# 6 Medication-related adverse events during hospitalisation: a retrospective record review study in the Netherlands

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## ABSTRACT

**Purpose**

Medication-related adverse events (MRAEs) are an important priority for patient safety. Results from Dutch AE studies showed that – despite various improvement initiatives - the incidence of preventable MRAEs did not decline. The aim of this study is to describe the characteristics of MRAEs during hospitalizations, using national patient data from records of patients admitted to Dutch hospitals in 2008 and 2011/2012.

**Methods**

Trained nurses and physicians reviewed the randomly selected records of 8,071 patients admitted to one of 20 hospitals in 2008 or 2011/2012, during a two-stage review process. Patient and admission characteristics were collected. After identification of a MRAE, physicians determined their potential preventability, drug type, related prescribing factors, and potential consequences.

**Results**

The physicians identified 928 AEs in 857 admissions, of which 218 (15.2%) were medication-related. They judged 55 (18.4%) of these as preventable. Preventability of MRAEs was high in anticoagulant treatment (42.5%). Haematoma (39.0%) and intra-cerebral haemorrhage (25.5%) were common types of anticoagulant-related AEs. Anticoagulant-related AEs were often related to dosage factors (46.9%) and often resulted in an intervention (80.2%), of which 40.2% was judged as preventable.

**Conclusions**

This study provided detailed information on MRAEs during hospital admissions in the Netherlands. A substantial proportion of AEs was medication-related (15.2%), of which 18.4% was judged to be preventable. As preventability in MRAEs was especially high in anticoagulant treatment (42.5%), those medications are a threat to patient safety. Future research and new safety programs should focus on prevention of AEs related to this medication group.

## INTRODUCTION

Patient safety continues to be a major challenge and a high priority in hospitals worldwide. Healthcare-related adverse events (AEs) are common and can be defined as unintended injuries that result in temporary or permanent disability, death, or prolonged hospitalization, caused by healthcare management rather than patients' underlying disease.[1-4]

Medication-related adverse events (MRAEs) occur as a consequence of medication errors or adverse drug reactions and are one of the most common types of healthcare-related AEs.[4-6] In the Netherlands, the first national AE study took place in 2004, in which the extent and nature of AEs and their preventability was evaluated in 21 Dutch hospitals.[7] Results from this study indicated that MRAEs comprise around 15% of all AEs, with almost 30% of them being preventable.[8-10] In addition, MRAEs were associated with considerable longer hospital stays and higher healthcare costs[9], imposing a high burden on patients, caregivers, and the healthcare system. These results were in line with findings from other AE studies[11-14] and also confirmed in systematic reviews and meta-analyses.[5,6]

Over the last years, the prevention of AEs has become an important priority for patient safety in the Netherlands. In 2008, the national program "Prevent Harm, Work Safely" was launched. The overall goal of this safety program was to reduce the number of preventable AEs in Dutch hospitals by 50% through the implementation of a Safety Management System in all hospitals and through improvement modules on 10 clinical themes, including medication processes such as medication reconciliation and high-risk medication.[15]

To keep track of changes in patient safety on a national level, a second and third measurement of the national AE study was conducted in 2008 and 2011/2012. In recent publications, general trends in AEs over time and main categories of preventable AEs have been assessed.[16,17] These studies showed that – despite various safety improvement initiatives such as the safety program - the incidence of preventable MRAEs did not decline over the years. Hence, the aim of the current study is to describe the characteristics of (potential preventable) MRAEs during hospitalizations, using national patient data from records of patients admitted to Dutch hospitals in 2008 and 2011/2012. This information could contribute to the design of future medication safety initiatives.



## METHODS

### Study design and population

We used the data from two of our previous AE studies[16, 17], in which patient records of hospital admissions in 2008 and 2011/2012 were assessed. Review of these admissions records took place in 2009/2010 and 2012/2013, respectively. In both studies, the same 20 hospitals of the in total 93 Dutch hospitals were included. The hospital samples were

both stratified by hospital type: university, tertiary teaching, and general hospitals. Within these strata, hospitals were randomly selected and a proper representation of urban and rural settings in the sample was verified. Per hospital, for each measurement year about 200 patient admissions were randomly selected: half of these consisted of admissions of patients discharged alive from the hospital after a stay of at least 24 hours, the other half consisted of inpatient deaths regardless of the length of hospital stay. In both studies, only one admission per patient was included. As was also common in other AE studies, records from patients admitted to the psychiatry or obstetrics department, and records of children younger than one year of age were excluded. Detailed information on the design of the studies was published previously.[7,17] Both study protocols were approved a priori by the medical ethics committee of the VU medical center, Amsterdam, the Netherlands.

**Patient record review**

Trained external nurses and external physicians reviewed the nursing and medical records of included admissions. The method of determining AEs, which was comparable to those of other international studies[18, 19] and based on the Canadian AE study[1], comprised two phases: first, a nurse screened the records by using triggers indicating potential AEs. In the second phase, a physician further reviewed admissions positive for at least one trigger. These physicians belonged to the specialties surgery, internal medicine, or neurology, and AE reviews were assigned based on their specialty. If needed, they could consult with specialties other than their own. Patient records of the index-hospital admission were reviewed, as were the patient records of patient admissions a year before and after the index-admission. Presence of AEs was determined by the physicians, based on a standardized procedure.

An AE was defined by three criteria:

1. An unintended physical or mental injury;
2. The injury resulted in prolongation of hospital stay, temporary or permanent disability or death;
3. The injury was caused by healthcare management rather than the patient's underlying disease.

To determine whether the injury was caused by health care management or the disease process a six-point Likert scale was used:

1. (Virtually) no evidence for management causation;
2. Slight to modest evidence of management causation;
3. Management causation not likely (<50/50, but borderline);
4. Management causation more likely (>50/50, but borderline);

5. Moderate to strong evidence of management causation;
6. (Virtually) certain evidence of management causation.

The cause of an AE was counted as caused by healthcare if the score was 4–6.

If an AE was identified, questions about the clinical process during which the AE occurred were asked. Physicians were able to choose from the following clinical processes: diagnostics, surgery, drug, medical procedure, other clinical management, discharge, and other. All AEs in which a drug was chosen to be the main clinical process during which the AE had occurred, were marked as medication-related AEs (MRAEs).

A MRAE was considered to be preventable when the care given fell below the current level of expected performance for practitioners or systems. In accordance with our previous studies, preventability was assessed on the following six-point Likert scale[7,9,16]:

1. Almost no evidence for preventability;
2. Slight to modest evidence for preventability;
3. Modest preventability (<50/50, but borderline);
4. Modest to strong evidence of preventability (>50/50, but borderline);
5. Strong evidence of preventability;
6. Almost certain evidence of preventability.

A score of 4-6 indicated that the reviewer regarded the MRAE as having a greater than 50% chance of being potentially preventable.

To add more structure to the implicit review process, the causation and preventability scores were each preceded by 13 questions to facilitate the final reviewers judgment. In addition, physicians were trained in assessing the causation and preventability prior to reviewing patient admissions, and frequent reflection meetings were organised to uphold a high quality of the review process.

After identification of a MRAE, the physician reviewers determined among others drug type, related prescribing factors, and potential consequences associated with the MRAE.[1] As for the timing of MRAEs, MRAEs that occurred during the patient's index-hospital admission and were detected during either the index-admission (n=147) or subsequent admissions over the following 12-month period (n=13) were counted. Also counted were MRAEs related to patient admissions in the same hospital within the 12 months preceding the index-admission but which were not detected until the index-admission (n=58). Exceptions were made for MRAEs related to hair loss due to cytostatic treatment and neutropenia without fever, as these were common side effects of cancer chemotherapy and therefore not counted as AEs in this study.

## STATISTICAL METHODS

### Weighting procedure

In accordance with our previous studies, during analyses all proportions were corrected for the oversampling of deceased patients and university hospitals. [8,9,16] In our sample, 50% of the patients were inpatient deaths, whereas in reality this is 3%. In the results we weighted our 50% back to the actual 3%. We followed the same procedure for the distribution of types of hospitals: in our sample 20% of the hospitals were university hospitals, whereas in reality this is 10%. Therefore, in the results we weighted our 20% back to the actual 10%. After weighting for this sample frame, the total study sample — that is, both discharged and deceased patients — was representative of the total Dutch population of hospitalised patients. Detailed information on the weighting procedure was published previously.[7] As a consequence of the weighting process, proportions are not directly comparable to the accompanying crude numbers.

### Conducted analyses

Summary and descriptive statistics for patient and admission characteristics were calculated for all reviewed patients, and for all patients who were assessed to have experienced an MRAE. SPSS complex samples were used to calculate weighted rates of patients who had experienced at least one MRAE during the admission, and their preventability (referred to as “MRAEs – admission level” in the accompanying Tables). As it was possible for patients to experience more than one MRAE during a hospital admission, we also assessed the total number of MRAEs and preventable MRAEs (referred to as “MRAEs – adverse event level” in the accompanying Tables). We further analysed medication type. For the drug type most frequently related to a preventable MRAE, we further analysed possible related prescribing factors as well as consequences. All statistical analyses were performed in SPSS 20.0 and STATA 13.

## RESULTS

**Table 1:** Patient and hospital characteristics of the study sample

| | Total population | | |
|---|---|---|---|
| | **N** | **unweighted%** | **weighted% †** |
| Inpatient admissions | 8,071 | | |
| Hospital admission year | | | |
| - 2008 | 4,023 | 49.9 | 49.8 |
| - 2011/2012 | 4,048 | 50.1 | 50.2 |
| Age in years, mean (median/sd) | | | 60.2 (64.0/20.8) |
| Age categories | | | |
| - 1-18 | 286 | 3.5 | 5.8 |
| - 19-40 | 533 | 6.6 | 10.8 |
| - 41-65 | 2,365 | 29.3 | 37.6 |
| - 66-79 | 2,665 | 33.0 | 29.0 |
| - 80 and older | 2,222 | 27.5 | 16.8 |
| Discharge status | | | |
| - Alive | 4,039 | 50.0 | 95.3 |
| - Inpatient death | 4,032 | 50.0 | 4.7 |
| Gender | | | |
| - Male | 4,155 | 51.5 | 50.0 |
| - Female | 3,916 | 48.5 | 50.0 |
| Patient admissions | | | |
| - University hospital | 1,593 | 19.7 | 13.9 |
| - Tertiary teaching | 2,843 | 35.2 | 44.1 |
| - General | 3,635 | 45.0 | 41.9 |
| Length of hospital stay, days (median/sd) | | | 6.5 (4.0/12.1) |
| Urgent admission | | | |
| - No | 2,496 | 30.9 | 45.6 |
| - Yes | 5,575 | 69.1 | 54.4 |
| Department to which patient was admitted | | | |
| - Cardiology | 814 | 10.1 | 11.1 |
| - Surgery | 1,410 | 17.5 | 21.7 |
| - Geriatrics | 163 | 2.0 | 1.1 |
| - Coronary Care Unit | 286 | 3.5 | 3.3 |
| - Intensive Care | 543 | 6.7 | 1.9 |
| - Paediatrics | 172 | 21.3 | 3.4 |
| - Internal medicine | 1,720 | 2.1 | 16.2 |
| - Orthopaedics | 510 | 2.2 | 11.1 |
| - Neurology | 695 | 9.9 | 7.2 |
| - Pulmonology | 802 | 8.6 | 6.5 |
| - Ear, nose and throat | 178 | 6.3 | 3.7 |
| - Urology | 251 | 3.1 | 5.0† |
| - Other | 527 | 6.5 | 7.8† |

† Weighted for overrepresentation of deceased patients and hospital type

**Table 2:** Patient and hospital characteristics of medication-related adverse events

| | MRAEs (n=204)* n (column %, weighted) † | Preventable MRAEs (n=53)* n (row %, weighted) † ‡ |
|---|---|---|
| Age categories | | |
| - 1-18 | 5 (4.2) | 0 (0.0) |
| - 19-40 | 9 (4.0) | 1 (22.6) |
| - 41-65 | 47 (25.1) | 7 (17.4) |
| - 66-79 | 88 (41.3) | 24 (17.9) |
| - 80 and older | 55 (25.5) | 21 (22.7) |
| Discharge status | | |
| - Alive | 67 (90.9) | 11 (17.2) |
| - Inpatient death | 137 (9.1) | 42 (30.7) |
| Gender | | |
| - Male | 104 (46.8) | 26 (18.1) |
| - Female | 100 (53.2) | 27 (18.7) |
| Patient admissions | | |
| - University hospital | 41 (14.5) | 8 (14.5) |
| - Tertiary teaching | 57 (36.9) | 13 (21.2) |
| - General | 106 (48.7) | 32 (17.5) |
| Urgent admission | | |
| - No | 44 (26.1) | 8 (14.0) |
| - Yes | 160 (73.9) | 45 (20.0) |
| Department to which patient was admitted | | |
| - Cardiology | 19 (8.5) | 9 (7.2) |
| - Surgery | 11 (2.2) | 3 (9.0) |
| - Geriatrics | 5 (1.4) | 2 (9.6) |
| - Coronary Care Unit | 5 (3.1) | 3 (7.6) |
| - Intensive Care | 15 (5.8) | 4 (29.2) |
| - Internal medicine | 75 (33.4) | 13 (6.9) |
| - Paediatrics | 2 (2.0) | - |
| - Ear, Nose, Throat | 2 (1.1) | - |
| - Pulmonology | 28 (15.1) | 8 (25.9) |
| - Neurology | 15 (6.9) | 4 (34.1) |
| - Orthopaedics | 8 (5.5) | 2 (29.0) |
| - Urology | 6 (7.1) | 3 (50.1) |
| - Other | 13 (7.8) | 2 (23.1) |

* MRAE's – admission level

† Weighted for overrepresentation of deceased patients and hospital type

‡ No preventability was shown if numbers of MRAEs were smaller than 5

MRAE=medication-related adverse event

**Table 3:** Drug type of medication-related adverse events

| | MRAEs (n=218)* n (column %, weighted) † | Preventable MRAEs (n=55)* n (row %, weighted) † ‡ |
|---|---|---|
| Antiasthmatic | 1 (0.0) | - |
| Antibiotic | 22 (13.6) | 3 (11.2) |
| Anticoagulant | 43 (17.1) | 17 (42.5) |
| Antidepressant | 1 (1.8) | - |
| Antiepileptic | 2 (1.1) | - |
| Antihypertensive | 4 (2.9) | - |
| Antiplatelet | 7 (6.3) | 1 (1.6) |
| Antipsychotic | 2 (0.1) | - |
| Chemotherapy | 58 (22.0) | 3 (0.7) |
| Cardiovascular | 11 (6.9) | 5 (4.4) |
| Diuretic | 5 (3.1) | 0 (0.0) |
| Insulin/ oral diabetic | 12 (5.0) | 7 (34.8) |
| Potassium | 1 (0.0) | - |
| Morphine/opioid | 9 (3.0) | 2 (5.3) |
| NSAID | 1 (0.0) | - |
| Sedative | 9 (1.4) | 4 (15.5) |
| Other | 30 (15.5) | 7 (27.8) |
| Total | 218(100) | 55 (18.4) |

* MRAEs - adverse event level
† Weighted for overrepresentation of deceased patients and hospital type
‡ No preventability is shown if numbers of MRAEs were smaller than 5
MRAE=medication-related adverse event; NSAID= Non-steroidal anti-inflammatory drug



In total, records of 8,071 patient admissions were included in the study, of which 4,023 of 2008 and 4,048 of 2011/2012. Patient and hospital characteristics of the study sample are described in Table 1.

**Medication-related adverse events**

The hospital admissions were assessed for the presence of AEs and MRAEs, and their preventability. In the second stage, the physicians identified 928 AEs in 857 admissions, of which 218 (15.2%) in 204 admissions were medication-related. They judged 55 (18.4%) of these MRAEs in 53 admissions as preventable. MRAEs often occurred in patients aged 66-79 years. The preventability of MRAEs was high in patients who died in-hospital, urgently admitted patients, patients admitted to a urology or neurology department, and patients admitted to tertiary teaching hospitals (Table 2).

Table 3 shows that the majority of MRAEs were adverse drug reactions related to cancer chemotherapy (n=58, 22.0%), anticoagulant treatment (n=43, 17.1%), and antibiotics (n=22, 13.6%). Preventability in MRAEs was especially high in anticoagulant treatment (n=17, 42.5%) and insulin/oral diabetics (n=7, 34.8%). MRAEs related to chemotherapy were seldom considered preventable: 0.7% (n=3) of all chemotherapy-related MRAEs.

**Anticoagulant-related adverse events**

As MRAEs related to anticoagulant treatment were common and often preventable, we further analyzed this type of medication. Although preventability in insulin/oral diabetic-related MRAEs was also found to be high, they only comprised 5.0% (n=12) of total MRAEs (Table 3). Therefore, due to power constraints we did not perform further analyses on this medication type.

Most anticoagulant-related AEs were related to coumarins (n=24, 55.8%) and heparins (n=13, 30.2%) (results not shown in Table). Although numbers were small, most of the anticoagulant-related AEs were among patients of 66 years or older and in patients urgently admitted. The preventability of anticoagulant-related AEs was high in urgently admitted patients and patients admitted to tertiary teaching hospitals. (Table 4).

Haematoma (n=5, 39.0%), intra-cerebral haemorrhage (n=8, 25.5%), and gastrointestinal bleeding (n=9, 12.6%) were common types of anticoagulant-related AEs. Anticoagulant-related AEs were often related to dosage factors (n=14, 46.9%), of which 66.2% (n=7) was judged as preventable. Although therapeutic factors were less often related to anticoagulant-related AEs, their preventability was high (n=4, 90.6%). Anticoagulant-related AEs often resulted in an intervention (n=26, 80.2%), of which 40.2% (n=10) was judged as preventable. In 18.9% (n=2), anticoagulant-related AEs resulted in readmission (Table 5).

**Table 4:** Patient and hospital characteristics of anticoagulant-related adverse events

| | **Anticoagulant-related AE (n=41)* n (column %, weighted) †** | **Preventable anticoagulant-related AE (n=17)* n (row %, weighted) † ‡** |
|---|---|---|
| Age categories | | |
| - 1-18 | 0 (0.0) | - |
| - 19-40 | 1 (0.3) | - |
| - 41-65 | 5 (14.0) | 2 (60.8) |
| - 66-79 | 17 (33.0) | 7 (39.0) |
| - 80 and older | 18 (52.7) | 8 (40.6) |
| Gender | | |
| - Male | 22 (38.6) | 10 (57.0) |
| - Female | 19 (61.4) | 7 (33.8) |
| Discharge status | | |
| - Alive | 11 (89.3) | 4 (42.6) |
| - Inpatient death | 30 (10.7) | 13 (44.1) |
| Urgent admission | | |
| - No | 10 (15.9) | 3 (6.5) |
| - Yes | 31 (84.1) | 14 (49.6) |
| Patient admissions | | |
| - University hospital | 6 (10.7) | 0 (0.0) |
| - Tertiary teaching | 9 (51.2) | 4 (59.7) |
| - General | 26 (38.2) | 13 (32.1) |
| Department to which patient was admitted | | |
| - Cardiology | 6 (2.1) | 4 (65.8) |
| - Surgery | 4 (1.4) | - |
| - Geriatrics | 1 (0.4) | - |
| - Coronary Care Unit | 3 (16.1) | - |
| - Intensive Care | 1 (0.3) | - |
| - Internal medicine | 13 (25.9) | 5 (37.0) |
| - Paediatrics | 0 (0.0) | - |
| - Ear, Nose, Throat | 1 (0.3) | - |
| - Pulmonology | 3 (19.6) | - |
| - Neurology | 3 (1.2) | - |
| - Orthopaedics | 2 (0.7) | - |
| - Urology | 4 (32.1) | - |
| - Other | 0 (0.0) | - |

* MRAEs – admission level

† Weighted for overrepresentation of deceased patients and hospital type

‡ No preventability was shown if numbers of MRAEs were smaller than 5

AE= adverse event

**Table 5:** Factors and consequences of anticoagulant-related adverse events

| | **Anticoagulant-related AEs (n= 43)* n (column%, weighted) †** | **Preventable anticoagulant-related AEs (n= 17)* n (row %, weighted) † ‡** |
|---|---|---|
| Prescribing factors | | |
| - Administrative/procedure | 0 (0.0) | - |
| - Dosage | 14 (46.9) | 7 (66.3) |
| - Therapeutic | 6 (10.1) | 4 (90.6) |
| - Delivery | 0 (0.0) | - |
| - Administering | 0 (0.0) | - |
| - Other | 22 (20.0) | 11 (20.0) |
| Type of adverse event | | |
| - Shock | 1 (0.4) | - |
| - Heart failure | 1 (0.4) | - |
| - Pulmonary embolism | 2 (0.7) | - |
| - Renal insufficiency | 1 (6.8) | - |
| - Other renal failure | 1 (0.4) | - |
| - Intra-cerebral haemorrhage | 8 (25.5) | 3 (38.6) |
| - Thromboembolism | 1 (0.4) | - |
| - Haematoma | 5 (39.0) | 1 (31.0) |
| - Gastro-intestinal bleeding | 9 (12.6) | 4 (14.2) |
| - Cerebrovascular accident | 7 (3.0) | 0 (0.0) |
| - Catheter-related blood infection | 1 (0.3) | - |
| - Pulmonary infection | 1 (0.4) | - |
| - Postsurgical haemorrhage | 1 (0.4) | - |
| - Other | 1 (9.9) | - |
| Consequences § | | |
| - Intervention | 26 (80.2) | 10 (40.3) |
| - Impairment at moment of discharge | 1 (4.9) | - |
| - Extended length of stay | 4 (5.9) | - |
| - Readmission | 2 (18.9) | - |
| - Death | 18 (12.1) | 4 (11.3) |
| - Outpatient visit | 1 (10.8) | - |
| - Other | 2 (11.1) | - |

* MRAEs - adverse event level

† Weighted for overrepresentation of deceased patients and hospital type

‡ No preventability was shown if numbers of MRAEs were smaller than 5

§ More than one answer was possible. Therefore the total percentage sums up to more than 100

AE=adverse event

## DISCUSSION

In the current study, a substantial proportion of all healthcare-related AEs were medication-related (n=218, 15.2%). Of all 218 identified MRAEs, 55 (18.4%) were deemed to be preventable. Preventability of MRAEs was especially high in anticoagulant treatment (n=17, 42.5%). Haematoma (n=5, 39.0%) and intra-cerebral haemorrhage (n=8, 25.5%) were common types of anticoagulant-related AEs. Anticoagulant-related AEs were often related to dosage factors (n=14, 46.9%) and they often resulted in an intervention (n=26, 80.2%), of which 40.2% (n=10) was judged as preventable.

The results of this study corroborate the findings of previous studies, demonstrating that MRAEs were responsible for 12-37% of all AEs [2,4,9,11-14,17], which was also confirmed in systematic reviews and meta-analyses [5,6,20-22]. In these earlier studies, 30-50% of MRAEs was judged to be preventable, whereas in our study this number was considerably lower (18.4%). The finding that anticoagulant treatment accounted for a substantial proportion of preventable MRAEs was also in line with previous research.[11,13,23-25] As compared to results of the first measurement of the national AE study [9], no visible differences were found in the occurrence of anticoagulant-related MRAEs (18.0% in 2004 vs. 17.1% in this study, respectively) but their preventability slightly decreased from 54.0% in 2004 to 42.5% in our study.

Over the past decades, several interventions have been developed to reduce MRAEs and improve medication safety. In the Netherlands, the national program “Prevent Harm, Work Safely” was launched in 2008 and aimed to reduce the number of preventable AEs in Dutch hospitals by 50%. The program included two improvement modules on medication processes: reducing events that involve high-risk medication and reducing medication errors on admission and discharge.[15]. Baines et al. (2015) concluded that during the safety program no visible improvements in medication safety were established.[16] MRAEs are therefore still a threat to patient safety, and our results indicate that especially on certain high-risk medications, such as anticoagulant treatment, many preventable MRAEs still occur.

Other intervention methods and tools to prevent MRAEs have also been proposed. The most commonly implemented interventions are “computerized physician order entry systems (CPOEs)”, a form of patient management software allowing health care providers to electronically enter patient treatment instructions.[26,27] While CPOE systems are well implemented in most hospitals, a considerable amount of MRAEs was still reported and CPOE systems introduced new types MRAEs as well. [28, 29]. Clinical pharmacy interventions have also been investigated, with a hospital pharmacist interacting and advising the healthcare team.[30,31] Though these interventions contributed to the reduction of (preventable) MRAEs, most of them are costly and time consuming and difficult to provide continuously.[31] Recent research showed that evidence-based drug rules seem promising in preventing MRAEs, but their clinical efficacy is yet to be tested.[32]

Although in the current study anticoagulant-related AEs were the most common types of preventable MRAEs, none of the aforementioned interventions specifically targeted this medication group. Anticoagulant care is considered complex and potential risks of bleeding and thrombosis should always be taken into account. In addition, various healthcare professionals are involved in the treatment of patients, including medical specialists, pharmacists, general practitioners, dentists, and the anticoagulation services. These different healthcare providers need to collectively coordinate anticoagulant care. It was previously argued that suboptimal communication and coordination within this "chain" of healthcare providers is common and associated with adverse patient outcomes.[33] In the Netherlands, several guidelines have been developed addressing these integrated care problems, but one of our recent studies showed that adherence to these guidelines is still trivial.[34] Future research is needed to further examine the complex nature of MRAEs, hereby focussing on hospital-related factors as well as suboptimal integrated care. This knowledge could contribute to the design of future medication safety initiatives, which should especially target the areas with the highest risk of preventable MRAEs, such as anticoagulant treatment.

**Strengths and limitations**

One of the strengths of the current study is that we reviewed 8,071 patient records over two periods in time based on an international, standardised assessment method of patient admissions. Although assessing patient records on AEs is a difficult process, retrospective chart studies currently offer the best method available to assess the incidence and is considered as the "golden standard".[35] This more implicit method also allows us to focus on a broad range of MRAEs instead of an explicit range of MRAEs and gives a good insight in the general state of medication safety in hospitals.

Retrospective review studies also have disadvantages. The incidence of preventable MRAEs may be underestimated because not all information is available or written down in the patient records.[36] However, hindsight bias may have been overestimated the incidence of MRAEs.[37] Knowing the outcome of an admission may have influenced the judgement of the causality and preventability of MRAEs. We found that anticoagulants still account for a large proportion of the total amount of preventable MRAEs. Unfortunately, we did not register the use of anticoagulants and other medications for *all* included patients. Therefore, a numerator was not available and the incidence of anticoagulant-related AEs could not be calculated.

## CONCLUSION

The current study provided detailed information on MRAEs during hospital admissions in the Netherlands. A substantial proportion of AEs was medication-related (n=218, 15.2%), of which 18.4% (n=55) was judged to be preventable. As preventability in MRAEs was especially high in anticoagulant treatment (n=17, 42.5%), those medications are a threat to patient safety. It is therefore recommended that future research and new safety programs focus on the prevention of AEs related to this high-risk medication group.

## REFERENCES


1. Baker GR, Norton PG, Flintoft V, et al. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. Canadian Medical Association Journal 2004; 170: 1678-1686.
2. Davis P, Lay-Yee R, Briant R, et al. Adverse events in New Zealand public hospitals I: occurrence and impact. New Zeal Med J 2002; 115: U271.
3. Wilson RM, Runciman WB, Gibberd RW, et al. The Quality in Australian Health Care Study. Med J Australia 1995; 163: 458-471.
4. Bates DW, Cullen DJ, Laird N et al. Incidence of adverse drug events and potential adverse drug events: Implications for prevention. Journal of the American Medical Association 1995; 274: 29-34.
5. Hakkarainen KM, Hedna K, Petzold M and Hägg S. Percentage of patients with preventable adverse drug reactions and preventability of adverse drug reactions – a meta-analysis. PLoS One 2012; 7: e33236.
6. de Vries EN, Ramrattan MA, Smorenburg SM, Gouma DJ and Boermeester MA. The incidence and nature of in-hospital adverse events: a systematic review. Qual Saf Health Care 2008; 17: 216-223.
7. Zegers M, de Bruijne MC, Wagner C, et al. Design of a retrospective patient record study on the occurrence of adverse events among patients in Dutch hospitals. BMC Health Serv Res 2007; 7: 27.
8. Zegers M, de Bruijne MC, Wagner C, et al. Adverse events and potentially preventable deaths in Dutch hospitals: results of a retrospective patient record review study. Qual Saf Health Care 2009; 18: 297-302.
9. Hoonhout LH, de Bruijne MC, Wagner C, et al. Nature, occurrence and consequences of medication-related adverse events during hospitalization: a retrospective chart review in the Netherlands. Drug Safety 2010; 33: 853-864.
10. de Bruijne MC, Zegers M, Hoonhout LHF and Wagner C. Onbedoelde schade in Nederlandse ziekenhuizen: dossieronderzoek van ziekenhuisopnames in 2004. Instituut voor Extramuraal Geneeskundig Onderzoek: Amsterdam, 2007.
11. Hakkarainen KM, Gyllensten H, Jönsson AK, et al. Prevalence, nature and potential preventability of adverse drug events – a population-based medical record study of 4970 adults. British Journal of Clinical Pharmacology 2014; 78: 170-183.
12. Davis P, Lay-Yee R, Briant R, et al. Adverse events in New Zealand public hospitals II: preventability and clinical context. New Zeal Med J 2003; 116: U624.
13. Leendertse AJ, Egberts AG, Stoker LJ, van den Bemt PA and Group HS. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Int Med 2008; 168: 1890-1896.

14. Sousa P, Uva AS, Serranheira F, Nunes C and Leite ES. Estimating the incidence of adverse events in Portuguese hospitals: a contribution to improving quality and patient safety. BMC Health Serv Res 2014; 14: 311.
15. VMS. VMS Safety Program. 2009; http://www.vmszorg.nl
16. Baines R, Langelaan M, de Bruijne M, Spreeuwenberg P and Wagner C. How effective are patient safety initiatives? A retrospective patient record review study of changes to patient safety over time. BMJ Qual Saf 2015;
17. Baines RJ, Langelaan M, de Bruijne MC, et al. Changes in adverse event rates in hospitals over time: a longitudinal retrospective patient record review study. BMJ Qual Saf 2013; 22: 290-298.
18. Brennan TA, Leape LL, Laird NM, et al. Incidence of adverse events and negligence in hospitalized patients. New England Journal of Medicine 1991; 324: 370-376.
19. Vincent C, Neale G and Woloshynowych M. Adverse events in British hospitals: preliminary retrospective record review. British Medical Journal 2001; 322: 517-519.
20. Beijer HJM and de Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. Pharmacy World and Science 2002; 24: 46-54.
21. Lazarou J, Pomeranz BH and Corey PN. Incidence of adverse drug reactions in hospitalized patients: A meta-analysis of prospective studies. Journal of the American Medical Association 1998; 279: 1200-1205.
22. Cano FG and Rozenfeld S. Adverse drug events in hospitals: a systematic review. Cadernos de Saude Publica 2009; 25 Suppl 3: S360-372.
23. Ruiter R, Visser LE, Rodenburg EM, et al. Adverse drug reaction-related hospitalizations in persons aged 55 years and over: a population-based study in the Netherlands. Drug Aging 2012; 29: 225-232.
24. van der Hooft CS, Dieleman JP, Siemes C, et al. Adverse drug reaction-related hospitalisations: a population-based cohort study. Pharmacoepidemiol Drug Saf 2008; 17: 365-371.
25. Jennings HR, Miller EC, Williams TS, Tichenor SS and Woods EA. Reducing anticoagulant medication adverse vents and avoidable patient harm. Joint Comm J Qual Patient Saf 2008; 34: 196-200.
26. Koppel R, Metlay JP, Cohen A et al. Role of computerized physician order entry systems in facilitating medication errors. Journal of the American Medical Association 2005; 293: 1197-1203.
27. Bates DW, Leape LL, Cullen DJ et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. Journal of the American Medical Association 1998; 280: 1311-1316.
28. Schiff GD, Amato MG, Eguale T, et al. Computerised physician order entry-related medication errors: analysis of reported errors and vulnerability testing of current systems. BMJ Qual Saf 2015; 24: 264-271.

29. Strom BL, Schinnar R, Aberra F et al. Unintended effects of a computerized physician order entry nearly hard-stop alert to prevent a drug interaction: a randomized controlled trial. Arch Int Med 2010; 170: 1578-1583.
30. Kucukarslan SN, Peters M, Mlynarek M and Nafziger DA. Pharmacists on rounding teams reduce preventable adverse drug events in hospital general medicine units. Archives of Internal Medicine 2003; 163: 2014-2018.
31. Kaboli PJ, Hoth AB, McClimon BJ and Schnipper JL. Clinical pharmacists and inpatient medical care: a systematic review. Archives of Internal Medicine 2006; 166: 955-964.
32. Ramrattan MA, Boeker EB, Ram K, et al. Evidence based development of bedside clinical drug rules for surgical patients. Int J Clin Pharm 2014; 36: 581-588.
33. Inspectie voor de Gezondheidszorg. Keten trombosezorg niet sluitend. Den Haag, 2010.
34. Damen N, Damen P, van Dijk L, de Bakker D and Wagner C. Implementatie Landelijke Standaard Ketenzorg Antistolling 2.0: stand van zaken. NIVEL: Utrecht, 2015.
35. Shojania KG and Marang-van de Mheen PJ. Temporal trends in patient safety in the Netherlands: reductions in preventable adverse events or the end of adverse events as a useful metric? BMJ Qual Saf 2015.
36. Zegers M, de Bruijne MC, Spreeuwenberg P, et al. Quality of patient record keeping: an indicator of the quality of care? BMJ Qual Saf 2011; 20: 314-318.
37. Henriksen K and Kaplan H. Hindsight bias, outcome knowledge and adaptive learning. Qual Saf Health Care 2003; 12 Suppl 2: ii46-50.