Preventable drug-related incidents of hemorrhage in nursing homes

a retrospective, descriptive research on preventable incidents of hemorrhage related to anticoagulation, antiplatelet and NSAID's use

University of Twente Faculty of Management and Governance

EXAMINATION COMMITEE
Dr. Jeannette van Manen & Prof. dr. Ron Kusters

WRITTEN BY
Sulaine Striebeek (s1228137)

December 2013

General Information:
Author: Sulaine Striebeek
Student number: s1228137
E-mail: s.m.striebeek@student.utwente.nl
Date of graduation: December, 2013
Title: Preventable drug-related incidents of hemorrhage in nursing homes. A retrospective, descriptive research on preventable incidents of hemorrhage related to anticoagulation, antiplatelet NSAID's use.

University of Twente:
Faculty: Management and Governance
Study direction: Health Sciences
Master track: Health Technology Assessment
Address: Drienerlolaan 5, 7522 NB Enschede

This thesis is written in article form.

Table of Contents

Acknowledgement

First of all I would like to offer my gratitude to strategist innovator H. Snijders MD for his collaboration with the University of Twente which has made this research possible. Being able to perform this research has been a valuable, interesting and rewarding experience.

I would also like to express my gratitude to my first and second supervisor dr. J.G. van Manen en prof. dr. G.C.M. Kusters for their guidance and advice throughout the research process. Without their support and guidance, it would have not been possible to complete this thesis.

Completing this work would have not been possible without the help of J.W. Rotman who has made it possible to get accessibility to the network of Carintreggeland. A. Wester MD, C. Span-Sluyter MD and H. Oldenhof who have provided me with the necessary information, guided me and supported me with their knowledge and experience within the nursing homes.

A special thanks to my friends and everybody who supported and helped me throughout the research process.

Finally, I would like to thank my family for their support throughout my study. Without their motivation, it would have not been possible to complete my study.

List of abbreviations and relevant definitions

ADR   Adverse Drug Reaction
HARM   Hospital Admissions Related to Medication
NSAID   Non-steroidal Anti-Inflammatory Drugs
GI   Gastro Intestinal
MRF   Medical Record Form
IRR   Incidents rate ratio
SD   Standard deviation
LOS   Length of stay
CAD   Catheter
NOAC   New Oral Anticoagulants
INR   International Normalized Ratio
FK   Farmacotherapeutisch Kompas
EPR   Electronic Patient Record

Medication error:
"Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer" [1].

Chronic prescription drugs:
Numbers of daily consumption of prescribe medications for chronicle disease.

Prescription rate:
Numbers of time anticoagulation, antiplatelet or NSAID were prescribed.

Drug-related hemorrhage:
Bleeding events which occurred after administration of anticoagulation, antiplatelet and NSAID's at the given prescription dosage or as result of an overdose.

Trauma:
Physical injury

Trombosedienst:
Is an institution which assists patients using anticoagulation. Every patient in Caritreggeland using anticoagulation is closely monitored by this institute [2].

High INR:
The INR is a measurement to determine the clothing tendency of the blood by the use of anticoagulation. Depending on the indication for the anticoagulation, the Trombosedienst will provide a target range and a dosage scheme for the particular patient. The INR range for anticoagulation users is between 2 and 4. A high INR were considered when the INR by measurement is higher than the target range provided by the Trombosedienst for the patient. A high INR increase the risk of bleeding [2].

Drug-drug interaction:
Drug-drug interaction is when another drug is simultaneously administered with anticoagulation, antiplatelet or NSAID's and affects the activity of the anticoagulation, antiplatelet or NSAID's and causes hemorrhage.

Preventable drug-related incidents of hemorrhage in nursing homes. A retrospective, descriptive research on preventable incidents of hemorrhage related to anticoagulation, antiplatelet and NSAID's use

Sulaine Striebeek

Abstract

Background: Patient safety, especially medication safety, is one of the main concerns in healthcare. Studies have pointed out a relationship between preventable drug-related ADR such as hemorrhages and the use of anticoagulation, antiplatelet and NSAID's. Conclusive information concerning the occurrence rate of preventable drug-related incidents of hemorrhage related to the use of these medications in nursing home is scarce.

Objective: To identify the prescription rate of anticoagulation, antiplatelet, NSAID's and combination of two or more of the drugs mentioned and to observe the occurrences of preventable drug related hemorrhage among nursing home residents using anticoagulation, antiplatelet and NSAID's.

Method: A retrospective, descriptive study was carried out among the residents of the 18 nursing homes of Carintreggeland living in the nursing homes in the period of January 2011 till April 2013. Medical records of 608 patients were reviewed for potential preventable drug-related incidents of hemorrhage. The collected data were summarized and placed in a MRF. Preventable drug-related incidents of hemorrhage were assessed using an adjusted version of the algorithm of Kramer et al. The severity of the harm was assessed using the NCC MERP Index for Categorizing Medication Errors and the NCC MERP Index for Categorizing Medication Errors Algorithm.

Results: The prescription rate of anticoagulation, antiplatelet, NSAID's and combination of two or more of these drugs were 33 per 100 patient years. The most prescribed drug was antiplatelet. The anticoagulation, antiplatelet and NSAID users had a total of 180 incidents of hemorrhage of which four were preventable. The nonusers had a total of 56 incidents of hemorrhage. The category of harm detected were circumstances or events that have the capacity to cause error; an error occurred that reached the patient but did not cause patient harm; an error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm. The preventable drug-related hemorrhages resulted in prolonged bleeding and temporary injury.

Conclusion: Anticoagulation, antiplatelet and NSAID users had a 1.9 fold greater risk on experiencing hemorrhage than nonusers. However, the incident rate of preventable drug-related hemorrhages in the nursing home is low. A total of four preventable incidents of hemorrhage were detected.

Introduction

Patient safety, especially medication safety, is currently one of the most important health care topics. Medicine use has the purpose of curing or palliating diseases, subsequently to improve the quality of life. [3, 4]. Yet, it is well known that the use of medicine can also cause adverse drug reaction (ADR), which in some cases might be life threatening. Consequently, the use or prescription of medication especially in elderly patients might be very challenging. Elderly patients are potentially at greater risk of getting ADR's. They are known to have multiple comorbid conditions and use multiple medications. These factors in combination with unforeseen physiological, pharmacokinetic and pharmacogenetic changes, age and additional medication errors can cause several ADR's [5-7].

ADR caused by medication error, is a crucial concern regarding medical safety in nursing homes. According to the HARM study, 5.6% of the acute hospital admissions in the Netherlands are drug-related. Approximately 46% of these hospital admissions could have been prevented, whereas 29% of these preventable drug-related hospitalizations are long-term care residents. The most occurred ADR is GI bleeding (14.5%) and the prominent drugs responsible are anticoagulation (6.3%), antiplatelet (8.7%), NSAID's (5.1%) and/or a combination of two or more of the drugs mentioned (10.5%). These drugs are being utilized for the treatment of cardiovascular and thrombotic morbidities and pain. They have proven to be beneficial in reducing the mortality and morbidity actuated by these conditions. These drugs however, can also cause critical ADR such as hemorrhage, which in some cases might be life threatening or might cause crucial disability amongst survivors. A higher risk of incidents of hemorrhage is shown in elderly patients. Risk factors of hemorrhage related to the use of these medications are: in ages >75, most consistent in males, decreased cognitive ability, multiple medications use, comorbidities, history of hemorrhage, helicobacter pillory, and history of peptic ulcer [8-11].

Studies have shown that anticoagulation use increases the hospitalization rate among elderly warfarin users by a factor of 1.26. The hospitalization rate for combine therapy (antiplatelet and anticoagulation) using aspirin and warfarin or aspirin and ticlopidin is 1.34 times higher than monotherapy [11-13]. When treatment is initiated with triple therapy (dual antiplatelet and anticoagulation), the risk of hemorrhage accelerates from 9.2% to 30% within 30 days after initiation. Blood transfusion and surgical intervention is required in 1% - 15% of the cases [12]. When NSAID's or corticosteroids are used together with anticoagulation drugs, it increases the risk of hemorrhage by a factor of 1.92 and 1.23 consecutively NSAID's monotherapy causes hospitalization regarding GI complication in elderly people (>65) with approximately 10 to 20 per 1,000 patients per year [8]. The incidents hemorrhage of the central nervous system is 1.64 times greater in warfarin users and 1.55 times greater in patients taking combination therapy with anticoagulation and antiplatelet. Treatment with antiplatelet monotherapy increases the risk of hospitalization due to antiplatelet related bleeding among nursing home residents with 1.07 [13].

Evidently, the use of anticoagulation, antiplatelet and NSAID's increases the risk of hemorrhage. This has been proven many times in several studies. However, according to our knowledge a study regarding preventable drug-related hemorrhages caused by the use of anticoagulation, antiplatelet and NSAID's in nursing homes has not yet been conducted. The HARM study have briefly mentioned this issue, but did not study it in depth [14].

The primary goal of this study was to identify the prescription rate of anticoagulation, antiplatelet NSAID's and the combination of two or more of the drugs mentioned and to observe the occurrences of preventable drug-related incidents of hemorrhage and their consequences. The secondary goal was to determine to what extent the prevalence of hemorrhage differs between the patients using anticoagulation, antiplatelet and NSAID's and the nonusers.

Method

Setting

A nursing home is an institute which provides special care and medical treatment (for a short- and long term) to patients who are in need of special care after discharge from the hospital or after experiencing a sever disorder. According to the latest data, there are approximately 479 nursing homes in the Netherlands [15, 16].

Carintreggeland is an innovative organization which offers housing welfare and care to patients in the region of Twente in the Netherlands. They offer a broad range of services such as nutrition and dietary advice, social work and welfare for elderly, home care, day care, short-term uptake and mediation for domestic help, nursing homes and long-term care facilities [17].

This retrospective, descriptive study was carried out in the 18 nursing homes of Carintreggeland in the period of March to June 2013. Medical records of 608 residents who live in the care facilities at any given moment in the period of January 2011 until April 2013 were reviewed.

Study population

The study population was divided in two groups, namely, the anticoagulation, antiplatelet and NSAID's users and the nonusers. Both groups were selected from the 1,950 patients living in the nursing homes in the period of January 2011 till April 2013. The selection of the anticoagulation, antiplatelet and NSAID's users were as followed, all the patient using all the types of anticoagulation, antiplatelet and NSAID's were selected from the pharmaceutical data. This added up to 1,024 patients. From the 1,024 patients, 400 patients were randomly selected. To find the total amount of nonusers, 1,024 was extracted from 1,950. This comes to a sum of 926 patients. Due to unknown reason, not all the data of all the 926 nonusers could have been obtained. It was possible to obtain data of 208 patients. All the 208 were included in the study. The day care patients were excluded from the study.

Figure 1. Selection of the study population
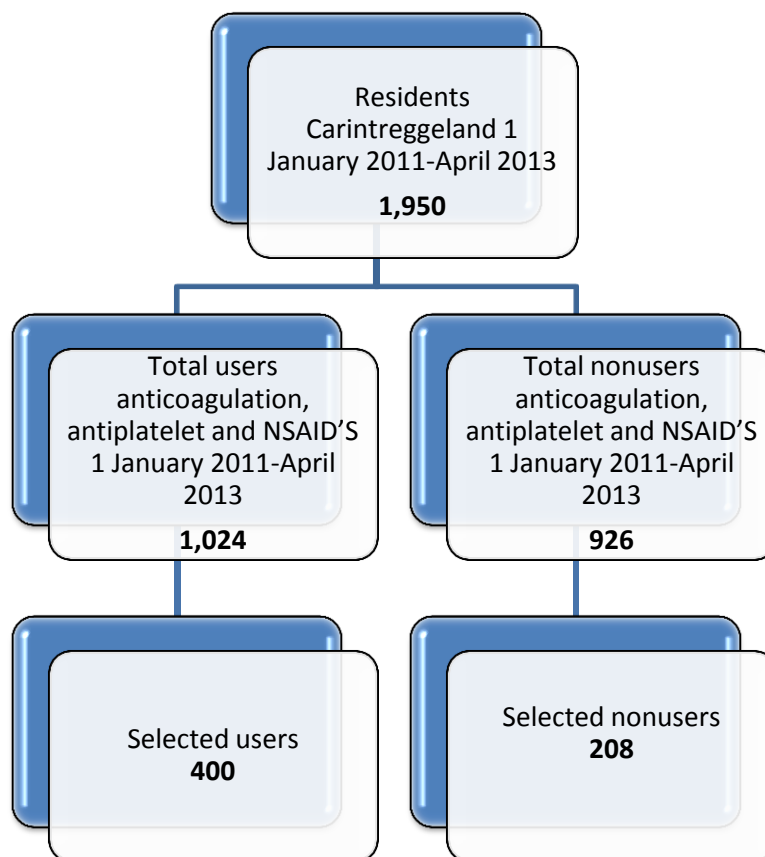
Data collection

Data on the prescription rate of anticoagulation, antiplatelet, NSAID's and the combination of two or more of the drugs mentioned, the occurrences of hemorrhage, drug-related hemorrhage and preventable drug-related hemorrhage were collected from the Electronic Patient Record (EPR) and the pharmaceutical data. The data analysis was performed according to the scheme shown in figure 2.

To calculate the prescription rate of anticoagulation, antiplatelet, NSAID's and the combination of two or more of the drugs mentioned, it was necessary to document every prescription of anticoagulation, antiplatelet, NSAID and the combination of two or more of the drugs mentioned prescribed in the period of January 2011 till April 2013 in the Medical Record Form (MRF). For a better overview of the use of the drugs studied, the three drug types were clustered in seven categories. Category 1: anticoagulation; category 2: antiplatelet; category 3: NSAID's; category 4: anticoagulation and antiplatelet; category 5: anticoagulation and NSAID's; category 6: antiplatelet and NSAID's; category 7: anticoagulation, antiplatelet and NSAID's. Combinations were considered as the use of two or more of the drugs mentioned at the same time.

Figure 2. Data analysis scheme
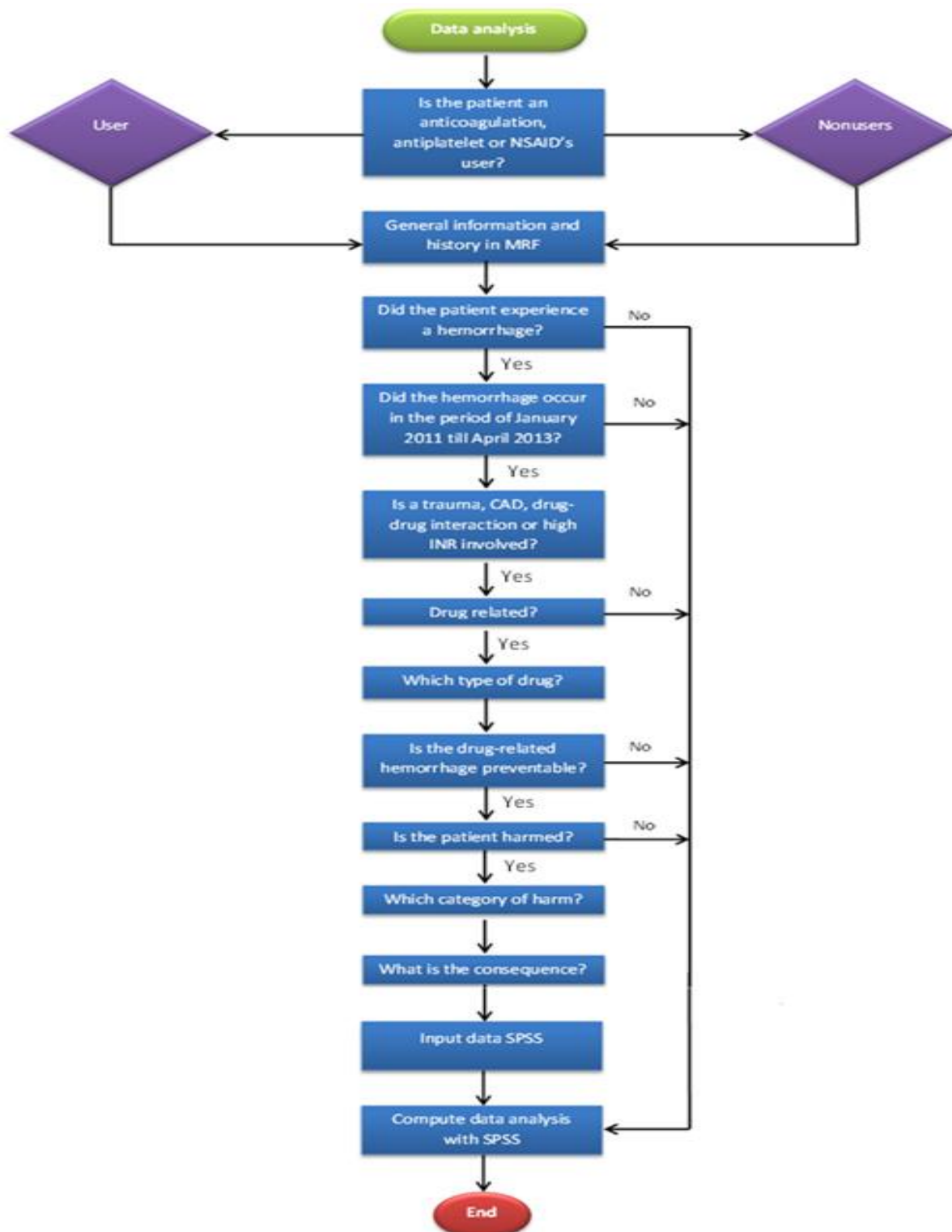
To calculate the occurrences of hemorrhage, every bleeding incident occurred and documented in the EPR at any given moment in the period of January 2011 till April 2013 was documented in the MRF of the patient who was being studied. Further, every hemorrhage was examined on drug-related hemorrhage. Drug-related hemorrhages were considered as bleeding events which occurred after the administration of anticoagulation, antiplatelet and NSAID's at the given prescription dosage or as result of an overdose. The examination was carried out under additional supervision of

physicians. To determine if the hemorrhages were drug-related, the following questions needed to be answered:

1) Did the hemorrhage occur after administration of the drug? (If the hemorrhage occurred one day after discontinuing the treatment, the hemorrhage was still considered as drug-related)

2) Is the hemorrhage, according to the Farmacotherapeutisch Kompas (FK), known as an universal side effect of the drug administered?

3) Did the patient experience any other disorder which can also cause hemorrhage when the incident occurred?

4) If the hemorrhage were as consequence of a disease, did the use of the drug involved increase the risk of hemorrhage? (If the answer to question three and four is yes, the hemorrhage was categorized as increase risk. This means that the hemorrhage was not drug related but the drug involved had an influence on the occurrence of the hemorrhage. This category was not further analyzed.)

Preventable drug-related hemorrhages were assessed using the algorithm of Kramer et al (appendix 1). This algorithm was designed to determine the cause of an observed clinical manifestation which in this case were hemorrhages [18]. In this study it was used to rank the probability of causation when an incident of hemorrhage was suspected to be a preventable ADR of the administered drug.

The algorithm has a scoring system of six axes, whereas four were relevant for this study. An extra axis (axis V) was added to the algorithm, which was applicable to assess the cases of drug-drug interaction in this study. It was assessed whether the hemorrhage was a common experienced ADR caused by the administered drug (axis I); if it was caused by another clinical condition (axis II); the timing compared to the drug administrated (axis III); if it was a consequence of an overdose (axis IV); if there were cases of drug-drug interaction (axis V).

For the definition of hemorrhage relating to a suspected ADR, the definition of ADR given by Kramer et al was modified. Hemorrhage was defined as "an undesirable bleeding that is consequent to and caused by the administration of anticoagulation, antiplatelet and NSAID's " [18].

Each axis was scored individually. Usually a score of 0, +1 or -1 was given to each axis to weight the evidence of hemorrhage as an ADR. An extra weight of +2 or -2 was given on Axis II and III. The weight of the scores depends on whether the evidence of the hemorrhage clearly shows a positive or negative association with the ADR. Thereupon, the scores of each individual axis were added up to acquire a total score. The total score can range from +7 to -7. If the score of +7 or +6 was obtained, the probability of ADR was definite. If the score of +5 or +4 was achieved, the probability of ADR was probable. If the score of +3, +2 or +1 was reached, the probability of ADR was possible. If the score of ≤0 was obtained, the probability of ADR was unlikely [18].

Only the probable and definite hemorrhages were used to establish the important causal link between the administered drug and the hemorrhage. These hemorrhages were further examined on harm and consequence of the hemorrhage. The nature and severity of the harm were assessed using the NCC MERP Index for Categorizing Medication Errors and the NCC MERP Index for Categorizing Medication Errors Algorithm (appendix 2 and 3)[19]. The results of the consequences of hemorrhages were classified in non-recurrent bleeding (bleeding events that happen a single time and was stopped shortly after the incidents), prolonged bleeding (bleeding events that last longer than one

day), temporary injury (when the patient experienced any type of deficiency due to the bleeding event or needed some intervention), hospitalization and death.

The collected data was summarized and placed in a MRF (appendix 4). The results of the data collected were assessed by a physician or specialist of Carintreggeland.

Statistical analysis

Statistical analysis was carried out using "IBM SPSS Statistic 21" software. Descriptive statistics was used to determine the general characteristics of the participants, the frequency of anticoagulation, antiplatelet, NSAID's use, hemorrhages, types of bleeding, harm and type of harm, the consequence and risk factors. Incidence rate ratio was calculated using the formula given by Cohen et al to determine if there was a statistical significant difference between the two groups studied. First the point estimate were calculated using the following formula: $\widehat{IR} = \dfrac{A_1/T_1}{A_0/T_0}$, where

A_0 is the total number of incidents of hemorrhage among the nonusers
A_1 is the total number of incidents of hemorrhage among the anticoagulation, antiplatelet and NSAID users
T_0 is the total patient years of the 208 nonusers
T_1 is the total patient years of the 400 anticoagulation, antiplatelet and NSAID users

Next the standard deviation of the log rate ratio were calculated using the following formula

$$\widehat{SD}[\ln(\widehat{IR})] = \left(\frac{1}{A_1} + \frac{1}{A_0} \right)^{1/2}$$

Finally the lower and upper limits of the rate ratio were calculated using the following formula

$\underline{IR}, \overline{IR} = \exp\{\ln(\widehat{IR}) \pm Z_\gamma \widehat{SD}[\ln(\widehat{IR})]\}$ [20]

Statistical significance was obtained when the confident interval was not one and differs by at least p-value ≤ 0.05.

The patient years was calculated by adding up the total admission time of every individual in the study population living in the nursing home in the period of January 2011 until April 2013.

The range of the comorbid disorders per patient was calculated by counting the numbers of comorbid disorders registered in the EPR in the period of January 2011 until April 2013.

The range of prescribed drugs per patient was calculated by counting the numbers of the prescribed drug registered in the EPR and the pharmaceutical data in the period of January 2011 until April 2013.

Results

General characteristics

A total of 608 residents of Carintreggeland were enrolled in the study. The group of anticoagulation, antiplatelet and NSAID's users comprised of 400 patients and the nonusers group comprised of 208 patients. Both groups differ with respect to gender (the nonusers had more female participants than the users), cognitive ability (most of the nonusers were dependent and most of the users were independent), comorbid disorder (most of the nonusers had zero to five comorbid disorders and most of the users had six or more comorbid disorders), and chronic prescription drugs (the users use more prescribed drugs than the nonusers). The mean age and LOS were similar between the two groups. An overview of the general characteristics of the participants is shown in table 1.

Table 1. General characteristics of the participants

Characteristics	Anticoagulation. antiplatelet and NSAID's users N=400 Observed patient years: 507.5		Nonusers N=208 Observed patient years: 306.5		All participants N=608	
	N	**%**	**N**	**%**	**N**	**%**
Gender						
Male	204	51	54	26	258	42.4
Female	196	49	154	74	350	57.6
Residential status						
Resident	205	51.3	126	60.6	331	54.4
Discharged	100	25	31	14.9	131	22.6
Death	95	23.7	51	24.5	146	24
Cognitive ability						
Dependent	153	38.3	108	51.9	261	42.9
Independent	247	62.7	100	48.1	347	57.1
Comorbid disorder						
Unknown	42	10.5	19	9.1	61	10
0-5	245	61.3	171	82.2	416	68.4
6-10	91	22.7	18	8.7	109	17.9
11-15	19	4.7	0		19	3.1
16-20	1	0.3	0		1	0.2
>21	2	0.5	0		2	0.3
Chronic prescription drugs						
0-5	67	16.8	107	51.4	174	28.6
6-10	193	48.2	84	40.4	277	45.6
11-15	100	25	16	7.7	116	19.1
16-20	32	8	0		32	5.3
>21	8	2	1	0.5	9	1.5
	Mean	**SD**	**Mean**	**SD**	**Total mean**	**Total SD**
Age	81.6	8.8	81.1	9.9	81.4	9.2
LOS*	29.6	32	33.2	30.6	30.8	31.5

*Length of stay in months

The prescription rate of anticoagulation, antiplatelet, NSAID's and combination

The prescription rate of anticoagulation, antiplatelet, NSAID's and the combination of two or more of the drugs mentioned among the 1,950 residents of Carintreggeland with an estimated 1,835.8 patient years comprised a total of 33 prescriptions per 100 patient years. The number of patients using anticoagulation, antiplatelet, NSAID'S and the combination of two or more of the drugs mentioned comes to 24 patients per patient years. Table 2 gives an overview of the prescription rate of anticoagulation, antiplatelet, NSAID and the combination of two or more of the drugs mentioned and the number of patients using these drugs.

Table 2. Prescription rate and number of patients using anticoagulation, antiplatelet, NSAID's and combination of two or more drugs for 1,950 residents living in the nursing home in the period of January 2011 till April 2013

Prescription rate and number of patients using anticoagulation, antiplatelet, NSAID's and combination of two or more drugs N=1,950 with 1,835.8 observed patient years				
	N	Number of *prescriptions* per 100 patient years	N	Number of *patients* with prescription per 100 patient years*
Anticoagulation	140	7.6	119	6.5
Antiplatelet	278	15.1	193	10.5
NSAID	94	5.1	54	3
Anticoagulation and antiplatelet	15	0.8	13	0.7
Anticoagulation and NSAID	30	1.6	26	1.4
Antiplatelet and NSAID	46	2.5	31	1.7
Anticoagulation, antiplatelet and NSAID	5	0.3	4	0.2
Total	**608**	**33**	**440**	**24**

* Multiple prescriptions per patient is possible

Occurrences and consequences of hemorrhage

The occurrences of hemorrhage among the anticoagulation, antiplatelet and NSAID's users and the nonusers

The occurrences of hemorrhage were observed among the 400 anticoagulation, antiplatelet and NSAID's users and the 208 nonusers. The anticoagulation, antiplatelet and NSAID's users had 1.9 times higher risk on hemorrhage compared to the nonusers. The risk of hemorrhage including the risk factors was 2 times higher by the anticoagulation, antiplatelet and NSAID's users compared to the nonusers. The top three most common types of hemorrhages were hematoma, hematuria, and rectal bleeding (table 3). Table 4 gives an overview of the risk of hemorrhages and risk factors for the anticoagulation, antiplatelet and NSAID's users and the nonusers.

There are some factors such as the use of catheter (CAD) and trauma that might increase the risk of bleeding. The users had a greater number of incidents (78.5 vs. 57.1 per 100 patient years) where traumas were involved and a greater number of incidents (126.4 vs. 93.5 per 100 patient years) were a CAD was used than the nonuser. Most of the incidents resulted in prolonged bleeding.

Table 3. Number of occurrences, types and consequences of hemorrhage (per 100 patient years) among the 400 anticoagulation, antiplatelet and NSAID'S users and the 208 nonusers living in the nursing home in the period of January 2011 till April 2013

	Anticoagulation, antiplatelet and NSAID's users N=400 with 507.5 0bserved patient years		Nonusers N=208 with 306.5 observed years		IRR	95% CI	
	N	Number of hemorrhages per 100 patient years	N	Number of hemorrhages per 100 patient years		UL	LL
Number of hemorrhages per 100 patient years							
	180	35.5	56	18.3	1.9	2.6	1.4
Number of patients with one or more hemorrhage per 100 patient years							
	N	Number of patients per 100 patient years	N	Number of patients per 100 patient years			
	91	17.9	43	14	1.3	1.7	1
Number of hemorrhage and type of hemorrhages per 100 patient year							
Gastro-intestinal bleeding	7	1.4	3	0.9	1.4	1.9	1
Hematoma/Subcutaneous hemorrhage	48	9.5	24	7.8	1.2	1.6	0.9
Sputum mixed with blood	7	1.4					
Nosebleed	6	1.2	2	0.7	1.8	2.5	1.3
Vaginal bleeding	8	1.6	3	0.9	1.6	2.2	1.2
Conjunctivae bleeding	6	1.2					
Rectal bleeding	10	1.9	6	1.9	1	1.4	0.7
Bleeding wound	4	0.8					

Hematuria	58	11.4	11	3.6	3.2	4.3	2.4
Vomit mixed with blood	4	0.8	3	0.9	0.8	1.1	0.6
Other	22	4.3	4	1.3	3.3	4.5	2.5
Number of the results of the consequences of hemorrhage per 100 patient years							
Prolonged bleeding	146	28.8	55	17.9	1.6	2.2	1.2
Non-recurrent bleeding	20	3.9					
Temporary injury	6	1.2					
Hospitalization	5	1.0					
Death	3	0.6	1	0.3	2	2.7	1.5
Factors that may increase the risk of hemorrhage							

Anticoagulation, antiplatelet and NSAID's users using CAD N=28 with 45.9 observed patient years		Nonusers using CAD N=6 with 10.7 observed patient years				
N	Number of hemorrhages related to CAD use per 100 patient years	N	Number of hemorrhages related to CAD use per 100 patient years			
58	126.4	10	93.5	1.4	3.4	0.6
Anticoagulation, antiplatelet and NSAID's users with Trauma N= 23 with 38.2 observed patient years		Nonusers with Trauma N=20 with 36.8 observed patient years				
N	Number of hemorrhages related to trauma per 100 patient years	N	Number of hemorrhages related to trauma per 100 patient years			
30	78.5	21	57.1	1.4	3.4	0.6

Table 4. Number of occurrences of hemorrhage (per 100 patient years) and risk factors among the 400 anticoagulation, antiplatelet and NSAID's users and the 208 nonusers living in the nursing home in the period of January 2011 till April 2013

	Anticoagulation, antiplatelet and NSAID's users N=400 with 507.5 observed patient years		Nonusers N=208 with 306.5 observed years		IRR	95% CI	
	N	Number of hemorrhages per 100 patient years	N	Number of hemorrhages per 100 patient years		UL	LL
Cognitive ability							
Dependent	96	18.9	29	9.5	2	2.7	1.5
Independent	84	16.5	27	8.8	1.9	2.5	1.4
Comorbid disorders							
0-5	153	30.2	47	15.3	2	2.7	1.5
6-10	20	3.9	6	1.9	2	2.7	1.5
11-15	1	0.20					
Chronic prescribe drugs							
0-5	25	4.9	30	9.8	0.5	0.7	0.3
6-10	54	10.6	24	7.8	1.4	1.8	1
11-15	86	16.9	1	0.3	51.9	70.1	38.5
16-20	12	2.4					
>21	3	0.6	1	0.3	1.8	2.5	1.3

Drug-related incidents hemorrhage

Among the 400 users of anticoagulation, antiplatelet and NSAID's, a sum total of 28 patients with an estimated 44.2 patient years have experienced one or more incidents of drug related hemorrhage. In total 55 drug-related hemorrhages and 97 hemorrhages which were not a direct consequence of the use of anticoagulation, antiplatelet and NSAID's but were potentially influenced by the use of these drugs, were observed. The 97 none directly drug-related hemorrhages were, for example hemorrhages caused by a urinary tract infection where the bleeding was prolonged due to the consummation of anticoagulation, antiplatelet or NSAID's. The main drugs involved were anticoagulation (49.8 per 100 patient years) and the combination of two or more drugs (47.5 per 100 patient years) (Table 5).

The occurrences of drug-related hemorrhage among patients with a dependent cognitive ability were 65.6 per 100 patient years and 58.8 per 100 patient years among the independent patients. Patients with 0-5 comorbid disorders had 110.9 drug-related incidents of hemorrhage per 100 patient years and 13.6 drug-related incidents of hemorrhage among patients with six or more comorbid disorders.

Patients using six or more chronic prescription drugs a day had a total of 124.4 drug-related incidents of hemorrhage per 100 patient years (table 6).

The most experienced types of drug-related hemorrhage were hematoma (24.9 per 100 patient years) and hematuria (43 per 100 patient years). The incidents of drug-related hemorrhage resulted in prolonged bleeding (110.9 per 100 patient years, temporary injury (6.8 per 100 patient years) and hospitalization (6.8 per 100 patient years) (tables 5 and 7). Consider that multiple occurrences of hemorrhages per patient were possible.

Table 5. Number of hemorrhages (per 100 patient years) among the 28 users of anticoagulation, antiplatelet and NSAID'S which experienced drug-related incidents of hemorrhage in the period of January 2011 till April 2013, per medication group

	Drug-related hemorrhage N=28 with 44.2 observed patient years	
	N	Number of hemorrhages per 100 patient years
Anticoagulation	22	49.8
Antiplatelet	8	18.1
NSAID's	4	9
Combination	21	47.5

Table 6. Number of hemorrhages in combination with the risk factors among the 28 patients which experienced drug-related hemorrhage in the period of January 2011 till April 2013 per 100 patient years

Drug-related incidents of hemorrhage and risk factors N=28 with 44.2 observed patient years		
	N	Number of hemorrhages peer 100 patient years
Cognitive ability		
Dependent	29	65.6
Independent	26	58.8
Comorbid disorders		
0-5	49	110.9
6-10	6	13.6
Polypharmacy		
0-5	5	11.3
>6	50	124.4

Table 7. Number of the type of hemorrhages in combination with factors that may increase the risk of hemorrhage and medication group, among the 28 patients which experienced drug-related hemorrhage in the period of January 2011 till April 2013 per 100 patient years

N=28 with 44.2 observed patient years								
Type of hemorrhage								
	N	**Number of hemorrhages per 100 patient years**						
Gastro-intestinal bleeding	4	9.1						
Hematoma/Subcutaneous hemorrhage	11	24.9						
Sputum mixed with blood	4	9.1						
Nosebleed	6	13.6						
Conjunctiva bleeding	6	13.6						
Rectal bleeding	2	4.5						
Bleeding wound	2	4.5						
Haematuria	19	43						
Other	1	2.3						
Occurrence of hemorrhage in high risk subgroups per 100 years								
	Drug-drug interaction N=6 with 11.2 observed patient years		**High INR N=6 with 9.9 observed patient years**		**CAD N=28 with 45.9 observed patient years**		**Trauma N=23 with 38.2 observed patient years**	
	N	**Number of hemorrhages per 100 patient years**	**N**	**Number of hemorrhages per 100 patient years**	**N**	**Number of hemorrhages per 100 patient years**	**N**	**Number of hemorrhages per 100 patient years**
Gastro-intestinal bleeding	2	17.9	3	30.3				
Hematoma/Subcutaneous hemorrhage							3	7.9
Sputum mixed with blood	1	8.9	1					

Haematuria	15	133.9	13		19	41.4		
Occurrence of hemorrhage in high risk subgroups per 100 years								
	Drug-drug interaction N=6 with 11.2 observed patient years		**High INR** N=6 with 9.9 observed patient years		**CAD** N=28 with 45.9 observed patient years		**Trauma** N=23 with 38.2 observed patient years	
	N	**Number of hemorrhages per 100 patient years**	**N**	**Number of hemorrhages per 100 patient years**	**N**	**Number of hemorrhages per 100 patient years**	**N**	**Number of hemorrhages per 100 patient years**
Anticoagulation	17	151.8	14	141.4	16	34.9	2	5.2
Antiplatelet					1	2.2		
NSAID's								
Combination	1	8.9			2	4.4	1	2.6
Consequence of drug-related hemorrhage								
	N				**Numbers in 100 patient years**			
Prolonged bleeding	49				110.9			
Temporary injury	3				6.8			
Hospitalization	3				6.8			

Preventable drug-related incidents of hemorrhage

Of the 55 drug-related hemorrhages, four of them were possibly preventable. The most occurred hemorrhage was: GI bleeding; sputum mixed with blood; conjunctiva bleeding; bleeding wound. The category of harm detected was: circumstances or events that have the capacity to cause error; an error occurred that reached the patient but did not cause patient harm; an error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm [18]. As consequence, 62.5 of the preventable drug-related hemorrhages per 100 patient years had resulted in prolonged bleeding and 20.83 per 100 patient years had resulted in temporary injury. All patients had recovered completely.

Discussion, limitations, conclusion and recommendations

Discussion

The purpose of this study was to determine the prescription rate of anticoagulation, antiplatelet, NSAID's and the combination of two or more of the drugs mentioned, to determine the occurrences of preventable drug-related hemorrhages and their consequences and to finally determine to what extent the prevalence of hemorrhage differs between the patients using anticoagulation, antiplatelet and NSAID's and the nonusers.

The findings of this study were as followed:

A total of 33 prescriptions of anticoagulation, antiplatelet, NSAID's and combination of two or more of the drugs mentioned per 100 patients years were prescribed at the Carintreggeland nursing homes. 35.5 hemorrhages per 100 patient years were detected among the users of anticoagulation, antiplatelet and NSAID's and 18.3 hemorrhages per 100 patient years were detected among the nonusers. Fifty-five drug-related hemorrhages, where four were preventable, were detected. As observed, the incidence rate of hemorrhages among the users of anticoagulation, antiplatelet and NSAID'S were 1.9 times greater than the nonusers. The preventable drug-related hemorrhages have resulted in prolonged bleeding and temporary injury.

Studies imply that the use of anticoagulation, antiplatelet and NSAID's increase the risk of hemorrhage (especially among elderly patients), where in some cases hospitalization, blood transfusion, or surgical intervention is required. When anticoagulation, antiplatelet or NSAID's are combined or used together with other drugs, the chance of hemorrhage further increases [8, 11, 13, 14]. In contrary, the results of this study shows an almost similar rate of hemorrhages between patients using anticoagulation (49.8 drug-related incidents of hemorrhage per 100 patient years) and combination of two or more of the drugs mentioned (47.5 drug-related incidents of hemorrhage per 100 patient years). The results of this study did not show an increase risk on hemorrhage by the use of combination drugs.

In comparison with other studies, this study shows a lower rate of preventable drug related incidents of hemorrhage. The HARM study stated that 46% of the acute drug-related hospital admissions are preventable and 29% of these preventable drug-related hospital admissions are residents of a long-term care facility [14]. Among the 400 anticoagulation, antiplatelet and NSAID's users, 55 incidents of drug-related hemorrhages within 28 patients of which four were preventable were detected. Hospitalization was needed by only one drug-related incident. Of the preventable drug-related incidents of hemorrhage, no hospitalizations were required. Every physician, specialist, health care facility and hospital established in the Netherlands should adhere to the guidelines provided by the Trombosedienst and the Dutch health care system to ensure the safety of the patients using certain drugs such as anticoagulation, antiplatelet and NSAID's. Therefore the assumption is made that the preventable drug-related incidents of hemorrhage are low due to the close monitoring of the patients using these drugs and the use of preventive medications when is needed.

Risk factors such as age, comorbid ability, polypharmacy, dependent cognitive ability, etc in combination with the use of anticoagulation, antiplatelet, NSAID's are known to increase the risk of

hemorrhage. [7-10]. When the risk factors in combination with the use of these drugs were analyzed, it was perceived that most of the risk factors did not increase the risk on hemorrhage. However, it was observed that the use of multiple medications (polypharmacy) has an increased risk on the occurrences of hemorrhage. This study shows a greater risk of hemorrhage among patients taking six or more prescription medication a day than patients taking less than six prescription medication a day. This corroborates the findings noticed in the other studies.

During the study it was observed that many patients having a hemorrhage did also experience a trauma or were wearing a CAD when the hemorrhage occurred. It was also discerned that the situations mention above in combination with the use of anticoagulation, antiplatelet and NSAID's increases the risk on hemorrhage (1.4 time higher risk of hemorrhage among the anticoagulation, antiplatelet and NSAID's users in comparison with the nonusers). Therefore the assumption is made that the use of CAD and having a trauma in combination with the use of anticoagulation, antiplatelet and NSAID's may increase the risk on hemorrhage. However, it is still uncertain if these situations are truly the cause of the hemorrhage or is it the drugs or the combination of the use of the drugs in combination with these situations.

Studies show that anticoagulation, antiplatelet and NSAID's users have a greater risk of experiencing hemorrhages than nonusers (1.3 times higher while using anticoagulation, 1.2 times higher using NSAID's and 1.3 to 1.9 times higher using combination therapy). Relatively, this study has also observed a greater risk on hemorrhage among the anticoagulation, antiplatelet and NSAID's users than the nonusers. A significant difference of 1.9 fold higher risk on hemorrhages was observed between the two groups. This rate is higher compared to the other studies. This might be due to the uneven distribution of the male and female gender especially among the nonusers. Studies imply that the male gender has a higher risk on experiencing hemorrhage in comparison with the female gender. The anticoagulation, antiplatelet and NSAID's users had a more even distribution of the gender, but had a greater amount of male in comparison with the nonusers. The nonusers group comprised of 74% female participants. Assumption is made that if the distribution of the genders were even in the nonusers group, the incidence rate of hemorrhage could have been different [5-7, 13].

The literature implies that GI bleeding and GI complication are the most occurred drug-related ADR [14]. According to the findings of this study, hematuria and hematoma were the most occurred drug-related hemorrhages. Rectal bleeding and GI bleeding were on the fourth and sixth place. The reason for this outcome is mainly due to the objective of this study. The main focus of this study was to determine the occurrences of preventable drug-related hemorrhage in general. Thus, from a minor bleeding that lasts longer than usual to a major bleeding that might require hospitalization or causes death. Contrary to this study, the main focus of most of the other studies conducted was hemorrhages which causes hospitalization or required an intervention or monitoring in order to prevent harm. Therefore hematoma and hematuria were not seen as the most common (preventable) drug-related hemorrhage. However, when the risk of hemorrhage among the anticoagulation, antiplatelet and NSAID users were compared with the nonusers, a noticeable increase on the risk of GI bleeding, vaginal bleeding, nose bleeding and conjunctivae bleeding was noticed. The risk on hematoma was the same within the two groups. Yet, the risk of hematuria was 3.2 times higher among the anticoagulation, antiplatelet and NSAID users. As it was observed before, the use of anticoagulation, antiplatelet and NSAID increases the risk of hemorrhage.

Limitations

One of the methods that were used to identify the preventable drug-related incidents of hemorrhage was the algorithm of Kramer at al. This algorithm was designed to observe drug-related ADR in general. In other words, it is a perfect tool to observe (new) clinical manifestation as an actual side effect of an administered drug. In this study, it is already known that hemorrhages are a universally known side effect of anticoagulation, antiplatelet and NSAID's. Due to this reason, a minimum score were automatically given to some axes. As a consequence, even though the hemorrhage was not a preventable drug-related incident, the scoring system considered it as possible preventable drug-related incidents.

Conclusion

Antiplatelet were the most prescribed drug among the three drugs that were being studied. In contrast with the literature revolving around this topic, this study shows a low incidents rate of preventable drug-related hemorrhages among elderly living in the nursing home. The preventable drug-related incidents of hemorrhage have resulted in prolonged bleeding and temporary injury. The risk of hemorrhage among the anticoagulation, antiplatelet and NSAID's users are 1.9 fold greater than nonusers. An increased risk coincides with the literature.

Recommendations

This study shows that preventable drug-related incidents of hemorrhage rarely occur among residents of the nursing homes of Carintreggeland. However, some particular points of interest that can be improved have been observed. To improve the quality of care of these nursing homes and the patient safety, following recommendations were formulated.

Anticoagulation and drug-drug interaction:
Anticoagulation is the most prescribed drug in this nursing home. Most hemorrhages caused by the use of anticoagulation were due to drug-drug interaction (in particular antibiotics). Hemorrhages due to drug-drug interaction between anticoagulation and antibiotics can be prevented by closer monitoring of these patients. Informing the "Trombosedienst" about the use of antibiotic and adjustment of the dosage of the anticoagulation, may decrease the number of incidents of hemorrhage caused by drug-drug interaction.

Further research:
The most common type of hemorrhages experienced by the residents of this nursing home was hematuria and hematoma. These types of hemorrhages can also be caused by a trauma or the use of CAD. In this study it was noticed that most of the incidents of hematoma and hematuria in both groups had a trauma or uses CAD. Therefore, it might be interesting to evaluate if these situations had an influence on the occurrences of hemorrhages and how they might be prevented.

NOAC are strong oral anticoagulation's that have been used for many years for the treatment of thrombosis after knee and hip surgery. Momentarily, NOAC is used as a replacement of the vitamin K-antagonist. This replacement has its advantages and disadvantages. The difference between these two types of anticoagulation is that the strict monitoring of INR, that is required with the use of vitamin K-antagonist, is not necessary when using NOAC. However, the use of vitamin K as an antidote in extreme bleedings, which is possible by vitamin K-antagonist, is not possible when using NOAC. It is uncertain what the consequence might be when using NOAC. It is interesting, therefore,

to ascertain if there is a difference in the occurrences of drug-related hemorrhages between these two medications and what the consequences are, it isrecommended to conduct a research regarding this topic.

This study was carried out in the 18 nursing homes of Carintreggeland. There are approximately 479 nursing homes in the Netherlands. Therefore, it might be interesting to evaluate how often the incidents of (preventable) drug-related hemorrhage do occurs in other nursing homes and what are the main consequences.

A follow-up study is recommended to ensure a high quality of care. It is the first time that a study on the occurrences of drug-related hemorrhages was carried out among residents of Carintreggeland. Therefore, to ascertain if the nursing home has improved in its quality of care provided to its clients, it is recommended to perform a follow-up study to compare the results of the actual study with the results of the follow-up study.

References

1.   Unknown. National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP).   [2012]; Available from: http://www.nccmerp.org/aboutMedErrors.html.

2.   Unknown. INR (International Normalized Ratio). Available from: http://www.trombosestichting.nl/patienten/behandeling/inr.html.

3.   Hui-Ling Liao ea. Analysis of drug–drug interactions (DDIs) in nursing homes in Central Taiwan. Archives of Gerontology and Geriatrics 2008;47:99-107.

4.   P.M.L.A. van den Bemt ea. Medication Administration Errors in Nursing Homes Using an Automated Medication Dispensing System. Journal of the American Medical Informatics Association. 2009;16:486–92.

5.   Maagd Gd. Nurses, who are at the front lines of health care in all areas of practice, should be aware of drugs that may cause serious problems for elderly patients. Geriatric Nursing. 1995;16:198-207.

6.   Johannes Oldenburg ea. Current pharmacogenetic developments in oral anticoagulation therapy: The influence of variant VKORC1 and CYP2C9 alleles. Journal of the International Society on Thrombosis and Haemostasis. 2007;98:570–8.

7.   Ronda G. Hughes ea. Medication Administration Safety. Patient Safety and Quality: An Evidence-Based Handbook for Nurses. San Francisco.
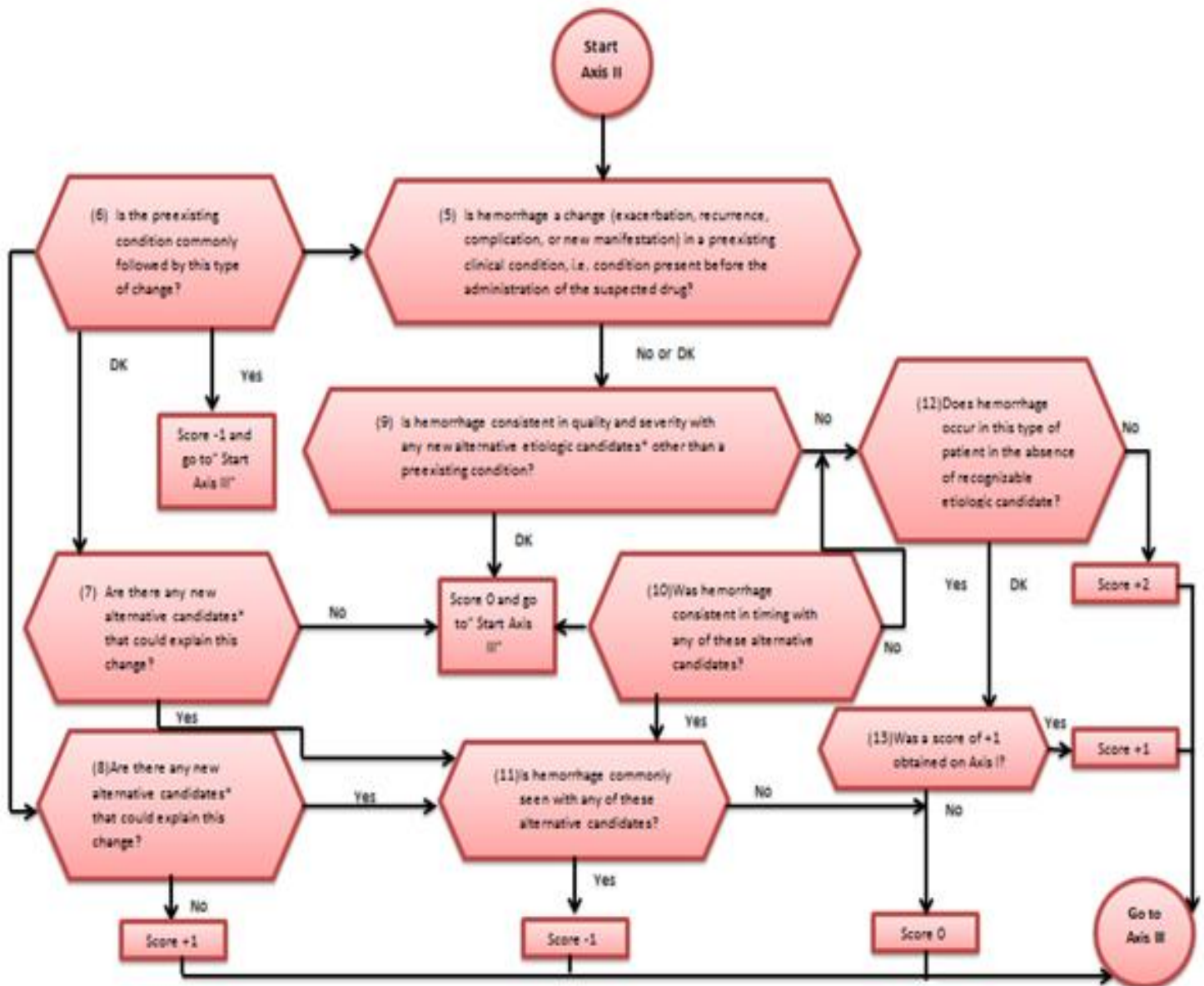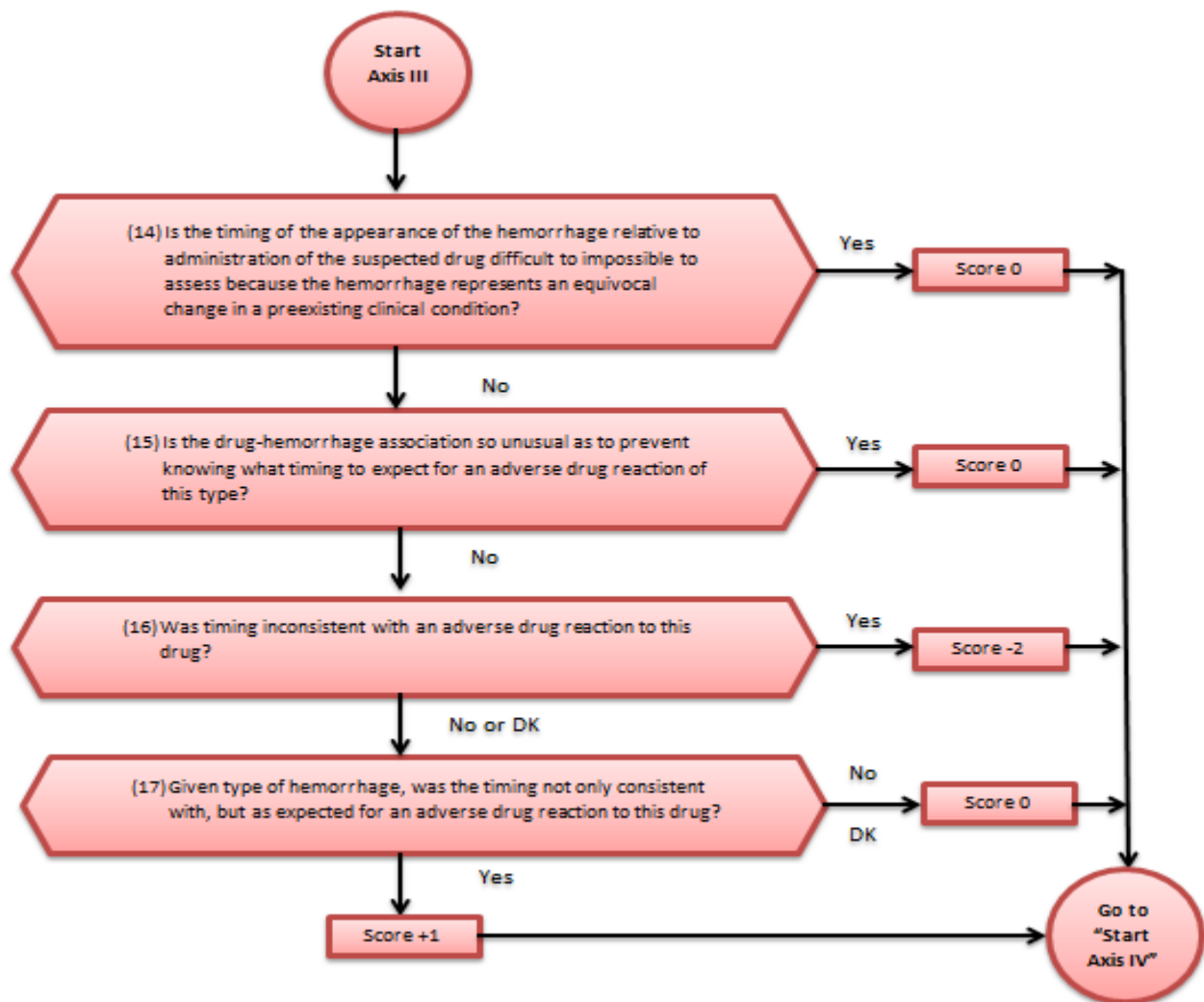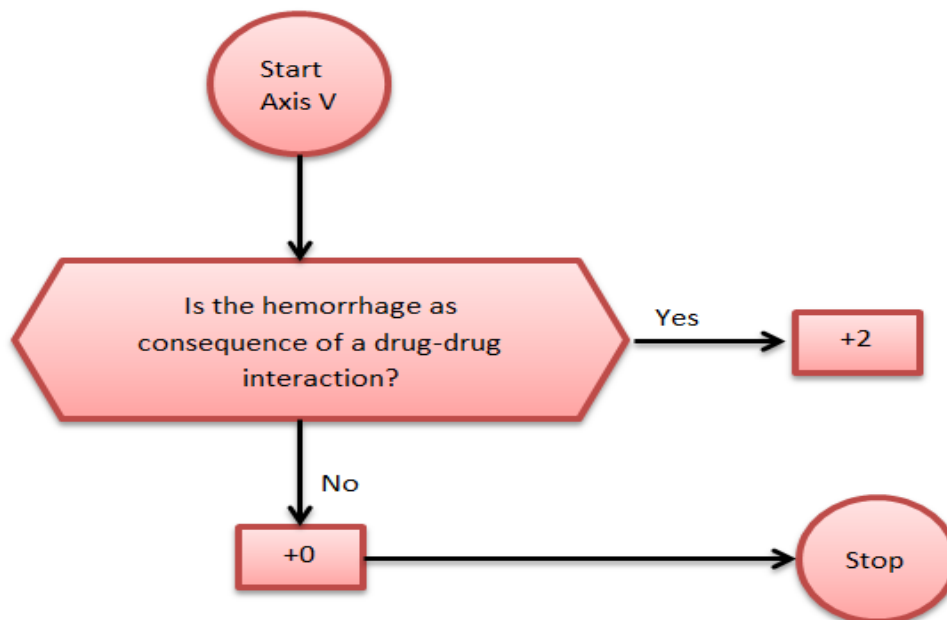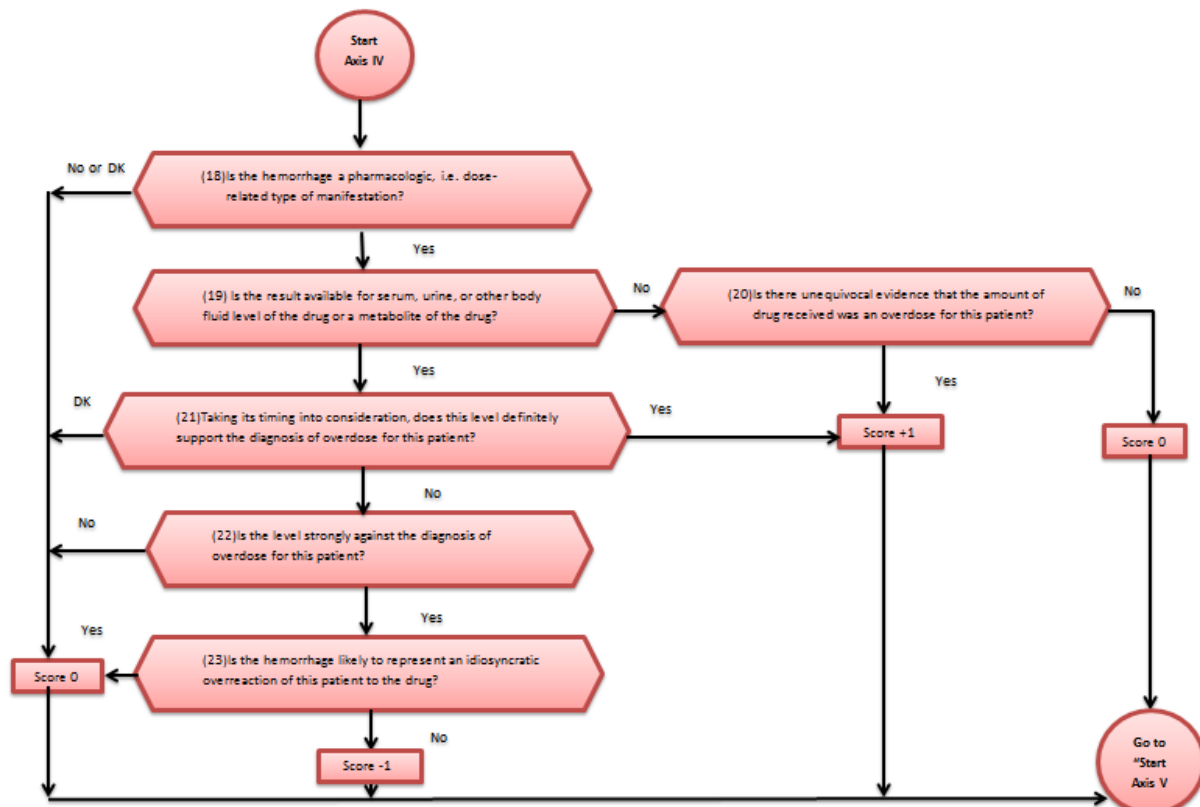
8.   C. Michael Stein ea. Educational Program for Nursing Home Physicians and Staff to Reduce Use of Non-Steroidal Anti-Inflammatory Drugs Among Nursing Home Residents. Medical Care. 2001;39(5):436-45.

9.   Peura DA. Gastrointestinal safety and tolerability of nonselective nonsteroidal anti-inflammatory agents and cyclooxygenase-2-selective inhibitors. Cleveland Clinic Journal of Medicine. 2002;69(1):31-9.

10.   Unknown. NSAID-gebruik en preventie van maagschade. Utrecht: Kwaliteitsinstituut voor de Gezondheidszorg CBO2003.

11.   Harold B. Oral Anticoagulation in Nursing Home Residents. JAMDA. 2003.

12.   Gualtiero Palareti ea. Bleeding with anticoagulation therapy – Who is at risk, and how best to identify such patients. Journal of the International Society on Thrombosis and Haemostasis. 2009;102:268–78.

13.   Brian J. Quilliam ea. Effect of Antiplatelet and Anticoagulant Agents on Risk of Hospitalization for Bleeding Among a Population of Elderly Nursing Home Stroke Survivors. Journal of the American Heart Association. 2001;32:2299-304.

14.   Medicatieveiligheid E. HARM-WRESTLING Een voorstel van de Expertgroep Medicatieveiligheid m.b.t. concrete interventies die de extramurale medicatieveiligheid op korte termijn kunnen verbeteren. The Hague: Ministerie van Volksgezondheid, Welzijn en Sport 2008.

15.   Unknown. Verpleeg- en verzorgingshuizen per gemeente 2009. 2009; Available from: http://www.zorgatlas.nl/zorg/langdurige-zorg/verpleging-en-verzorging/verpleeg-en-verzorgingshuizen-per-gemeente-2009/.

16.   Unknown. Verpleeghuizen en verzorgingshuizen. Available from: http://www.rijksoverheid.nl/onderwerpen/verpleeghuizen-en-verzorgingshuizen/vraag-en-antwoord/wat-is-het-verschil-tussen-een-verzorgingshuis-en-een-verpleeghuis.html.

17.   Unknown. Over Carintreggeland Available from: http://www.carintreggeland.nl/content/1/3/over_carintreggeland.aspx.

18.   Michael S. Kramer ea. An Algorithm for the Operational Assessment of Adverse Drug Reactions

I. Background, Description, and Instructions for Use. JAMA. 1979;242:623-32.

19.   Prevention. NCCfMERa. NCC MERP Index for Categorizing Medication Errors. 2001.

20.   MS Cohen ea. Calculation of incidence rate ratios and 95% confidence intervals. The New England Journal of Medicine. 2011;365:493-505.

Appendix 1: Algorithm of Kramer et al

```
            ┌─────────┐
            │  Start  │
            │ Axis I  │
            └─────────┘
                 │
                 ▼
```

(1) Is hemorrhage widely known and universally accepted as an adverse drug reaction to the suspected drug?   —— Yes ——▶   (2) Is hemorrhage widely known to occur at the dosage received in this   —— Yes ——▶   Score +1

No or DK ↓   No   DK

(3) Consult the Farmacotherapeutisch Kompas. Is hemorrhage listed as an adverse reaction to the suspected drug in the dosage received?   —— Yes ——▶

No ↓

(4) Has enough clinical experience accumulated with the drug so that most incidence of hemorrhage to it is likely to have been previously reported?   —— No / DK ——▶   Score 0

Yes ↓

Score -1   ——————————————————▶   Go to Axis II

Appendix 2: NCC MERP Index for Categorizing Medication Error Algorithm

Circumstances or events that have the capacity to cause error

Did an actual error occur? — NO → **Category A**

YES ↓

Did the error reach the patient? * — NO → **Category B**

YES ↓

Did the error contribute to or result in patient death? — YES → **Category I**

NO ↓

Was the patient harmed?

NO → **Was intervention to preclude harm or extra monitoring required?**
 - NO → **Category C**
 - YES → **Category D**

YES ↓

Did the error require an intervention necessary to sustain life?

NO → **Was the harm temporary?**
 - YES → **Did the error require initial or prolonged hospitalization?**
   - NO → **Category E**
   - YES → **Category F**
 - NO → **Category G**

YES ↓

Was the harm permanent?
 - YES → **Category G**
 - NO → **Category H**

Harm
Impairment of the physical, emotional, or psychological function or structure of the body and/or pain resulting therefrom.

Monitoring
To observe or record relevant physiological or psychological signs.

Intervention
May include change in therapy or active medical/surgical treatment.

Intervention Necessary to Sustain Life
Includes cardiovascular and respiratory support (e.g., CPR, defibrillation, intubation, etc.)

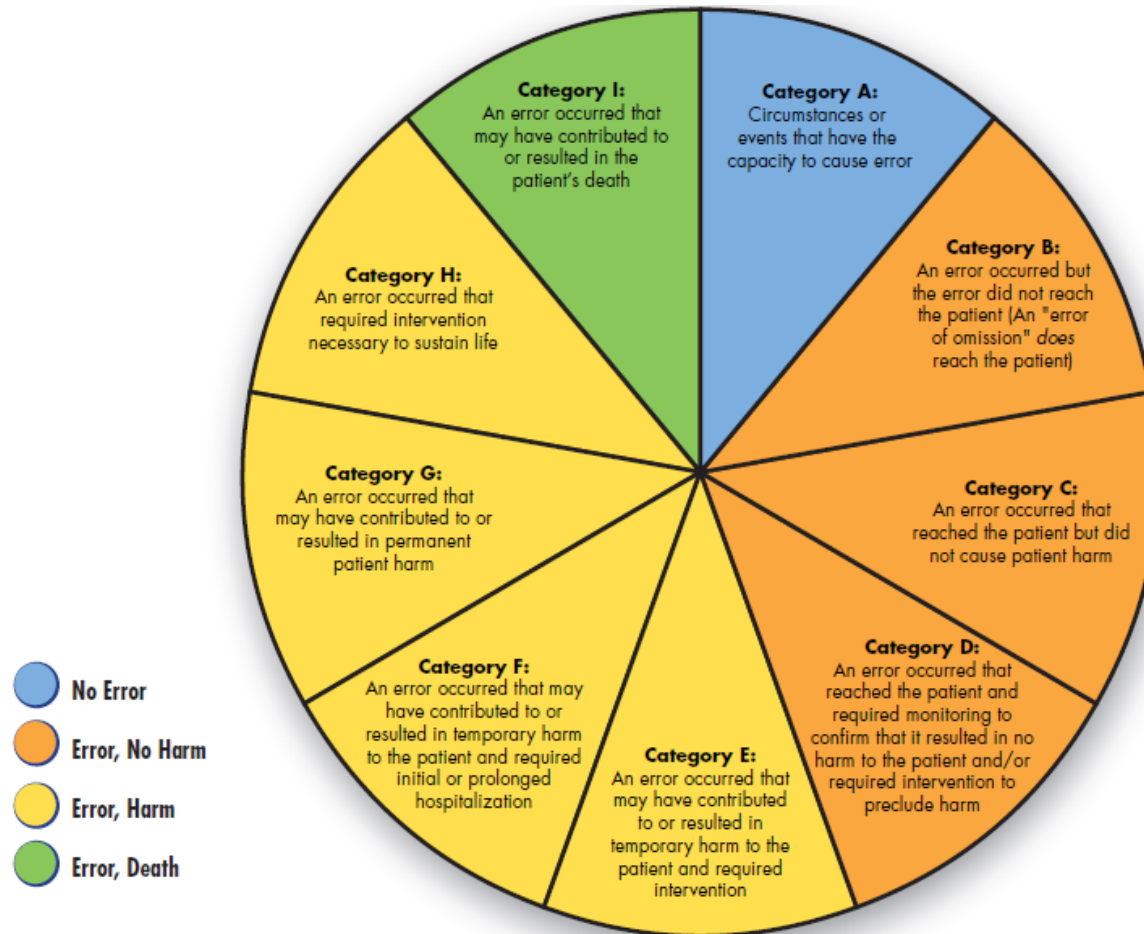*An error of omission does reach the patient.

© 2001 National Coordinating Council for Medication Error Reporting and Prevention. All Rights Reserved.

* Permission is hereby granted to reproduce information contained herein provided that such reproduction shall not modify the text and shall include the copyright notice appearing on the pages from which it was copied.

PSF030X

Appendix 3: NCC MERP Index for Categorizing Medication Errors

Category I:
An error occurred that may have contributed to or resulted in the patient's death

Category A:
Circumstances or events that have the capacity to cause error

Category B:
An error occurred but the error did not reach the patient (An "error of omission" does reach the patient)

Category H:
An error occurred that required intervention necessary to sustain life

Category C:
An error occurred that reached the patient but did not cause patient harm

Category G:
An error occurred that may have contributed to or resulted in permanent patient harm

Category D:
An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm

Category F:
An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization

Category E:
An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention

Legend:
- No Error
- Error, No Harm
- Error, Harm
- Error, Death

Definitions

Harm
Impairment of the physical, emotional, or psychological function or structure of the body and/or pain resulting therefrom.

Monitoring
To observe or record relevant physiological or psychological signs.

Intervention
May include change in therapy or active medical/surgical treatment.

Intervention Necessary to Sustain Life
Includes cardiovascular and respiratory support (e.g., CPR, defibrillation, intubation, etc.)

PSF0306

Appendix 4: Medical Record Form

No.	Date:	
General information		
Resident, discharge or death		
Patient number		
Date of birth		
Gender		
Name of the nursing home		
Ward		
Length of stay (LOS)		
Cognitive ability		
Trauma		
CAD		

History		
Disorder(s)	Before admitted	Reason admission
Total chronic medicatoion		
Ended		
OTC		
Extra medication		
Chronic and OTC		

Adverse events			
Hemorrhage			
Type(s) of hemorrhage	1)		
	2)		
	3)		
	4)		
	5)		
Duration hemorrhage	Start date	End date	Duration in months
	1)		
	2)		
	3)		
	4)		
	5)		
Reason	1)		
	2		
	3		
	4		
	5		
Total number of incidents			