaban
2nd anticoagulant (LMWH)	Enoxaparin 100mg subcutaneously once daily
Override justification	One dose of enoxaparin post initial dose of rivaroxaban
Prescribing outcome	Enoxaparin prescription cancelled as LMWH not indicated. No duplicate anticoagulant therapy administered
Patient Outcome	No patient harm. *Duplication prevented. Low molecular weight heparin is not indicated during the initiation of rivaroxaban.*

3. Actions inappropriate – duplicate not cancelled

1st anticoagulant (DOAC)	Apixaban
2nd anticoagulant (LMWH)	Enoxaparin 120mg subcutaneously STAT
Override justification	, (Only a comma typed into justification text box)
Prescribing outcome	Two anticoagulant doses administered 2 hours apart. Apixaban administered at 6pm Enoxaparin administered at 8pm
Patient Outcome	No patient harm.

	Duplicate anticoagulant doses were administered but there was no evidence of patient harm on review of clinical notes.