TARGETING OUTPATIENT DRUG SAFETY: RECOMMENDATIONS OF THE DUTCH HARM-WRESTLING TASK FORCE

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ACKNOWLEDGEMENTS SECTION:

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Competing interest

All authors declare that there were no competing interests.

Contributors

PdS contributed to conception and study design. PvdB and MS provided access to the anonymized crude data of HARM and IPCI. MW and PdS combined these into a single database and used it for further analysis. PdS collected and aggregated the background literature. The Task Force (including PvdB,MS,MW, CK and PdS) interpreted the data and developed the recommendations. All authors contributed to the drafting of the manuscript and, and approved the final version of the report.

Funding

This multidisciplinary consensus was funded by the Dutch ministry of Health, Welfare and Sport. They played no role in the design and conduction of the study, nor in the collection, management, analysis, interpretation of the data, review or approval of the manuscript.

Acknowledgements

We would like to thank members of the Task Force: H. Buurma, F. Boersma, H. Folmer, J.L.M. van Klundert, M.E.A.P. Kokenberg and R.J. van Marum. Furthermore we would like to thank A.M. Linssen for her assistance to create a schematic overview of the guidelines for secondary prevention of arterial thrombosis and M. Roukens for her correction on typographic errors on the final report.

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ABSTRACT

Background: Two Dutch observational studies (HARM and IPCI) have shown that approximately 5% of all unplanned hospital admissions are due to adverse drug reactions of which 40-46% are avoidable. These studies prompted the initiation of a Dutch multidisciplinary Task Force with the assignment to reduce the number of prescriber-related hospital admissions related to medications (HARMs) in a quick win way.

Objective: To develop a limited number of recommendations for concrete interventions, which should be feasible and relatively easy to convert into computerized drug safety alerts.

Method: To identify the major adverse drug reactions (ADRs), crude data of HARM and IPCI were reanalyzed and compared with different international studies, followed by structured literature searches for further characterization of the identified ADRs, their risk factors and potential risk reduction strategies. Based on this information, the Task Force drew up general and drug-specific recommendations. As the recommendations of the Task Force are a mixture of evidence-based and expert-based risk-reducing strategies, they have been graded in accordance with the GRADE methodology.

R**esults:** Seven pharmacologically predictable ADRs associated with ten drug classes were responsible for more than half of all potentially preventable hospital admissions in the HARM and IPCI studies, which was comparable to the results of international studies. Gastrointestinal and other bleedings were the most frequent ADR, followed by electrolyte disturbances, fractures, disturbances of diabetes control, renal insufficiency and heart failure. Nine general and thirty-four drug-specific recommendations were developed.

Conclusions: As HARMs constitute a significant public health problem, the Task Force underlines the need to implement its recommendations as soon as possible. They do not replace existing guidelines, but reinforce, complement and fine-tune existing national and international guidelines. Further research is still required to assess the cost-consequences and cost-effectiveness of some recommendations, and to monitor the implementation of the recommendations and their effect on the incidence of potentially preventable HARMs.

1 BACKGROUND

After a Dutch literature review in 2002 had shown that hospital admissions due to adverse drug reactions (ADRs) pose a significant, expensive and partially avoidable public health problem[1], two Dutch research groups performed studies to establish the nature, volume and preventability of drug-related hospital admissions in The Netherlands.

First, a retrospective cohort-study in the "Integrated Primary Care Information" database (hereafter designated as the IPCI study) evaluated the extent, characteristics and determinants of ADR-related hospitalizations [2;3]. Hospital admissions due to deliberate or unintentional overdose or due to non-adherence were excluded and the avoidability of the drug-related reasons for hospital admission was assessed applying the algorithm of Hallas et al. [4] and the criteria of Schumock and Thornton [5]. The IPCI study identified 3515 hospital admissions, of which 2238 were unplanned. 115 cases of these unplanned admissions were medication related. Its outcome was that 5.1% of all unplanned hospital admissions in The Netherlands were definitely or probably caused by ADRs [2;3].

Subsequently a larger prospective case-control study, the so-called HARM (Hospital Admissions Related to Medication) study, looked at unplanned medication-related hospitalizations and determined their potential preventability and associated risk factors [6;7]. During 40 days all unplanned admissions (exclusion criteria were age below 18 years, admission for obstetric indications, psychiatric admissions, and admissions for self poisoning) were evaluated for their potential relation to drug use by using the algorithm of Kramer et al.[8]. The preventability of the admissions was assessed applying a modified version of the criteria of Schumock and Thornton [5]. The HARM study identified 13,000 unplanned hospital admissions of which 714 were related to medication. The study showed that 5.6% of all unplanned hospitalizations in The Netherlands were drug-related and that 46% of these were potentially preventable[6;7].

These studies prompted the Dutch Ministry of Health, Welfare and Sport to initiate a multidisciplinary task force with the assignment to make concrete recommendations on how to reduce the observed potentially preventable HARMs in a quick win way ("low hanging fruit").

2 METHODS

The Task Force successively took the following steps:

1) Identification of the most relevant ADRs.
2) Further analysis of their epidemiology and identification of their risk factors.
3) Identification of HARM-reducing strategies.
4) Structured approach for drawing up concrete recommendations.
5) Identification of prominent general issues.

2.1 IDENTIFICATION OF THE MOST RELEVANT ADVERSE DRUG REACTIONS

Crude data of all potentially preventable HARMs in the IPCI and HARM studies were retrieved in anonymized form from the researchers, combined into one data set and

reanalyzed to identify the responsible drug(s), the clinical reason for the hospital admission and any further potentially relevant details. This analysis was complemented by looking at international studies of drug-related hospital admissions.

Since the Task force aimed to reduce the number of HARMs with a limited number of concrete interventions, the identification of medications and drug groups as 'risk medications' was more based on absolute numbers than on the relative incidence of potentially preventable hospital admissions. Furthermore, only ADRs related to prescribing errors were included, since user-related complications would require different kinds of interventions [9].

Pooling the IPCI and HARM results yielded a total of 829 medication related hospital admissions, of which 367 (44%) had been rated as potentially avoidable. When only the prescriber-related problems were taken into consideration, seven types of ADR associated with ten different drug groups accounted for more than half of all these potentially preventable admissions (Table I).

These results were in line with the results of international studies[10-12] .

Table I. Major potentially preventable ADRs and their corresponding drug classes according to the HARM/IPCI data.

Potentially preventable adverse effects	Number of cases[a]	Most important drug class(es)
Gastrointestinal and other bleedings	84 (40.8%)	Vitamin K antagonists platelet aggregation inhibitors NSAIDs
Electrolyte disturbances	30 (14.6%)	Diuretics RASI (hyperkalaemia)
Fractures	26 (12.6%)	CNS medications (through falls) Corticosteroids (through osteoporosis)
Disturbances of diabetic control	32 (15.5%)	Blood-glucose lowering drugs (mainly hypoglycaemia) Corticosteroids (hyperglycaemia)
Renal failure/ heart failure	13 (6.3%)	RASI (renal failure) NSAIDs (renal failure and heart failure)
Constipation	11 (5.3%)	Opioids
Bradycardia	10 (4.9%)	Cardiac drugs (sotalol/digoxin)
Total (367 potentially preventable admissions)	**206 (56%)**	

NSAIDs = non-steroidal anti-inflammatory drugs; **RASI** = Renin angiotensin system inhibitors; **CNS** = central nervous system

a The percentages between brackets are derived from a total of 367 potentially preventable admissions.

2.2 FURTHER ANALYSIS AND IDENTIFICATION OF RISK FACTORS.

According to the IPCI and HARM studies, patients at risk for HARMs are characterized by advanced age, polypharmacy, multiple co-morbidity (four or more), impaired cognition, non-adherence to medication, impaired renal function and/or a dependent living situation[2;7]. To obtain further information about the epidemiology of the identified ADRs and their risk factors, various literature searches were performed. The initial basic search strategy consisted of searching Medline through on-line consultation of PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed – entrez date from Jan 01 2000 up to Dec 31 2007) for pertinent articles. Further Medline searches on selected topics were performed in October 2008 and October 2009. Searches usually focused on the Medical Subject Heading (MeSH) of a specific drug or drug group with the qualifier "adverse effects" (e.g. Anti-inflammatory agents, non-steroidal/ adverse effects) and/or on the MeSH term for a specific adverse effect with the qualifier "chemically induced" (e.g. Hemorrhage/chemically induced) without ticking the MeSH boxes for "Restrict search to major topic headings only" or "Do not explode this term". This basic approach was supplemented with an incremental search strategy that looked at the bibliography of every useful reference retrieved for additional references and that iterated this procedure if necessary. The identification of risks and risk factors was not only based on randomized double-blind studies, but also on well designed and performed observational studies, since randomized studies are not necessarily designed to compare the safety of different drug treatments. Furthermore, high risk patients are often excluded in randomized trials [13;14].

2.3 IDENTIFICATION OF HARM-REDUCING STRATEGIES.

Following the example of many current guidelines, the Task Force decided to look not only for well-proven HARM-reducing strategies but to consider potentially relevant strategies as well. Strategies were particularly identified by searching Medline for combinations of the MeSH terms used in the previous step with the MeSH "intervention studies" or with the Publication Type "Clinical Trial". This basic approach was supplemented with an incremental search strategy that looked at the bibliography of every useful reference retrieved and that iterated this procedure if necessary, and at current national and international guidelines.In addition the references retrieved in step 2 were screened for information about risk reduction.

2.4 DRAWING UP CONCRETE RECOMMENDATIONS.

The Task Force developed and executed a structured approach for the drawing up of concrete recommendations on the basis of the previous steps. Firstly, it made its assignment to focus on "low-hanging fruit" operational by stipulating that it should be feasible and relatively easy to convert each recommendation into a computerized drug safety alert and to build in these alerts into the current decision support systems for safe prescribing and dispensing by general practitioners, community pharmacists and outpatient clinics. For instance, the Task Force decided to advise against the prescribing of glibenclamide to patients ≥ 70 years (because the risk of a potentially serious hypoglycaemia is relatively high) but it did not drew up concrete recommendations on how to improve the self-management of patients with diabetes.

This stipulation of easy integration into current prescribing and dispensing systems does not only offer the advantage that the recommendations can be integrated relatively smoothly into daily practice, but also facilitates the structural monitoring of adherence to the recommendations by means of quality indicators (for instance, by measuring over time how often glibenclamide is still being prescribed and dispensed to patients ≥ 70 years).

As the Task Force recommends a mixture of evidence-based and expert-based risk-reducing strategies, all its recommendations were graded in accordance with the grading method of the GRADE (short for Grading of Recommendations Assessment, Development and Evaluation) Working Group[15-17]. Each recommendation is provided here with a code that is composed of:

- a number to indicate the power of the recommendation: 1 = strong; 2 = weak;
- a letter for the methodological quality of the underlying evidence: A = high quality evidence from RCTs without important limitations or exceptionally strong evidence from observational studies; B = moderate quality evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies; C = low quality evidence from observational studies with at least one critical outcome, case series, or from RCTs with serious flaws or indirect evidence.

To further acceptance and implementation, the Task Force geared its recommendations as much as possible to existing national and international guidelines. They do not replace existing guidelines, but reinforce, complement and fine-tune them.

The Task Force also presented a preliminary draft of its report to various medical and pharmaceutical professional societies in The Netherlands with the request to pass on any constructive criticism. Finally, the Task Force made an effort to minimize unnecessary discrepancies between its separate recommendations (for instance, by preferring the same general age limit of 70 years wherever possible).

2.5 IDENTIFICATION OF PROMINENT GENERAL ISSUES

In the course of its work, the Task Force identified several general issues that needed to be addressed in addition to its specific recommendations:

2.5.1 REDUCTION OF UNINTENTIONAL RECHALLENGES

Studies have shown that a drug which has been stopped during a hospital stay because of an ADR, may be represcribed to the patient after his or her hospital discharge [18-20]. Yet a previous ADR can be an important risk factor for the recurrence of an ADR, if the patient is exposed again to the same medication [21-24]. It is therefore important that the hospital-based specialist does not only pass on to the general practitioner in a clear way *that* the drug has been discontinued in the hospital but also *why* this has happened.

2.5.2 INFORMING PATIENTS ABOUT ALARM SIGNS AND SYMPTOMS

Besides its recommendations to improve computerized prescribing and dispensing, the Task Force would like to demand special attention to the recognition of alarm signs and symptoms

by the drug users themselves. The direct reason was that, according to some of the discharge letters that were analyzed in the IPCI study, melaena had already been present in the days preceding hospitalization because of a GI bleeding. Information about alarm signs and symptoms should be presented, of course, very carefully (preferably in the form of oral communication supported by written material[25]) to prevent that the patient is frightened by this information in such a way that he decides on his own not to take the prescribed risk medication.

2.5.3 ECONOMIC ANALYSES

Although the performance of economic analyses was beyond its assigned scope, the Task Force recognized that some of its recommendations needed to be submitted to formal cost-consequence and cost-effectiveness analyses, because they require additional medications (e.g. gastric protection) or laboratory testing (e.g. creatinine and potassium) which will therefore generate extra costs.

2.5.4 OTHER GENERAL ISSUES

The Task Force identified several other general mechanisms which increase the risk of HARMs and therefore require due attention (see Table II: Summary of general recommendations).

Table II. Summary of general recommendations

nr	Recommendation
1	Discussions on the improvement of drug safety in outpatients should not only focus on short-term quick wins, but also on longer-term risk reducing strategies. Among the subjects to be considered are[9]: a) The reduction of potentially preventable HARMs which occur less frequently. b) The reduction of potentially preventable adverse effects which do not lead to hospital admission. c) The prevention, screening and reduction of nonadherence to therapy and other user-related problems affecting drug safety. d) To extend the attention which this review already pays to risk factors and to improve current computerized medication surveillance systems by taking such risk factors (and their mutual interactions) more systematically into consideration. In complex cases it may be desirable to estimate the patient's individual risk of an adverse drug effect by means of an especially developed risk model[9]. e) The furthering of adhering to the principles of "clinical risk management" by healthcare professionals[26;27]. Examples of questions which should be answered in this context are: • Which risk situations and processes need additional attention? • Can high risk health care professionals be identified besides high risk medications, high risk patients and high risk processes? • Do health care professionals have an adequate culture with respect to drug safety[28;29] ? • Is it possible to improve the current prioritization of computerized medication surveillance signals? • What is the optimal way to surveil each individual risk? f) The use of new ICT options, such as consultation and application of electronic patient records through connections between the different computer systems of health care professionals and institutions in primary and secondary care. g) Implementation of a centre for the nationwide collection and evaluation of medication errors in outpatients.
2	Healthcare professionals should be aware of the fact that a substantial part of the potentially preventable HARMs are due to a limited number of well-known pharmacologically predictable adverse drug reactions caused by a limited number of well-established drug classes. They implement risk reducing strategies in the short term which are specifically aimed to these drug-related problems.
3	When an elderly patient uses at least five or more chronic medications, prescribed by different physicians, these prescribers should reach agreement on which physician is the overall director of drug therapy (which is not necessarily the same as assuming all responsibility in the legal sense). They record this overall director in their patient records and also communicate this to the dispensing pharmacist(s) of that particular patient.

(Table II continued)

nr	Recommendation
4	When a risk medication is initiated which is not intended by definition for prolonged use (e.g., a VKA, NSAID, opioid, benzodiazepine) the prescriber informs, if possible, any other relevant physician and the dispensing pharmacist about the expected length of this drug therapy. This expected length should be recorded in the computerized file of that patient. If the expected length cannot yet be established, because it should first become clear whether a drug will have the desired effect (e.g. in the case of an antidepressant), a date is selected on which the effectiveness of the drug therapy is evaluated and on which the expected length of the therapy can be determined.
5	When a medical specialist initiates a drug treatment, which is subsequently continued by a general practitioner, both health care professionals agree and document who is responsible for periodic controls, re-evaluation, repeat prescriptions, and the length of therapy. General practitioners who take over repeat prescribing from a medical specialist, are responsible for these repeat prescriptions, unless there is a well-documented agreement with the specialist (e.g. in the form of a discharge letter) that the latter remains responsible [30].
6	In elderly patients on polypharmacy, physicians and pharmacists periodically evaluate which drugs could or should be continued by means of a medication review. Since elderly patients on polypharmacy are not only at risk of overtreatment, but also of undertreatment[31;32], it should also be assessed whether any essential drug is unjustly missing. Health care professionals are aware that medication reviews are only appropriate to identify problems which gradually emerge but that they are less effective for the prevention of HARMs which primarily become manifest within 1-2 weeks after the start or adjustment of a drug treatment.
7.	The computer systems of the prescribing physicians and dispensing pharmacists should support the implementation of the recommendations in this report as well as possible. If the systems cannot provide adequate support for this implementation, they should be made more suitable for this task. The Task Force particularly has in mind: - Recording which physician is the overall director of drug therapy, and who is responsible for the indication and expected length of therapy of each risk medication. - The recording of laboratory values (such as creatinine, sodium, potassium) in such a way that it allows automatic use in the computerized medication surveillance of patients on risk medications. - Recording of earlier ADRs, impaired cognition, and other risk factors in such a way that it allows automatic use in the computerized medication surveillance of patients on risk medications. - The identification of complex risk patients and the proposal of potential actions which are desirable in these particular patients. Computer systems should be designed in such a way that quality control of the execution of specific recommendations can be realized relatively easily.[a]

(Table II continued)

nr	Recommendation
8.	When medication is discontinued in hospital because of a significant adverse effect, the physician quickly and adequately informs the patient himself, other physicians and pharmacists who are directly involved in the treatment of the patient. This is preferably communicated through a special note documenting the discontinuation of the drug (e.g. a pharmaceutical discharge letter). The physician should not only communicate which drug is discontinued, but should also provide the motivation and (if relevant) which alternative medication has been selected. Each physician and pharmacist involved documents this information in his computer system in such a way that it allows automatic surveillance to prevent that the drug in question or a closely related one is accidentally restarted. When a drug has caused a serious adverse effect, but has to be continued in spite of this (for example, in the case of an antithrombotic drug), the prescriber rapidly and accurately informs the patient himself and other physicians and pharmacists who are directly involved in the drug treatment of that patient.
9.	If a drug is added to improve safety of a risk medication, the former should be discontinued when the latter is stopped. Software systems should produce an alert when this does not happen.

a For instance, an intervention trial has shown that the combination of brief physician education and the generation of computer alerts improves the prescribing of gastroprotection to high risk NSAID users[33].

nr = number; **HARM** = Hospital Admission Related to Medication; **NSAID** = non-steroidal anti-inflammatory drug; **ADRs** = Adverse Drug Reactions; **VKA** = vitamin K antagonist

3 GASTROINTESTINAL AND OTHER BLEEDINGS

3.1 HARM AND IPCI DATA

Combination of the HARM and IPCI data yielded 84 potentially preventable admissions due to bleeding complications (64 gastrointestinal (GI) and 20 other/unspecified bleedings). From these 84 cases, 39 (46%) concerned patients of 80 years or older.

In all cases the bleeding had been induced by a vitamin K antagonist (VKA), platelet aggregation inhibitor (PAI) and/or non-steroidal anti-inflammatory drug (NSAID). In 47 of the 84 cases (56%) other interacting medications were also involved (Table III).

In the 64 cases of GI bleeding, 11 (17%) patients already had an existing GI problem and adequate gastric protection was lacking in 28 cases (44%). In some of the cases of GI bleeding, the first sign (melaena) had already become manifest days before the ultimate hospital admission. We therefore suggest that users of VKAs, PAIs and NSAIDs should be informed about the alarm symptoms of gastrointestinal bleeding, especially when they are at increased risk. Such information should be presented, of course, very carefully (preferably in the form of oral communication supported by written material[25]) to prevent that the patient is frightened by this information in such a way that he decides on his own not to take the prescribed risk medication.

Table III. HARM/IPCI cases of hospitalization due to gastrointestinal and other bleedings (numbers of cases between brackets).

Gastrointestinal bleedings		
Associated with	**Pre-existing gastrointestinal problems**	**Further comments**
VKA (9)	Ulcer (1)	Irregular VKA use due to alcohol abuse (1) Combination of VKA and antibiotics (excluded co-trimoxazole) (4) including at least 2 cases without extra monitoring of INR)
VKA + NSAID (2)[a] **VKA + NSAID + 2 corticosteroids (1)** **VKA + NSAID + unspecified antidepressant (1)** **VKA + NSAID + unspecified interacting drug (2)**	Diverticular disease (1)	Rectal bleeding (1) VKA non-adherence (1) Poor VKA monitoring (1) No/inadequate gastric protection with PPI (2) Adequate gastric protection (1)
PAIs (12)	ulcer(s) (3) diverticulitis (1) unspecified gastric problem (1)	No/inadequate gastric protection with PPI (4) No hard indication for PAI (1)
NSAIDs (5)		No/inadequate gastric protection with PPI (3) Overdosing in patient with impaired renal function (1)
VKA + PAI (3) **PAI + PAI (6)**[b]	Diverticulitis (1) Gastric resection (1)	No/inadequate gastric protection with PPI (2) No hard indication for combination (2)
PAI +NSAID (8) **PAI + coxib (1)** **PAI+ corticosteroid(7)** **PAI + SSRi (1)** **PAI + unspecified interacting drug (2)** **PAI + NSAID + corticosteroid (1)**	Diverticulitis (1) Previous gastrointestinal bleeding (1)	Diverticular bleeding (3) including 1 case with additional rectal bleeding No/inadequate gastric protection with PPI (14) including 1 case of ranitidine 150mg/day and 2 cases of nonadherence to PPI
NSAID + corticosteroid (2) **NSAID + unspecified interacting drug (1)**		No/inadequate protection with PPI 93)
Subtotal (64)	**ulcer(s) (4)** **diverticular disease (1)** **diverticulitis (3)** **previous gastrointestinal bleeding(1)** **other (2)**	**No/inadequate gastric protection with PPI (28)**

(Table III continued)

Other and unspecified bleedings		
Associated with	**Specification of bleedings**	**Further comments**
VKA (8)	Intracranial bleeding (2) Epistaxis (2) Haemoptoe (1) Abdominal wall haematoma (1) Not specified bleeding (2)	Previous bleeding(s) (2) Inadequate monitoring (1) Combination with antibiotics (other than co-trimoxazole) without extra monitoring of INR (4)
VKA +PAI (2)	Intracranial bleeding (1) Haemoptoe(1)	
VKA + NSAID (2) **VKA + SSRI (1)** **VKA + unspecified antidepressant (1)** **VKA + unspecified interacting drug (2)**	Intracranial bleeding (2) Haemoptoe (1) Bladder bleeding (1) Psoas hematoma (1) unspecified bleeding (1)	Inadequate VKA monitoring (1) Patient started NSAID on his own initiative (1)
PAI (3)	Intracranial bleeding/ cerebral vascular accident (2) Haemoptoe (1)	Relatively high dose level of PAI (1) Fatal case in spite of discontinuation of PAI (1)
PAI + NSAID (1)	Postsurgical bleeding from perineal wound (1)	Temporary discontinuation of PAI before surgery would have been better (1)
Subtotal (20)		
Total (84)		

a One case involved a combination of two NSAIDs.

b Two cases involved a combination of dipyridamole with another PAI.

VKA = vitamin K antagonist; **PAI** = platelet aggregation inhibitor; **NSAID** = non-steroidal anti-inflammatory drug; **SSRI** = selective serotonin reuptake inhibitor; **PPI** = proton pump inhibitor; **INR** = International Normalized Ratio; **coxib** = COX-2 selective inhibitor.

3.2 VITAMIN K ANTAGONISTS

3.2.1 PATHOPHYSIOLOGY

VKAs induce anticoagulation by antagonizing vitamin K and thereby impairing the biological activity of vitamin K-dependent coagulation factors (factor II, VII, IX and X.) Their most common side effect (haemorrhage) reflects their mode of action and narrow therapeutic index. An international normalized ratio (INR) level above 6 increases the risk of haemorrhage considerably [34]. The bleeding risk of a VKA therapy aimed at an INR of 2.5 (range 2.0-3.0) is lower than that of a treatment aimed at an INR > 3[35;36].

3.2.2 EPIDEMIOLOGY

The annual incidence of major haemorrhage ranges between 0.8 and 7.8 episodes per 100 patients years.[1] GI bleeding is the most frequent form (66%)[37].

3.2.3 RISK FACTORS

Risk factors for VKA-induced major bleedings include: intensity of anticoagulant effect, shorter time in therapeutic range, initiation of VKA therapy, increased duration of therapy, advanced age, polypharmacy, history of bleeding, peripheral vascular diseases, cerebral vascular diseases, serious heart diseases, renal insufficiency, presence of malignancy, diverticulitis, history of alcohol abuse, liver diseases, increased plasma trombomodulin, treated hypertension, diabetes mellitus, ischemic stroke, intercurrent diarrhoea and fever, insufficient patient education, Factor IX Ala-10 mutations, cytochrome p450 CYP2C9 and VKORC1 polymorphisms and interfering drugs[21;22;34-41].

According to a recent review it is possible to use warfarin and acenocoumarol in patients with chronic renal insufficiency without dose adjustment since these drugs are metabolised by the liver[42]. Unpublished analyses of acenocoumarol and phenprocoumon users in the Erasmus Rotterdam Health and the Elderly (ERGO) database did not demonstrate an association between renal insufficiency and VKA dose levels or INR levels ≥ 6 (the latter was only analyzed in acenocoumarol users since there were not enough phenprocoumon users) [43]. Close monitoring of the INR in patients with chronic renal insufficiency is nevertheless recommended, because there is some evidence that the pharmacokinetics of VKAs in these patients may be altered, which might increase their risk of adverse effects[42;44].

Several investigators have developed bleeding prediction models for major bleeding during VKA therapy[21;45]. While these rules can be helpful when deciding if therapy should be started, they are inaccurate during long-term treatment of outpatients[34].

Lifestyle factors such as low body mass index, recent weight loss ≥ 2 kg, below-average level of physical activity, history of excessive alcohol intake, having never-smoked and holidays are also risk factors for overanticoagulation (INR≥ 6.0) [46]. Furthermore irregular VKA use and/or changes in dietary habits can cause increases as well as decreases of the INR level[46-48].

Many drugs can increase the bleeding risk of VKAs through a drug-drug interaction: miconazole (including topical creams), phenylbutazone, analgesic acetylsalicylic acid (ASA))/carbasalate calcium , allopurinol, amiodarone, propafenone, protease inhibitors, efavirenz, androgens, anabolic steroids, benzbromarone, cimetidine, danazol, disulfiram, fibrates,

fluconazole, voriconazole, ketoconazole, itraconazole, antibacterial agents (in particular co-trimoxazole, parenteral cefamandole, metronidazole and isoniazid), disopyramide, quinidine, selective serotonin reuptake inhibitors (SSRIs), tamoxifen, rosuvastatin, thyroid drugs, capecitabine, fluorouracil and sitaxentan.
In a Dutch observational study, the main interactive drugs that were associated with major bleeding during VKA therapy under everyday circumstances were low-dose ASA/carbasalate calcium, NSAIDs, and antibacterial drugs[49]. These drugs were also involved in 19/34 (56%) potentially preventable HARM/IPCI cases of VKA-related bleeding.
For the bleeding risk of the concurrent use of VKA with a PAI or NSAID we refer to sections 3.3 and 3.4 of this report, respectively.
Antibacterial agents can be subdivided into agents that interfere with VKA pharmacokinetics (co-trimoxazole, metronidazole, isoniazid) and those that do not[50]. Co-trimoxazole can almost always be substituted and should preferably not be prescribed to VKA users[51]. An exception to this rule can be made for the prophylactic or therapeutic use of co-trimoxazole in opportunistic infections in immunocompromised patients (such as HIV-infected patients)[52;53].
When antibacterial agents without pharmacokinetic interactions with VKAs are used, they can still be associated with an increased risk of an INR ≥6.0 and serious bleeding in VKA users, because these drugs are commonly used in diseases with fever, which is associated with an increased risk of an INR ≥6.0 approximately three by itself[54]. In 8/34 (24%) of the HARM/IPCI cases of potentially preventable bleedings during VKA use, the patient had taken an antibacterial agent without a pharmacokinetic interaction with VKAs and in at least 6 of these cases, there had been no extra control of the INR.

3.2.4 RISK REDUCING STRATEGIES

For general guidance on VKA therapy, the Task Force refers the reader to the clinical practice guidelines of the American College of Chest Physicians (ACCP), the European Society of Cardiology (ESC) and the Dutch Institute for Health Care improvement (CBO)[40;55;56]. To reduce the bleeding risk in VKA users the following startegies should be especially considered:

a) *Careful weighing of the expected benefits and possible risks (without continuing the VKA therapy longer than is strictly necessary).*
   The target range should not only depend on the indication for VKA use, but also on patients characteristics[57].[2] Risk factors, such as irregular use, a pre-existing GI disease or a previous bleeding caused by VKA therapy need to be included in the decision to initiate a VKA therapy[6;21]. Since the duration of VKA-therapy depends on the indication and varies between short-term (six weeks up to six months) and long-term (years up to lifelong), it is crucial that duration of therapy is chosen accurately and communicated with the patient and the other healthcare providers involved.

b) *Careful weighing of the expected benefit of VKAs plus interacting drugs against the possible risk of such combinations.*
   Careful weighing is particularly important when the VKA will be combined with low-dose ASA or an NSAID, since these ulcerogenic drugs increase the bleeding risk without

altering the INR (which makes it impossible for an anticoagulation clinic to prevent the consequences of the interaction by adjusting the VKA dose on the basis of the INR). See section 3.3.

According to a recent meta-analysis the risk of major bleeding was higher in patients treated with low-dose ASA and VKA compared to VKA therapy alone [OR=1.4;1.0-2.0] . In patients with a mechanical heart valve the risk for arterial thromboembolism was lower when they received combined therapy with ASA and VKA compared to VKA alone [OR=0.3; 0.2-0.5]. A similar benefit was not observed in patients with atrial fibrillation [OR=1.0; 0.5-2.1] or coronary artery disease [OR = 0.7; 0.4-1.4], which seriously questions the combined use of ASA and VKA for these latter indications[58].

Table IV gives a systematic overview of the indications for which current guidelines recommend or suggest a combination of VKA with ASA for the secondary prevention of arterial thrombosis. Table V gives an overview of indications for which triple therapy (VKA + ASA + other PAI) can be taken into consideration.Generally, there is no hard indication for double or triple therapy if that indication is not listed in tables IV and V. For some indications, guidelines explicitly discourage double or triple therapy (see table VI).

When the prescriber decides (after careful consideration) to combine a VKA with ASA or an NSAID, it is desirable to add a proton pump inhibitor (PPI) to reduce the risk of serious upper gastrointestinal events (UGIEs). This proposal is based on studies which showed positive effects of a PPI in users of ASA or NSAIDs (section 4.3 and 4.4). Obviously such gastric protection will not reduce the risk of bleeding in the lower GI tract or outside the GI tract. There are no published studies of the effectiveness and safety of PPI protection in users of a VKA in addition to ASA or an NSAID[37;57;59]. The Netherlands' Pharmacovigilance Centre Lareb recently reported 16 cases of an increased VKA effect associated with PPI use (most often related to omeprazole in acenocoumarol users)[57]. However, earlier studies have not yielded evidence that omeprazole significantly interacts with acenocoumarol therapy in healthy volunteers or long-term acenocoumarol users[60;61].

Table IV. Indications for VKA plus ASA as recommended in international and national guidelines.

Indication	Recommended duration of therapy	Gradation[a]		Guidelines
		grade	class	
Mechanical prosthetic heart valves in presence of additional risk factors for arterial thrombosis [b]	Long-term		I-B	ACC/AHA[62]
	Long-term	1B		ACCP[63]
	Long-term	1C+		CBO[40]
	Long-term		IIa-C	ESC [64]
Mechanical prosthetic heart valves and systemic embolism despite therapeutic INR	Long-term		I-B	ACC/AHA [62]
	Long-term		IIa-C	ESC [64]
	Long-term	2C		ACCP [63]
	Long-term	1C+		CBO [40]
Mechanical prosthetic heart valve in the 2nd and 3rd trimester of pregnancy			IIa-C	ACC/AHA[62]
Bioprosthetic heart valves in presence of additional risk factors for arterial thrombosis [b,c]	Long-term		I-B	ACC/AHA[62]
	Long-term	2C		ACCP [63]
	Long-term		IIa-C	ESC [64]
Rheumatic mitral valve disease and atrial fibrillation; or rheumatic mitral valve and systemic embolism or left atrial thrombus despite therapeutic INR	Long-term	2C		ACCP[63]
	Long-term	1C		CBO[40]
PCI and atrial fibrillation (after triple therapy)	12 months		IIa-C	ESC[65]
Revascularization therapy and atrial fibrillation	12 months		IIb-C	ESC[65]
Patient with myocardial infarction in health care settings in which close INR monitoring of VKA therapy is available.	Up to 4 years	2B		ACCP[66]
In high risk patients with myocardial infarction (an with large anterior MI, significant heart failure, intracardiac thrombus visible on transthoracic echocardiography, atrial fibrillation or a history of a thromboembolic event)	At least 3 months	2A		ACCP[66]
In post-STEMI patients who have no stent implanted and who have indications for VKA[d]	Long-term		IIa-B	ACC/AHA[67]
In patients with NSTEMI/UA with high CHD risk and low bleeding risk who do not require or are intolerant for clopidogrel [c,e]	Long-term		IIb-B	ACC/AHA[68]
In NSTEMI/UA patients who have indication for anticoagulation [d]	Long-term		IIb-B	ACC/AHA[68]

(Table IV continued)

Indication	Recommended duration of therapy	Gradation[a] grade	class	Guidelines
In patients with STEMI with or without acute ischemic stroke who have cardiac source of embolism (AF, mural thrombus, or akinetic segment)	At least 3 months		I-B	ACC/AHA[67]
	Long-term if source is AF		I-B	ACC/AHA[67]
In post-STEMI patients younger than 75 years without specific indication for VKA who can have their level of anticoagulation monitored reliably[d]	Unspecified		IIa-B	ACC/AHA [67]
In patients with STEMI at high risk of thromboembolic events (e.g. with AF)	unspecified		IIa-B	ESC [69]
In patients with recent stent placement plus indication for VKA and increased risk of bleeding[c,d]	unspecified		IIb-C	ESC[69]
In patients with CABG and strong concomitant indication for VKA[d]	unspecified	2C		CBO[40]
	Long-term	2C		ACCP[66]
In patients with infrainguinal bypass operation and high risk for total occlusion or amputation	Long-term	2B		CBO[40]
	unspecified	2B		ACCP[70]

a The ACCP and CBO guidelines graded their recommendations according to the system of GRADE work-group[16;17]. Each recommendation is provided with a code that is composed of a number to indicate the power of the recommendation: 1 = strong; 2 = weak) and a letter for the methodological quality of the underlying evidence: A = high quality evidence from RCTs without important limitations or exceptionally strong evidence from observational studies; B = moderate quality evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies; C = low quality evidence from observational studies with at least one critical outcome, case series, or from RCTs with serious flaws or indirect evidence.

The ESC and ACC/AHA guideline weighted and graded their recommendations according to predefined scales[62;64;65;67-69]. A therapy/treatment is classified as class I when it should be performed/administered, is is classified as class IIa when it is reasonable to be performed/administered and it is classified as class IIb when the therapy/treatment may be considered. Level of evidence A means that dat is derived from multiple randomized clinical trials or meta-analyses, level of evidence B means that dat is derived from a single randomized clinical trial or large non-randomized studies and level of evidence C means that it is a consensus of opinion of the experts and/or small studies, retrospective studies or registries.

b According to the ACC/AHA guidelines risk factors include atrial fibrillation, previous thromboembolism, left ventricular dysfunction and hypercoagulable condition[62]. According to the ACCP guideline risk factors include: atrial fibrillation, hypercoaguble state, low ejection fraction, or a history of atherosclerotic vascular disease or heart valve replacement[63;66]. According to the ESC guideline risk factors include: atrial disease, coronary disease and other significant atherosclerotic disease[64]. According to the CBO guideline risk factors include: atrial fibrillation, an enlarged left atrium , low ejection fraction, or who have a history of myocardial infarction[40].

c Except patients with a specified risk factors for bleeding: age > 80 years, history of GI bleeding[63].

d Indication for VKA: atrial fibrillation, left ventricular thrombus, mechanical prosthetic valve or extensive regional wall-motion abnormality[67-69].

e High CHD risk is defined as chronic kidney disease, diabetes mellitus, atherosclerosis in vascular beds or > 20 % Framingham 10-year risk. The Framingham risk score is based on gender, age, total cholesterol, HDL-cholesterol, smoking status, systolic blood pressure, and treatment for hypertension[68].

ASA = acetylsalicylic acid; **AF** = atrial fibrillation; **VKA** = vitamin K antagonist; **TIA** = transient ischaemic attack; **INR** = international normalized ratio; **PCI** = percutaneous coronary intervention; **STEMI** = ST-elevation myocardial infarction; **NSTEMI** = non-ST-elevation myocardial infarction; **UA** = unstable angina pectoris; **CHD** = coronary heart disease; **CABG** = coronary artery bypass grafting; **ACC** = American College of Cardiology; **AHA** = American Heart Association; **ACCP** = American College of Chest Physicians; **ESC** = European Society of Cardiology; **CBO** = The Dutch Institute for Health Care Improvement.

Table V. Overview of indications for simultaneous use of ASA, clopidogrel and VKA. (triple antithrombotic therapy).

Indication	Recommended duration of therapy	Grading of recommendation[a]		Guidelines
		grade	class	
PCI with BMS placement and strong concomitant indication for VKA[b]	At least 2 weeks	1C		CBO[40]
	4 weeks	2C		ACCP[66]
	Minimum of 1 month		IIa-C	ESC[65]
	1 month		IIb-B	ACC/AHA[68]
PCI with DES placement (type not specified) and strong concomitant indication for VKA[b,c]	At least 12 months		IIb-B	ACC/AHA[68]
	12 months	2C		ACCP[66]
PCI with DES placement (sirolimus-stent) and AF as strong indication for VKA[b,c]	At least 3 months		IIa-C	ESC[65]
PCI with DES placement (paclitaxel-stent) and AF as strong indication for VKA[b,c]	At least 6 months		IIa-C	ESC[65]
In patients with NSTEMI and a compelling indication for VKA	Short		IIa-C	ESC[71]
	unspecified		IIb-B	ACC/AHA[68]

a The ACCP and CBO guidelines graded their recommendations according to the system of GRADE work-group[16;17]. Each recommendation is provided with a code that is composed of a number to indicate the power of the recommendation: 1 = strong; 2 = weak) and a letter for the methodological quality of the underlying evidence: A = high quality evidence from RCTs without important limitations or exceptionally strong evidence from observational studies; B = moderate quality evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies; C = low quality evidence from observational studies with at least one critical outcome, case series, or from RCTs with serious flaws or indirect evidence.

The ESC and ACC/AHA guideline weighted and graded their recommendations according to predefined scales[62;64;65;67-69]. A therapy/treatment is classified as class I when it should be performed/administered, is is classified as class IIa when it is reasonable to be performed/administered and it is classified as class IIb when the therapy/treatment may be considered. Level of evidence A means that dat is derived from multiple randomized clinical trials or meta-analyses, level of evidence B means that dat is derived from a single randomized clinical trial or large non-randomized studies and level of evidence C means that it is a consensus of opinion of the experts and/or small studies, retrospective studies or registries.

b Indication for VKA: atrial fibrillation, left ventricular thrombus, mechanical prosthetic valve or extensive regional wall-motion abnormality[67-69].

c If long-term oral anticoagulation is required, use of a bare mental stent rather than a drug-eluting stent will expose the patient to a shorter duration of triple therapy and hence to a lower bleeding risk.

ASA = acetylsalicylic acid; **VKA** = vitamin K antagonist; **PCI** = percutaneous coronary intervention; **BMS** = bare metal stent; **DES** = drug-eluting stent; **STEMI** = ST-elevation myocardial infarction; **NSTEMI** = non-ST-elevation myocardial infarction; **ACC** = American College of Cardiology; **AHA** = American Heart Association; **ACCP** = American College of Chest Physicians; **ESC** = European Society of Cardiology; **CBO** = The Dutch Institute for Health Care Improvement.

Table VI. Indications in which combination antiplatelet therapy is discouraged by international and national guidelines.

Indication	Recommended therapy	Discouraged combination(s)	Grading of recommendations[a]		Guidelines
			Grade	Class	
CABG	ASA	There is never an indication for addition of dipyridamole	1A 1A		ACCP[66] CBO[40]
		VKA should not be added without concomitant indication for VKA[b]	1C		ACCP[66]
IMA	ASA	VKA should not be added without concomitant indication for VKA[b]	1C		ACCP[66]
Infrainguinal bypass operation	ASA therapy	VKA should not be added in patients without high risk for total occlusion or amputation	1A		CBO[40]
Nonoperative patients with asymptomatic carotid stenosis (primary or recurrent)	ASA therapy	No dual antiplatelet therapy with ASA and clopidogrel in this patient group.	1B		ACCP[70]
In STEMI patients with history of stroke and TIA for whom PCI is planned	ASA or ASA plus clopidogrel therapy[d]	Prasugrel is not recommended as part of dual antiplatelet therapy regimen.		III	ACC/AHA [72]

a The ACCP and CBO guidelines graded their recommendations according to the system of GRADE work-group[16;17]. Each recommendation is provided with a code that is composed of a number to indicate the power of the recommendation: 1 = strong; 2 = weak) and a letter for the methodological quality of the underlying evidence: A = high quality evidence from RCTs without important limitations or exceptionally strong evidence from observational studies; B = moderate quality evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies; C = low quality evidence from observational studies with at least one critical outcome, case series, or from RCTs with serious flaws or indirect evidence.

The ESC and ACC/AHA guideline weighted and graded their recommendations according to predefined scales[62;64;65;67-69]. A therapy/treatment is classified as class I when it should be performed/administered, is is classified as class IIa when it is reasonable to be performed/administered and it is classified as class IIb when the therapy/treatment may be considered. Level of evidence A means that dat is derived from multiple randomized clinical trials or meta-analyses, level of evidence B means that dat is derived from a single randomized clinical trial or large non-randomized studies and level of evidence C means that it is a consensus of opinion of the experts and/or small studies, retrospective studies or registries.

b Indication for VKA: atrial fibrillation, LV thrombus, mechanical prosthetic valve or extensive regional wall-motion abnormality[67-69].

c High risk of bleeding: history of bleeding or age above 80 [63].

d The ACC/AHA guideline recommend to weigh the benefits and risks of prescribing clopidogrel and ASA in patients with a recent history of TIA or stroke. Given prasugrel's greater tendency to cause intensive inhibition of platelet aggregation in general and the findings of increased levels of bleeding compared with clopidogrel in this population, the guideline discourages the use use of prasugrel as part of a dual antiplatelet therapy regimen in patients with prior stroke or TIA[72].

ASA = acetylsalicylic acid; **VKA** = vitamin K antagonist; **ACS =** acute coronary syndrome**; IMA =** internal mammary artery;**CABG** = coronary artery bypass grafting; **ACCP** = American College of Chest Physicians; **ESC** = European Society of Cardiology; **CBO** = The Dutch Institute for Health Care Improvement.

c) *Adequate communication between physicians, pharmacists and outpatient anticoagulation clinics.*

In The Netherlands, VKA treatment of outpatients is monitored by specialized anticoagulation clinics[73]. For adequate monitoring of the INR, the anticoagulation clinic should be well informed about each temporary risk situation that may lead to overcoagulation, including the initiation of drugs which interfere with the pharmacokinetics of VKAs (Table VII). A Dutch study has shown that this is not always the case[73]. For this reason dispensing pharmacists should inform the anticoagulation clinic by themselves instead of advising the patient to do this. Pharmacists should also inform the anticoagulation clinic whenever a VKA user starts an antibiotic, since fever increases the risk of overcoagulation.

Coagulation clinics should also be informed when drugs with a pharmacokinetic interaction are discontinued, since well-adjusted patients are at increased risk of bleeding when an INR reducing drug, such as preparations with phytomenadione (including dietary vitamin supplements), aminoglutethimide, enzyme-inducing antiepileptics (carbamazepine, phenobarbital, phenytoin, primidone), St John's wort , rifampicin, rifabutin, bosentan, azathioprine, mercaptopurine or aprepitant are discontinued. Ideally, the prescriber should inform the pharmacist of such discontinuations with a special "this drug will be discontinued" message, so that the pharmacist can inform the anticoagulation clinic. Physicians should inform the anticoagulation clinic and the pharmacist when other relevant changes occurs (e.g. deterioration of heart failure, arrhythmia, trauma or haemorrhage, elective surgery or a planned tooth extraction)[41].

d) *Dosing VKAs on the basis of pharmacogenetic testing*

Observational studies have shown that allele variants of cytochrome P450 2C9 (CYP2C9*2 and CYP2C9*3) decrease liver clearance. Consequently, they lower steady-state daily doses and increase bleeding risk and make it more difficult to reach stable anticoagulation in users of warfarin or acenocoumarol. With respect to phenprocoumon, reaching stable anticoagulation is also hampered, but the association with lower steady-state daily doses and increased bleeding risk is less clear[74]. Genetic polymorphisms of vitamin K epoxide reductase complex 1(VKORC1) enzyme increase the sensitivity to all VKAs in the same way. Each VKORC1 A allele decreases the steady-state dose level and the VKORC1 A/A genotype is an important risk factor for bleeding[74;75]. The US Food and Drug Administration (FDA) has therefore demanded that the package insert of warfarin mentions that a lower start dose should be considered in patients with certain genetic VKORC1 and CYP2C9 variants[75].

According to most experts it is still too early for routine VKORC1 and CYP2C9 testing before the start of a VKA therapy. It is advisable to await the results of current and planned intervention studies of this issue[74;76-80]. In the meanwhile, however, the diagnostic use of VKORC1 testing (and in the case of acenocoumarol also CYP2C9 testing) can be considered, when the VKA dose level in an individual patient is unusually low or when a usual dose level produces INR values that are unusually high[76;78].

Table VII. Drug-drug interactions with VKA (derived from Dutch guideline on the management of VKA interactions) [50].

Characterization of drug-drug interaction		Interacting drug (class)
Effect on INR	**Seriousness**	
INR increases(Increased VKA effect)	Very strong interaction (contraindicated)	Miconazole Phenylbutazone Analgesic ASA /carbasalate calcium (> 300mg/day)
	Strong interaction	Allopurinol Amiodarone, propafenone Protease inhibitors, efavirenz Androgens, anabolic steroids Benzbromarone Cefamandole Cimetidine Co-trimoxazole Danazol Disulfiram Fibrates Fluconazole, voriconazole, ketoconazole, itraconazole Thyroid drugs Capecitabine, fluorouracil Sitaxentan
	Moderate or unclear interaction	Antibiotics (other than co-trimoxazole) Disopyramide Quinidine Isoniazid Selective serotonin reuptake inhibitors Tamoxifen Rosuvastatin
INR decreases (reduced VKA effect)	Very strong interaction (contraindicated)	Combination preparations with vitamin K (including dietary supplements)
	Very strong interaction	Aminoglutethimide Enzyme-inducing antiepileptics (carbamazepine, phenobarbital, phenytoin, primidone) Hypericum Rifampicin, rifabutin
	Strong interaction	Colestyramin Griseofulvin Thyreostatic drugs Ritonavir Bosentan
	Moderate or unclear interaction	Azathioprine, mercaptopurine Enteral nutrition with vitamin K Aprepitant
No effect on INR		NSAIDs (analgesic salicylates > 300mg/day excluded) [a] Antithrombotic ASA/carbasalate calcium (≤300mg/day)[b]

a NSAIDs increase the risk of major bleeding, but do not change the INR. For this reason anticoagulation clinics cannot compensate by adjusting the VKA dose. If possible, NSAIDs should be avoided. When a VKA is nevertheless combined with an NSAID, gastric protection (PPI or misoprostol) is advized.

b Low-dose ASA and carbasalate calcium increase the risk of major bleeding, but do not change the INR. For this reason anticoagulation clinics cannot compensate by adjusting the VKA dose.

VKA= vitamin K antagonist; **ASA**= acetylsalicylic acid; **NSAID** = non-steroidal anti-inflammatory drug; **INR** = international normalized ratio; **PPI** = proton pump inhibitor.

e) Addition of low-dose vitamin K in patients receiving long-term VKA therapy with a variable INR response.

According to the 8th clinical practice guidelines of the ACCP, studies suggest that adding a daily low-dose of oral vitamin K (100 to 200 µg) could be considered, with close monitoring of the INR and warfarin dose adjustment, in patients receiving long-term warfarin therapy with a variable INR response not attributable to any of the usual known causes for instability[57;81]. Further prospective research is necessary to decide if this intervention strategy can indeed be broadly recommended, and also for users of acenocoumarol or phenprocoumon.

f) VKA users and/or their partner should receive adequate and regular education.
In patients who are suitably selected and trained, patient self-testing or patient self-management is an effective treatment model which can reduce the variability of the INR response and the risk of thromboembolism[57;64;82;83]. However, since this alternative type of therapeutic management falls outside the scope of the low-hanging fruit approach, this report confines itself to the recommendation that VKA users should be well informed about gastrointestinal alarm symptoms (see section 3.1) and about the risks of fever and changes in lifestyle or diet.

g) Substitution with a novel type of anticoagulant
The possibility of reducing the bleeding risk of a VKA by substituting it with a direct thrombin inhibitor or direct factor Xa inhibitor should be briefly examined here. In patients with atrial fibrillation, the direct thrombin inhibitor dabigatran (150 mg/day) gave better protection against stroke or systemic embolism than warfarin and a similar rate of major bleeding, whereas a lower dose of 110 mg/day was associated with similar protection as warfarin and a lower rate of bleeding[84]. In patients with acute venous thromboembolism, dabigatran was as effective as warfarin, but both drugs showed a similar rate of major bleeding[85]. Dabigatran does not require monitoring of its therapeutic effect but a specific antidote is not available when a user develops a bleeding[86]. The direct factor Xa inhibitor rivaroxaban has been approved in Europe for the prevention of VTE after major orthopedic surgery, but in May 2009, the US FDA did not approve it, because of a concern that it could lead to bleeding events in significantly more patients than enoxaparin[87].

3.3 PLATELET AGGREGATION INHIBITORS

3.3.1 PATHOFYSIOLOGY

PAIs increase bleeding time and decrease platelet adhesiveness. Inherent to their mode of action they increase the risk of haemorrhages, particularly GI bleedings[88]. In principle, the side effects, precautions, contraindications and interactions that apply to high doses of ASA as analgesic or antipyretic also apply to the use of low-dose ASA as PAI. The serious side effects of clopidogrel are more or less similar to those of low-dose ASA.

3.3.2 EPIDEMIOLOGY

According to a recent review of observational studies, the relative risk (RR) of UGIEs in patients on low-dose ASA (≤ 325 mg/day) lies between 2.0 [1.7-2.3] and 4.0 [3.2-4.9] [89]. In a Spanish study, low-dose ASA was responsible for no less than 8.2% and no more than 12.2%

of all non-fatal and fatal GI bleedings attributed to NSAIDs and ASA[90]. Pooling of the IPCI and HARM studies shows that PAIs were – in absolute numbers - an important cause of potentially preventable HARMs (64% vs 28% for VKA related cases and 33% for NSAID related cases). There is no evidence that dosage forms of carbasalate calcium cause less GI complications than plain ASA preparations[91].

Table VIII shows a summary of recently published observational studies which evaluated not only the relative risk of UGIEs associated with ASA, but also those associated with clopidogrel and dipyridamole.

The results with regard to clopidogrel are contradictory. Two studies showed identical increases in bleeding risk for clopidogrel and ASA, a third study showed no effect of clopidogrel, while a fourth study showed a non-significant increase for clopidogrel (Table VIII). A possible explanation may be that clopidogrel is more often prescribed to patients with an increased risk of bleeding ("channelling"). The large-scaled randomized CAPRIE trial showed less serious GI bleedings with clopidogrel (75mg/day during 1-3 years) than with ASA (325mg/day) (0.49% versus 0.71%; $p<0.05$) [92]. However, several types of risk patients were excluded in the CAPRIE study, which makes it uninformative about the bleeding risk in risk groups. Although clopidogrel seems safer than ASA in low-risk patients, this does not exclude the possibility that clopidogrel increases bleeding risk in risk patients (see section 3.3.3).

The observational studies in table VIII show also contradictory results concerning dipyridamole: one study showed an increased risk while another study did not. Again, "channelling" may have played a role here. The European Stroke Prevention study 2 (ESPS 2) did not show a significant difference between modified-release dipyridamole and placebo (1.5% vs 1.3%) with respect to moderate and serious bleedings[93]. Again, these findings do not exclude the possibility of an increased risk in risk patients, since patients with an increased risk of bleeding were excluded from the study.

Since dipyridamole is usually combined with VKA or another PAI, it is particularly important to know the bleeding risk of such combinations. See section 3.3.3. for the bleeding risk of dipyridamole plus ASA or a VKA.

Table VIII. Observational studies investigating the relationship between upper gastrointestinal bleeding and the use of risk medications.

Reference	Risk medication(s)	$RR_{adj}/OR_{(adj)}$ [95% CI]
Lanas et al.[94]	ASA (all doses)	5.3 [4.5-6.3]
	100mg/day	2.7 [2.0-3.6]
	300mg/day	6.1 [4.3-8.7]
	Clopidogrel/ticlopidine [a]	2.8[1.9-4.2]
	NSAID	5.3 [4.5-6.2]
	Low/medium doses	4.0 [3.2-5.0]
	High doses	6.8 [5.3-8.8]
	Rofecoxib	2.1 [1.1-4.0]
	Celecoxib	1.0 [0.4-2.1]
	Low-dose ASA+ NSAID	12.7 [7.0-23.0]
	Low-dose ASA + COX-2 selective inhibitor	14.5 [3.3-63.9]
	Acetaminophen	0.9 [0.7-1.1]
Ibanez et al. [95]	ASA (all doses)	4.0 [3.2-4.9]
	≤ 100mg/day	3.8 [2.8-5.2]
	> 200mg/day	3.9 [2.5-5.9]
	Clopidogrel	2.3 [0.9-6.0]
	Dipyridamole	0.9 [0.4-2.0]
	ASA + PPI	1.1 [0.5-2.6]
	ASA + H_2 receptor antagonist	3.0 [1.6-5.4]
	ASA + antacids	6.6 [4.5-9.8]
	ASA + misoprostol	5.0 [1.5-16.8]
	PAI (other than ASA) + PPI	0.9 [0.4-2.3]
Hallas et al. [96]	Low-dose ASA	1.8 [1.5-2.1]
	Clopidogrel	1.1 [0.6-2.1]
	Dipyridamole	1.9 [1.3-2.8]
	VKA	1.8 [1.3-2.4]
	ASA + clopidogrel	7.4 [3.5-15]
	ASA + VKA	5.3 [2.9-9.5]
	ASA + dipyridamole	2.3 [1.7-3.3]
Delaney et al. [97]	Warfarin	1.9 [1.6-2.3]
	Low-dose ASA	1.4 [1.3-1.5]
	Clopidogrel	1.7 [1.3-2.2]
	NSAID	1.8 [1.6-2.0]
	COX-2 selective inhibitor	1.6 [1.3-2.1]
	Warfarin + ASA	6.5 [4.3-9.9]
	Warfarin + NSAID	4.8 [2.8-8.2]
	Warfarin + COX-2 selective inhibitor	4.6 [1.5-14.4]
	ASA + clopidogrel	3.9 [2.8-5.5]
	Clopidogrel + non-selective NSAID	2.9 [1.6-5.4]
	Clopidogrel + COX-2 selective inhibitor	2.6 [1.1-6.2]

a The risks of clopidogrel and ticlopidine separately were comparable.

VKA = Vitamin K antagonist; **PAI** = platelet aggregation inhibitor; **ASA** = acetylsalicylic acid; **PPI** = proton pump inhibitor; **NSAID** = non-steroidal anti-inflammatory drug; $\mathbf{RR_{adj}}$ = adjusted relative risk; $\mathbf{OR_{adj}}$ = adjusted odds ratio.

Low gastrointestinal bleeding

PAIs are not only associated with UGIEs but also with lower GI bleeding. Of the 53 HARM/IPCI cases with GI bleeding in PAI and/or NSAID users (Table III), 4 cases (8%) were associated with diverticulitis/diverticulosis and another 3 cases with diverticular bleeding (in 1 case preceded by intestinal bleeding).

Several observational studies have looked at the association between lower GI bleeding and the use of non-selective NSAIDs (NS-NSAIDs) and/or PAIs. According to a recent review, a significant association was found in seven of eight case-control studies (with ORs varying between 1.9 and 18.4)[98].

In some studies, NS-NSAIDs gave an increased RR of lower GI tract complications that was comparable to the increase in the RR of UGIEs. According to the same review, the use of NS-NSAIDs was significantly higher among cases in 4/5 case-control studies of diverticular complications (such as perforations) (with ORs varying from 1.8 to 11.2) [98].

Specific data about lower GI bleedings due to the use of PAIs are still scarce. In a large randomized trial, 300 mg and 1200 mg of ASA daily increased the risk of fresh blood per rectum (as a measure of low gastrointestinal bleeding) only insignificantly, when compared to placebo[99]. However, patients with a high risk of ASA-related complications had been excluded from this study.

In a Swiss observational study, 16% of all GI bleedings were diverticular bleedings and, when these bleedings occurred in elderly patients, they were strongly associated with the use of ASA[100].

3.3.3 RISK FACTORS

Low-dose ASA

Table IX shows which risk factors predispoe patients receiving low-dose ASA for UGIEs. Among these factors, a history of a prior complicated ulcer is the strongest predictor[101;102].

Table IX. Risk factors for upper gastrointestinal complications in patients on low-dose ASA [89].

Risk factors
History of peptic ulcer or ulcer complication
History of gastrointestinal bleeding
Infection with *Helicobacter pylori*
Advanced age (especially >70 years)
Serious co-morbidity (?) [a]
Use of NS-NSAID or COX-2 selective inhibitor
Use of VKA
Interaction with other risk medication (see table XI)

a Although this risk factor is listed in the underlying article, it is not substantiated with study results.

NSAID = non-steroidal anti-inflammatory drug; **VKA**= vitamin K antagonist

The ASA-related risk factors are largely comparable to the risk factors for UGIEs in NSAID users (Table X). However, there is growing evidence to suggest that the mechanism by which low-dose ASA induces UGIEs may be different from that of NSAIDs[103;104]. For practical

purposes, it seems important to take into account that the risk of UGIE complications in patients on low-dose ASA is only half of the risk of NSAID users[101].

Several studies have shown that the bleeding risk associated with low-dose ASA is related to the dose level[105;106], but this has been questioned by others[107;108](see also the conflicting evidence in Table VIII). There is no convincing evidence that a daily dose below 100 mg ASA is safer than 100 mg a day. Several studies have shown that a daily dose 75 mg ASA can double the risk of GI bleedings[109;110]. It is even questionable whether10 mg ASA daily is always safe [111].

In addition, resistance to ASA is increasingly recognised as a clinically relevant problem[112] and it is not yet clear to what extent resistance to ASA might increase if its daily dose is reduced to a level that lies far below 100mg daily[113].

Table X. Plausible risk factors for upper GI complications in patients receiving NSAIDs (according to the Dutch CBO guideline on NSAID-use and gastric damage)[24].

Plausible risk factors[a]	$OR_{adj}/RR_{adj}/HR_{adj}$ [95%CI]	Comments
High doses	1.4[1.0-2.0]	For double the maximum dose (compared to the maximum dose)
Use of more than one NSAID concurrently	Varying between 7.8 and 11.0	
Duration of therapy		There is little reason to assume that the risk of upper GI complications would decrease as the duration of NSAID use increases
Higher age	1.04 [1.02-1.06]	For each additional year
GI ulcer/complication patient's history	Varying between 1.6 and 2.5	
***Helicobacter pylori* infection**		Results are still inconclusive according to other sources [24;114]
Diabetes	3.1 [1.2-4.3]	
Heart failure	5.9 [2.3-13.1]	
Seriously invalidating rheumatoid arthritis	1.3 [1.0-1.7]	
Concurrent use of VKA	3.8 [1.9-7.8]	
Concurrent use of low-dose ASA	1.9 [1.2-2.8]	
Concurrent use of oral corticosteroid	Varying between 1.8 and 4.4	
Concurrent use of SSRI	Varying between 2.8 and 4.6	

OR_{adj} = adjusted Odds Ratio; **RR_{adj}** = adjusted Relative Risk; **HR_{adj}** = adjusted Hazard Ratio; **BMI** = body mass index; **VKA** = vitamin K antagonist; **ASA** = acetylsalicylic acid; **SSRI** = selective serotonin reuptake inhibitor; **NSAID** = non-steroidal anti-inflammatory drug.

In 32 of the 47 HARM/IPCI cases (68%) of PAI-related bleedings, a drug-drug interaction was noted. Table VIII shows how the bleeding risk is increased when a VKA, clopidogrel, an NS-NSAID or COX-2 selective inhibitor is added to ASA. A number of observational studies have noted a 2 to 4-fold increased risk of UGIEs associated with the concomitant prescription of NSAIDs with low-dose ASA compared to low-dose ASA alone[115].

According to reference sources on drug-drug interactions, the clinical evidence for an interaction between ASA and heparin or an LMWH (low-molecular-weight-heparin) is less substantial than the evidence for ASA plus VKA[116]. For instance, a study in healthy volunteers did not reveal a clinically significant interaction between ASA and the LMWH danaparoid[117]. Yet a recent US consensus document indicates that the risk of major bleeding (especially from the upper GI tract) is not only significantly increased when ASA is combined with an oral VKA, but also when it is used together with heparin or an LMWH. This consensus recommends that patients on this latter type of combination should also receive a PPI[115]. The evidence underpinning this statement refers particularly to the use of high doses of heparin or an LMWH in acute situations[118-121].

The risk of ASA-related UGIEs can increase further, when different risk factors come together in the same patient. For instance, in a recent observational study of patients with acute myocardial infarction treated with different combinations of antithrombotic drugs, the adjusted HRs for bleeding were 1.33 for clopidogrel, 1.23 for VKA, 1.47 for ASA plus clopidogrel, 1.84 for ASA plus VKA, 3.52 for clopidogrel plus VKA, and 4.05 for triple therapy (compared to ASA as reference)[122]. In another study, triple therapy in patients on VKA treatment (who required the addition of ASA plus clopidogrel because of coronary stenting) was associated with a major bleeding HR of 6.6[123]. As a result, triple therapy should only be given to patients in whom the expected cardiovascular benefits outweigh the significant GI risks. According to the US consensus document on reducing the GI risks of PAI therapy and NSAID use, it would seem prudent to add a protective PPI in these cases[115]. The document also refers to an earlier US guideline which recommended a target INR of 2.0 to 2.5, when a patient is treated with triple therapy[124][Grade 1C recommendation according to King[124]]. It adds the annotation, however, that an INR target of 2.0 to 2.5 may be too low in patients with certain mechanical heart valves, in which case their individual thrombotic and bleeding risks need to be assessed[115]. Further data on the drug interaction potential of low-dose ASA are summarized in table XI.

Table XI. Drug-drug interactions between ASA and other drugs.

Interacting drug	Comments
NS-NSAID	Several studies show an increased risk of upper gastrointestinal bleeding (between 2 and 4), when ASA is combined with an NS-NSAID [88;94;115;125] Vice versa, there is an increased risk between 1.3 and 2.4 when ASA is combined with an NS-NSAID compared to an NS-NSAID alone[94;125;126].
Ibuprofen	In healthy volunteers, platelet aggregation inhibition by low dose enteric coated ASA was reduced when ibuprofen (single dose of 400mg) was administered 2 hours *before* ASA. The ASA-related inhibition was not reduced when the same dose of ibuprofen (400mg) was administered 2 hours *after* ASA. A similar interaction was not seen with acetaminophen (1000mg) or rofecoxib (25mg). When ibuprofen was given for 6 days (400mg 3 times a day) 2 hours *after* ASA, the same interaction was observed but no interaction occurred when the ibuprofen was replaced by diclofenac (75mg twice daily)[127]. A possible explanation is that ibuprofen binds reversibly to the COX-1 enzyme and thereby prevents the irreversible binding of ASA. Since ASA has a short half-life, a part of ASA will already have been eliminated by the time ibuprofen leaves the binding site, which results in a reduced platelet aggregation inhibitting effect[128;129]. Six observational studies of the clinical significance of the interaction between ASA and ibuprofen have produced contradictory results. Three studies did not show a detrimental effect[130-132], whereas the other three studies did [133-135]. According to a large unpublished cohort study, simultaneous use of ASA removed the risk of cardiovascular events in users of celecoxib, sulindac, meloxicam and indomethacin but not in users of ibuprofen[136]. A detrimental effect of ibuprofen was also evident in five out of six prospective *ex vivo* studies[137-142]. All in all it is advisable not to combine low-dose ASA with ibuprofen and to give acetaminophen instead, if possible[143;144].[12] When an NSAID is needed, it is not easy to decide, on basis of the available literature, which NSAID should be preferred. COX-2 selective inhibitors are not a good choice because of their cardiovascular contraindications and precautions (section 3.4.4.). The Dutch General Practitioners' guidance on pain relief recommends diclofenac or meloxicam on the basis of ex vivo studies [145], but this decision is not supported well by the available randomized and observational studies. According to the guidelines of the American College of Gastroenterology and other recent expert opinions, preference may be given to naproxen, if patients at high risk (including users of low-dose ASA) need an NSAID[104;146-148].
Diclofenac	In an ex vivo study [127] diclofenac did not interact with ASA. However, several randomized and observational studies of the cardiovascular risks of NS-NSAIDs suggest that diclofenac (certainly when used in high doses of 150mg/day) may be relatively unsafe[136].
Meloxicam	In several ex vivo studies no interaction with ASA was seen[149-151]. However there are no data from RCTs to support the simultaneous use of meloxicam and ASA and the data from observational studies are still limited[136].
Naproxen	According to randomized and observational studies naproxen may be a relatively safe NSAID for the combination with ASA[136]. In a recent observational study, in which the addition of ibuprofen seemed to reduce secondary prevention of myocardial infarction by ASA, such a detrimental effect was not seen for the addition of naproxen[135]. However, this favourable outcome has not beem confirmed in the recent ADAPT trialin which 220mg of naproxen sodium per day led more often than placebo to a thrombo-embolic cardiovascular event or congestive heart failure in

(continuance)

Interacting drug	Comments
Naproxen	patients ≥ 70 years [HR = 1.6; 1.0-2.6], whereas 400 mg celecoxib per day (in a third study arm) did not show such an effect[152]. The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) compared 400mg lumiracoxib per day with either 2400mg ibuprofen per day (substudy A) or with 1000mg naproxen per day (substudy B) during 12 months. When only the patients on low-dose ASA in substudy A were considered, serious trombotic events (cardiovascular mortality, non-fatal myocardial infarctions and cerebrovascular accidents) were seen significantly more often in users of ibuprofen ± ASA than in users of lumiracoxib ± ASA [2.1% vs 0.3%], whereas such a difference was not observed in substudy B between the naproxen + ASA users and the lumiracoxib + ASA users [1.6% vs 1.5%]. Remarkably, these different outcomes were more due to a difference between two lumiracoxib groups [0.3% vs 1.5%] than by the difference between the ibuprofen and naproxen groups [2.1% vs 1.6%]. Moreover, none of the two substudies was sufficiently large to confirm or refute cardiovascular risks indisputably[136]. ASA users showed congestive heart failure (a secondary endpoint in the TARGET analysis) more often in ibuprofen users than in lumiracoxib users [0.9% vs 0.3%] but this difference was not signifycant. In substudy B, heart failure was not observed more often in naproxen users than in lumiracoxib users [0.6% vs 0.5%] [153]. Four cases have been reported of an inadequate PAI response to ASA during concomitant use with naproxen, which disappeared after discontinuation of the naproxen[140]. A detrimental effect of naproxen on the PAI effect of ASA has also been observed in one *ex vivo* study[140], but was not found in three other studies[138;154;155]. There are also studies which support that naproxen may have some antiplatelet effect of its own[156-158].
Selective COX-2 inhibitor	In an endoscopic trial, addition of a COX-2 selective inhibitor to ASA increased the risk of an ulcer from 7.3% to 16.1%[159]. Of the non-ASA users in the TARGET trial, the patients on lumiracoxib showed a significantly lower risk of ulcer complications than those on ibuprofen or naproxen [HR = 0.2; 95% CI 0.1-0.4]. In those taking ASA, however, the difference was much smaller and no longer significant [HR = 0.8; 0.4-1.6] [160]. In observational studies the gastrointestinal benefits of COX-2 selective inhibitorsalso disappeared when ASA was added [94;125;126]. In one of these studies the risk of gastrointestinal bleeding was significantly lower in users of a COX-2 inhibitor plus low-dose ASA than in users of an NS-NSAID plus low-dose ASA [126], but this was not the case in one of the two other studies[94]. All in all it is likely that low dose ASA should not be combined with a COX-2 selective inhibitor.
Corticosteroids	It is likely that addition of corticosteroids to ASA increases the risk of gastrointestinal bleeding[88]. An observational study showed an RR for upper gastrointestinal bleedings of 5.3 [2.9-8.8] in patients using ASA and corticosteroids[161]. This risk was not directly compared with that of patients receiving ASA without corticosteroids, but for the latter risk, a standardized incidence ratio of 2.6 [2.2-2.9] was found in another study using the same data base [162]. A retrospective review of more than 40 randomized studies showed no difference in the incidence of ulcers between users of corticosteroids and users of placebo [163]. However, patients with a total intake of 1000mg of prednisone equivalents or more seemed to have more ulcers than patients with a total dose below 1000mg (in patients who take a dose of 5 mg of prednisone equivalents every day, this limit is reached after 6.6 months.)

(Table XI continued)

Interacting drug	Comments
SSRIs	Observational studies suggest that concurrent use of ASA and SSRIs increases the risk of gastrointestinal bleeding. However, this effect appears to be smaller than that of combined use of SSRIs and NSAIDs[164;165]. A case control study showed an RR of 7.2 [3.1-17.1] in patients receiving SSRIs and ASA versus an RR of 2.6 [1.7-3.8] in patients receiving SSRIs without ASA[166]. In a cohort study the risk with concurrent use of SSRIs and ASA was 5.2 [3.2-8.0] versus 3.6 [2.7-4.7] for monotherapy with SSRIs[167]. Both studies reported an interactive effect between SSRIs and ASA. Unfortunately none of the studies reported an RR in patients receiving ASA only. On basis of the available information it is advisable to take an increased risk of gastrointestinal complications with concurrent use of SSRIs and ASA into account.
Spironolactone	Following case reports of gastric ulceration induced by spironolactone [168;169] and a controlled trial in which spironolactone reduced the beneficial effect of carbenoxolone on gastric ulceration [170], the risk of upper gastrointestinal events in users of spironolactone was investigated in a case control study. Concurrent use of spironolactone and an ulcerogenic drug (defined as a PAI, NSAID, VKA or corticosteroid) led to a distinctly higher OR_{adj} [7.3; 2.9-18.7] than spironolactone itself [2.5; 1.9-3.3] [171]. Two subsequent studies have confirmed that patients receiving spironolactone (as such or especially in high doses) are at increased risk of upper gastrointestinal bleeding [172;173]. In both studies, the risk increased with higher doses of spironolactone. One study found a HR of 2.30 [95% CI 1.62-3.62] for upper gastrointestinal bleeding in subjects exposed to doses of spironolactone higher than 37.5mg/day[172]. In the other study, the OR_{adj} for upper gastrointestinal bleeding in spironolactone users was 2.7 [95% CI 2.2-3.2], but increased to 5.4 [95% CI 3.4-8.6] in users of 100mg tablets[173]. Neither study showed that the risk increased by concurrent use of NSAIDs. In view of the evidence, that spironolactone may impair healing of gastric or duodenal erosions[170;171], the Task Force has nevertheless concluded that an interaction between spironolactone and ulcerogenic agents is a real possibility and that gastric protection may be advisable when patients receive ASA or an NSAID concurrently with spironolactone .

NS-NSAID = non-selective Non-steroidal anti-inflammatory drug; **ASA** = low-dose acetylsalicylic acid; **PAI** = platelet aggregation inhibitor; **VKA** = vitamin K antagonist; **ADAPT** = Alzheimer's Disease Anti-inflammatory Prevention Trial; **RCT** = randomized clinical trial; **HR** = Hazard Ratio; **RR** = relative risk; **OR_{adj}** = adjusted Odds Ratio; SSRIs = selective serotonin reuptake inhibitors; **TARGET =** the Therapeutic Arthritis Research and Gastrointestinal Event Trial

<u>Clopidogrel</u>

Specific risk factors for clopidogrel-related bleedings are less well-documented than those for ASA-related bleedings. In a retrospective cohort-study on the safety of clopidogrel (75mg/day)with a median follow-up of one year, 9 of 70 (12%) patients with a previous history of a non-ASA-related peptic ulcer or with a history of an ASA-related GI complication (peptic ulcer or dyspepsia) developed a GI bleeding and one patient had a perforated ulcer[174]. In two randomized trials, recurrence of ulcer complications was found much more often in patients using clopidogrel compared to the combined use of ASA plus a PPI (Table XII). Finally, there are two observational studies in which GI complications were seen more often in patients using clopidogrel and ASA concomitantly than in users of clopidogrel alone (Table VIII).

Table XII. Randomized double-blind studies investigating the benefits of PPIs in PAI users at increased risk for upper GI complications.

Reference[a]	Study population	intervention[b]	Results
Lai et al. 2002[175]	123 patients with a history of healed ulcer complications after use of low dose ASA and in whom *H. pylori* infection had first been eradicated.	During 12 months (A) 100mg ASA + placebo (B) 100mg ASA + PPI	Recurrent ulcer complications (A) 14.8% (B) 1.6%
Chan et al.2005[176]	320 *H.pylori* negative patients with a history of a healed ulcer after ASA use.	During 12 months (A)75mg clopidogrel + placebo (B)80mg ASA + PPI	Recurrent bleeding ulcers (A) 8.6% (B) 0.7%
Lai et al. 2006[177]	170 patients with a history of healed ulcer complications after ASA use in whom *H. pylori* infection had first been eradicated.	During 12 months (A)75mg clopidogrel + placebo (B)100mg ASA + PPI	Recurrent ulcer complications (A) 13.6% (B) 0%
Yeomans et al.2008[178]	991 patients ≥ 60 yr without pre-existing gastroduodenal ulcer	75-325 mg ASA for 26 weeks + (A) placebo (B) 20 mg esomeprazole	Gastric/duodenal ulcer (A) 5.4% (B) 1.6%
Taha et al. 2009[179]	404 patients ≥ 18 yr without pre-existing ulcer	75-325 mg ASA for 12 weeks + (A) placebo (B) 40 mg famotidine	Gastric resp duodenal ulcer (A) 15% resp 8.5% (B) 3.4% resp 0.5%
Ng et al. 2010[180]	160 patients with ASA-related peptic ulcers/erosions with or without history of bleeding (in whom *Helicobacter* had first been eradicated if necessary)	80 mg ASA during 48 weeks + (A) 2x 40 mg famotidine (B) 20 mg pantoprazole	Recurrent ulcers/ erosions[c] (A) 20% (B) 0%

a As non-Caucasians have an increased risk for NSAID-induced ulcer complications[181;182], it is probably not without significance that three of the five studies were conducted in Hong Kong. Another limitation of these studies is that they only evaluated GI outcomes without simultaneous assessment of cardiovascular outcomes[183].

b Reported doses are daily doses.

c This was the primary end point; there was also a significant difference in gastrointestinal bleeding of 7.7% in group (A) vs 0% in group (B).

UGIE = upper gastro intestinal event; **ASA** = low-dose acetylsalicylic acid; **PPI** = proton pump inhibitor; **yr** = year; **NSAID** = non-steroidal anti-inflammatory drug

All in all, so long as more information is not available, it seems advisable to assume that clopidogrel has the same risk factors for UGIEs as low-dose ASA, (Table IX). A guideline-based overview of hard indications for the combined use of clopidogrel and low-dose ASA is presented in Table XIII.

Table XIII. A systematic overview of indications for using simultaneous ASA and clopidogrel according to internation and national guidelines.

Indication	Recommended duration	Grade of recommendation[a]		Guidelines
		Grade	**Class**	
PCI with BMS	At least 12 months[b]		I-B	ACC/AHA[72]
	12 months			
	4 weeks[c]	1A		ACCP[66]
	At least 1 month[d]		I-A	ESC[184]
		1A		CBO[40]
PCI after vascular brachytherapy	12 months		1C	ESC[185]
PCI with DES (not further specified)	3-4 months	1A		ACCP[66]
	4-12 months	1B		ACCP[66]
	>12 months[e]	2C		ACCP[66]
	At least 12 months		I-B	ACC/AHA[72]
	Beyond 15 months			
	6-12 months		IIb-C	ACC/AHA[72]
	12 months			
			I-C	ESC[185]
		1C		CBO[40]
STEMI or NSTEMI patients and PCI without reperfusion therapy	12 months		IIa-C	ACC/AHA[124]
Irrespective of (acute) treatment of STEMI	Up to 12 months	1B		CBO[40]
	At least 2 weeks			
	Long-term (eg 1 year)		I-B	ACC/AHA[124;186]
	12 months			
	2-4 weeks		IIa-C	ACC/AHA[186]
	Up to 12 months			
			IIa-C	ESC[69]
		1A		ACCP[66]
		2B		ACCP[66]
In NSTEMI/UA patients with CABG	9-12 months	2B		ACCP[66]
Irrespective of (acute) treatment of NSTEMI/UA	6-12 months	1A		CBO[40]
	Up to 12 months		I-B	ACC/AHA[187]
	12 months			
	12 months	1A		ACCP[66]
			I-A	ESC[71]
NSTEMI/UA patients selected for invasive approach			I-A	ACC/AHA[72]
Symptomatic CAD		2B		ACCP[66]
Patients at high risk for trombotic events or for whom stent thrombosis can be fatal	12 months	1C		CBO [40]

a The ACCP and CBO guidelines graded their recommendations according to the system of GRADE work-group[16;17]. Each recommendation is provided with a code that is composed of a number to indicate the power of the recommendation: 1 = strong; 2 = weak) and a letter for the methodological quality of the underlying evidence: A = high quality evidence from RCTs without important limitations or exceptionally strong evidence from observational studies; B = moderate quality evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies; C = low quality evidence from observational studies with at least one critical outcome, case series, or from RCTs with serious flaws or indirect evidence.
The ESC and ACC/AHA guideline weighted and graded their recommendations according to predefined scales[62;64;65;67-69]. A therapy/treatment is classified as class I when it should be performed/administered, is is classified as class IIa when it is reasonable to be performed/administered and it is classified as class IIb when the therapy/treatment may be considered. Level of evidence A means that dat is derived from multiple randomized clinical trials or meta-analyses, level of evidence B means that dat is derived from a single randomized clinical trial or large non-randomized studies and level of evidence C means that it is a consensus of opinion of the experts and/or small studies, retrospective studies or registries.

b If the risk of morbidity due to bleeding outweighs the anticipated benefit of clopidogrel or prasugrel therapy, earlier discontinuation should be considered. (Level of Evidence: I-C) [72]

c It is recommended to prescribe both ASA and clopidogrel to post-PCI BMS-stented patients with high bleeding risk for at least 2 weeks. Risk factors for bleeding risk are include advanced age, poorly controlled hypertension, and low body weight. (Grade 1B / I-B) [68;124]

d With stable CAD.

e After the first year of treatment, the ACCP guideline suggests that treatment with ASA plus clopidogrel may be continued indefinitely if there are no bleeding or other tolerability issues [66]

ASA = acetylsalicylic acid; **STEMI** = ST-elevation myocardial infarction; **NSTEMI** = non-ST-elevation myocardial infarction; **UA** = unstable angina pectoris; **CAD** = coronary artery disease; **BMS** = bare metal stent; **DES** = drug-eluting stent; **PCI** = percutaneous coronary intervention; **CABG** = coronary artery bypass grafting; **ACC** = American College of Cardiology; **AHA** = American Heart Association; **ACCP** = American College of Chest Physicians; **ESC** = European Society of Cardiology; **CBO** = The Dutch Institute for Health Care Improvement**.**

Prasugrel

Prasugrel is more potent than clopidogrel and thus entails a higher risk of serious bleeding particularly in patients older than 75 years of age[188].

Dipyridamole

One observational study showed no significant increased risk with concurrent use of ASA and dipyridamole versus receiving only ASA or only dipyridamole (See Hallas et al.[96]) in Table VIII). In several large-scaled randomized studies of secondary prevention after cerebral ischemia or cerebral bleeding, haemorrhages were not present more often in patients receiving ASA plus dipyridamole than in those using only ASA. However, a higher incidence of bleedings was found in patients on ASA plus dipyridamole as compared to patients receiving clopidogrel alone[93;189;190].

According to a review of studies in patients with heart valve prostheses, bleeding risk is not only increased by the addition of low-dose ASA to VKA, but also by the addition of dipyridamole[191]. When the results of four comparative studies are combined, the percentage of major bleedings was 6.0% (23/386) in patients using a VKA and dipyridamole vs 2.7% (11/404) for patients using a VKA without dipyridamole.

3.3.4 RISK REDUCING STRATEGIES

a) Eradication of Helicobacter pylori

Since an infection with *Helicobacter pylori (H. pylori)* increases the risk of an upper GI bleeding in users of ASA significantly [OR= 4.7;2.0-10.9] [192], the literature recommends to eradicate *H. pylori* in high risk users of ASA[89]. In a randomized clinical trial of 250 Asian patients with a history of an upper GI bleeding who were infected with *H. pylori* and received ASA the probability of recurrent bleeding during a six-month period was comparable between those who received omeprazole 20mg daily and those who received eradication therapy (0.9% vs 1.9%)[193]. A later study showed that *H. pylori* eradication plus PPI was superior to *H.pylori* eradication alone (see Table XII; Lai et al.[175]). Since non-Caucasian patients have an increased risk of NSAID-related ulcer complications[181], one should realize that three out of the five studies in this Table were carried out in Hong Kong .

The US consensus document on reducing the GI risks of PAIs and NSAIDs recommends to test for and, if necessary, to eradicate *H. Pylori* in patients with a history of ulcer disease before starting chronic PAI therapy. Unlike the results of studies among non-ASA NSAID users, case-control studies have consistently shown that *H. Pylori* is an important risk factor for ulcer and ulcer bleeding in users of low-dose ASA[115]. A possible explanation may be that low-dose ASA is not as ulcerogenic as NSAIDs and probably provokes bleeding in pre-existing *H. pylori* ulcers. As curing the infection heals *H. pylori* ulcers, resumption of low-dose ASA alone may be insufficient to induce recurrent

ulceration. However large-scale, long-term studies are still required to evaluate the true benefit of *H. pylori* eradication in low-dose ASA users who are at increased risk of ulcer complications[104;148].

b) Addition of gastric protection

Low-dose ASA

When patients at risk for UGIEs (Table IX) receive ASA, gastric protection, is recommended. The US consensus document on reducing the GI risks of PAIs and NSAIDs considers PPIs as the preferred agents for the prophylaxis and therapy of ASA-associated injury[115] and this preference is also expressed in other secondary sources[194].

In view of the similarity in risk factors between low-dose ASA and NSAIDs users (see section 3.3.3), the Task Force has deliberately geared its recommendations on the addition of a PPI in ASA users to the recommendations in the Dutch CBO guideline on the prevention of gastric damage in NSAID users[24]. However, the Task Force has emphatically taken into account that the risk of UGIEs in ASA users is roughly a factor of 2 lower than the risk in NSAID users with comparable risk factors[101,3]. The Task Force also carefully considered the US ACCF/ACG/AHA 2008 expert consensus recommendations on reducing the GI risks of PAIs and NSAIDs[115]. According to the Dutch Institute for Health Care improvement (CBO) guideline, the risk of gastric damage can be reduced by standard doses of a PPI, by misoprostol (800 µg/day) or by double doses of a H_2 receptor antagonist (H_2RA) (Table XIV). PPIs have the advantage that their effects have been repeatedly demonstrated (Table XII). As pharmacotherapeutic differences between the PPIs are small, the price level should play a major role in choosing the specific PPI. Misoprostol has the disadvantage that it is less well tolerated than PPIs, especially when given in its full dose of 800 µg/day.

Observational studies suggest that PPIs reduce UGIEs in users of low-dose ASA and/or clopidogrel more markedly and consistently than H2RAs[195-197]. In an RCT involving low-dose ASA users at average risk, a normal dose of the H_2RA famotidine (40mg/day) was more effective than placebo in the prevention of gastric/duodenal ulceration[179]. However, in a Hong Kong study of high risk patients on 80mg of ASA/day (who had pre-existing peptic ulcers/erosions and who had first received *Helicobacter* eradication if necessary), a relatively low-dose of pantoprazole (20mg/day) was superior to high-dosed famotidine (80mg/day) in the prevention of recurrent ulcers/erosions and GI bleeding[180](cf Table XII). There is also a cross-over study in Helicobacter-negative healthy volunteers treated with 100mg of ASA per day, in which 15mg lansoprazole daily for 7 days was superior to 40mg famotidine per day in the prevention of gastric mucosal injury[198].

Table XIV. Strategies to prevent gastric damage in users of NSAIDs according to the Dutch CBO Guideline on NSAID use and gastric damage [24].

Strategies	Conclusions
Helicobacter pylori eradication	- It is likely that eradication before NSAID use decreases the risk of ulcers and related complications[a] - There is evidence that the risk is still increased after eradication.
Addition of antacids or sucralfate	- There is no evidence that sucralfate is efficacious
Addition of H_2-receptor antagonists	- Standard doses of ranitidine or famotidine are insufficient - Double doses of ranitidine (2 x 300mg per day) provided effective prevention of gastrointestinal ulcers in an endoscopic study [199]
Addition of PPIs	- Omeprazole (20mg), lansoprazole (15mg) and pantoprazole (40mg) all reduce the risk of endoscopic ulcers.
Addition of misoprostol	- 400-800 µg per day reduces the risk of ulcers - 800µg per day reduces the risk of GI ulcer complications (perforation, obstruction, bleeding) - All dose levels produce diarrhoea more often than placebo and patients receiving 800µg per day stop treatment more often than patients receiving placebo[b].
Replacement by meloxicam or nabumetone	- There is no supporting evidence from sufficiently poweredstudies, with clinical endpoints.and adequate lengths of follow-up
Replacement by COX-2 selective inhibitors	- A reduced risk of clinically relevant ulcers has been proven for rofecoxib and is likely for celecoxib.

a See for more information section 3.4.4 sub a.

b 800µg of misoprostol per day appears to be more effective to prevent gastric ulcers than 400µg daily [RR = 0.2; 0.1-0.3 vs RR = 0.4; 0.3-0.5]. A reduction of the risk of clinical complications of NSAID-induced gastric ulcers has only been demonstrated for 800µg daily [OR = 0.6; 0.4-1.0] [199;200]. A disadvantage of misoprostol is that it is less well tolerated than PPIs, because diarrhoea often develops. This side effect is seen more often with 800µg per day than with 400µg per day, but even this lower dose level can still lead to diarrhoea[199].

NSAID = non-steroidal anti-inflammatory drug; **PPI** = proton pump inhibitor; **GI** = gastrointestinal; **RR** = relative risk; **OR** = odds ratio

The preference for PPIs raises the question of whether these agents may compromise the antiplatelet activity of low-dose ASA. So far, there is insufficient evidence to postulate the existence of such an interaction. In a case-control study, patients with coronary artery disease showed a reduced anti-platelet response to uncoated ASA (75mg/day) when they were treated simultaneously with a PPI[201]. However, no reduction in antiplatelet activity was observed in other human studies, which prospectively assessed combinations of enteric coated ASA (75-125mg/day) with omeprazole (20mg/day)[202], lansoprazole (30mg/day)[203], or pantoprazole (40mg/day)[204]. A pharmacokinetic evaluation of ASA (325mg/day) and esomeprazole(40mg/day) in healthy volunteers also failed to demonstrate a significant interaction[205]. In contrast, the H_2RA ranitidine (300mg/day) has been reported to lower blood salicylate levels and modestly reduce the antiplatelet effects of ASA (325mg/day) in healthy volunteers[206].

It has been repeatedly demonstrated that the gastrointestinal safety of ASA plus PPI is superior to that of clopidogrel without a PPI (Table XII). Hence it is not recommended to replace ASA by clopidogrel in *H.pylori* negative patients who have developed an upper GI bleeding, while receiving ASA. There are no randomized studies addressing the effectiveness of PPIs in patients receiving ASA who have other risk factors for bleeding than a gastrointestinal complication in their' history. Yet gastric protection seems also relevant in patients at an advanced age (Table IX), patients with concurrent use of VKA (Table IV, V and VI), clopidogrel (Table XIII), NS-NSAIDs, COX-2 selective inhibitors, corticosteroids, SSRIs, high doses heparin/LMWH and/or spironolactone (Table XI).

The expected benefits of PPI therapy for low-dose ASA users at substantial risk for UGIEs weigh more strongly than their known potential disadvantages, such as an increased risk of pneumonia[4] or fractures[5207].

As indicated in the introduction, cost-effectiveness analyses with respect to the addition of a PPI in different categories of ASA users fall outside the scope of this report. The task force has taken note of a US analysis in which the addition of a PPI in patients ≥ 65 years using low-dose ASA with a moderate risk of upper GI bleeding was cost-effective when over-the-counter (OTC) prices of PPIs were used for the analysis. When prescription costs of PPIs were used, cost effectiveness was only reached in patients at high risk[208]. An accompanying commentary on this study pointed out that the real effectiveness of PPIs in ASA users with a moderate risk might be lower than the 66% reduction which was assumed in the analysis[209]. It also pointed at remaining uncertainties about certain risks of PPI use (fractures, pneumonia and other unrecognized adverse effects). The Task Force considers it desirable that such cost-effectiveness analyses are performed for different subgroups of ASA users.

<u>Clopidogrel</u>

Concomitant use of a PPI reduces the risk of upper GI bleeding not only in users of low-dose ASA, but also in users of other PAIs[95;195]. In one observational study, PPI use reduced the risk in users of clopidogrel or ticlopidine to an RR of 0.19 [95% CI 0.07–0.49] [195]. The ACCF/ACG/AHA 2008 expert consensus on reducing the gastrointestinal

risks of PAI and NSAID use suggested accordingly that PPI co-therapy may be beneficial to reduce the gastrointestinal risks of clopidogrel[115]. Several observational studies subsequently showed an association between simultaneous PPI use and decreased effectiveness of clopidogrel (Table XV).

Table XV. Observational studies about simultaneous PPI use and decreased effectiveness of clopidogrel on clinical end points.

Reference	Clinical End Point(s)	Type of PPI	Risk Increase [95% CI]
Pezalla, Day and Pulliadath 2008[210]	Acute myocardial infarction	All PPIs [a]	RR_{adj} = 3.37 [a]
Dunn et al. 2008[211b]	Myocardial infarction /stroke/ death	All PPIs	HR = 1.5 [1.1–2.1]
Juurlink et al. 2009[212]	Rehospitalization with new myocardial infarction	All PPIs	OR_{adj} = 1.27 [1.03–1.57]
		Pantoprazole	OR_{adj} = 1.02 [0.70–1.47]
		Other PPIs	OR_{adj} = 1.40 [1.10–1.77]
Ho et al. 2009[213]	Rehospitalization for acute coronary syndrome or all-cause mortality	All PPIs	OR_{adj} = 1.25 [1.11-1.41]
		Omeprazole [c]	OR_{adj} = 1.24 [1.08-1.41]
		Rabeprazole [c]	OR_{adj} = 2.83 [1.96-4.09]
Stanek et al. 2009[214] [b]	Serious cardiovascular event (myocardial infarction, unstable angina, TIA/stroke, coronary revascularization or cardio-vascular mortality)	All PPIs	HR_{adj} = 1.51 [1.39-1.64]
		Omeprazole	HR_{adj} = 1.39 [1.22-1.57]
		Esomeprazole	HR_{adj} = 1.57 [1.40-1.76]
		Pantoprazole	HR_{adj} = 1.61 [1.41-1.88]
		Lansoprazole	HR_{adj} =1.39 [1.16-1.67]
Wang et al. 2009[215]	Myocardial reinfarction (in Taiwanese patients)	All PPIs	OR = 1.62 [1.01-2.59]
Rassen et al 2009[216]	Myocardial infarction hospitali-zation, death, revascularization (after PCI or hospitalization for ACS)	All PPIs	Propensity score-adjusted rate ratios: 1.22 [0.99-1.51] for MI or death 1.20 [0.84-1.70] for death 0.97 [0.79-1.21] for revascularization
O'Donoghue et al. [217]	Cardiovascular death/myocardial infarction/stroke	All PPIs	HR_{adj} = 0.94 [0.80-1.11]
		Omeprazole	HR_{adj} = 0.91 [0.72-1.15]
		Esomeprazole	HR_{adj} = 1.07 [0.75-1.52]
		Lansoprazole	HR_{adj} = 1.00 [0.63-1.59]
		Pantoprazole	HR_{adj} = 0.94 [0.74-1.18]
Ray ea 2010[218]	Serious cardiovascular disease (fatal or nonfatal myocardial infarction or sudden cardiac death, stroke, or other cardiovascular death)	All PPIs	HR = 0.99 [0.82–1.19]
		Omeprazole	HR = 0.79 [0.54–1.15]
		Esomeprazole	HR = 0.71 [0.48–1.06]
		Lansoprazole	HR = 1.06 [0.77–1.45]
		Pantoprazole	HR = 1.08 [0.88–1.32]
		Rabeprazole	HR = 0.54 [0.30–0.97] [d]

[a] In subjects with high PPI exposure (which was based on PPI adherence rates.)

[b] So far only published as an abstract.

[c] Lansoprazole and pantoprazole were not analyzed separately because of the low numbers of users.

[d] Smallest number of person years.

PPI = proton pump inhibitor; TIA = transient ischaemic attack; PCI = percutaneous coronary intervention; ACS= acute coronary syndrome; HR_{adj}= adjusted hazard ratio; MI= myocardial infarction; OR_{adj}= adjusted odds ratio

This negative effect was neither seen in a recent analysis by O'Donoghue et al. 2009[217] nor in the so-called Clopidogrel and Optimization of Gastrointestinal Events (COGENT) trial which compared a combination product of clopidogrel plus omeprazole to placebo in patients requiring clopidogrel for at least 12 months. While the rate of upper GIbleeding or pain of presumed gastrointestinal origin with underlying multiple erosive disease was significantly higher in the placebo group, there was no difference in the rates of serious cardiovascular events. The COGENT trial was halted prematurely, however, with a mean follow-up of only 133 days, and the results reproduced here were taken from a secondary non-peer reviewed source[219].

Randomized and cross-over studies of the influence of PPIs on the antiplatelet action of clopidogrel have yielded varying results as well. The antiplatelet activity of clopidogrel was significantly decreased by omeprazole in one study[220], while another study showed a non-significant reduction for lansoprazole[221]. A third study suggested that 20 mg of omeprazole affected the platelet response to clopidogrel significantly more often than 20 mg of pantoprazole did[222].

In November 2009, the FDA reported new unpublished clinical evidence that omeprazole reduced the active metabolite levels of clopidogrel by 45% and its antiplatelet activity by 47%. These reductions were also seen when both drugs were given 12 hours apart, so separate administration did not reduce their interaction. On the basis of these and earlier data, the FDA concluded that concomitant use of omeprazole and clopidogrel should be avoided and that this warning also extended to esomeprazole (because this PPI is a component of omeprazole). The FDA added that the applicability of the COGENT results was limited because of the study design and follow-up and that specific recommendations about the co-administration of clopidogrel and PPIs other than omeprazole and esomeprazole could not be made because of insufficient information[223]. Following the FDA lead, the Dutch Working Group on Pharmacotherapy and Drug Information decided to restrict computerized drug interaction alerts to combinations of clopidogrel with omeprazole or esomeprazole without generating alerts for combinations with other PPIs[224].

<u>Prasugrel</u>

Data about the risk of combining the related PAI prasugrel with a PPI are scarce. In one study, lansoprazole reduced the bioavailability of prasugrel's active metabolite by 13% without affecting its antiplatelet activity. In this study, lansoprazole did not significantly affect the antiplatelet action of clopidogrel either [221]. PPI use did not significantly influence the risk of cardiovascular death, myocardial infarction or stroke in prasugrel users[HR_{adj} = 1.00; 95% CI 0.84–1.20] in an observational analysis by O'Donoghue[217]. This was also seen for individual PPIs (omeprazole, pantoprazole; esomeprazole, lansoprazole). It seems premature, however, to draw definitive conclusions about the safety of these combinations without additional evaluations of prasugrel plus PPIs (particularly omeprazole).

c) *Strict reasons for use*

Adhering to strict reasons for use will also help to reduce the GI complications of ASA. This is especially important in patients with a history of diverticular complications or lower GI bleedings (as it is impossible to reduce the risk of a lower GI bleeding by the addition of a PPI) and for patients using a combination of ASA and VKA or of ASA and a second PAI (Tables IV, V, VI and XIII).

d) *Substitution of clopidogrel with prasugrel*

Substitution of clopidogrel by prasugrel does not appear to be a viable option to decrease the risk of serious bleeding, since the more potent prasugrel entails a higher risk in this respect than clopidogrel, particularly in patients older than 75 years of age[188].

e) *Restricting the OTC availability of ASA*

In the HARM study, one case of a bleeding cerebral vascular accident was attributed to an OTC product of ASA. The advisability to provide OTC ASA products with a 'Pharmacy Only' status will be explained in detail in section 3.4.4.

f) *Reduction of the ASA dose level*

The Task force did not adopt a suggestion in the literature to reduce the dose level of ASA to doses lower than 100mg per day[89], since the effectiveness of this proposal is uncertain (see above) and since it cannot be excluded that this might increase the clinically relevant problem of resistance to ASA[112;113].

3.4 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

3.4.1 PATHOPHYSIOLOGY

GI adverse effects of NSAIDs vary in seriousness from stomach complaints (such as nausea, stomach pain and heartburn) to GI ulcers complicated by perforation, obstruction and/or haemorrhage. The relation between mild complaints and the development of serious complications is limited. The latter are primarily based on inhibition of the enzyme cyclo-oxygenase (COX). This results in the suppression of the synthesis of prostaglandins, which in turn leads to reduction of the protective function of the gastric intestinal mucosa. Furthermore, NS-NSAIDS can also prolong bleeding clotting time through platelet aggregation inhibition. Since the NSAID effect on the synthesis of prostaglandins is a systemic effect, NSAIDs can produce their serious GI adverse effects also when taken via another route than oral administration[24].

The anti-inflammatory effects of NSAIDs rest on inhibition of the COX-2 subtype, while their GI harm is due to inhibition of COX-1. Some NSAIDS (such as meloxicam and nabumetone) are *in vitro* more selective inhibitors of COX-2 than others, but it has not been convincingly demonstrated that these agents also have superior GI safety in daily clinical practice[24;225]. There is evidence from large randomized clinical trials that the GI risks of the newly developed COX-2 selective inhibitors (such as rofecoxib and celecoxib) are reduced[160;226-228]. However, these studies are not without limitations, since they do not provide enough insight into the effects in high risk patients or into long-term GI safety[225]. In two of the studies, the

superior GI safety of the COX-2 selective inhibitor disappeared, when only ASA users were evaluated. One of these studies has also been criticized for leaving out data on its second half year, since this may have flattered its results[229].

3.4.2 EPIDEMIOLOGY

According to a meta-analysis of 16 trials in which NSAIDs were compared with placebo the RR of NSAID users for developing a UGIEs is 5.4 [1.8-16.1]. Pooling of 9 cohort studies yielded an RR of 2.7 [2.1-3.5], and 23 case-control studies gave an RR of 3.0 [2.5-3.7][230]. Five to ten percent of these UGIEs were fatal[225]. On basis of a Dutch database (PHARMO) it has been calculated for 2000 that 2823 hospital admissions in the Netherlands were due to NSAIDs and that 165 of these (5.8%) were fatal[24]. This concerned a period, however, when the addition of a gastroprotective agent was still less common[231].

Recent observational studies assessing the risk on UGIEs for different types of NSAIDs are summarized in Table XVI. These studies do not only confirm the increased risk of NS-NSAIDs, but also show an increased risk for meloxicam, nabumetone and COX-2 selective inhibitors. However, patients receiving COX-2 selective inhibitors may have had GI risk factors more often than users of NS-NSAIDs[232]. COX-2 selective inhibitors have been associated with a significant lower risk of GI complications than NS-NSAIDS after correction for this 'channelling'[233].

Patients receiving NS-NSAIDs are not only at a higher risk of UGIEs, but also of lower GI bleeding[225]. According to a recent overview, six of eight case-control studies assessing lower GI complications showed an RR between 1.9 [1.2-3.1] and 3.8 [1.8-7.9] with one outlier of 18.4 [5.1-66.2][98]. Large-scale observational studies of the risk of lower GI bleeding in patients receiving COX-2 selective inhibitors are not yet available.

3.4.3 RISK FACTORS

Table X shows an overview of independent risk factors that have been correlated with UGIEs in patients receiving NSAIDs. Besides VKAs, PAIs, corticosteroids and SSRIs, spironolactone should also be considered as a drug which can increase the GI risk of NSAIDs (Table XI).

Potential risk factors for the development of UGIEs in patients receiving COX-2 selective inhibitors include length of therapy, elderly user, a history of bleeding GI ulcer, and concurrent use of a VKA, PAI or NS-NSAID[114;181;234;235]. Comparison of these risk factors to those in Table X suggests that there are clear parallels with the risk factors for NS-NSAIDs.

Data about the risks of COX-2 selective inhibitors in combination with oral corticosteroids or SSRIs are still scarce. In an observational study the risk of concurrent use of COX-2 selective inhibitors and SSRIs compared to monotherapy with a COX-2 selective inhibitor was not significantly increased [OR_{adj} 1.3; 0.7-2.5][236].

According to reference sources on drug-drug interactions, clinical evidence for an interaction between NSAIDs and heparin/LMWH is limited to sporadic case reports and a prospective study of ketorolac plus LMWH dalteparin in healthy subjects[116;224;237]. Nevertheless, combining an NSAID with heparin/LMWH is considered controversial and appropriate caution is recommended if such drugs are given together[224;238]. Consequently, it seems

prudent to extend the US consensus document which recommends the addition of a PPI if patients are treated with ASA plus heparin/LMWH (see section 3.3.3) to patients on an NSAID plus high-dose heparin/LMWH as well.

Table XVI. Observational studies investigating the relationship between gastrointestinal events anddifferent types of NSAIDs.

References[a] (GI endpoint)	Type(s) of NSAIDs	RR [95%CI]
Laporte et al. 2004[239] (upper GI bleeding)	Aceclofenac	1.4[0.6-3.3]
	Dexketoprofen	4.9 [1.7-13.9]
	Meloxicam	5.7 [2.2-15.0]
	Nimesulide	3.2 [1.9-5.6]
	Celocoxib	0.3 [0.03-4.1]
	Rofecoxib	7.2 [2.3-23.0]
Ashworth et al. 2005[240] (GI bleeding)	Diclofenac + misoprostol (as combination preparation)	Reference
	Naproxen	7.9 [3.9-15.9]
	Nabumetone	2.6 [1.0-6.6]
	Diclofenac + separate cytoprotective agent	6.8 [3.5-13.4]
Hippisley-Cox, Coupland, and Logan 2005 [241] (GI bleeding, perforation, surgery)	Ibuprofen	1.6 [1.4-1.8]
	Diclofenac	2.1 [1.8-2.4]
	Naproxen	2.0 [1.5-2.6]
	Rofecoxib	1.8 [1.4-2.3]
	Celecoxib	1.3 [0.9-1.7]
Lanas et al. 2006 [94] (upper GI bleeding)	Non-selective NSAIDs	5.3 [4.5-6.2]
	Rofecoxib	2.1 [1.1-4.0]
	Celecoxib	1.0 [0.4-2.1]
García Rodríguez and Barreales 2007 [125] (upper GI bleeding, perforation)	Non-selective NSAIDs	3.7[3.1-4.3]
	Half-life of ≥12 hours[b]	4.5 [3.3-6.2]
	slow release	6.5 [4.7-8.9]
	COX-2 selective inhibitors	2.6 [1.9-3.6]

a When there was more than one endpoint in a study, the most serious endpoint was selected

b Including naproxen, piroxicam, sulindac, meloxicam and nabumetone .

NSAID = non-steroidal anti-inflammatory drug; **RR** = relative risk

3.4.4 RISK REDUCING STRATEGIES

The conclusions of the Dutch CBO guideline on NSAID-related gastric damage about the effectiveness of different preventive strategies are summarized in Table XIV[24]. A British systematic review of this topic reached somewhat different conclusions[200]. According to the Task Force, this latter review does not provide enough impetus to reject the recommendations of the Dutch CBO guideline. Firstly, the review only focused on symptomatic ulcers and serious GI complications, whereas the literature often considers endoscopic ulcers as a useful surrogate for more serious GI complications[242]. Secondly, only 15 of the 51 studies in the British review, concerned drugs which are also available in the Netherlands, and several studies were characterized by relatively low exposure to NSAIDs (low dose level, short duration of the study) or "tolerability" as endpoint[24].

To reduce the bleeding risk in NSAID users the following strategies could be especially considered:

(a) Strict decisions whether to prescribe an NSAID or not

In all patients at risk for UGIEs, the possibility of giving acetaminophen instead of an NSAID should always be considered. For example, acetaminophen can be as effective as an NSAID in individual patients with osteoarthritis[243-245]. N of 1 trials can be used to investigate to which patients this applies[246;247].

When one considers the prescribing of an NSAID, not only the risk of GI complications should be taken into account, but also the risks of renal insufficiency and heart failure (see section 4.5 and 4.6).

(b) Eradication of H.pylori

The CBO guideline recommends to test patients with a history of a GI ulcer complication for *H. pylori* infection and to eradicate an untreated infection before an NSAID is started, as this may reduce the risk of ulcers and complications.

Eradication of *H. pylori* infection has been presented as the most cost-effective strategy for primary prevention of NSAID-associated ulceration in patients >50 years[248]. However, it remains unclear whether a test and treat strategy would be cost effective for the large group of patients who take NSAIDs intermittently and often for only short periods of time. Futhermore, eradication of *H. pylori* alone is not sufficient for the secondary prevention of peptic ulcer bleeding in chronic NSAID users[148].

The available trials reporting on the benefit of *Helicobacter* eradication in NSAID-users show varying results. According to a meta-analysis of five randomized studies, 7.4% of the eradicated NSAID users developed a peptic ulcer versus 13.3% of the non-eradicated users [OR =0.4; 0.2-0.9]. Further analyses showed a significant risk reduction in patients who had not been treated with NSAIDs prior to eradication [OR= 0,3; 0.1-0.5], but not in patients who had received NSAIDs before [OR =1.0: 0.5-1.7]. A bleeding ulcer was found in 0% of the eradicated patients versus 1.2% of the non-eradicated patients [OR = 0.1; 0.02-0.9]. In two studies comparing eradication with PPI treatment, the former strategy

seemed to prevent a peptic ulcer less effectively to than the latter (2.6% versus 0% OR = 7.4; 1.3-43.6) [249]. A more recent study in long-term NSAID users (48% of whom were on gastroprotective drug therapy) did not show a favourable effect of eradication either[250].

(c) Addition of gastric protection

The Dutch CBO guideline recommends to give gastric prevention (PPI or misoprostol) always if the patient has a history of an UGIE or if the patient is > 70 years. The guideline recommends to consider gastric protection if the patient is between 60 and 70 years old; if the NSAID is used concurrently with a VKA, PAI, corticosteroid or SSRI; if the patient suffers from serious invalidated rheumatoid arthritis, heart failure or diabetes; or if the patient receives a high dose level of the NSAID. According to the guideline these risk factors are cumulative, so the risk increases when a patient has more than one risk factor. The Task force has decided to follow the CBO guideline with regards to its strict recommendations and to convert its noncommittal suggestions (which leave much room to refrain from preventive action in certain risk situations) into the more strict recommendation of the recent ACG guidelines[148] which recommend gastric protection if there are multiple risk factors.

This means that the Task Force recommends adequate gastric protection in all NSAID users who have at least two of the following risk factors:

- Age between 60 and 70 years;
- intake of high doses of an NSAID for a prolonged period (e.g., the upper dose limit of the recommended dosage range for more than 3 weeks);
- concurrent use of an interacting drug which enlarges the risk for a GI complication (VKA, ASA, clopidogrel, systemic corticosteroid, SSRI, spironolactone, high doses of heparin/LMWH) (cf. Table XI)
- seriously invalidating rheumatoid arthritis, heart failure or diabetes.

This also applies to patients who receive the NSAID shortly or intermittently. After careful consideration of Table XIV, observational studies[251-254] and recent reviews[148;194;253] the Task Force has decided to give preference to a PPI in normal doses for the prevention of NSAID-related GI toxicity.[6]

It is important that the patient adheres to the gastric protective treatment regimen[251;255] and that the gastric protective drug is discontinued, when the NSAID is discontinued[256].

(d) Replacement by COX-2 selective inhibitor

According to a Cochrane review, COX-2 selective inhibitors produce significantly fewer gastroduodenal ulcers (RR=0.26;95% CI0.23-0.30) and ulcer complications (RR = 0.39; 95% CI 0.31-0.50) than NS-NSAIDs[247]. However, when there are no significant risk factors for UGIEs, there is insufficient reason to prefer a COX-2 selective inhibitor over an NS-NSAID. And when there are significant risk factors, COX-2 selective inhibitors are not necessarily safer than NS-NSAIDs in all situations. There is clinical evidence, for instance, that the GI advantage of a COX-2 selective inhibitor disappears, when ASA is used concurrently[160;227]. There are also several trials in which a COX-2 selective inhibitor

was compared head-to-head with an NS-NSAID in patients with a history of an UGIE (Table XVII).

COX-2 selective inhibitors were not really safer in these studies than a NS-NSAID combined with a PPI. In one recent trial, however, a COX-2 selective inhibitor plus a double-dose PPI was safer than this inhibitor without the addition of a PPI[257]. This suggests that the combination of a COX-2 selective inhibitor plus a double-dose PPI may be considered in those patients, who have a history of one or more UGIEs during NSAID use despite adequate gastric protection and in whom alternative approaches (such as substitution of the NSAID by acetaminophen or the discontinuation of an interacting drug) are not feasible. However, the trial did not have a third arm evaluating a NS-NSAID plus a PPI, so it did not directly address the comparative GI safety of the COX-2 inhibitor plus PPI versus that of a NS-NSAID plus PPI.

Discussions of whether NS-NSAIDs should be replaced by COX-2 selective inhibitors should also take into account the recent data about the cardiovascular risks of these two drug groups, which depend on[225;258;259]:

- Cardio renal effects (hypertension, heart failure, oedema), which may occur with all types of NSAIDs, are dose-dependent and may make an important contribution to the cardiovascular risks of NSAIDs in the long term. (see sections 4.5 and 4.6), Cox-2 selectivity does not appear to have an impact on the degree of cardiorenal effects.
- Thrombotic effects, especially the risks of myocardial infarction and cerebral vascular accidents[260].

According to the European Medicines Agency (EMEA), COX-2 selective inhibitors have such cardiovascular risks that they should be used in the lowest effective dose for the shortest possible duration of treatment. These drugs should be avoided in patients with ischaemic heart disease or stroke, and etoricoxib should also be avoided in uncontrolled hypertension. Furthermore, EMEA has recommended caution when COX-2 inhibitors are to be prescribed to patients with risk factors for heart disease (such as hypertension, hyperlipidaemia, diabetes and smoking)[259].

This viewpoint of EMEA raises the question, however, to which extent NS-NSAIDs are safer for cardiovascular patients, because there is increasing evidence to suggest that high doses of NS-NSAIDs also entail an increased risk of thrombotic effects[136;261-263]. The recommendation to prescribe COX-2 selective inhibitors in patients with cardiovascular risk factors in the lowest effective dose for the shortest possible duration of treatment, therefore also applies to NS-NSAIDs[225;258]. In line with this, the cardiovascular contraindications for COX-2 selective inhibitors (see above) probably also apply to high-dose NS-NSAIDs.

Table XVII. Randomized double-blind studies of the gastrointestinal safety of selective COX-2 inhibitors versus NS-NSAIDs in patients with a history of NSAID-related ulcer complications[a.]

Reference	Research population	Interventions	Results
Selective COX-2 inhibitor *without* a PPI			
Chan et al.2002[234]	287 *Helicobacter* negative patients with healed NSAID induced GI ulcer bleeding	Duration: 6 months (A) 400 mg celecoxib + placebo (B) 150 mg diclofenac + 20 mg omeprazole	Recurrent ulcer bleeding (A) 4.9% (B) 6.4% (difference not significant)
Lai et al. 2005[264]	224 *Helicobacter* negative patients with healed NSAID induced GI ulcer bleeding	Duration: 5.5 months (A) 200 mg celecoxib (B) 750 mg naproxen + 30 mg lansoprazole	Recurrent ulcer complications (A) 4% (B) 6% (difference not significant)
Goldstein et al. 2007[265]	854 analyzable cardiovascular patients on low-dose ASA without gastroduodenal ulcer at baseline	During 12 weeks (A) 200 mg celecoxib + 81-325 mg ASA (B) 1000 mg naproxen + 30 mg lansoprazole + 81-325 mg ASA	Gastroduodenal ulcers (A) 9.9% (B) 8.9%
Selective COX-2 inhibitor *with* PPI			
Chan et al. 2007 [257]	441 *Helicobacter* negative patients with healed NSAID-induced upper GI bleeding	Duration: 12 months (A) 400 mg celecoxib (B) 400 mg celecoxib + 40 mg esomeprazole b	Recurrent ulcer bleeding (A) 9% (B) 0%
Goldstein et al.2007 [266]	440 patients with gastric ulcer ≥ 5mm and <25mm on continued therapy with COX-2 selective inhibitor or NS-NSAID therapy	Duration: 8 weeks (A) COX-2 selective inhibitor + 40mg esomeprazole (B) COX-2 selective inhibitor + 20mg esomeprazole (C) COX-2 selective inhibitor + ranitidine 150mg twice daily (D) NS-NSAID + 40mg esomeprazole (E) NS-NSAID + 20mg esomeprazole (F) NS-NSAID + ranitidine 150mg twice daily	Gastric ulcer healing rates (A) 13 out of 14 = 92.9% (B) 10 out of 12 = 83.3% (C 16 out of 21 = 76.2% (D) 101/119 = 84.9% (E)107/126 = 84.9% (F)90/117 = 76.9%

a Since non-Caucasian patients have an increased risk for ulcer complications due to NSAIDs[181;182], it is probably not unimportant to notice that all studies, except Goldstein et al. 2007 [265] are performed in Hong Kong. Another limitation of these studies is that the studies only evaluated gastrointestinal outcomes without simultaneous assessment of cardiovascular outcomes[183].

b The usual dose of esomeprazole for the prevention of NSAID-associated gastroduodenal ulcers is 20mg daily.

NSAIDs = non-steroidal anti-inflammatory drugs; **ASA**= acetylsalicylic acid; **PPI** = proton pump inhibitor

The ACG guidelines for the prevention of NSAID-related ulcer complications gear their recommendations to the GI and cardiovascular risk profiles of the individual user (see Table XVIII for a summary). Similar tailoring strategies are propagated in other recent sources[104;147;253;267].

Table XVIII. Summary of the ACG recommendations for prevention of NSAID-related ulcer complications[1,2148].

	Low gastro-intestinal risk [3]	**Moderate gastro-intestinal risk** [3]	**High gastro-intestinal risk** [3]
Low cardio-vascular risk [4]	NS-NSAID alone [5]	NS-NSAID + PPI/misoprostol [6]	Alternative therapy if possible or COX-2 inhibitor + PPI/ misoprostol [6]
High cardio-vascular risk [4]	Naproxen + PPI/misoprostol [6]	Naproxen + PPI/misoprostol [6]	Avoid NSAIDs or COX-2 inhibitors. Use alternative therapy

1 All patients with a history of ulcers who require NSAIDs should be tested for *H. pylori*, and if the infection is present, eradication therapy should be given.

2 The ACG guidelines summarize the advantages and disadvantages of the available treatment options as follows:

(a) Misoprostol is very effective in preventing ulcers and ulcer complications in patients taking NSAIDs when given in full doses (800 μg/day). Unfortunately, the usefulness of this dose level is limited by its gastrointestinal side effects (cf Table XIV).

(b) PPIs significantly reduce gastric and duodenal ulcers and their complications in patients taking NSAIDs or COX-2 inhibitors.

(c) COX-2 inhibitors are associated with a significantly lower incidence of gastric and duodenal ulcers when compared to traditional NS-NSAIDs. However, this beneficial effect is negated when the patient is taking concomitant low-dose ASA. The usefulness of these agents has also been reduced by their association with myocardial infarction and other thrombotic cardiovascular events. The lowest possible dose of celecoxib should be used to minimize the risk of cardiovascular events.

(d) High-dose H2RAs can reduce the risk of NSAID-induced endoscopic peptic ulcers. They are significantly less effective than PPIs, however, and there are no clinical outcome data to prove that this strategy prevents ulcer complications.

3 The ACG guidelines stratify gastrointestinal risks into:

(a) Low risk – no risk factors.

(b) Moderate risk – 1-2 risk factors: age >65 years; high dose NSAID therapy; previous history of uncomplicated ulcer; concurrent use of ASA (in low or high doses), corticosteroid or VKA.

(c) High risk – more than 2 risk factors, or a history of a previously complicated ulcer (especially recent).

4 The ACG guidelines arbitrarily define high cardiovascular risk as the requirement for low-dose ASA.

5 The least ulcerogenic NSAID in the lowest effective dose.

6 The ACG guidelines claim that lower doses of misoprostol (400-600 μg/day) also confer a significant protective effect with less side effects[148]. While there is clinical evidence that 400-800 μg/day of misoprostol reduces the risk of endoscopic ulcers, a favourable effect on relevant endpoints (upper gastrointestinal complications) has only been demonstrated for 800 μg/day[24]

NS-NSAIDs = non-selective non-steroidal anti-inflammatory drugs; **PPI**= proton pump inhibitor; **ACG**= American College of Gastroenterology; **H2AR** = Histamine-2 antagonist; **ASA** = acetylsalicylic acid; **VKA**= vitamin K antagonist

In the spirit of this approach, the Task Force has amended the Dutch CBO guideline for prevention of NSAID-related GI damage from 2003[24] as follows:

- If NSAID therapy is considered necessary for patients at high GI risk (e.g., with a prior UGIE), preference should be given to a COX-2 selective inhibitor plus a PPI. However, further studies are still desirable to confirm the relative efficacy of this combined therapy[253]. Furthermore, it is not an attractive option for patients who are also at high cardiovascular risk because such patients are sensitive to the cardiovascular side effects of the COX-2 selective inhibitor and will often be treated with low-dose ASA (which nullifies the increased GI safety of the COX-2 selective inhibitor).
- If NSAID therapy is considered necessary for patients at high cardiovascular risk (e.g., patients on low-dose ASA or clopidogrel), preference should be given to naproxen. Protective therapy with a PPI should be provided, if additional GI risk factors besides naproxen and the PAI are present.

It is still insufficiently clear, however, whether naproxen is really a favourable exception within the group of NS-NSAIDs. On the one hand, this drug has emerged as a relatively safe agent from the pooled results of randomized trials and observational studies[262;263]. On the other hand, in a recent comparative randomized trial, naproxen sodium (220 mg b.i.d.) gave a higher HR for serious cardiovascular and cerebral vascular events than placebo [HR = 1.6; 1.0-2.6], whereas such an effect was not observed for celecoxib (200 mg b.i.d.)[152]. Furthermore, it has not yet been convincingly demonstrated that naproxen completely lacks the adverse drug-drug interaction with low-dose ASA, which has been reported for ibuprofen (cf. Table XI)[135;136;138;143;153]. If an NSAID-related bleeding has developed, the risk of a recurrent ulcer after healing is increased, even when a PPI is added or when a NS-NSAID is replaced by a COX-2 selective inhibitor (Table XVII, Chan et al. [234]). Even the risk of endoscopic ulcers (in absence of a ulcer complication) was not significantly different: 18.7% [11.3%-26.1%] vs 25.6% [17.1%-34.1%][268]. All by all none of the two investigated treatment strategies are exceedingly effective for this type of high risk patients. Data about combining COX-2 selective inhibitors with a PPI in risk patients are still limited[257;269].

(e) Reducing the Over-The-Counter availability of NSAIDs and ASA

OTC NSAIDs and ASA may not only cause GI and other bleedings (this part), but can also induce renal insufficiency (section 4.5) and worsen heart failure (section 4.6) or asthma. In addition, ibuprofen may decrease the platelet inhibitory effects of ASA (Table X).

Observational studies suggest that OTC NSAID products entail a low risk of serious GI complications, when used in patients without any risk factors and when used intermittedly and in low doses. However, the risk of UGIEs significantly increases, when patients are at high risk (Table IX) and when high doses are used for a prolonged period[270-273]. It is open to question whether all patients can judge for themselves if their risk of GI complications is neglibly small. In a recent French study, 12% of patients using ibuprofen as an OTC drug had a contraindication and 38% should have consulted a physician before starting the drug[274].

At the time of the HARM study, Pharmacy Only products of NSAIDs and ASA were not available in The Netherlands, but only OTC and Prescription Only products. The HARM researchers did not systematically discriminate between these two categories of products, but they did record, whether patients had been using these drugs "on their own initiative". This would not only reflect OTC use, but also the unauthorized use of Prescription Only drugs (e.g., the remainder of an earlier prescription or a product obtained from someone else) In total, the HARM researchers associated ten cases of HARM with NSAIDs or ASA that had been used "on the user's own initiative":

- Four cases involved a NSAID which was definitely Prescription Only (three times diclofenac and once 600 mg ibuprofen); one of these cases was assessed as unavoidable by the HARM researchers
- Three cases definitely involved an OTC product (two times ASA and once ibuprofen)
- In three cases it remained unclear whether the NSAID had been an OTC product or had been obtained through an earlier prescription (two times ibuprofen and once naproxen).

On the one hand, these findings show that there should be more awareness of the risk that patients may use prescription only NSAIDs or ASA on their own initiative (3/332; i.e., 0.9% of the potentially avoidable causes). On the other hand, at least three (0.9%) cases and possibly six (1.8%) cases of the 332 potential avoidable cases involved an OTC product. At a total of 16.000 potentially avoidable drug-related admissions to Dutch hospitals per year, this would correspond to 144 and 288 cases per year, respectively.

The Task Force therefore recommended in the first draft of its report to consider a "Pharmacy Only" status for OTC products of NSAIDs and ASA.[7] This will only be beneficial, however, if pharmacies treat such medications as Prescription Only drugs. This implies that:

- These products should always be dispensed for a single user (that is, provided with a personalized label), so that the user knows that the dispensed product is only meant to be used by himself.
- These products should always be recorded in the patient's pharmacy record, so that they will be consistently included in the automatic medication surveillance of their users.

Following this preliminary recommendation, the Dutch Medicines Evaluation Board reconsidered the legal status of OTC products of NSAIDs. As this board strives for risk minimization[275]. Therefore they do not only take into account the properties of the active ingredient, but also the strength and the package size of the product. The Dutch Medicines Evaluation Board decided to change the legal status of high doses of naproxen (550mg) and diclofenac 25mg into "Pharmacy Only" [276]. Unfortunately ibuprofen 200mg kept its 'General Sale'status.

3.5 RECOMMENDATIONS RELATED TO BLEEDINGS

Bleeding (section 3)

Recommendation 1.

Antithrombotic agents are prescribed only on strict indication (Grade 1C). The prescribing physician records this indication and passes it on, together with the intended duration of therapy, to all healthcare professionals who are directly involved in the treatment of the patient. This general recommendation applies particularly when patients are at increased risk of bleeding, e.g.(Grade 1B):

a) Because they have a history of bleeding during antithrombotic therapy.
b) Because they will be treated with a VKA plus PAI or with two PAIs.

Bleeding resulting from Vitamin K antagonists (section 3.2)

Recommendation 2.

Before starting VKA therapy, the treating physician assesses the risk of irregular use (e.g. due to impaired cognition or alcohol abuse) (Grade 1B).

Recommendation 3.

VKA users with a history of bleeding or with an unstable INR with supratherapeutic peaks ≥ 6 require meticulous monitoring (Grade 1B).

The physician, who diagnoses a major bleeding in a VKA user, passes this information on to all healthcare professionals who are directly involved in the treatment of the patient (Grade 2C).

The physician who observes a change in the co-morbidity of a VKA user that requires intensified INR monitoring (e.g., decreased diabetic control or worsening heart failure) passes this information on to the clinic or service which is monitoring the anticoagulation intensity of that patient (Grade 1C). Reversely, the latter informs the healthcare professionals who are directly involved in the treatment of the patient when INR values are unstable with supratherapeutic peaks ≥ 6 (Grade 1C).

Recommendation 4.

When a VKA user start another medication that is known to give a pharmacokinetic interaction with VKAs, the physician or pharmacist reports this directly to the clinic or service which is monitoring anticoagulation intensity without leaving this to the patient (Grade 1C).

As the simultaneous use of a VKA with co-trimoxazole produces a considerable increase in INR and as substitution of co-trimoxazole with another antibacterial agent is almost always feasible, the combination of co-trimoxazole with a VKA should be avoided as much as possible, especially when it would be used for more than one day (Grade 1B). An exception may be necessary for VKA users with HIV infection (Grade 2C).

When a medication that gives a strong pharmacokinetic interaction with VKAs is discontinued in a VKA user, the physician reports this by means of a discontinuation note to the dispensing pharmacist who in turn informs the monitoring clinic or service (Grade 1C).

Computerized medication surveillance systems should produce an alert when antibiotic treatment is started in a VKA user. Pharmacists should pass this information on directly to the monitoring clinic or service without leaving this to the patient (Grade 1C).

Recommendation 5.
Genotyping of VKORC1 (and CYP2C9 in the case of acenocoumarol) should be considered as a diagnostic tool, when the INR response to normal VKA doses is unusually high or when VKA dosage is unusually low in an individual user (Grade 2B).

Recommendation 6.
VKA users should be well informed about the risks and management of intercurrent diseases and changes in lifestyle or diet (Grade 1B).
VKA users at increased risk of gastrointestinal bleeding receive oral and written information about its alarm symptoms (Grade 2C).
Patient self-management is recommended for those VKA users who can perform this adequately after being suitably selected, educated and trained (Grade 2B).

Bleeding resulting from PAIs (section 3.3) and NSAIDs (section 3.4)
Recommendation 7.
If possible NSAIDs are avoided if:
a) Patients are older than 70 years (Grade 1C).
b) Patients have a history of one or more UGIEs (Grade 1B).
c) Patients have a history of diverticular disease or lower gastrointestinal bleeding (Grade 1B).
d) The addition of the NSAID will result in a high dose level of the NSAID or in the combination of two different NSAIDs (Grade 1B).
e) Patients will be treated concurrently with a VKA, selective COX-2 inhibitor, systemic corticosteroid, low-dose ASA, clopidogrel, prasugrel(Grade 1B); heparin/LMWH (Grade 1C); SSRI or spironolactone (Grade 2B).
f) Patients have heart failure, diabetes (Grade 1B) or severe rheumatoid arthritis(Grade 1C).

NSAID users who are at increased risk of gastrointestinal bleeding receive oral and written information about its alarm symptoms (Grade 2C).

Recommendation 8.

Adequate gastric protection by means of a proton pump inhibitor (PPI) is needed when NSAID users[1]:

a) Have a history of one or more UGIEs (Grade 1B).
b) Are older than 70 years (Grade 1C).
c) Have two or more of the following risk factors (Grade 1C):
   - are 60-70 years old;
   - need long-term treatment with a high dose level of the NSAID;
   - are treated simultaneously with another medicine that increases the risk of gastrointestinal complications (VKA, ASA, clopidogrel, prasugrel, systemic corticosteroid, SSRI, spironolactone, high doses of heparin/LMWH);
   - have serious co-morbidity (such as severe rheumatoid arthritis, heart failure or diabetes).

Recommendation 9.

Adequate gastric protection with a PPI is necessary when users of low-dose ASA[1]:

a) Have a history of one or more UGIEs (Grade 1B).
b) Are at least 60 years and treated simultaneously with two or more medications that increase the risk of gastrointestinal complications (VKA, NSAID, selective COX-2 inhibitor, clopidogrel, prasugrel, high doses of heparin/LMWH, oral corticosteroid, SSRI and/or spironolactone)(Grade 1C).
c) Are at least 70 years old and are treated simultaneously with one other medication that increases the risk of gastrointestinal complications (VKA, NSAID, selective COX-2 inhibitor, clopidogrel, high doses heparin/LMWH, oral corticosteroid, SSRI and/or spironolactone) (Grade 1C).
d) Are at least 80 years old (Grade 1C).

To err on the safe side of caution, this recommendation also applies to clopidogrel and prasugrel (grade 1C).

Users of PAIs who are at increased risk of gastrointestinal bleeding receive oral and written information about its alarm symptoms (Grade 2C).

[1] *It is advisable to submit these recommendations to further cost-effectiveness analyses as they are only based on clinical considerations.*

One has to realize that lower gastrointestinal complications cannot be prevented by the addition of a gastric protective agent.

Recommendation 10.
When a gastric protective agent is added to NSAID or low-dose ASA treatment to reduce the risk of upper gastrointestinal complications, the prescriber and pharmacist inform the patient about the importance of good adherence to this protective therapy (Grade 1C).
When the NSAID or low-dose ASA is discontinued, the gastric protective agent should be discontinued as well (Grade 1B).

Recommendation 11.
When an NSAID or low-dose ASA is started in a patient with a history of UGIEs (together with a PPI for gastric protection), the patient is tested for the presence of *Helicobacter pylori* as soon as possible and, if necessary, treated with eradication therapy, if the patient has not been tested and treated before (Grade 1B).

Recommendation 12.
When a *Helicobacter* negative ASA user has a history of healed ASA-associated upper gastrointestinal bleeding, the combination of low-dose ASA plus a PPI is preferable to clopidogrel without a PPI (Grade 1B).

Recommendation 13.
When a selective COX-2 inhibitor is combined with low dose ASA, this compromises the relative gastrointestinal safety of the selective COX-2 inhibitor. Consequently, the recommendations for the simultaneous use of ASA and a non-selective NSAID also apply to the combination of low-dose ASA and a selective COX-2 inhibitor (Grade 1B).

Recommendation 14.
In view of the potential health risks of NSAIDs and ASA, it is advisable to reclassify current OTC products with an NSAID or ASA as “Pharmacy Only“ products. This makes it possible to dispense these products to named users and to enter these products into the personal pharmacy record of their users so thatthey can be systematically taken into account in the medication surveillance programme of the pharmacy computer system (Grade 2B).

Recommendation 15.
Selective COX-2 inhibitors are contraindicated for patients with established ischaemic heart disease or stroke and their application in patients with peripheral arterial disease or risk factors for heart disease (such as hypertension, hyperlipidaemia, diabetes, and smoking, or peripheral arterial disease) should be kept as low and as short as possible (Grade 1B).
Non-selective NSAIDs should also be avoided as much as possible in patients with established ischaemic heart disease or stroke. When a non-selective NSAID cannot be avoided, its use should be as low and short as possible. This also applies to the use of non-selective NSAIDs in patients with peripheral arterial disease or risk factors for heart disease (Grade 1B).

4 ELECTROLYTE DISTURBANCES, RENAL DYSFUNCTION AND HEART FAILURE

4.1 HARM AND IPCI DATA

In the combined HARM and IPCI cases, 44 potentially preventable admissions due to electrolyte disorders, renal failure and/or heart failure were found. From these 44 cases, 29 (66%) were aged above the age of 80 years. The following associations came to the fore (Table XIX):

- Thiazide diuretics and hyponatraemia (8);
- Potassium-losing diuretics and hypokalaemia (7) or dehydration (8);
- Renin angiotensin system inhibitors (RASIs) (a collective name for angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs)) potassium-sparing diuretics and hyperkalaemia (7); in one case it was explicitly documented that hyperkalemia developed despite adequate monitoring .
- RASIs/ NSAIDs and renal insufficiency (8);
- NSAIDs and heart failure (5); in at least two of these cases, the patients had renal insufficiency and in 4 cases the NSAID had been given to patients with an already existing cardiac disease.

4.1 HYPONATRAEMIA ASSOCIATED WITH THIAZIDE DIURETICS

4.1.1 PATHOPHYSIOLOGY

Thiazide diuretics and thiazide-like diuretics (such as chlorthalidone and indapamide) can cause hyponatraemia in sensitive patients by inducing hypovolemia which leads to increased antiduretic hormone (ADH)-secretion. Loop diuretics also show these effects, but to a lesser extent. Thiazide-induced hypokalaemia can exacerbate hyponatraemia by transporting potassium to the extracellular compartment, while sodium moves to the intracellular compartment. Severe hyponatraemia is less common than mild asymptomatic hyponatraemia, but it can lead to significant morbidity and mortality[277].

Hyponatraemia in patients receiving thiazide diuretics, usually arises in the first 2 to12 days of therapy, although it can also occur after this period[277-280]. In patients with a history of hyponatraemia due to thiazide use, a single dose may be sufficient to reduce the sodium level by 5.5mmol/L[281].

In mild cases of asymptomatic hyponatraemia, careful observation is required, but it will not always be necessary to discontinue the causing agents. In more severe cases, it may be necessary to limit fluid intake and to discontinue the causative agent[282;283].

Table XIX. HARM/IPCI data of electrolyte disorders, dehydration, renal failure and heart failure.(Numbers of cases between brackets).

Symptoms	Accompanied by	Associated with	Potentially relevant co-medication	Additional Comments
Hyponatraemia (8)	Hypokalaemia and dehydration (1) Renal insufficiency (3)	Thiazides (8)	NSAID (1)	Sodium level already low before start of therapy or before dose increase (2) 25mg HCT per day in patient ≥ 85 years (2) Previous hyponatraemia during HCT (1)
Hypokalaemia (7)[a]	Hypomagnesaemia (1) Dehydration as a result of diarrhoea (1) Renal insufficiency (3)	Thiazides (2) Thiazide + RASI (1) Thiazide + potassium sparing diuretic+ polystyrene sulfonate (1) Loop diuretic (3)	Digoxin (1) Macrogol (1)	Diarrhoea due to macrogol (1)
Dehydration (8) [b]	Collapse (1) Cardiac shock (2) Possible pneumonia (1) Diarrhoea (1) Renal insufficiency (5)	Thiazides (3) Thiazide + potassium sparing diuretic(1) Loop diuretic (1) Thiazide + potassium sparing diuretic+ loop diuretic (2) RASI (1)		25mg HCT per day in patient ≥ 85 years (1) Dehydration as a result of renal insufficiency by RASI (1)
Electrolyte disturbance (1)		Thiazide + potassium sparing diuretic(1)		Unspecified electrolyte disturbance as a result of insufficient monitoring (1)
Hyperkalaemia (7)	Dehydration (1) Metabolic acidosis (1) Renal insufficiency(5)	Thiazide + potassium sparing diuretic(1) RASI + potassium sparing diuretic (1) RASI + 2nd RASI + potassium sparing diuretic + polystyrene sulfonate (1)	Digoxin (1) Beta-blocker + co-trimoxazole (1)	No action taken on previous measurements (1) Preexisting renal function unknown (1) Adequate monitoring (1)
Renal insufficiency (8)[c]	Dehydration (1)	RASI (1) RASI + thiazide (1) RASI cardiac drug RASI + NSAID (1) RASI+ NSAID + loop diuretic (1) NSAIDs (3)		NSAID started in patients with preexisting renal insufficiency (3) Patient started NSAID on his own initiative (1) Dose of RASI too high in view of renal function (1)
Heart failure (5)	Renal insufficiency(2) Possible pneumonia ((1)	NSAID (1) NSAID + loop diuretic (1) NSAID + RASI + loop diuretic (1) NSAID + RASI + corticosteroid (2)		NSAID started in patient with preexisting heart disease (4)
Total (44)				

a Excluding one case in which hyponatraemia and dehydration were also documented.

b Excluding one case of dehydration due to renal insufficiency and three cases in which hyponatraemia, hypokalaemia or hyperkalaemia were also documented.

c Excluding three cases in which hyperkalaemia was also documented.

RASI = renin-angiotensin-sytem inhibitor; **HCT**= hydrochlorothiazide; **NSAID** = non-steriodal anti-inflammatory drug.

4.1.2 EPIDEMIOLOGY

In a British study, hyponatraemia was seen in 130 of 951 (13.7%) thiazide users in primary care. In nine cases (approximately 1% of all thiazide users) the sodium level decreased to a level at which symptoms could be expected (i.e., <125 mmol/l)[280].

4.1.3 RISK FACTORS

A case-control study carried out in Hong Kong compared 223 thiazide users who had been hospitalized because of serious symptomatic hyponatraemia with 216 thiazide users without hyponatraemia and found the following risk factors upon univariate analysis:

- Higher age (76 ± 9 years versus 66 ± 13 years);
- Lower serum potassium level (3.4 ± 0.9 mmol/L versus 4.0 ± 0.6mmol/L);
- Institutionalisation in an elderly home and physical immobility.

There were no significant correlations between hyponatraemia and sex, renal function, duration of thiazide use, concomitant use of loop diuretics, ACEIs or NSAIDs[279]. In another study, however, women were at higher risk of developing diuretic-induced hyponatraemia[278]. Serious hyponatraemia may develop during the first weeks after the addition of an SSRI or venlafaxine to a thiazide diuretic[284-287]. Venlafaxine acts as an SSRI in low doses, whereas it also inhibits the reuptake of norepinephrine in high doses[284]. SSRIs and venlafaxine have the ability to stimulate the secretion of ADH[282;283]. Since the action of duloxetine is closely related to that of venlafaxine, it is plausible that this drug may also interact with thiazides. An increased risk of hyponatraemia in patients receiving thiazide diuretics has also been attributed to other drugs that stimulate ADH secretion or increase the sensitivity to this hormone, such as NSAIDs, loop diuretics, and carbamazepine[277;282;283].

4.1.4 RISK REDUCING STRATEGIES

a) Monitoring of sodium levels

It is not clear when and how often the sodium level should be measured to prevent serious hyponatraemia in users of thiazides cost-effectively. According to the Task Force, however, striving to improve monitoring in daily practice should not be postponed until the frequency of such monitoring has been established accurately by further research. Based on the risk factors mentioned in section 4.2.3, the Task Force established some risk situations in which measuring the sodium level seems to be meaningful[277;283;288]:[8]

- *When therapy with a thiazide diuretic is initiated or when the dose level of a thiazide diuretic is increased*, the sodium level should be determined in the first 5-9 days thereafter, if the patient is ≥ 80 years old or if the patient is ≥ 70 years old and also uses a SSRI, venlafaxine or related drug, NSAID, carbamazepine or loop diuretic.
- *When an interacting drug (SSRI, venlafaxine or related drug, NSAID, carbamazepine or loop diuretic) is added to a thiazide diuretic or when the dose level of an interacting drug is increased in a thiazide user*, the sodium level should be determined in the first 5-9 days if the patient is ≥ 70 years old.

When an intercurrent illness (e.g. diarrhoea, vomiting, fever) increases the risk of electrolyte disturbances, careful observation is necessary (if needed supplemented with a determination of the sodium level), if the patient is ≥ 70 years old and uses a thiazide diuretic.

b) Counselling of risk patients and promotion of self-management

Patients at increased risk of a hyponatraemia should be informed orally and in written form about this risk, about the first symptoms of hyponatraemia and about risk increasing

situations that may cause additional fluid and salt loss (e.g. infections, vomiting, diarrhoea, fever, great physical strain, hot weather – see section 4.3.4 *sub c*)[224;289].
Vulnerable elderly users of thiazides may require additional support, when they are temporarily at increased risk of fluid and/or salt loss (e.g. hot weather, diarrhoea, fever, vomiting etc.).

4.2 HYPOKALAEMIA/DEHYDRATION ASSOCIATED WITH POTASSIUM-LOSING DIURETICS

4.2.1 PATHOPHYSIOLOGY

Thiazide and loop diuretics increase the availability of sodium in the more distal segments of the kidney and thereby promote the active exchange of sodium and potassium. Hypovolemia and underlying diseases (e.g. heart failure, liver cirrhosis) may also increase potassium release by stimulating the secretion of aldosterone.
Diuretics can cause dehydration and reduce the effective circulating volume, as a result of which weakness, malaise, orthostatic hypotension and muscle cramps may develop. This may not only occur in aggressively treated patients, but also when lower doses are given to sensitive patients (e.g. elderly users) [290].
Despite several investigations and years of discussion, the relation between low doses of thiazide diuretics and the risk of arrhythmias or sudden heart death is still controversial[291-297].

4.2.2 EPIDEMIOLOGY

A British study investigating the use of thiazide diuretics in primary care showed that hypokalaemia was less common than hyponatraemia: 8.5% (79/951 patients) versus 13.7% (130/951 patients). In ten patients (approximately 1% of all thiazide users) the serum potassium was severely reduced (< 3.0 mmol/L)[280].

4.2.3 RISK FACTORS

The risk of diuretic-induced hypovolemia is increased by the following factors[295]:

- Excessive diuretic dose (especially when treatment is started or adapted);
- Improved adherence to drug therapy(e.g., after outpatient medication review or coincident with hospitalization);
- Reduction of dietary sodium intake (e.g., due to new dietary measures, improved compliance to dietary measures coincident with hospitalization, or anorexia or nausea because of an intercurrent illness)
- Development of extrarenal sodium losses (e.g. from diarrhoea or an enteric fistula);
- Discontinuation of medications that may impair diuretic potency (e.g. NSAIDs);
- Improvement in the underlying condition with reduced tendency to retain sodium or augmented diuretic potency (congestive heart failure, nephrotic syndrome, liver cirrhosis).

4.2.4 RISK REDUCING STRATEGIES

a) Monitoring of potassium and creatinine levels.

It is not yet clear when and how often the potassium level should be measured to prevent serious hypokalaemia in users of potassium-losing diuretics cost-effectively.

According to the Task Force, striving to improve monitoring in daily practice should not be postponed until the frequency of monitoring has been established accurately by further research. Based on the risk factors mentioned in 4.3.3. and on current guidelines and other authoritative sources, potassium and creatinine should be measured in the following risk situations[298-300]:

a. *Before the start of a potassium-losing diuretic* if the patient:
   - is ≥ 70 years old;
   - is on a combination of a potassium-losing diuretic and a potassium-sparing diuretic;
   - uses digoxin in the absence of a potassium-sparing agent (RASI, potassium-sparing diuretic)
   - is at increased risk *of* hypokalaemia or *from* hypokalaemia (e.g. pre-existing hypokalaemia, arrhythmias or coronary heart disease);

Within 1- 2 weeks after the start of a potassium-losing diuretic and subsequently each year and also after each dose increase, if the patient:

a. is ≥ 80 years old;
b. is ≥ 70 years old and uses a combination of a potassium-losing diuretic and a potassium-sparing diuretic;
- is ≥ 70 years old and uses a combination of a potassium-losing diuretic and digoxin in the absence of a potassium-sparing agent (RASI, potassium-sparing diuretic);
- is ≥ 70 years old and at increased risk *of* hypokalaemia or *from* hypokalemia (e.g. pre-existing hypokalaemia, arrhythmias or coronary heart disease).

b) Combination with potassium-sparing diuretics

When a thiazide diuretic is used in low doses for the treatment of hypertension, problems are usually rare. However, there are circumstances which may intensify a mild decrease of the potassium level (3.0-3.5mmol/L), such as stress reactions (probably due to increased influx of potassium into the cells by the beta2-adrenergic effect of norepinephrine, activation of the renin-angiotensin system (RAS) (particularly during strict salt restriction), excessive vomiting and diarrhoea, and excessive consumption of liquorice.

The addition of a potassium-sparing diuretic is meaningful, when there is:

- an increased risk *of* hypokalaemia (e.g., use of corticosteroids, high doses of thiazide or loop diuretics)
- an increased risk *from* hypokalemia (e.g., arrhythmias, coronary heart disease, digitalized patients,
- a serious reduction of the potassium level (≤ 3.0 mmol/L).

Monitoring of the potassium level remains necessary, since a potassium-sparing diuretic does not automatically nullifies the risk of hypokalaemia.

c) Counselling of risk patients and promotion of self-management

Patients at increased risk of hypokalaemia and/or dehydration should be informed orally and in written form about this risk, the first symptoms of hypokalaemia and the situations that may cause additional fluid and salt loss .

In cases of additional fluid and salt loss due to vomiting, diarrhoea, or hot weather, the Dutch CBO/General Practitioners guideline on Cardiovascular Risk Management recommends that the patient prevents further dehydration and hyponatraemia by temporary adaptation of the dose of the diuretic (e.g. halving the daily dose or using it on alternate days), either in direct consultation with the precriber or following a previously reached agreement with the prescriber[298;299].

For vulnerable elderly users of diuretics, additional support may be necessary, when they are temporarily at an increased risk of fluid and salt loss (e.g. hot weather, diarrhoea, vomiting, feveretc.).

According to a Dutch textbook, patients should drink sufficiently to prevent a reduction in the circulating volume. This is especially important when a loop diuretic is used. However, too much intake of fluid can lead to hyponatraemia, so regular monitoring of the degree of hydration, sodium and potassium is recommended, particularly in users of a loop diuretic[301].

4.3 HYPERKALAEMIA ASSOCIATED WITH RASIS AND POTASSIUM-SPARING DIURETICS

4.3.1 PATHOPHYSIOLOGY

The use of RASIs may increase potassium levels by reducing the secretion of aldosterone. Without additional risk factors serious hyperkalaemia is an unusual complication[302].

4.3.2 EPIDEMIOLOGY

In a US study of 1818 outpatients on ACEIs, hyperkalaemia (potassium > 5.1 mmol/L) was found in 194 (11%) patients; in 37 (19%) of these patients the potassium serum was ≥ 5.6 mmol/L and in three cases (1.5%) a serious hyperkalaemia was observed (≥ 6.0mmol/L). Out of the 155 patients continuing their ACEI, 15(9.7%) developed a potassium level ≥ 6.0 mmol/L[303].

4.3.3 RISK FACTORS

Hyperkalaemia and deterioration of renal function in users of RASIs particularly occur in the treatment of heart failure, since the cardiovascular and renal system is more dependent on RAS in this condition. Potassium-sparing diuretics (spironolactone, eplerenone, triamterene, amiloride) and potassium salts can enhance the effect on the potassium level and the risk also increases in combination with beta-blockers (which are often used in patients with chronic heart failure). The risk is further increased if an NSAID is used simultaneously or if the patient has diabetes mellitus or impaired renal function.

Further risk factors are shown in Table XX[302]. Special risk situations are the onset of therapy, increases in dose level and intercurrent events such as surgery[304].

Table XX. Risk factors for hyperkalaemia during RASI use [302].

Risk factors	Comments
Advanced age	When users continue a RASI in spite of hyperkalaemia, an age above 70 years is a significant risk factor for the development of serious hyperkalaemia[303]
Chronic kidney disease	Particularly if the glomerular filtration rate is less than 30ml/min[a]
Diabetes mellitus	
Heart failure	Between one-third and half of the patients with heart failure also have renal insufficiency
Hypovolaemia	Cave intercurrent acute events which may lead to dehydration[304]
Concomitant use of drugs which interfere with the renal excretion of potassium[b]	Non-selective NSAIDs COX-2 selective inhibitors Beta-blockers Calcineurin inhibitors (ciclosporin, tacrolimus) Heparin Ketoconazole Potassium-sparing diuretic Trimethoprim Pentamidine
Potassium supplements	Including salt substitutes and certain herbs rich in potassium (such as noni juice (*Morinda citrifolia),* alfalfa (*Medicago sativa),* dandelion (*Taraxacum officinale),* horsetail *(Equisetum arvense)* and nettle *(Urtica dioica).*

a Serum creatinine levels are by themselves not sufficient to obtain a reliable picture of the glomerular filtration rate. Instead, this rate should be calculated by using the MDRD (Modification of Diet in Renal Disease Study) formula or the creatinine clearance should be estimated by using the Cockcroft–Gault formula[302]. Both formulas have their limitations: the Cockroft-Gault formula is inaccurate in obese and elderly people, while the MDRD is less useful in patients with underweight and in muscular athletes [305;306].

b In addition, non-selective beta-blockers may lead to an increased potassium level under certain circumstances by interfering with the potassium uptake in cells which is mediated by beta-2-adrenergic receptors[307]. This effect is less marked with beta-1 selective blockers[308].

NSAIDs = non-steroidal anti-inflammatory drugs; **RASI** = Renin angiotensin system inhibitors

Routine monitoring of electrolytes and renal function is not only recommended in users of RASIs with additional risk factors for hyperkalaemia and deterioration of renal function, (but also when users of the renin inhibitor aliskiren are at increased risk [309]. Aliskiren increases serum potassium only infrequently (<1%), but this risk may be higher in risk patients (e.g. concomitant use of a RASI or other drug increasing serum potassium) [309]. For instance, 2% of 588 hypertensive patients treated with aliskiren plus valsartan (with or without hydrochlorothiazide) developed potassium levels > 5.5 mmol/L; only one patient (0.2%) showed potassium levels ≥ 6.0 mmol/L[310]. In a study comparing aliskiren plus losartan to losartan alone in hypertensive patients with type 2 diabetes with nephropathy, 4.7% of 301 patients receiving the combination treatment showed at least one serum potassium ≥ 6.0 mmol/L compared to 1.7% of 298 patients on losartan. Nine of the 14 aliskiren-treated patients with hyperkalemia should have been excluded at baseline because of a serum potassium ≥ 5.1 mmol/L[311].

Aliskiren has also been associated with isolated cases of renal dysfunction and acute renal failure in patients at increased risk (e.g., because of dehydration, unrecognized pre-existing renal insufficiency, advanced age and/or concomitant use of an NSAID or spironolactone) [309].

4.3.4 RISK REDUCING STRATEGIES

Table XXI gives an overview of the measures which should be taken into consideration when users of RASIs are at increased risk of hyperkalaemia[302].

Risk reducing strategies are:

a) *Monitoring of potassium and creatinine*

Patients who are at the highest risk of hyperkalaemia, are those who also benefit the most from a RASI[302]. In other words, when a patient has one or more risk factors it is not necessary to discontinue the RASI, but careful monitoring of the potassium level is required. A US study has shown that such monitoring is not yet performed systematically[304;312;313]. It is not clear when and how often the potassium level should be measured to prevent serious hyperkalaemia in users of RASIs cost-effectively[302;304]. A Dutch trial has shown, however, that the monitoring of electrolytes and renal function as part of an intensive support programme for patients with heart failure class III or IV by physicians and nurses (both expert in heart failure) reduced the amount of hospital admissions and/or deaths significantly[314]. In the study period of 1 year, there were 9 patient checkups which involved inter alia laboratory measurements of electrolytes, anaemia and renal function (3 times the full spectrum and 6 times an incomplete range)[315]. In the intervention group, the average number of hospital admissions due to heart failure (combined with mortality due to all causes) was only half (23/118 = 0.19 per patient) of that in the control group (47/122 = 0.38 per patiënt) [314]. The benefit of intensive support programs for outpatients with heart failure has also been shown in other countries[316-318].

Table XXI. Measures to reduce the risk of hyperkalaemia in patients using RASIs.

Measures
- If possible discontinue drugs that interfere with the renal excretion of potassium (e.g. NSAIDs and COX-2 selective inhibitors) - Inform patients about the risk of using salt substitutes and herbal preparations or dietary supplements rich in potassium - Prescribe a thiazide or loop diuretic (the latter is necessary when the estimated glomerular filtration rate is < 30ml/min)[a] - Prescribe sodium bicarbonate to correct metabolic acidosis in patients with chronic kidney disease: 8-16mEq (=0.65-1.3g) twice daily (but first ensure effective diuretic therapy to reduce the risk of volume overload); - Initiate RASI therapy in a low dose - Reduce the dose of RASI, if the potassium increases to ≥5.5mmol/L. If the patient uses a combination of an ACEI, an ARB, and an aldosterone-receptor blocker, consider to discontinue one agent and to recheck the serum potassium level. - If potassium is > 5.5 mMol/L despite the steps described above, discontinue the RASI. - Addition of a potassium-sparing diuretic requires careful monitoring; the daily dose of spironolactone should not exceed 25mg when it is combined with a RASI; this combination is contraindicated when the glomerular filtration rate < 30ml/min; - Give particular attention to patients with underlying disturbances of cardiac conduction, since even mild degrees of hyperkalemia can precipitate heart block**.**

a Serum creatinine levels are by themselves not sufficient to obtain a reliable picture of the glomerular filtration rate. Instead, this rate should be calculated by using the MDRD (Modification of Diet in Renal Disease Study) formula or the creatinine clearance should be estimated by using the Cockcroft–Gault formula[302]. Both formulas have their limitations: the Cockroft-Gault formula is inaccurate in obese and elderly people, while the MDRD is less useful in patients with underweight and in muscular athletes [305;306].

NSAIDs = non-steroidal anti-inflammatory drugs; **RASI** = Renin angiotensin system inhibitors (a collective name for angiotensin converting enzyme inhibitors and angiotensin receptor blockers); **ACEI** = angiotensin converting enzyme inhibitor; **ARB** = angiotensin receptor blocker; **MDRD** = modification of Diet in Renal Disease Study

According to the Task Force, striving to improve monitoring in daily practice should not be postponed until the frequency of monitoring has been established accurately by further research. According to current guidelines and other authoritative sources, potassium and creatinine levels should be measured in the following risk situations[298-300;319].

- If a RASI or renin inhibitor is started potassium and creatinine levels are checked beforehand if:
  a. The patient is at least 70 years.
  b. There is an increased risk of hyperkalaemia or an increased risk from hyperkalaemia (e.g. heart failure, cardiac conduction disorder, diabetes mellitus, renal insufficiency, simultaneous use of an aldosterone antagonist).
- Within 1-2 weeks after the start of a RASI or renin inhibitor, subsequently each six months and after each dose increase, if there is an increased risk of hyperkalaemia (e.g. heart failure, cardiac conduction disorder, diabetes mellitus, renal insufficiency, age ≥ 70 years[9] or concurrent use of thiazide and loop diuretics).
- Within 1-2 weeks after the addition of spironolactone or another potassium-sparing diuretic to a RASI and after each dose increase of a potassium-sparing diuretic.[10]

b) Stringent assessment of hazardous co-medications

Concomitant use of drugs which interfere with the renal excretion of potassium should be avoided if possible. This is particularly relevant for NS-NSAIDs and COX-2 selective inhibitors[302].

c) Counselling of patients and promotion of self-management

Patients at increased risk of hyperkalaemia should be informed orally and in written form about the first symptoms of hyperkalaemia and additional risk situations (Table XX). For example, patients should be informed about the risks of intercurrent events that may lead to dehydration[304] and the risks of salt substitutes and herbal preparations or dietary products that are rich in potassium (Table XX).

For vulnerable elderly users of RASIs, additional support may be necessary, when they are temporarily at increased risk of fluid and salt loss (e.g. hot weather, diarrhoea, vomiting, fever etc.).

4.4 RENAL DYSFUNCTION ASSOCIATED WITH RASIS AND NSAIDS

4.4.1 PATHOPHYSIOLOGY

RASIs

Besides hyperkalaemia, renal insufficiency is one of the most important adverse effects of RASIs. In general, RASIs do not affect renal function, but in patients with renal arterial stenosis or pre-existing renal impairment the intraglomerular pressure and glomerular filtration rate (GFR) may be severely decreased. When renal arterial stenosis is unilateral, functional loss of the affected kidney may develop without an increase in creatinine level. The risk of renal arterial stenosis should be especially considered in patients with generalized atherosclerosis.

The use of RASIs can also lead to renal insufficiency, when the effective circulating volume is reduced (e.g. as a result of moderate to serious heart failure) or when there is an absolute reduction in intravascular volume (e.g. gastroenteritis, forced diuresis, or inadequate fluid intake). In these situations, angiotensin II counteracts the reduction of the GFR (which would otherwise develop under the influence of decreased renal perfusion pressure) by constriction of the efferent arteriole[320]. Although the risk of developing acute renal insufficiency due to a RASI is greatest immediately after the start of therapy, a risk persists throughout therapy[300].

NSAIDs

NSAIDs increase the risk of renal insufficiency by their inhibitory effect on the prostaglandin synthesis. In normal circumstances, prostaglandins have no important role in maintaining renal perfusion and GFR, but when the effective circulating volume is reduced (e.g. as a result of heart failure, cirrhosis, chronic renal insufficiency or dehydration) the prostaglandin production will increase to maintain renal perfusion. Since NSAIDs inhibit this effect, they may lead to excessive vasoconstriction followed by reduction of the renal perfusion and the GFR. This can even produce acute renal failure (ARF)[321].

4.4.2 EPIDEMIOLOGY

RASIs

In a British study, 9/135 (7%) of the hospital admissions due to uraemia were related to the use of an ACEI. In three of these cases, a renovascular disease was present, while in the other six cases heart failure combined with an intercurrent illness was involved. This rather old study also showed that, in a large British GP practice, renal function was only monitored in 29% of the patients after the start of an ACEI[322].

NSAIDs

In a study assessing the relationship between NSAIDs and ARF, NSAID-use tripled the risk [RR_{adj}= 3.2; 1.8-5.8][323]. COX-2 selective inhibitors have also been associated with an increased risk of AFR [324].

An effect of NSAID use on the progression of chronic renal failure has been reported as well. In patients older than 65 years, the risk of a reduced GFR was significantly increased by using a high-dose NSAID [OR=1.3; 1.0-1.5]. Hereby a linear relationship was seen between the cumulative NSAIDS dose and the alteration of the GFR. The risk of COX-2 selective inhibitors was similar to that of NS-NSAIDs[325].

4.4.3 RISK FACTORS

RASIs

Besides the risk factors mentioned in section 4.5.1, sepsis and calcineurin inhibitors (ciclosporin, tacrolimus) also increase the risk of ARF in patients receiving RASIs. The underlying mechanism is similar to that of the RASIs themselves[320].

In general, concurrent use of an ACEI and a low-dose thiazide diuretic does not affect renal function. However, the combination of an ACEI with a loop diuretic may lead to uraemia, when diuresis is so strong that it can no longer be compensated for by the mobilization of oedematic fluids, which then results in a decrease in the effective arterial volume[320].

NSAIDs

An Australian study found a weak relationship between impaired renal function and NSAID use in the previous month [OR_{adj} 1.8; 1.0-3.4], but the OR_{adj} was considerably higher in patients with renal disease [6.6; 0.8-57.8] or with a history of gout or hyperuricaemia [7.2; 1.3-40.2][326]. The latter finding is remarkable, since NSAIDs are generally considered as drugs of first choice in gouty arthritis[327].

The above mentioned study of the relationship between NSAID use and ARF has yielded evidence to suggest that NSAID use increases the risk of ARF in a more than additive way in patients with heart failure [RR_{adj} = 7.6; 2.7-21.6] or hypertension [RR_{adj}= 6.1; 2.5-14.8] and in users of diuretics [RR_{adj} = 11.6; 4.2-32.2] or calcium channel blockers [RR_{adj} = 7.8; 3.0-20.5] [323].

Combinations of RASIs and NSAIDs

In a Dutch case-control study, the risk for hospitalization due to functional renal impairment in patients receiving ACEIs was higher, when an NSAID had been initiated in the previous three months [OR_{adj} = 2.2; 1.1 – 4.5]. This increase in risk was most marked in patients above

70 years [OR_{adj} = 2.7; 1.0-7.2] and in patients who had started an NSAID in the previous three months and had received at least three NSAID prescriptions [OR_{adj} = 7.1; 1.8-28.7][328].
Since ACEIs, NSAIDs and diuretics are all capable of reducing renal function, the literature cautions against a so-called "triple whammy", in which all three types of drugs are combined with each other[329]. This warning also applies to ARBs [330]and to COX-2 selective inhibitors[331;332]. No epidemiological studies have been found in literature, that explored the extent to which such triple therapy is more dangerous than double therapy with two of these agents.

4.4.4 RISK REDUCING STRATEGIES

RASIs

The Task Force already outlined in section 4.4.4 (sub a) a number of risk situations in which measurements of potassium and creatinine are advisable. Renal function should also be monitored in patients with generalized atherosclerosis (because of the risk of renal arterial stenosis).
One should be particularly aware of the risk of impaired renal function when there is:

- *Pre-existing renal impairment or renal arterial stenosis*. The potential disadvantages of renal effects of RASIs should be carefully balanced against the benefits of these agents in patients with kidney diseases, including diabetic nephropathy. A systematic analysis of randomized studies investigating the progression of renal insufficiency in users of ACEIs with pre-existing renal insufficiency (with or without diabetic mellitus or heart failure) showed that continuation of the ACEI was preferable when GFR was reduced and/or when the serum creatinine level was increased, if the latter did not rise more than 30% above baseline[333].
- All ACEIs except fosinopril have active metabolites which can accumulate, when renal function is decreased, which increases the risk of adverse effects. The initial dose and maximum dose of these drugs are therefore dependent on the creatinine clearance[224]. On the other hand, only the initial dose of olmesartan has to be adjusted in renal insufficiency with a creatinine clearance > 10 ml/min, while this is not necessary for the other ARBs (candesartan, eprosartan, irbesartan , losartan, telmisartan, valsartan) [224]. However, all ARBs can have a negative effect on renal function by affecting the RAS system.
- A *reduction of the effective circulating volume* e.g., due to heart failure (cave: intercurrent illnesses such as gastroenteritis), inadequate fluid intake or forced diuresis. The risk of uraemia by concurrent use of loop diuretics can be reduced by titrating the dose until the patient does not lose more than 1 kg of body weight per day[224].
- *Sepsis*
- *Use of an NS- NSAID or COX-2 selective inhibitor* (see above)
- *Use of a calcineurin inhibitor* (ciclosporin, tacrolimus).

NSAIDs

The most important precautionary measure to prevent that NS-NSAIDs and COX-2 selective inhibitors lead to impaired renal function, is a careful weighing of their pros and cons in each patient, whereby the following points should be taken into consideration:

- *Cardiovascular contraindications and precautions* (see section 3.4.4. sub c), including *pre-existing heart failure and hypertension;*
- *Renal disease or a history of gout/ hyperuricaemia;*
- *A reduced effective circulating volume* (not only in patients with heart failure, but for instance also in patients with cirrhosis, chronic renal impairment and dehydration)
- *Concomitant use of drugs which may reduce renal function* (such as a RASI or diuretic – see also below). If an NSAID is to be added to a diuretic, the risk assessment should also take into consideration that the indication of the diuretic (hypertension or heart failure) plays an important role [224]. If a loop diuretic is started in a patient who is already on an NSAID, it is possible that the former is added to treat an adverse effect of the latter[224].

Preferably, another kind of analgesic should be selected (such as acetaminophen). If an NSAID cannot be avoided, it should be prescribed as shortly as possible in the lowest possible dose .

Before prescribing NSAIDs to patients with gouty arthritis, careful attention should be paid to their cardiovascular and renal risks. Gouty arthritis is often associated with cardiovascular disorders (in which case NSAIDs should preferably be avoided if possible) and renal function impairment in these patients is mainly related to their vascular risk factors[327;334]. If NSAIDs are considered undesirable in such patients because of their potential cardiovascular and renal effects, a corticosteroid may be given instead (under the proviso of adequate monitoring for metabolic bone disease). If a corticosteroid is also considered undesirable (e.g. because it will increase the risk of bleeding or glucose intolerance), colchicine may be a reasonable alternative[327;335;336].

To reduce the risk of renal function loss in patients with chronic gout, one should not only consider avoidance of NSAIDs but also strive for optimal control of hyperuricaemia, because a combination of these two measures has been reported to improve renal function in these patients[334].

For patients who belong to the above-mentioned risk groups, it is recommended to check the renal function before and one week after initiating an NSAID [224].

Combinations of a RASI and an NSAID

Concurrent use of a RASI and an NSAID entails an increased risk, if the patient is over 70 years old, and it seems particularly hazardous when a diuretic is being used as well (see section 4.5.3). The combination of a RASI and an NSAID should certainly be avoided, if there is a history of renal hypoperfusion or impaired renal function[321].

Furthermore it is important to consider the reason for prescribing the RASI[224]:

- in *nephropathy* and *after a myocardial infarction,* the only risk to be considered is renal impairment.
- in *hypertension,* the NSAID may also reduce the blood pressure lowering effect of the diuretic, especially if the NSAID is used for more than two weeks.

- in *heart failure*, there is a risk that this condition is deteriorated by the use of the NSAID in such a way that hospital admission becomes necessary (see section 4.6.4). Preferably, NSAIDs should be avoided in users of RASIs with heart failure. If an NSAID cannot be avoided, the prescriber should monitor renal function and diuresis and should avoid aggressive dehydration. Furthermore, the patient should be informed about the possible symptoms of deteriorating heart failure[224]. Patients who are at increased risk may monitor and document their body weight on a daily basis under identical circumstances. Symptoms that require the attention of the prescriber are an increase in body weight of > 2 kg in a few days, a reduction in exercise capacity, and worsening of dyspnoea or shortness of breath[289].

4.5 HEART FAILURE ASSOCIATED WITH NSAIDS

4.5.1 PATHOPHYSIOLOGY

The use of NSAIDs can exacerbate pre-existing heart failure. The proposed mechanism is that renal function is reduced by the inhibitory effect of the NSAID on the prostaglandin synthesis. Under normal circumstances, prostaglandins do not play a major role in maintaining renal perfusion and GFR, but when the effective circulating volume is reduced (e.g. heart failure, cirrhosis, chronic renal insufficiency and dehydration) the production of prostaglandins is increased to sustain renal perfusion (cf. section 4.5.1.). NSAIDs inhibit this effect and can thereby lead to excessive vasoconstriction followed by a reduction of the renal perfusion and the GFR. This can then lead to oedema and sodium retention resulting in (the aggravation of) heart failure[321].

NSAIDs can produce adverse interactions with drugs that are commonly prescribed to patients with heart failure. In patients with a decreased circulating volume due to heart failure, NSAIDs may reduce the effect of loop diuretics and subsequently cause a serious retention of fluid. Under normal circumstances, the concomitant use of NSAIDs and RASIs does not significantly affect the kidney. However, when renal perfusion or renal function is reduced, both types of drugs will interfere with the physiological mechanism that sustains the GFR[321].

4.5.2 EPIDEMIOLOGY

Several studies have investigated the relationship between NSAID use and heart failure. In two different studies, NSAIDs increased the risk for hospital admission due to heart failure considerably in patients with a history of heart disease [OR = 26.3 and RR_{adj} = 9.9, respectively], but not in patients without pre-existing heart disease[23;337].

4.5.3 RISK FACTORS

Besides a history of heart disease, concurrent use of corticosteroids is also a risk factor. Corticosteroids can cause sodium and fluid retention as a result of their mineral corticosteroid activity[289].

4.5.4 RISK REDUCING STRATEGIES

a) Avoidance of NSAID

Since a history of heart disease obviously increases NSAID-related hospital admissions and since NSAIDs can interfere with drugs used in patients with heart failure, NSAIDs should preferably be avoided in patients with heart failure[289;321]. Agents such as sulindac or nabumetone are no suitable alternatives, since they are as nephrotoxic as other NSAIDS [321].This is also true for COX-2 selective inhibitors, which have similar effects on the kidney as NS-NSAIDs[153;321].

b) Intensive monitoring and promotion of self-management

When an NSAID is necessary after all, intensive monitoring of the renal function and clinical symptoms is of great importance[321]. In such cases patients should be instructed on how tomonitor their clinical status by themselves .

c) Discouragement of OTC NSAIDs

See section 3.4.4 (sub e)

4.6 RECOMMENDATIONS RELATED TO ELECTROLYTE DISTURBANCES, RENAL INSUFFICIENCY AND HEART FAILURE

Electrolyte disturbances, general (section 4)

Recommendation 16.

Patients at increased risk of an electrolyte disturbance (hyponatraemia, hypokalaemia, hyperkalaemia) receive oral and written information about this risk. This information should not only outline the first symptoms of the electrolyte disturbance but also the risk situations that can lead to increased fluid and salt loss (such as infection, vomiting, diarrhoea, physical exertion, high environmental temperature) (Grade 2C). Vulnerable elderly are monitored more closely, when they are temporarily at increased risk of fluid and salt loss (Grade 2C).

Hyponatraemia due to thiazide diuretics (section 4.2)

Recommendation 17.

When a thiazide diuretic is started or when its dose level is increased, the sodium level should be checked in the first 5-9 days if (Grade 1C):

(a) The patient is at least 80 years old.
(b) The patient is at least 70 years old and also uses a SSRI, venlafaxine or a related drug, NSAID, carbamazepine or loop diuretic.

When a thiazide user is at least 70 years old and starts to use an interacting drug (SSRI, venlafaxine or related drug, NSAID, carbamazepine or loop diuretic), the sodium level should be checked in the first 5-9 days (Grade 1C).

A thiazide user who is at least 70 years old requires careful observation (if necessary supplemented with a check of the sodium level), when an intercurrent disease (such as diarrhoea or vomiting) increases the risk of an electrolyte disturbance (Grade 1C).

Hypokalaemia/dehydration due to potassium-losing diuretics (section 4.3)

Recommendation 18.

If a potassium-losing diuretic is started, potassium and creatinine levels are checked beforehand if (Grade 1C):

(a) The patient is at least 70 years old.
(b) one of the following situations applies:
- The potassium-losing diuretic is combined with a potassium-sparing diuretic.
- There is an increased risk of hypokalaemia or an increased risk from hypokalaemia (e.g. pre-existent hypokalaemia, cardiac arrhythmia or coronary heart disease).
- The potassium-losing diuretic is combined with digoxin in absence of a potassium-sparing agent (RASI, renin inhibitor or potassium-sparing diuretic).

Potassium and creatinine levels are checked again within 1-2 weeks after the start of a potassium-losing diuretic and then every year and following every dose increase in any of the following situations (Grade 1C):

a. If the patient is 80 years or older.
b. If the patient is ≥ 70 years old and uses a combination of a potassium-losing diuretic and a potassium-sparing diuretic.
c. If the patient is ≥ 70 years old and simultaneous uses a potassium-losing diuretic and digoxin in absence of a potassium-sparing agent (RASI, renin inhibitor or potassium-sparing diuretic).
d. If the patient is ≥ 70 years old and there is an increased risk of hypokalaemia or an increased risk from hypokalaemia (e.g. pre-existent hypokalaemia, cardiac arrhythmia, coronary heart disease or age ≥ 70 years).

Hyperkalaemia due to RASIs and potassium-sparing diuretics (section 4.4)

Recommendation 19.

If a RASI or renin inhibitor is started, potassium and creatinine levels are checked beforehand if:

(a) The patient is at least 70 years old (Grade 1C).
(b) There is an increased risk of hyperkalaemia or an increased risk from hyperkalaemia (e.g. heart failure, cardiac conduction disorder, diabetes, renal insufficiency, simultaneous use of a potassium-sparing diuretic (Grade 1B); simultaneous use of a thiazide diuretic and loop diuretic (Grade 1C).

Potassium and creatinine levels are checked again within 1-2 weeks after the start of the RASI or renin inhibitor and then at least every six months and following every dose increase in any of the following situations:

(a) There is an increased risk of hyperkalaemia or an increased risk from hyperkalaemia (e.g. heart failure, cardiac conduction disorder, diabetes, renal insufficiency, simultaneous use of a potassium-sparing diuretic (Grade 1B); simultaneous use of a thiazide diuretic and loop diuretic (Grade 1C), age ≥ 70 years (Grade 1C);
(b) Within 1-2 weeks after the addition of a potassium-sparing diuretic to a RASI or renin inhibitor and after every dose increase of such a potassium-sparing diuretic (Grade 1B).

Recommendation 20.
When the user of a RASI is at increased risk of hyperkalaemia (Table III), the prescribing of NSAIDs (including COX-2 selective inhibitors) should be avoided if this is in any way possible (Grade 1B).

Renal insufficiency due to RASIs (section 4.5)
Recommendation 21.
When prescribing a RASI, one should carefully weigh the expected benefits against the increased risk of renal insufficiency and monitor the creatinine level in any of the following situations:
- Pre-existing renal insufficiency or renal artery stenosis (cave: generalised atherosclerosis) (Grade 1B).
- Reduced effective circulating volume (cave: heart failure, intercurrent diseases, inadequate fluid intake or aggressive diuresis with a loop diuretic) (Grade 1C).
- Sepsis (Grade 1C).
- Simultaneous use of an NSAID (including COX-2 selective inhibitor) or calcineurin inhibitor (ciclosporin, tacrolimus) (Grade 1C).

Recommendation 22.
In patients with existing renal insufficiency, one should take into consideration that most ACEI may further compromise renal function through accumulation of an active metabolite. Dose adjustment is not necessary for fosinopril and for most AT_1-antagonists (with the exception of olmesartan) (Grade 1B).

Renal insufficiency/heart failure due to NSAIDs (sections 4.5 and 4.6)
Recommendation 23.
If it is in any way possible, the prescribing of NSAIDs (including selective COX-2 inhibitors) should not only be avoided in cardiovascular risk patients, including patients with heart failure and hypertension (recommendation 15), but also in the following risk situations (Grade 1B):
- A history of renal disease.
- Reduced effective circulating volume (not only in patients with heart failure, but also, for instance, in patients with hepatic cirrhosis, chronic renal insufficiency and dehydration).
- Simultaneous uses of drugs which may also compromise renal function, such as a RASI and/or a diuretic (the combination of these two drugs with an NSAID seems particularly hazardous).

Before prescribing an NSAID to a patient with a history of gout/hyperuricaemia, one should carefully assess the cardiovascular and renal risks, because gouty arthritis is often associated with cardiovascular disorders (in which case NSAIDs should preferably be avoided – cf. recommendation 15) and because gout/hyperuricaemia has been associated with an increased risk of NSAID-induced renal insufficiency (Grade 1B).

If an NSAID cannot be avoided in a patient at increased risk, the NSAID should be prescribed as short and as low as possible. Renal function should be checked before and one week after the start of the NSAID (Grade 1C). The patient receives oral and written information on how to recognize deterioration (Grade 2C).

5 OTHER ADVERSE DRUG REACTIONS

5.1 FRACTURES DUE TO FALL INCIDENTS

5.1.1 HARM AND IPCI DATA

In the HARM study 20 potentially avoidable hospital admissions were related to fractures due to falls, 12 (60%) of which concerned patients over 80 years old. All of these cases involved at least one psychotropic drug. In 13 (65%) cases different psychotropic drugs and/or alcohol abuse played a role and in four (20%) cases three or four psychotropic drugs were involved. In six (30%) cases it was remarkable that at least one psychotropic drug had been prescribed at a dose level that was high considering the age and/or renal function of the patient.

5.1.2 PATHOPHYSIOLOGY

Psychotropic agents (benzodiazepines, sedatives/hypnotics, antidepressants, and antipsychotics) increase the risk on fall incidents in elderly patients[338;339]. Different kinds of mechanisms can play a role, such as delayed responsiveness, induction of muscular hypotonia, dizziness, orthostatic hypotension and balance disturbances (which may also be related to extrapyramidal side effects)[301;340].

Certain *cardiovascular drugs* (antiarrhythmics Type 1a, digoxin and diuretics) can also increase the risk of falls[341]. In the case of diuretics, dizziness may be induced by orthostatic hypotension [342] and the tendency to fall may also be increased by muscle weakness due to hypokalaemia.

5.1.3 EPIDEMIOLOGY

Falls are a common problem in elderly people living at home: 30% of elderly ≥ 65 years old fall at least once a year and in half of these cases the elderly falls again within the next 12 months. Falls occur even more frequently in homes for the elderly and nursing homes: 30-70% of the residents fall at least once a year and 15-40% fall twice a year or more often[343;344].

Approximately 10% of the fall incidents in the elderly lead to a severe injury, including hip fractures (1-2%), other fractures (3-5%), trauma of the soft tissue and head injury (5%). Especially hip fractures are characterized by an increased risk of permanent dependence and increased mortality. In The Netherlands, 28,900 elderly people are annually hospitalized after a fall, including 3,600 residents of nursing homes[343;344].

In a Dutch study of 106 hospitalized patients ≥ 70 years, 25 (24%) hospitalizations were related to serious ADRs and in five of these patients (i.e., 5% of all hospital admissions) the hospitalization had been preceded by a severe fall incident[345].

5.1.4 RISK FACTORS

Drugs increasing the risk of falling are only one of the many risk factors for fall incidents in independently living elderly people. Table XXII lists which factors have been identified as independent risk factors in at least two different studies.

There is evidence to suggest that the risk of falling increases if more than one hazardous drug is being used simultaneously[338;346].

Benzodiazepines do not only increase the risk of falling, but also increase the risk of a hip fracture by at least 50%[347].

It has been reported more than once that the dose level of benzodiazepines can play an important role[344;348-350]. As a result, the risk of falling may be reduced not only by discontinuing a benzodiazepine altogether, but also by reducing its dose to a lower (geriatric) level. Initial reports that short-acting benzodiazepines were safer than long-acting ones have not been confirmed in later studies[338;351;352].

Table XXII. Independent risk factors for fall incidents in the independently living elderly [343].

Independent risk	OR/RR/DR
Mobility impairment (balance, walking, musculoskeletal problems)	0.5-3.9[a]
Previous fall	1.2-3.3
Psychotropic drugs	**1.6-28.3**
Parkinson's disease	7.7-9.5
Joint disorders	2.0-2.7
Dizziness	1.8-2.0
Difficulties with daily living activities	1.5-3.8
Urinary incontinence	1.6-1.7
Visual impairment	1.2-2.3
Physical activity	0.4-0.6
Age	0.6-8.1
Polypharmacy	**2.6-4.5**
Female gender	1.6-2.1
Depressive symptoms	1.4-2.2
Cognitive impairment	1.1-5.0

a The value of 0.5 was from a study which showed that the ability to stand up quickly from one's seat may be a protective factor against falling.

OR =odds ratio; **RR** = relative risk; **DR**= density ratio (number of cases per 10.000 persons' days of the exposed group divided by the number of cases per 10.000 person's days of the unexposed group).

5.1.5 RISK REDUCING STRATEGIES

a) Do not initiate or continue psychotropic drugs if it is not necessary to do so

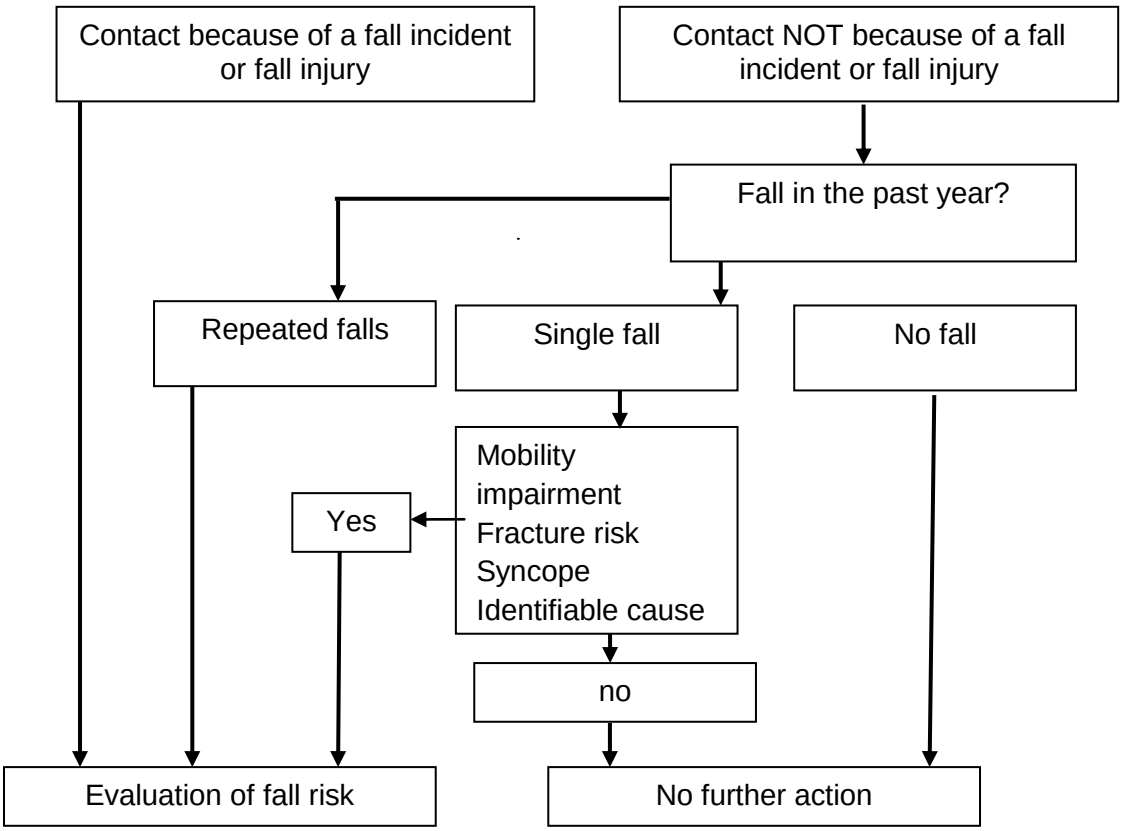
The need to initiate psychotropic drugs in elderly patients only on strict indication does not only apply to benzodiazepines, but also to other psychotropic drugs, such as antipsychotics (including the atypical agents) and antidepressants. The prescriber should realize that the prescription of combinations of psychotropic drugs is generally not

evidence-based, whereas such combinations may entail an increased risk of falling. For patients > 70 years old, the prescriber should assess whether there is an increased risk of falling based on the patient record and a few short questions. The following factors are among the most important clues that the risk of falling is increased[343]:

- The *occurrence of one or more falls* in the preceding year (which usually is a strong predictor of future fall incidents);
- A *suspicion of impaired mobility* (which can often be established based on the patient record, direct observation or a simple test, such as the "get-up and go" test).

Elderly who are potentially prone to falling, can then be subjected to a more detailed evaluation. Hereby it is advisable to assess the risk of fractures as well. This latter risk depends on the risk of falling, the bone strength, and the so-called impact of falling. Bone strength is determined by bone density, bone structure and bone quality, while the impact of falling is associated inter alia with a low body mass index and the ability to react with a protective response during a fall[343]. In Figure 1 an algorithm is presented, which may help to estimate the risk of falling and the risk of injuries in daily practice. This algorithm has been based on the available literature, expert opinion and the feasibility of its implementation in daily practice, but it has not yet been validated scientifically. An additional factor that may be taken into account is the vitamin D status of elderly people, because adequate supplementation of vitamin D appears to reduce their risk of falling with more than 20% and because higher levels of vitamin D seem to improve their muscular strength[343].

Figure 1. Algorithm for the detection of fall risks and fall injury risks (reproduced taken from the Dutch CBO guideline on prevention of fall incidents in the elderly)[343].



Prescribers should not continue psychotropic treatment any longer than is strictly necessary. This calls for formal moments of evaluation, in which the physician assesses in a personal contact whether therapy is still indicated. This evaluation should also look at falls or dizziness which may have occurred after the start of therapy. For benzodiazepine derivatives and antipsychotic drugs the first re-evaluation should take place after 1-2 weeks. In the case of antidepressants used for a depression it is more convenient to schedule the first reevaluation after 4-6 weeks (because their effects develop more gradually). When long-term use cannot be avoided, the use of each psychotropic drug should be evaluated at least yearly.

b) Intervention programmes

Judging from the available intervention studies, multidisciplinary and interdisciplinary intervention programmes which first perform a multifactorial analysis and then take targeted, if necessary multiple measures, seem to be the most useful. Elderly patients are eligible for such programmes, if they have actually fallen and/or if they have known risk factors for falling and injuries due to falling (including use of drugs increasing the risk of falling). This is particularly relevant when elderly people have visited an emergency room because of a fall[343;353].

Studies which have assessed how discontinuation of fall-promoting drugs affects the frequency of falls and the severity of their consequences are still rare. In a double blind study from New Zealand, gradual withdrawal of psychotropic drugs in elderly users aged 65 years was compared to the continuation of psychotropic drugs. After 44 weeks, the intervention group showed a significantly lower risk of falling [HR = 0.3; 0.2-0.7]. The researchers add, however, that permanent withdrawal was difficult to achieve[354].

In most studies that evaluated the discontinuation of drugs increasing the risk of falling, this intervention was part of a multifactorial approach, whereby it is impossible to determine in retrospect which part of the total effect can be contributed to this part of the intervention[343;353]. One could reason, however, that when an effective multifactorial approach consisted inter alia of a critical review of drugs increasing the risk of falling, the omission of this intervention from the total approach might compromise its effectiveness. According to the Task Force, such a critical review should not only pay attention to psychotropic drugs, but also to fall-risk-increasing cardiovascular drugs. In a Dutch study of elderly patients, discontinuation of cardiovascular risk medications gave a similar reduction of the risk of falling as the discontinuation of psychotropic drugs: HR = 0.4 [0.2-0.8] vs 0.6 [0.2-1.4][355].

Benzodiazepines and related agents

According to a Dutch textbook on drug therapy and GP guidelines on the treatment of anxiety and sleeping disorders[301;356],the GP should first of all try to avoid that a new user becomes a chronic user (i.e. for more than 1-2 months). If this fails, the GP should attempt at least once to encourage the patient by means of a minimal intervention strategy to discontinue the benzodiazepine or to come over for a consultation (e.g. by sending the patient a letter, which informs the patient about the risks of continuing the

benzodiazepine, or which refers the patient to a website application for individualized counselling). This type of intervention is not labour-intensive and can be effective in approximately 20-25% of the general patient population[357-359]. Another type of strategy is the use of a gradual tapering scheme. This approach is labour-intensive, since it requires gradual reduction of the dose to minimize the risk of withdrawal symptoms, but it may be successful in up to two out of three patients[358;360].

5.2 FRACTURES ASSOCIATED WITH GLUCOCORTICOIDS

5.2.1 HARM AND IPCI DATA

In the HARM study, 6 hospital admissions concerned fractures following the use of oral corticosteroids without the addition of a bisphosphonate. Two patients were younger than 75 years, one patient was between 75 and 80 years old and three patients were 80 years or older.

5.2.2 PATHOPHYSIOLOGY

Oral glucocorticoids can adversely affect bone quality. Inhibition of bone formation and stimulation of apoptosis of osteocytes play an important role. Several studies suggest that the increased risk of fractures can only partially be explained by the reduction of bone mineral density and that changes in bone quality also make a significant contribution[361].

5.2.3 EPIDEMIOLOGY

Observational studies have demonstrated that oral glucocorticoids are associated with an increased risk of fractures [361]. In the largest study to date (performed in the British GPRD = General Practice Research Database) the following relative risks were found[362]:

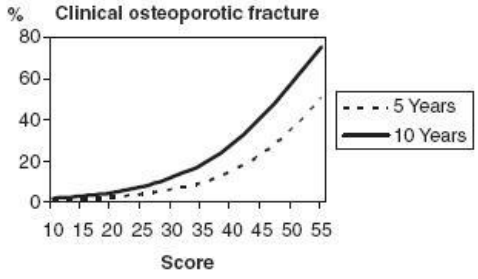
- RR = 1.3 [1.3-1.4] for non-vertebral fractures;
- RR = 1.6 [1.5-1.8] for hip fractures;
- RR = 2.6 [2.3-2.9] for vertebral fractures.

5.2.4 RISK FACTORS

The increased risk of fractures in oral glucocorticoid users is dose-dependent and is especially increased in the first three months of therapy[361]. A retrospective GPRD analysis showed that even daily doses as low as 2.5mg of prednisolone equivalents (PEs) can be associated with an increased risk[363]. This study identified various other predictors as well and was able to present a risk score on the basis of these risk factors, which estimates the long-term risk of fractures in patients using glucocorticoids (Table XXIII)[363].

Table XXIII. Risk score for estimating the probability of a clinical osteoporotic fracture due to a glucocorticoid[363].

Specific age (in years)	**50**	**65**	**80**
Daily doses of 7.5 mg PEs	8	6	**5**
Daily doses of 15 mg PEs	11	9	**7**
All ages			
Age (for each 10 years of age)	**4**		
Male sex	**- 6**		
Body Mass Index < 20	**3**		
Body Mass Index ≥ 26	**- 1**		
Smoker	**1**		
History of fall in past 6 months	**8**		
Fracture history prior to GC use	**6**		
Other osteoporotic fracture during GC treatment	**Not applicable**		
Disease/drug related risk factor (for each factor)[a]	**2**		
Recent hospitalization for underlying disease	**4**		
GC used for rheumatoid arthritis	**1**		
GC used for non-infectious enteritis and colitis	**1**		



Total Score	**5-year risk for fracture**
30	**6.2 % (6.0– 6.4)**
40	**15.3 % (14.9–15.7)**
50	**35.2 % (33.7–36.6)**

a In a previous GPRD study, the following diseases and drugs were associated with an increased risk of fractures: a history of anaemia, dementia, and cerebrovascular disease, or prescriptions in the previous 6 months for anticonvulsants, antiarrythmics, hypnotics/anxiolytics, antidepressants or anti-Parkinsonian drugs[364].

PEs = prednisone equivalents; **GC** = glucocorticoid; **RA** = rheumatoid arthritis

The GPRD has also been used to investigate the risk of intermittent treatment with high daily doses of ≥ 15mg of PEs per day. If the cumulative exposure was low (a total dose of ≤ 1g) the risk for osteoporotic fractures was increased only slightly, but if the cumulative exposure was high (a total dose of > 1g) the risk was significantly increased[365].

Discontinuation of the glucocorticoid reduces the risk of fractures to its background level, except when the patient has been exposed to a high cumulative amount[361].

Users of inhalation corticosteroids are also at increased risk of fractures, especially when higher dosages are used. It is likely, however, that this risk is mainly related to the underlying respiratory disorder[361].

5.2.5 RISK REDUCING STRATEGIES

a) Addition of a bisphosphonate

Dutch Guidelines on the prevention and treatment of osteoporosis recommend the addition of a bisphosphonate in the following situations[366-368]:

- if the patient will use more than 15 mg PEs per day for more than three months: always
- if the patient will use a dose between 7.5-15 mg per day for more than three months:: only if the patient is a postmenopausal female, a male aged > 70 years or has abnormally reduced bone density (since the risk of fractures is strongly increased in these patients).

Care should be taken that these patients have an adequate intake of vitamin D and calcium.[11]

The bisphosphonate should be continued for as long as the corticosteroid therapy lasts[366]. So far, its recommended maximum duration of therapy has been five years[301]. There are no studies which demonstrate that the continuation of the bisphosphonate has beneficial effects after discontinuation of the corticosteroid. Consequently, when the latter is discontinued, the former can also be stopped, except when the risk of fractures remains high after the corticosteroid has been stopped[366].

5.3 LOSS OF DIABETIC CONTROL ASSOCIATED WITH BLOOD GLUCOSE-LOWERING AGENTS

5.3.1 HARM AND IPCI DATA

The HARM and IPCI studies comprised 26 potentially preventable cases due to disturbances of diabetic control, which included at least 14 cases of hypoglycaemia and 6 cases of hyperglycaemia. Nineteen (73%) patients used one or more types of insulin, while the other 27% were only treated with oral blood glucose-lowering agents. In 15(58%) cases the patient was younger than 75 years, while in 6 cases the patient was 80 years or older. Possible reasons for the loss of diabetic control are summarized in Table XXIV.

In 15 (58%) cases it was likely that the patient himself could have prevented hospital admission; in 8 of these patients the insulin dosage had not been sufficiently tuned to the dietary pattern or to an intercurrent illness. The remaining 11 (42%) cases might have been avoided, if professional assistance and monitoring would have been more adequate. A remarkable example was a case in which the insulin dosage remained unchanged even though the body weight of the patient decreased significantly due to an ENT malignancy.

These results raise the question of how the education and professional guidance of insulin users can be further improved. According to the Task Force, a general answer lies outside the scope of its assignment to identify improvements of the "low hanging fruit" type. Instead, this section is restricted to the reduction of hypoglycaemia in users of sulphonylurea (SU) derivatives, which caused 4 of the 26 HARM/IPCI cases (15%) in which hospitalization was due to a potentially preventable disturbance of diabetic control.

Table XXIV. Possible reasons of 26 HARM/IPCI cases of potentially preventable diabetic dysregulation. (Numbers refer to numbers of cases).

Possible reasons	Type of treatment		Comments
	Insulin	No insulin	
Suboptimal self-management	**13**	**2**	
Intercurrent disease	5		Vomiting, diarrhoea and/or fever (4) Malaise without extra glucose monitoring (1)
Unwanted dietary pattern	3	2	No or insufficient food intake (4)
Suboptimal support/monitoring	**6**	**5**	In home for the elderly or a nursing home (3)
Undertreatment/underdosing	2	1	Chronic therapy with 5mg prednisone per day (1) Diabetic pump was not filled well after cleaning (1)
Overtreatment	2	1	Too much insulin was given by caretaker (1) Insulin dose unaltered, in spite of weight reduction due to ENT malignancy (1)

5.3.2 PATHOPHYSIOLOGY

Severe hypoglycaemia is the most important adverse effect of SU derivatives and related agents. This complication is especially seen with the long-acting glibenclamide (glyburide). Because of its long duration of action, the hypoglycaemia can be quite prolonged and can return after treatment has initially produced an improvement[369].

5.3.3 EPIDEMIOLOGY

In a retrospective cohort study in elderly users of blood glucose-lowering agents (≥ 65 years) the risk of severe hypoglycaemia was 1.2 [1.1-1.4] per 100 person years for users of SU derivatives versus 2.8 [2.5-3.1] for users of insulin[370].

5.3.4 RISK FACTORS

In the above mentioned cohort study, the strongest predictor of hypoglycaemia was a recent hospital discharge (in ≤ 30 previous days) [RR= 4.5; 3.5-5.7]. Other independent risk factors included advanced age [RR = 1.8; 1.4-2.3], a black race [RR = 2.0; 1.7-2.4], and simultaneous use of at least 5 medications [RR = 1.3; 1.1-1.5].

Other studies have shown that the start of an SU derivative, pre-existing renal insufficiency, a CYP2C9 genotype *3/*3 or *2/*3, the use of glibenclamide (versus other SU derivatives) and interactions with drugs that potentiate SU derivatives all increase the risk of a severe or less severe hypoglycaemia[371-374].

In a large case-control study in elderly patients, the risk of severe hypoglycaemia due to glibenclamide was significantly increased, when co-trimoxazole was used simultaneously [OR_{adj}= 6.6; 4.5-9.7][375].

Beta-blockers may increase the severity of hypoglycaemia and delay the recovery. They modify and partially block the warning signs. Selective beta-blockers have these effects to a lesser extent than non-selective beta-blockers. However, the 'safety' of selective beta-blockers is only relative and may be lost when higher dose levels are used[224]. RASIs may decrease the blood glucose level in patients with diabetes and can thus increase the risk of hypoglycaemia due to SU derivatives[224].

5.3.5 RISK REDUCING STRATEGIES

a) Avoidance of glibenclamide, especially in elderly patients

The Dutch GP practice guideline on Diabetes Mellitus Type II discourages the prescribing of glibenclamide because of its relatively high risk of hypoglycaemia (which can sometimes be severe). Moreover, this guideline cautions that hypoglycaemia can return after a few hours because of the long-acting effect of glibenclamide[376].

The Task Force therefore recommends to add glibenclamide to the so-called Beers list of medications, which are considered inappropriate for the use in elderly patients because they entail the risk of severe adverse effects[9;377].

b) Counselling of patients

Counselling of insulin users should not only pay attention to the importance of a geared diet, but also to the risk of intercurrent illnesses.

The risk of hypoglycaemia during the use of SU derivatives is not only increased by advanced age and renal insufficiency, but also by unusual physical exercise, and irregular or reduced food intake [301]. Users of SU derivatives should therefore be informed on how to deal with these risk factors. Especially if they are at increased risk of hypoglycaemia (e.g. because of renal insufficiency or a potential drug-drug interaction) they should be informed orally and in written form about its first symptoms.

5.4 LOSS OF DIABETIC CONTROL ASSOCIATED WITH GLUCOCORTICOIDS

5.4.1 HARM AND IPCI DATA

In the HARM study, six cases of serious hyperglycaemia were associated with the use of glucocorticoids. Three (50%) patients were younger than 75 years. In three patients latent diabetes became manifest, in two cases pre-existing diabetes deteriorated, and in one case this remained unclear.

5.4.2 PATHOPHYSIOLOGY

Glucocorticoids can cause hyperglycaemia by decreasing the sensitivity of the liver and peripheral tissue to insulin. Therefore gluconeogenesis in the liver can increase while the uptake of glucose in muscle and fat tissue is reduced [224].

5.4.3 EPIDEMIOLOGY

In a randomized study of the effects of a high-dose course of glucocorticoids in patients with COPD, hyperglycaemia was developed in 24/160 (15%) of the corticosteroid users versus 4/111 (4%) of the placebo users. In the corticosteroid users, hyperglycaemia usually developed in the first few days after the onset of therapy, and 16/24 (67%) patients had a history of diabetes [378].

An observational case-control study has shown that oral glucocorticoid users are at increased risk for a hyperglycaemia requiring blood glucose-lowering therapy compared to non-users [OR = 2.2; 1.9-2.6] [379].

5.4.4 RISK FACTORS

In the above mentioned observational study the risk of hyperglycaemia was highest during the first six weeks of the glucocorticoid therapy. The dose-level seemed to be relevant as well[379].The risk gradually increased from an OR = 1.8 [1.5-2.0] for exposures below 10 mg PEs per day to OR = 10.3 [3.2-33.9] for exposures ≥ 30mg PEs per day.

Braithwaite et al. assert that the risk of severe or prolonged hyperglycaemia is not that high, when only a single injection of glucocorticoid is given or when the steroid is tapered quickly within 2 weeks[380].

In a study of patients with primary renal diseases, 17/42 (41%) patients developed diabetes during corticosteroid therapy. Advanced age and a high body mass index were independent risk factors for the occurrence of this adverse effect[381].

5.4.5 RISK REDUCING STRATEGIES

a) *Monitoring of blood glucose levels and, if necessary, initiation/adaption of blood glucose-lowering treatment*

A hyperglycaemic effect is often only noticeable, when ≥7.5mg PEs per day are used. In such cases, it is advisable to monitor the glucose level regularly during and after discontinuation of the corticosteroid therapy and to adjust the dose level of the blood glucose-lowering treatment, if hyperglycaemia occurs[224].

Braithwaite et al. advise to measure the glucose level prior to corticosteroid therapy and each 1-2 weeks after the start of the therapy. They also raise the possibility that the patient can self-monitor the presence of glucose in the urine during the first 4 weeks of treatment. If diabetes develops, self-monitoring of the blood glucose level should be considered[380].

The literature is divided about the issue whether an oral blood glucose-lowering agent is adequate or inadequate, when glucocorticoid users develop mild hyperglycaemia. It is more obvious that more severe cases of hyperglycaemia should be treated with insulin, especially if the patient is already known to have diabetes. Since corticosteroids can increase the resistance of diabetic patients to insulin, their need for insulin may become 1.5 to 2 times as high. It may even be necessary to adapt the insulin dosage on a daily basis[380;382].

In general, the effects of glucocorticoids on the glucose level subside quickly after their discontinuation (i.e, within 2 days after stopping the steroid) [382]. One should be aware of the risk of hypoglycaemia when a blood glucose-lowering treatment has been started or

adjusted because of a glucocorticoid therapy and that glucocrticoid is subsequently discontinued[380].

b) *Counselling of the patient*

When a glucocorticoid therapy is initiated, diabetic patients should be informed about the risk of hyperglycaemia and its first symptoms (thirst, dry mouth, frequent miction, and fatigue). If necessary, patients should contact their physician[224].

5.5 BRADYCARDIA ASSOCIATED WITH DIGOXIN AND/OR SOTALOL

5.5.1 HARM AND IPCI DATA

Fourteen potentially preventable hospital admissions were associated with relatively high dose levels of digoxin and/or sotalol. In 10 (71%) of these cases bradycardia (with or without a collapse) was documented. In at least 12 cases, one of the following risk factors was present: renal impairment (8x), age ≥ 80 years (7x), concomitant use of verapamil or diltiazem (3x), concurrent use of sotalol with metoprolol and amiodarone (1x), and simultaneous use of two dose levels of digoxin (0.25 and 0.125 mg/day) after the old dose level of 0.25 mg/day) had been revised to a dose level of 0.125mg/day (1 x).

The Task Force focuses on digoxin and sotalol, because in the pooled HARM/IPCI data, bradycardia was most often related to these two drugs. Only one case of bradycardia concerned metoprolol and one other case concerned amiodarone, whereas 10 cases of bradycardia were associated with digoxin and/or sotalol.

5.5.2 PATHOPHYSIOLOGY

Digoxin

As digoxin has a narrow therapeutic window, most cases of adverse effects involve an intoxication. Digoxin does not only increase cardiac contractility (positive inotropic effect), but also reduces heart frequency (negative chronotropic effect) and depresses A-V conduction (negative dromotropic effect). A toxic digoxin level can lead to severe bradycardia and blockade of the A-V conduction[383].

Sotalol

The risk of bradycardia during the use of sotalol is inherent to the pharmacological effect of this beta-blocker. In addition, sotalol may produce torsade de pointes (ventricular arrhythmia) by prolonging the QT interval[384].

5.5.3 EPIDEMIOLOGY

Digoxin

In a Dutch study of the risk of hospitalization due to intoxication with digoxin, there were 1286 of such admissions (0.04% of all acute admissions) in 2001-2004. The incidence was 48.5 [45.9-51.2] per 100,000 prescriptions, which corresponded to 1.94 admissions per 1000 treatment-years[385].

Sotalol

The literature has not yielded epidemiological data about the chance that sotalol leads to hospitalization because of severe bradycardia .

5.5.4 RISK FACTORS

Digoxin

In observational studies, the risk of digoxin toxicity was univariately related to such factors as advanced age, renal impairment, hypokalaemia, hypomagnesaemia, hypercalcaemia, hypoxia, ischemic heart disease, hypothyroidism, and concurrent use of interacting drugs (e.g. amiodarone, propafenone, quinidine, verapamil and clarithromycin) [375;386-388]. In one study, the only risk factor which remained after multivariate analysis was the dose level of digoxin[388]. In another study, a high dose of digoxin (≥25mg/day), advanced age (≥80 years), renal insufficiency and drug-drug-interactions were independent risk factors[387]. The Task Force is of the opinion that the prescribing of digoxin to an elderly patient (i.e., ≥ 70 years) requires adequate knowledge of the renal function of that particular patient. The dispensing pharmacist should have access to that information to verify that the prescribed dose of digoxin corresponds to the patient's renal function.

There are divergent opinions about the contributory role of that hypokalaemia may play in the development of digoxin toxicity (and thereby about the advisability to monitor potassium on a regular basis if digoxin is combined with a potassium-losing diuretic) [224;288]. On the one hand, there is actual evidence that hypokalaemia can increase the risk of digoxin toxicity from a study in twelve patients with advanced heart failure. In this study all patients received a high-dose loop diuretic in addition to digoxin and had normal digoxin and potassium levels, until hypokalaemia was created by stopping their potassium supplement or potassium-sparing diuretic. In 6 cases, this led to cardiac arrhythmias that resembled a digoxin intoxication (while they continued to have normal digoxin levels)[389]. A subsequent study showed that hypokalaemia can lower the clearance of digoxin by reducing its tubular secretion[390]. On the other hand, the risk of diuretic-induced hypokalaemia in patients with heart failure is less likely, since these patients are usually also treated with one or more potassium-sparing agents (RASI, aldosterone antagonist)[391;392]. All in all, the monitoring of the potassium level seems to be especially relevant, when digoxin is combined with a potassium-losing diuretic without the addition of a potassium-sparing drug.

Sotalol

The risk of sotalol toxicity is increased by renal insufficiency and by the concurrent use of interacting drugs (e.g. verapamil and diltiazem)[224]. The risk that sotalol leads to prolongation of the QT interval and torsade de pointes is increased by hypokalaemia[393].

5.5.5 RISK REDUCING STRATEGIES

Digoxin

Digoxin should be given in lower initial and maintenance doses in elderly patients, patients with impaired renal function or impaired thyroid function. Renal function and serum electrolytes should be regularly measured[301].

The risk of toxicity in digoxin users is also increased by interacting drugs such as quinidine, amiodarone, propafenone, cyclosporine, macrolides, itraconazole, verapamil and diltiazem [224]. According to a recent report of the Dutch Inspectorate, combinations of digoxin with macrolides or itraconazole should not be dispensed[394].

Sotalol

Before sotalol is initiated or before its dosage is increased, it is advisable to check the ECG as well as the renal function and electrolyte levels of the patient. If renal impairment is present, the dose level should be reduced under the guidance of the creatinine clearance[29].

One should be aware that the risk of sotalol toxicity is also increased by concurrent use of verapamil or diltiazem[224]. As the risk of bradycardia due to sotalol is based upon the pharmacological action of this beta-blocker, no other beta-blockers should be given simultaneously (although there are exceptions to this rule in cardiologic practice).

5.6 SEVERE CONSTIPATION ASSOCIATED WITH OPIOIDS

5.6.1 HARM AND IPCI DATA

In the HARM and IPCI studies, 11 cases of serious constipation and ileus were seen, in which an opioid had been used, either without the addition of any laxative or in combination with an unsuitable laxative (e.g. psyllium). At least 6 of these patients were below the age of 75 years.

5.6.2 PATHOPHYSIOLOGY

Among the various effects of opioids on the GItract are reduction of bowel motility, bowel secretion and blood circulation, which may result in dry hard faeces. When opioids are used chronically, constipation is the most frequent adverse reaction and patients rarely develop tolerance to this effect[395].

5.6.3 EPIDEMIOLOGY

Estimates of the frequency of constipation in opioid users, who developed constipation in randomized trials, vary between 15% and 90%[395]. Of the terminal patients using opioids, 90% may need a laxative[396].

5.6.4 RISK FACTORS

No observational studies have been found in the literature which looked at risk factors for developing severe constipation during opioid therapy. According to reviews, it seems likely that strongly acting opioids entail a larger risk than weakly acting ones[395] and that elderly patients are at increased risk compared to younger ones[397].

5.6.5 RISK REDUCING STRATEGIES

It is generally recommended to combine opioids with a laxative to prevent constipation, unless there is an obvious reason for not doing so (e.g. acute abdominal pain of unknown cause, intestinal obstruction or diarrhoea) [395;397;398]. Studies in the Netherlands and elsewhere suggest that opioid users do not always receive a laxative and that there is room for improvement in this respect[397;399-401]. However, one should be aware that laxatives only

counteract constipation without preventing all gastrointestinal adverse effects of opioids[395;402] and there are also patients who do not really require a laxative. The report even suggests that it it may be useful to discontinue laxative therapy in terminal patients[403]. Consequently, a laxative should not be added routinely, but always as the result of a conscious decision. If one decides to withhold laxative co-therapy, this should be properly documented in the patient record so that it can be audited how often one has omitted a laxative unintentionally.
There are no comparative randomized trials which indicate the most suitable laxative in users of opiates. Emollients as monotherapy are usually not effective[395;397;398]. Bulk-producing laxatives have the disadvantage that they have to be taken with sufficient amounts of fluid, which is often problematic in terminal patients. With insufficient fluid intake, they may develop a gelatinous mass which may lead to complete obstruction, especially if a subobstruction is already present[395;396].
The literature often prefers a combination of a contact laxative (e.g. senna) with an emollient (docusate sodium) on the basis of practical experience[395;397;398] Dutch sources advise to start with an osmotic laxative (e.g. lactulose or macrogol) and to add a contact laxative if this produces insufficient results[145;404]. In a study in terminal patients, 27 (77%) of 35 opioid users who received a laxative (principally lactulose) were still constipated. In these patients the dose of lactulose used was too low to be effective, while higher (effective) doses would have produced adverse GI effects[396].

5.7 RECOMMENDATIONS RELATED TO REMAIN ADRS

Fractures due to fall incidents (section 5.1)

Recommendation 24.

Psychotropic drugs (benzodiazepines and related agents, classical and atypical antipsychotic agents, tricyclic and non-tricyclic antidepressants) may only be started in elderly patients on strict indication (cave combinations) (Grade 1B).
When patients are ≥ 70 years old, the prescriber asks about fall incidents in the past year and assesses (on the basis of direct observation and the medical record) to which extent the patient has impaired mobility. If this assessment shows an increased risk of falling, the risk of fall injury should be examined more closely (Grade 1C).

Recommendation 25.

The prescriber assesses periodically in a personal consultation with the elderly patient, whether it is still necessary to continue psychotropic drugs and those cardiovascular drugs which also increase the risk of falling (antiarrhythmic agents type Ia, digoxin, diuretics) (Grade 1B).
The first reassessment of treatment should take place at 1-2 weeks after starting a benzodiazepine or antipsychotic agent and at 4-6 weeks after starting an antidepressant (Grade 1C).
If long-term treatment cannot be avoided, the use of all drugs which increase the risk of falling is reassessed at least annually (Grade 1C).

Recommendation 26.
Elderly patients who have fallen repeatedly within one year and/or have visited an emergency department because of a fall, qualify for a multifactorial intervention which does not only encompass reconsideration of all drugs, which increase the risk of falling but also pays sufficient attention to other risk factors (Grade 1C).

Recommendation 27.
If a benzodiazepine (or related agent) is used to treat insomnia or anxiety for a longer period, one should try at least once to discontinue the therapy by means of a minimal intervention strategy (such as a discontinuation letter or a derivative web application) or by means of gradual dose tapering (Grade 1B).
If an elderly user does not succeed in the complete discontinuation of the benzodiazepine, an attempt should be made to reduce the dose level (Grade 1B).

Fractures due to glucocorticoids (section 5.2)
Recommendation 28.
When a patient will use ≥ 7.5 mg prednisone equivalents per day for more than three months, the addition of a bisphosphonate is recommended in the following situations (Grade 1B):
- For doses > 15mg per day: always.
- For doses of 7.5-15mg per day: when the patient is a postmenopausal female or a male > 70 years old or when bone density is abnormally reduced.

Besides the bisphosphonate, an adequate intake of calcium and vitamin D is relevant (Grade 1B).
The bisphosphonate is continued for as long as the corticosteroid therapy is continued, with a maximum of five years (Grade 1C).
After discontinuation of the corticosteroid, the bisphosphonate can also be discontinued, unless the risk profile is still increased (Grade 1C).
When a glucocorticoid is used in high intermittent doses of ≥ 15mg prednisone equivalents per day, protective therapy should be emphatically considered, when the total cumulative exposure of the patient exceeds 1g prednisone equivalents (Grade 2B).

Hypoglycaemia due to blood glucose-lowering agents (section 5.3)
Recommendation 29.
It is not advisable to prescribe glibenclamide to patients ≥ 70 years, because the risk of a potentially serious hypoglycaemia is relatively high (Grade 1B).

Recommendation 30.
Users of oral blood glucose-lowering sulphonylurea derivatives should be informed about the risks of unusual physical exercise, an irregular dietary pattern or reduced food intake, and also about how to manage these risks (Grade 2C).
They should also receive oral and written information about the first symptoms of hypoglycaemia, especially when they are at increased risk of hypoglycaemia (e.g., because of renal insufficiency or a potential drug-drug interaction) (Grade 2C).

Hyperglycaemia due to glucocorticoids (section 5.4)

Recommendation 31.

When a glucocorticoid therapy with ≥ 7.5mg prednisone equivalents per day is started, the blood glucose level should be checked (unless the treatment consists of a single injection) (Grade 1C). If necessary, blood glucose-lowering treatment is initiated or adapted under guidance of these test results. In more severe cases of hyperglycaemia, insulin is preferable to an oral blood glucose-lowering agent (Grade 1C). Patients are advised to be attentive to symptoms of hyperglycaemia (thirst, dry mouth, increased diuresis, fatigue) and to consult their physician if necessary (Grade 2C).

When there is no evidence that the patient has diabetes, the glucose level is checked before therapy is started and 3-7 days after its start. When a risk factor is present (e.g., a renal disease or a high corticosteroid dose of ≥ 15mg prednisone equivalents per day) one or more additional checks should be considered (Grade 2C).

When the patient is known to have diabetes or develops hyperglycaemia during corticosteroid use, it is advisable to check the glucose level more frequently (every 1-2 weeks in the beginning of therapy) (Grade 2C).

Recommendation 32.

When blood glucose-lowering treatment has been started or adapted because of glucocorticoid-induced hyperglycaemia, the risk that hypoglycaemia may develop when the corticosteroid treatment is discontinued again should be considered (Grade 1A).

Bradycardia due to sotalol and/or digoxin (section 5.5)

Recommendation 33.

When digoxin and/or sotalol are given to elderly users, risk factors for the development of bradycardia should be carefully considered:

- Renal function should be checked before the start of the treatment, before each dose increase and subsequently at least once a year (Grade 1B).
- Combinations with other cardiovascular agents that can enhance their effects (such as verapamil and diltiazem) should only be given on strict indication (Grade 1B).
- Sotalol should only be combined with another beta-blocker on strict indication (Grade 1B).
- The risk of drug-drug interactions between digoxin and potentiating non-cardiovascular drugs (macrolides, itraconazole, ketaconazole) should be carefully controlled (Grade 1B).
- When digoxin is added to a potassium-losing diuretic without the addition of a potassium-sparing agent (RASI, potassium-sparing diuretic), the potassium level should be checked before the start of the therapy, before each increase in dose, and subsequently at least once a year (Grade 1C).

Serious constipation due to opioids (section 5.6)

Recommendation 34.

Each opioid user should be simultaneously treated with a laxative, except when there is a good reason not to do so (e.g. a joint decision by prescriber and patient to effectuate this measure not immediately). In such cases, the prescriber records the specific reason and periodically reassesses the need for a laxative (Grade 1C).

The prescriber who selects an osmotic laxative (e.g. lactulose or macrogol) as monotherapy, , regularly inquires whether this agent is effective and adds a contact laxative (e.g. sennosides or bisacodyl) if necessary (Grade 1C).

6 DISCUSSION

The HARM-wrestling Task Force established that seven types of pharmacologically predictable adverse effects (haemorrhages; electrolyte disturbances; fractures; disturbances of diabetic control; renal insufficiency and heart failure; constipation; and bradycardia) with ten long existing drugs classes (VKAs, PAIs, NSAIDs, diuretics, RASI, central nerve system (CNS) medication, corticosteroids, blood-glucose lowering drugs, opioids and cardiac drugs (sotalol/digoxin)) were responsible for more than half of all the potentially preventable hospital admissions. As a consequence, clinical drug risk management should focus not only on pharmacovigilance to detect new risks of new drugs but also on intervention measures to reduce specific old risks of specific old drugs.

The Task Force drew up 34 specific recommendations to reduce these potentially preventable HARMs in a quick win way. Many of these recommendations were already present in prevailing clinical practice treatment guidelines, so pursuing a rapid reduction of the observed HARMs is more about implementing and reinforcing existing guidelines than about replacing them[405]. The recommendations do not only focus on risk medications, but also on risk patients and risk situations . More often than not, recommendations could not be based on definitive randomized trials but had to be derived from well-designed and well-performed observational studies and general pharmacological common sense.

Besides specific recommendations, the Task Force identified 9 general issues, such as the need to assign one main physician to each complex risk patient, the need to provide timely feedback about actual HARMs from the hospital to general practice (to avoid that patients are injudiciously reexposed after discharge), and the need to inform patients about first alarm symptoms and signs without frightening them.

Roughly speaking, half of the recommendations of the Task Force are about appropriate prescribing (e.g., giving drugs only on strict indication or adding a protective drug), a quarter about careful follow-up (e.g., laboratory monitoring and appropriate duration of therapy), and another quarter about adequate communication (with the patient and with other healthcare

providers). Many of the recommended actions cannot be postponed until the next medication review but should already be carried out as soon as a treatment is started or changed.

Both the specific and the general issues can only be implemented if different health care parties recognize their importance and stimulate better communication between health care professionals.

Although economic analyses were beyond the assigned scope of the Task Force, the time has come to vigorously execute implementation strategies that are as much evidence-based as possible; to target barriers to change and their underlying causes; to recognize and distinguish risk medications, risk patients, risk processes, and risk healthcare providers; and to consider that different prescribers may require different methods of implementation [406]. It should be emphasized that many of the recommended actions cannot be postponed until the next medication review but should already be carried out as soon as a treatment is started or changed[405].

The beneficial and adverse effects of the recommended interventions should be monitored, not only to assess the progress of implementation but also to increase our current evidence base. When interpreting the results of monitoring, it is not realistic to expect total success, since individual HARMs may be less preventable in practice than in theory. Moreover, prescribers may have a sound reason to disregard an advice in an individual patient. If this is the case, the reason for the deviation should be recorded to facilitate transfer of patient data, to advance quality assessment, and to enrich future scientific analyses[405].

7 CONCLUSIONS

Two independent studies (the IPCI study and the HARM study) have shown that 5.1%- 5.6% of all unplanned hospital admissions in The Netherlands are medication related[6;407]. Pooling of their data yielded a total of 829 HARMs (hospital admissions related to medications), of which 44% were judged as potentially avoidable.

Seven types of pharmacologically predictable adverse effects with ten long existing drugs classes were identified. 34 drug-specific recommendations and 9 general issues were developed. More often than not, recommendations could not be based on definitive randomized trials but had to be derived from well-designed observational studies and general pharmacological common sense.

More than 50% of the potentially avoidable HARMS are due to ten well-known old drug classes and these as HARMs constitute a significant public health problem. Therefore, the Task Force underlines the need to implement its recommendations into current clinical practice.

Further research is still needed to assess the cost-consequences and cost-effectiveness of some recommendations, and to monitor the implementation of the recommendations and their effect on the incidence of potentially preventable HARMs.

8 FOOTNOTES

1 This variation is partially caused by different definitions [22].

2 If a VKA therapy is restarted after a bleeding incident, it is important to eliminate risk factors. Depending on the therapeutic range (INR 2-3, 2.5-3.5, or 3-4), it may be possible to lower the target range (e.g., to 2.0-2.5). However it is not easy to establish a target range that is only 0.5 INR wide, especially not in users of acenocoumarole. Phenprocoumon levels are more stable, but is the long action of this drug can be a disadvantage for patients at risk[408].

3 Table XXV shows the numbers of high GI complications per 1000 person years for NSAID and/or ASA users in different age categories and with different gastrointestinal histories. This table is derived from figure 3 in reference[101], which was based on the following assumptions concerning the numbers of complications per 1000 person years:

- Approximately one in the general population;
- Exponential increase from <1 below the age of 60 to > 5 at the age of 85;
- In each age group, the risk is two times higher for men than it is for women;
- If the patient has a history of upper gastrointestinal pain/dyspepsia, an uncomplicated ulcer or a complicated ulcer, the risk is increased by a factor of 2, 6, and 10, respectively;
- NSAID use increases the risk by a factor of 3-4 (without an ulcer in the patient's history) or 2.5 (with an ulcer in the patient's history);
- ASA increases the risk by a factor of 2.

Table XXV: Numbers of upper gastrointestinal complications per 1000 person years in patients using NSAID and/or ASA in different age categories[101].

Drug Use	NSAID without ASA[a]		ASA without NSAID[a]		NSAID plus ASA[a]	
Ulcer(complication) in the history	No	yes	No	Yes	No	Yes
Age category						
20-60 years	1.6 - 6.4	7.2 - 20.0	0.8 - 3.2	4.8 - 16.0	3.2 - 12.8	14.4 - 40.0
60-69 years	4.8 - 19.2	21.6 - 60.0	2.4 - 9.6	14.4 - 48.0	9.6 - 38.4	43.2 - 120.0
70-79 years	7.2 - 28.8	32.4 - 90.0	3.6 - 14.4	21.6 - 72.0	14.4 - 57.6	64.8 - 180.0
≥ 80 years	12.0 - 48.0	54.0 – 150.0	6.0 - 24.0	36.0 – 120.0	24.0 - 96.0	108.0 - 300.0

a The numbers have been reproduced as white characters against a black background if the Dutch CBO Guideline on the prevention of gastric damage in NSAID users recommends to take preventive action (age above 70 years or ulcer (complication) in the patient's history). The numbers have been reproduced as blak characters against a grey background if the Dutch CBO Guideline recommends that the taking of preventive action should be seriously considered(age between 60 and 70 years or, concurrent use of NSAID and ASA). These CBO recommendations come down to the taking of preventive action when the expected number of cases per 1000 person years is ≥ 7.2 and to the consideration of preventive action when the expected number of cases per 1000 person years is ≥ 3.2. These limits have been applied to mark when preventive action should be taken or considered in the spirit of the Dutch CBO Guideline[24].

NSAIDs = non-steroidal anti-inlammatory drugs; **ASA =** acetylicsalicylic acid.

4 In a Dutch study PPIs increase the risk of pneumonia [OR_{adj} =1.73;1.33-2.25]; the OR_{adj} varied between 1.23 [0.78-1.9] 3 for doses < 1 DDD (defined daily dose) and 2.28 [1.26-4.10] for doses > 1DDD[409]. An increased risk for pneumonia (mainly in the first week after the start of the PPI) was also shown by Danish researchers. However, the latter study did not show a significant effect of different dose levels[410]. In a third study, the start of PPI therapy within the last 2 weeks was associated with an OR_{adj} of 3.21 [2.46 to 4.18], but no statistically significant association was seen for longer-term PPI therapy[411]. Other recent studies have associated PPI use with an RR_{adj} = 1.16 [1.03–1.31] [412]; with an OR_{adj} = 1.55 [1.38–1.77] [413], but without a significant impact on short-term and long-term mortality in pneumonia cases[414]; and with an adjusted rate ratio of 1.16 [1.11-1.22][415]. According to a comment accompanying the latter study, its result can be equated with 4 extra hospitalisations for pneumonia each year for every 1000 elderly people prescribed a PPI. The comment adds as a cautionary note that the study did not firmly establish a causal association and that the increase might also have been due to unidentified confounders (e.g., co-morbid conditions giving rise to an increased risk of pneumonia in the first place) [416]. It is widely accepted that it is hazardous to interpret increased risks from case-control studies as real evidence of increased risk, when they have a low magnitude (i.e., an OR_{adj} or RR_{adj} < 2), because bias (e.g., due to residual confounding factors, misclassication of diagnoses, or selection bias) may account for such apparently weak associations[417-420].

5 A positive association between long-term PPI use and the development of osteoporotic fractures (especially hip fractures) has been found in five of the six case-control studies

which addressed this issue (see Table XXVI). The magnitude of the association was mostly low (i.e., OR_{adj} or $RR_{adj} < 2$) which raises a question of whether the reported increases in risk were real (cf. note 4). The possibility of a real association is supported by increased responses to higher daily doses and/or longer duration of PPI use in some of the studies. In the only negative study, no increased risk was seen after the exclusion of patients with major medical risk factors (e.g., alcoholism, convulsions/epilepsy, psychotic conditions, fall incidents, confusion/ agitation, Parkinson's disease, etc.), which suggests that the associations observed in the other studies may have been the result of residual confounding or effect modification[421]. In another study, an excess fracture risk was only present in long-term PPI users with at least one additional risk factor for the development of fractures (e.g., alcohol abuse, arthritis, diabetes, kidney disease, glucocorticoid use). The overall fracture incidence in subjects with ≥ 1 yr supply of PPIs was 3.24 per 1000 person-years compared to 2.14 per 1000 person-years in persons not exposed to PPIs[422]. Commentators[416;423;424] and the reporting investigators themselves generally conclude that these findings are insufficient to relinquish PPI use, when patients have a clear indication for treatment (such as the prevention of NSAID-related complications). Some add as cautionary notes that PPIs should not be used in higher doses or for longer duration than is necessary and that patients who require long-term PPI therapy should be encouraged to take the recommended daily amounts of calcium and vitamin D. In a cross-sectional study, PPI use was only associated with an increased risk of non-vertebral fractures in men, who were not taking calcium supplements (HR = 1.49; 1.04–2.14) [425]. So far, however, no other studies have reported on the extent to which interventions with calcium and vitamin D supplementation may modify the association between PPI use and fracture risk[422]. If calcium supplementation in PPI users is considered desirable, calcium citrate is preferable to calcium carbonate, because calcium absorption from the latter is significantly decreased when the patient is on PPI therapy[426-428].

Table XXVI. Case-control studies of the association between PPI use and fractures

Reference	Study End	Outcome (95% CI)
Vestergaard et al. [429]	Any fracture	OR_{adj} for PPI use within last year 1.18 [1.12-1.43] OR_{adj} for different types of fracture 1.45 [1.28-1.65] for hip fractures 1.60 [1.25-2.04] for spine fractures OR_{adj} for different exposures to PPIs within last year 1.16 [1.06-1.26] for exposure to <25 DDDs 1.34 [1.26-1.42] for exposure to 25-99 DDDs 1.14 [1.09-1.19] for exposure to ≥ 100 DDDs
Yang et al. [427]	Hip fracture in subjects > 50 yr	OR_{adj} for PPI use > 1 yr 1.44 [1.30-1.59] OR_{adj} with increasing duration of PPI use 1.22 [1.30-1.59] for 1 yr 1.41 [1.28-1.56] for 2 yr 1.54 [1.37-1.73] for 3 yr 1.59 [1.39-1.80] for 4 yr OR_{adj} below or above average daily dose of 1.75 1.40 (1.26-1.54) for daily dose ≤ 1.75 2.65 [1.80-3.90] for daily dose > 1.75
Targownik et al. [430]	Osteoporotic fracture (hip, vertebra, wrist) in subjects ≥ 50 yr	OR_{adj} for osteoporotic fracture with increasing duration of PPI use 1.28 [0.93-1.77] for ≤ 6 yr 1.92 [1.16-3.18] for ≥ 7 yr OR_{adj} for hip fracture with increasing duration of PPI use 1.43 [0.97–2.11] for ≤ 4 yr 1.62 [1.02–2.59] for ≤ 5 yr 2.49 [1.33–4.67] for ≤ 6 yr 4.55 [1.68–12.29] for ≥ 7 yr
Kaye et al. [421]	Hip fracture in subjects aged 50-79 yr without major risk factors	RR_{adj} for any PPI prescription 0.9 [0.7–1.1] RR_{adj} with increasing number of PPI prescriptions 1.0 [0.7–1.4] for 1 prescription 1.0 [0.7–1.3] for 2-9 prescriptions 0.9 [0.6–1.4] for 10-29 prescriptions 0.5 [0.3–0.9] for ≥ 30 prescriptions
Roux et al. [431]	Vertebral and non-vertebral fracture in women aged 55-79 yr	RR_{adj} for omeprazole use 3.50 [1.14–8.44] for vertebral fracture no significant increase for non-vertebral fracture
Corley ea 2010[422]	Hip/femur fracture in subjects ≥ 18 yr	OR_{adj} for long term PPI use (supply ≥ 2 yr) 1.30 [1.21–1.39] OR_{adj} with increasing PPI dosage 1.12 [0.94-1.33] for < 0.74 pills/day 1.30 [1.19-1.42] for 0.75-1.49 pills/day 1.41 [1.21-1.64] for ≥ 1.5 pills/day OR_{adj} with increasing duration of PPI use no substantially increases with longer durations OR_{adj} for ≥ 2 yr PPI supply in absence/presence of other risk factor(s) 0.66 [0.38-1.12] in absence of other risk factor 1.25 [1.16-1.35] in presence of other risk factor(s)

OR_{adj} = adjusted odds ratio; **RR_{adj}** = adjusted relative risk; **PPI** = proton pump inhibitor; **DDD** = daily defined doses; **yr** = years

6 There appears to be only one large RCT which has compared the preventive effectiveness of PPIs in NSAID users head-to-head with that of H2ARs[253]. In this Australian trial, 432 patients (who had been successfully treated for gastroduodenal ulcers/erosions and required continuous NSAID treatment) were randomized to either omeprazole (20 mg/day) or ranitidine (300 mg/day). After 6 months, the proportions of patients in remission (defined as the absence of a relapse of lesions, dyspeptic symptoms, and

adverse events leading to the discontinuation of treatment) were 72% in the omeprazole group vs 59% in the ranitidine group. Gastric and duodenal ulcers had recurred in 5.2% resp. 0.5% of the patients on omeprazole compared to 16.3% resp. 4.2% of the patients on ranitidine[432]

7 In the wake of this recommendation The Dutch Medicines Evaluation Board revaluated the OTC availability of NSAID products on the Dutch market and decided to assign a "Pharmacy Only" status to a part of them.

8 The time period of three to five days and the age limits of 70 and 80 years have been chosen because of the following considerations:

- Hyponatraemia in patients receiving thiazide diuretics usually arises in the first 2 to12 days of therapy[280].
- Thiazide diuretic users older than 70 years are at increased risk for hyponatraemia compared to younger people[280].
- In the age above 80 the chance of being a vulnerable elderly is relatively high.

The recommendations of the Task Force correspond to:

- A recommendation of the Dutch General Practitioners' guideline on heart failure , which recommends to pay extra attention to sodium, potassium and creatinine monitoring in patients with concurrent use of a thiazide diuretic and a loop diuretic[289]
- A Dutch textbook on computerized medication alerts which recommends to check the sodium level in patients with concurrent use of a thiazide diuretic and SSRI/venlafaxine and one or more of the following risk factors: age above 65 years, concurrent use of a loop diuretic, heart failure, intercurrent infection, diarrhoea or vomiting[288]

9 This relatively arbitrary age limit has been chosen because an age older than 70 years is a significant risk factor for the development of severe hyperkalaemia in patients who continue RASI therapy in spite of a hyperkalaemia [303].

10 When a RASI is combined with spironolactone, the daily doses of spironolactone should not exceed 25mg. This combination is contraindicated in patients with a GFR ≤ 30ml/min (Table XXI).

11 If a long-term user of corticosteroids has a dietary intake of calcium < 1000-1200mg per day, supplementation with 500mg of elementary calcium per day is recommended.

12 Pain management guidelines sometimes propose tramadol as a treatment option for mild-to-moderate pain in patients at high risk of gastrointestinal side effects (including peptic ulcer disease)[433].In an observational study, this agent was not associated with an increased risk of upper gastrointestinal bleeding[434],but concern has been raised that its analgesic effects may mask the symptoms of peptic ulcer complications and may thereby increase the time to appropriate treatment. In a Danish study of patients hospitalized with peptic ulcer perforation, users of tramadol (alone or in combination with NSAIDs) had adjusted 30-day mortality rate ratios of 2.02 [95% CI 1.17-3.48] and 1.32 [95% CI 0.89-1.95], respectively, compared to patients who had used neither tramadol nor NSAIDs[433].

9 REFERENCE LIST

(1) Beijer HJ, de Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. Pharm World Sci 2002; 24(2):46-54.

(2) van der Hooft CS, Dieleman JP, Siemes C, Aarnoudse AJ, Verhamme KM, Stricker BH et al. Adverse drug reaction-related hospitalisations: a population-based cohort study. Pharmacoepidemiol Drug Saf 2008; 17(4):365-371.

(3) Sturkenboom MCJM, Dieleman JP. [Hospital admissions due to adverse drug reactions-A inventarisation. Final report]. Rotterdam: ErasmusMC; 2006.

(4) Hallas J, Harvald B, Gram LF, Grodum E, Brosen K, Haghfelt T et al. Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. J Intern Med 1990; 228(2):83-90.

(5) Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm 1992; 27(6):538.

(6) Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med 2008; 168(17):1890-1896.

(7) Van den Bemt PMLA, Egberts ACG, Leendertse A. Hospital Admissions Related to Medication (HARM). [A prospective, multi-centre research to drug related hospital admissions.-Final report]. Utrecht: Division of Pharmacoepidemiology & Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences; 2006.

(8) Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An algorithm for the operational assessment of adverse drug reactions. I. Background, description, and instructions for use. JAMA 1979; 242(7):623-632.

(9) De Smet PAGM, Denneboom W, Kramers C, Grol R. A composite screening tool for medication reviews of outpatients. General issues with concrete examples. Drugs Aging 2007; 24(9):733-760.

(10) Schneeweiss S, Hasford J, Gottler M, Hoffmann A, Riethling AK, Avorn J. Admissions caused by adverse drug events to internal medicine and emergency departments in hospitals: a longitudinal population-based study. Eur J Clin Pharmacol 2002; 58(4):285-291.

(11) Howard RL, Avery AJ, Slavenburg S, Royal S, Pipe G, Lucassen P et al. Which drugs cause preventable admissions to hospital? A systematic review. Br J Clin Pharmacol 2007; 63:136-147.

(12) Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 2004; 329(7456):15-19.

(13) Stricker BH, Psaty BM. Detection, verification, and quantification of adverse drug reactions. BMJ 2004; 329(7456):44-47.

(14) Vandenbroucke JP. When are observational studies as credible as randomised trials? Lancet 2004; 363(9422):1728-1731.

(15) Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, onso-Coello P et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336(7650):924-926.

(16) Anonymous. GRADE working group. 2010.
Ref Type: Data File

(17) Guyatt GH, Cook DJ, Jaeschke R, Pauker SG, Schunemann HJ. Grades of recommendation for antithrombotic agents: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133(6 Suppl):123S-131S.

(18) Visser LE, Graatsma HH, Stricker BH. Contraindicated NSAIDs are frequently prescribed to elderly patients with peptic ulcer disease. Br J Clin Pharmacol 2002; 53(2):183-188.

(19) van der Linden CM, Kerskes MC, Bijl AM, Maas HA, Egberts AC, Jansen PA. Represcription after adverse drug reaction in the elderly: a descriptive study. Arch Intern Med 2006; 166(15):1666-1667.

(20) Zhang M, Holman CD, Preen DB, Brameld K. Repeat adverse drug reactions causing hospitalization in older Australians: a population-based longitudinal study 1980-2003. Br J Clin Pharmacol 2007; 63(2):163-170.

(21) Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. Am J Med 1998; 105(2):91-99.

(22) Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(3 Suppl):204S-233S.

(23) Feenstra J, Heerdink ER, Grobbee DE, Stricker BH. Association of nonsteroidal anti-inflammatory drugs with first occurrence of heart failure and with relapsing heart failure: the Rotterdam Study. Arch Intern Med 2002; 162(3):265-270.

(24) Anonymous. [The Dutch Institute for Health Care improvement (CBO) guideline NSAID use and prevention of gastric damage]. Utrecht: The Dutch Institute for Health Care improvement CBO; 2003.

(25) Raynor DK, Blenkinsopp A, Knapp P, Grime J, Nicolson DJ, Pollock K et al. A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines. Health Technol Assess 2007; 11(5):iii, 1-iii160.

(26) Buurma H, De Smet PAGM, Kruijtbosch M, Egberts AC. Disease and intolerability documentation in electronic patient records. Ann Pharmacother 2005; 39(10):1640-1646.

(27) Buurma H, Schalekamp T, Egberts ACG, De Smet PAGM. Compliance with national guidelines for the management of drug-drug interactions in Dutch community pharmacies. Ann Pharmacother 2007; 41(12):2024-2031.

(28) Ashcroft DM, Parker D. Development of the Pharmacy Safety Climate Questionnaire: a principal components analysis. Qual Saf Health Care 2008; in press.

(29) Ashcroft DM, Morecroft C, Parker D, Noyce PR. Safety culture assessment in community pharmacy: development, face validity, and feasibility of the Manchester Patient Safety Assessment Framework. Qual Saf Health Care 2005; 14(6):417-421.

(30) De Smet PAGM, Dautzenberg M. Repeat prescribing: scale, problems and quality management in ambulatory care patients. Drugs 2004; 64:1779-1800.

(31) Kuijpers MA, van Marum RJ, Egberts AC, Jansen PA. Relationship between polypharmacy and underprescribing. Br J Clin Pharmacol 2008; 65(1):130-133.

(32) Denneboom W, Dautzenberg M, Grol RP, De Smet PAGM. Analysis of polypharmacy in older patients in primary care using a multidisciplinary expert panel. Br J Gen Pract 2006; 56:504-510.

(33) Cote GA, Rice JP, Bulsiewicz W, Norvell JP, Christensen K, Bobb A et al. Use of physician education and computer alert to improve targeted use of gastroprotection among NSAID users. Am J Gastroenterol 2008; 103(5):1097-1103.

(34) Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133(6 Suppl):257S-298S.

(35) Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer FJ, Vandenbroucke JP, Briet E. Optimal oral anticoagulant therapy in patients with mechanical heart valves. N Engl J Med 1995; 333(1):11-17.

(36) van der Meer FJ, Rosendaal FR, Vandenbroucke JP, Briet E. Assessment of a bleeding risk index in two cohorts of patients treated with oral anticoagulants. Thromb Haemost 1996; 76(1):12-16.

(37) Schulman S. Oral anticoagulation. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ, Seligsohn U, editors. William Hematology. 6th edition. New York: McGraw-Hill; 2001. 1777-1792.

(38) Kuijer PM, Hutten BA, Prins MH, Buller HR. Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism. Arch Intern Med 1999; 159(5):457-460.

(39) Reitsma PH, van der Heijden JF, Groot AP, Rosendaal FR, Buller HR. A C1173T dimorphism in the VKORC1 gene determines coumarin sensitivity and bleeding risk. PLoS Med 2005; 2(10):e312.

(40) Anonymous. [The Dutch Institute for Health Care improvement (CBO) guideline for the prevention of venous thromboembolic complications and arterial thrombosis] . Utrecht: The Dutch Institute for Health Care improvement CBO; 2009.

(41) Pauwe OMD. [Opinion report approach of risky medication]. Voorschoten: Federatie van Nederlandse Trombosediensten; 2008.

(42) Grand'Maison A, Charest AF, Geerts WH. Anticoagulant use in patients with chronic renal impairment. Am J Cardiovasc Drugs 2005; 5(5):291-305.

(43) Teichert M, Stricker BHC. Persoonlijke mededeling. 2007. Rotterdam, Department of Epidemiology & Biostatistics Erasmus Medical Center.
Ref Type: Data File

(44) Dreisbach AW, Japa S, Gebrekal AB, Mowry SE, Lertora JJ, Kamath BL et al. Cytochrome P4502C9 activity in end-stage renal disease. Clin Pharmacol Ther 2003; 73(5):475-477.

(45) Landefeld CS, McGuire E, III, Rosenblatt MW. A bleeding risk index for estimating the probability of major bleeding in hospitalized patients starting anticoagulant therapy. Am J Med 1990; 89(5):569-578.

(46) Penning-van Beest FJ, Geleijnse JM, van ME, Vermeer C, Rosendaal FR, Stricker BH. Lifestyle and diet as risk factors for overanticoagulation. J Clin Epidemiol 2002; 55(4):411-417.

(47) Kumar S, Haigh JR, Rhodes LE, Peaker S, Davies JA, Roberts BE et al. Poor compliance is a major factor in unstable outpatient control of anticoagulant therapy. Thromb Haemost 1989; 62(2):729-732.

(48) van der Meer FJ, Briet E, Vandenbroucke JP, Sramek DI, Versluijs MH, Rosendaal FR. The role of compliance as a cause of instability in oral anticoagulant therapy. Br J Haematol 1997; 98(4):893-900.

(49) Penning-van Beest F, Erkens J, Petersen KU, Koelz HR, Herings R. Main comedications associated with major bleeding during anticoagulant therapy with coumarins. Eur J Clin Pharmacol 2005; 61(5-6):439-444.

(50) Anonymous. [Dutch guideline for management of drug-drug interactions with coumarines]. [available at: http://www.fnt.nl/pdf/cumarine%20interactiesjuli2007.pdf [geraadpleegd op 5 dec 2007]]. 2007. Voorschoten, Federation of Dutch Thrombosis Services.
Ref Type: Data File

(51) Schalekamp T, van Geest-Daalderop JH, Kramer MH, van Holten-Verzantvoort AT, de BA. Coumarin anticoagulants and co-trimoxazole: avoid the combination rather than manage the interaction. Eur J Clin Pharmacol 2007; 63(4):335-343.

(52) Grimwade K, Swingler, G. Cotrimoxazole prophylaxis for opportunistic infections in adults with HIV. Cochrane Database Syst Rev 2003;(3):CD003108.

(53) Green H, Paul M, Vidal L, Leibovici L. Prophylaxis of Pneumocystis pneumonia in immunocompromised non-HIV-infected patients: systematic review and meta-analysis of randomized controlled trials. Mayo Clin Proc 2007; 82(9):1052-1059.

(54) Penning-van Beest FJ, van ME, Rosendaal FR, Stricker BH. Characteristics of anticoagulant therapy and comorbidity related to overanticoagulation. Thromb Haemost 2001; 86(2):569-574.

(55) ACCP guidelines. 2010. Northbrook, United States of America, American College of Chest Physicians.
Ref Type: Data File

(56) ESC Clinical Practice guidelines. 2010. Les Templiers, France, European Society of Cardiology.
Ref Type: Data File

(57) Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133(6 Suppl):160S-198S.

(58) Dentali F, Douketis JD, Lim W, Crowther M. Combined aspirin-oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease: a meta-analysis of randomized trials. Arch Intern Med 2007; 167(2):117-124.

(59) Schulman S. Clinical practice. Care of patients receiving long-term anticoagulant therapy. N Engl J Med 2003; 349(7):675-683.

(60) de Hoon JN, Thijssen HH, Beysens AJ, Van Bortel LM. No effect of short-term omeprazole intake on acenocoumarol pharmacokinetics and pharmacodynamics. Br J Clin Pharmacol 1997; 44(4):399-401.

(61) Vreeburg EM, De Vlaam-Schluter GM, Trienekens PH, Snel P, Tytgat GN. Lack of effect of omeprazole in oral acenocoumarol anticoagulant therapy. Scand J Gastroenterol 1997; 32(10):991-994.

(62) Bonow RO, Carabello BA, Chatterjee K, de LA, Jr., Faxon DP, Freed MD et al. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation 2008; 118(15):e523-e661.

(63) Salem DN, O'Gara PT, Madias C, Pauker SG. Valvular and structural heart disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133(6 Suppl):593S-629S.

(64) Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G et al. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J 2007; 28(2):230-268.

(65) Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace 2010; 12(10):1360-1420.

(66) Becker RC, Meade TW, Berger PB, Ezekowitz M, O'Connor CM, Vorchheimer DA et al. The primary and secondary prevention of coronary artery disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133(6 Suppl):776S-814S.

(67) Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation 2004; 110(9):e82-292.

(68) Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, Jr. et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Circulation 2007; 116(7):e148-e304.

(69) Van de Werf F., Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 2008; 29(23):2909-2945.

(70) Sobel M, Verhaeghe R. Antithrombotic therapy for peripheral artery occlusive disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133(6 Suppl):815S-843S.

(71) Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernandez-Aviles F et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. The Task Force for the Diagnosis and Treatment of Non-ST-

Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology. Eur Heart J 2007; 28(13):1598-1660.

(72) Kushner FG, Hand M, Smith SC, Jr., King SB, III, Anderson JL, Antman EM et al. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (updating the 2005 Guideline and 2007 Focused Update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2009; 120(22):2271-2306.

(73) Schalekamp T, Smit C, van Geest-Daalderop JH, de Vries-Goldschmeding H, de BA. Discrepancies between medication records of anticoagulation clinics and pharmacy records. Pharmacoepidemiol Drug Saf 2006; 15(11):823-828.

(74) Becquemont L. Evidence for a pharmacogenetic adapted dose of oral anticoagulant in routine medical practice. Eur J Clin Pharmacol 2008; 64(10):953-960.

(75) Anonymous. Coumadin labeling. [Available at: http://www.fda.gov/cder/foi/label/2007/009218s105lblv2.pdf [accessed Oct 5 2008]]. 2007. Rockville, Food and Drug Administration. Ref Type: Data File

(76) Flockhart DA, O'Kane D, Williams MS, Watson MS, Flockhart DA, Gage B et al. Pharmacogenetic testing of CYP2C9 and VKORC1 alleles for warfarin. Genet Med 2008; 10(2):139-150.

(77) Shurin SB, Nabel EG. Pharmacogenomics--ready for prime time? N Engl J Med 2008; 358(10):1061-1063.

(78) Stehle S, Kirchheiner J, Lazar A, Fuhr U. Pharmacogenetics of oral anticoagulants: a basis for dose individualization. Clin Pharmacokinet 2008; 47(9):565-594.

(79) Limdi NA, Veenstra DL. Warfarin pharmacogenetics. Pharmacotherapy 2008; 28(9):1084-1097.

(80) McClain MR, Palomaki GE, Piper M, Haddow JE. A rapid-ACCE review of CYP2C9 and VKORC1 alleles testing to inform warfarin dosing in adults at elevated risk for thrombotic events to avoid serious bleeding. Genet Med 2008; 10(2):89-98.

(81) Sconce E, Avery P, Wynne H, Kamali F. Vitamin K supplementation can improve stability of anticoagulation for patients with unexplained variability in response to warfarin. Blood 2007; 109(6):2419-2423.

(82) Fitzmaurice DA, Gardiner C, Kitchen S, Mackie I, Murray ET, Machin SJ. An evidence-based review and guidelines for patient self-testing and management of oral anticoagulation. Br J Haematol 2005; 131(2):156-165.

(83) Heneghan C, onso-Coello P, Garcia-Alamino JM, Perera R, Meats E, Glasziou P. Self-monitoring of oral anticoagulation: a systematic review and meta-analysis. Lancet 2006; 367(9508):404-411.

(84) Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361(12):1139-1151.

(85) Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009; 361(24):2342-2352.

(86) Crowther MA, Warkentin TE. Managing bleeding in anticoagulated patients with a focus on novel therapeutic agents. J Thromb Haemost 2009; 7 Suppl 1:107-10.:107-110.

(87) Garcia D, Libby E, Crowther MA. The new oral anticoagulants. Blood 2010; 115(1):15-20.

(88) Laine L. Review article: gastrointestinal bleeding with low-dose aspirin - what's the risk? Aliment Pharmacol Ther 2006; 24(6):897-908.

(89) Lanas A, Scheiman J. Low-dose aspirin and upper gastrointestinal damage: epidemiology, prevention and treatment. Curr Med Res Opin 2007; 23(1):163-173.

(90) Lanas A, Perez-Aisa MA, Feu F, Ponce J, Saperas E, Santolaria S et al. A nationwide study of mortality associated with hospital admission due to severe gastrointestinal events and those associated with nonsteroidal antiinflammatory drug use. Am J Gastroenterol 2005; 100(8):1685-1693.

(91) Van Oijen MGH, Dieleman JP, Laheij RJF, Sturkenboom MCJM, Jansen JBMJ, Verheugt FWA. Peptic ulcerations are related to systemic rather than local effects of low-dose aspirin. Clin Gastroenterol Hepatol 2008; accepted for ublication.

(92) CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996; 348(9038):1329-1339.

(93) Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996; 143(1-2):1-13.

(94) Lanas A, Garcia-Rodriguez LA, Arroyo MT, Gomollon F, Feu F, Gonzalez-Perez A et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. Gut 2006; 55(12):1731-1738.

(95) Ibanez L, Vidal X, Vendrell L, Moretti U, Laporte JR. Upper gastrointestinal bleeding associated with antiplatelet drugs. Aliment Pharmacol Ther 2006; 23(2):235-242.

(96) Hallas J, Dall M, Andries A, Andersen BS, Aalykke C, Hansen JM et al. Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: population based case-control study. BMJ 2006; 333(7571):726.

(97) Delaney JA, Opatrny L, Brophy JM, Suissa S. Drug drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. CMAJ 2007; 177(4):347-351.

(98) Laine L, Smith R, Min K, Chen C, Dubois RW. Systematic review: the lower gastrointestinal adverse effects of non-steroidal anti-inflammatory drugs. Aliment Pharmacol Ther 2006; 24(5):751-767.

(99) Slattery J, Warlow CP, Shorrock CJ, Langman MJ. Risks of gastrointestinal bleeding during secondary prevention of vascular events with aspirin--analysis of gastrointestinal bleeding during the UK-TIA trial. Gut 1995; 37(4):509-511.

(100) Geyer M, Stamenic I, Buhler H, Bertschinger P. [Epidemiology of gastrointestinal bleeding in the elderly]. Schweiz Rundsch Med Prax 2006; 95(19):757-765.

(101) Hernandez-Diaz S, Garcia Rodriguez LA. Cardioprotective aspirin users and their excess risk of upper gastrointestinal complications. BMC Med 2006; 4:22.

(102) Cryer B. Reducing the gastrointestinal risks of low-dose aspirin. Gastroenterology 2010; 138(1):30-33.

(103) Yeomans ND, Hawkey CJ, Brailsford W, Naesdal J. Gastroduodenal toxicity of low-dose acetylsalicylic acid: a comparison with non-steroidal anti-inflammatory drugs. Curr Med Res Opin 2009; 25(11):2785-2793.

(104) Malfertheiner P, Chan FK, McColl KE. Peptic ulcer disease. Lancet 2009; 374(9699):1449-1461.

(105) García Rodríguez LA, Hernandez-Diaz S, de Abajo FJ. Association between aspirin and upper gastrointestinal complications: systematic review of epidemiologic studies. Br J Clin Pharmacol 2001; 52(5):563-571.

(106) Serebruany VL, Steinhubl SR, Berger PB, Malinin AI, Baggish JS, Bhatt DL et al. Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials. Am J Cardiol 2005; 95(10):1218-1222.

(107) Laine L, McQuaid K. Bleeding complications related to aspirin dose. Am J Cardiol 2005; 96(7):1035-1036.

(108) McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. Am J Med 2006; 119(8):624-638.

(109) Weil J, Colin-Jones D, Langman M, Lawson D, Logan R, Murphy M et al. Prophylactic aspirin and risk of peptic ulcer bleeding. BMJ 1995; 310(6983):827-830.

(110) Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998; 351(9118):1755-1762.

(111) Cryer B, Feldman M. Effects of very low dose daily, long-term aspirin therapy on gastric, duodenal, and rectal prostaglandin levels and on mucosal injury in healthy humans. Gastroenterology 1999; 117(1):17-25.

(112) Pamukcu B. A review of aspirin resistance; definition, possible mechanisms, detection with platelet function tests, and its clinical outcomes. J Thromb Thrombolysis 2007; 23(3):213-222.

(113) Bode-Boger SM, Boger RH, Schubert M, Frolich JC. Effects of very low dose and enteric-coated acetylsalicylic acid on prostacyclin and thromboxane formation and on bleeding time in healthy subjects. Eur J Clin Pharmacol 1998; 54(9-10):707-714.

(114) Zullo A, Hassan C, Campo SM, Morini S. Bleeding peptic ulcer in the elderly: risk factors and prevention strategies. Drugs Aging 2007; 24(10):815-828.

(115) Bhatt DL, Scheiman J, Abraham NS, Antman EM, Chan FK, Furberg CD et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2008; 52(18):1502-1517.

(116) Baxter K. Stockley's Drug Interactions. A source book of interactions, their mechanisms, clinical importance and management, 8th edn. London: Pharmaceutical Press; 2008.

(117) de BA, Danhof M, Cohen AF, Magnani HN, Breimer DD. Interaction study between Org 10172, a low molecular weight heparinoid, and acetylsalicylic acid in healthy male volunteers. Thromb Haemost 1991; 66(2):202-207.

(118) Bhatt DL, Scheiman J, Abraham NS, Antman EM, Chan FK, Furberg CD et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2008; 52(18):1502-1517.

(119) Van Loenen AC. [Pharmacotherapeutic compass]. [Available at: http://www.fk.cvz.nl/ [Accessed various times in jan - aug 2010]]. 2010. Amstelveen, College voor zorgverzekeringen.
Ref Type: Data File

(120) Van Loenen AC. [Pharmacotherapeutic compass]. [Available at: http://www.fk.cvz.nl/ [Accessed various times in jan - aug 2010]]. 2010. Amstelveen, College voor zorgverzekeringen.
Ref Type: Data File

(121) Collins R, MacMahon S, Flather M, Baigent C, Remvig L, Mortensen S et al. Clinical effects of anticoagulant therapy in suspected acute myocardial infarction: systematic overview of randomised trials. BMJ 1996; 313(7058):652-659.

(122) Sorensen R, Hansen ML, Abildstrom SZ, Hvelplund A, Andersson C, Jorgensen C et al. Risk of bleeding in patients with acute myocardial infarction treated with different

combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. Lancet 2009; 374(9706):1967-1974.

(123) Khurram Z, Chou E, Minutello R, Bergman G, Parikh M, Naidu S et al. Combination therapy with aspirin, clopidogrel and warfarin following coronary stenting is associated with a significant risk of bleeding. J Invasive Cardiol 2006; 18(4):162-164.

(124) King SB, III, Smith SC, Jr., Hirshfeld JW, Jr., Jacobs AK, Morrison DA, Williams DO et al. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Writing Group to Review New Evidence and Update the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention, Writing on Behalf of the 2005 Writing Committee. Circulation 2008; 117(2):261-295.

(125) García Rodríguez LA, Barreales TL. Risk of upper gastrointestinal complications among users of traditional NSAIDs and COXIBs in the general population. Gastroenterology 2007; 132(2):498-506.

(126) Rahme E, Bardou M, Dasgupta K, Toubouti Y, Ghosn J, Barkun AN. Hospitalization for gastrointestinal bleeding associated with non-steroidal anti-inflammatory drugs among elderly patients using low-dose aspirin: a retrospective cohort study. Rheumatology (Oxford) 2007; 46(2):265-272.

(127) Catella-Lawson F, Reilly MP, Kapoor SC, Cucchiara AJ, DeMarco S, Tournier B et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. N Engl J Med 2001; 345(25):1809-1817.

(128) Anonymous. Concomitant use of Ibuprofen and Aspirin: Potential for Attenuation of the Anti-Platelet Effect of Aspirin. Food and Drug Administration Science Paper 9/8/2006. [Availabe at: http://www.fda.gov/cder/drug/infopage/ibuprofen/Science_Paper.pdf [accessed Jan 01, 2008]]. 2006. Rockville, Food and Drug Administration. Ref Type: Data File

(129) Ellison J, Dager W. Recent FDA warning of the concomitant use of aspirin and ibuprofen and the effects on platelet aggregation. Prev Cardiol 2007; 10(2):61-63.

(130) Curtis JP, Wang Y, Portnay EL, Masoudi FA, Havranek EP, Krumholz HM. Aspirin, ibuprofen, and mortality after myocardial infarction: retrospective cohort study. BMJ 2003; 327(7427):1322-1323.

(131) Garcia Rodriguez LA, Varas-Lorenzo C, Maguire A, Gonzalez-Perez A. Nonsteroidal antiinflammatory drugs and the risk of myocardial infarction in the general population. Circulation 2004; 109(24):3000-3006.

(132) Patel TN, Goldberg KC. Use of aspirin and ibuprofen compared with aspirin alone and the risk of myocardial infarction. Arch Intern Med 2004; 164(8):852-856.

(133) MacDonald TM, Wei L. Effect of ibuprofen on cardioprotective effect of aspirin. Lancet 2003; 361(9357):573-574.

(134) Kimmel SE, Berlin JA, Reilly M, Jaskowiak J, Kishel L, Chittams J et al. The effects of nonselective non-aspirin non-steroidal anti-inflammatory medications on the risk of nonfatal myocardial infarction and their interaction with aspirin. J Am Coll Cardiol 2004; 43(6):985-990.

(135) Hudson M, Baron M, Rahme E, Pilote L. Ibuprofen may abrogate the benefits of aspirin when used for secondary prevention of myocardial infarction. J Rheumatol 2005; 32(8):1589-1593.

(136) Strand V. Are COX-2 inhibitors preferable to non-selective non-steroidal anti-inflammatory drugs in patients with risk of cardiovascular events taking low-dose aspirin? Lancet 2007; 370(9605):2138-2151.

(137) Cryer B, Berlin RG, Cooper SA, Hsu C, Wason S. Double-blind, randomized, parallel, placebo-controlled study of ibuprofen effects on thromboxane B2 concentrations in aspirin-treated healthy adult volunteers. Clin Ther 2005; 27(2):185-191.

(138) Capone ML, Sciulli MG, Tacconelli S, Grana M, Ricciotti E, Renda G et al. Pharmacodynamic interaction of naproxen with low-dose aspirin in healthy subjects. J Am Coll Cardiol 2005; 45(8):1295-1301.

(139) Renda G, Tacconelli S, Capone ML, Sacchetta D, Santarelli F, Sciulli MG et al. Celecoxib, ibuprofen, and the antiplatelet effect of aspirin in patients with osteoarthritis and ischemic heart disease. Clin Pharmacol Ther 2006; 80(3):264-274.

(140) Gengo FM, Rubin L, Robson M, Rainka M, Gengo MF, Mager DE et al. Effects of ibuprofen on the magnitude and duration of aspirin's inhibition of platelet aggregation: clinical consequences in stroke prophylaxis. J Clin Pharmacol 2008; 48(1):117-122.

(141) Gladding PA, Webster MW, Farrell HB, Zeng IS, Park R, Ruijne N. The antiplatelet effect of six non-steroidal anti-inflammatory drugs and their pharmacodynamic interaction with aspirin in healthy volunteers. Am J Cardiol 2008; 101(7):1060-1063.

(142) Schuijt MP, Huntjens-Fleuren HW, de MM, Vollaard EJ. The interaction of ibuprofen and diclofenac with aspirin in healthy volunteers. Br J Pharmacol 2009; 157(6):931-934.

(143) Steinhubl SR. The use of anti-inflammatory analgesics in the patient with cardiovascular disease: what a pain. J Am Coll Cardiol 2005; 45(8):1302-1303.

(144) Le Comte M, Heersche A, Wensveen B. [New advise for drug-drug interactions]. Pharm Weekbl 2007; 142(nr.50):38.

(145) Verduijn MM, Folmer H. [The pharmacotherapeutic guideline 'pain relief' of the Dutch College of General Practitioners. Version october 2007]. [Available at: http://nhg.artsennet.nl/upload/104/standaarden/FTR/Pijnbestrijding.html [Accessed Nov 25, 2007]]. 2007. Utrecht, The Dutch College of General Practitioners. Ref Type: Data File

(146) Vonkeman HE. NSAID complications – the balance of risks. Ph.D. Thesis. Enschede: Universiteit Twente; 2007.

(147) Chan FK, Abraham NS, Scheiman JM, Laine L. Management of patients on nonsteroidal anti-inflammatory drugs: a clinical practice recommendation from the First International Working Party on Gastrointestinal and Cardiovascular Effects of Nonsteroidal Anti-inflammatory Drugs and Anti-platelet Agents. Am J Gastroenterol 2008; 103(11):2908-2918.

(148) Lanza FL, Chan FK, Quigley EM. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol 2009; 104(3):728-738.

(149) Hovestad-Witterland AHI, Klein Gunnewiek JMT, De Metz M, Vollaard EJ. [A closer look to COX-2-preferential NSAIDs. Effect of meloxicam and nabumetone on thrombosis prophylaxis with acetylsalicylic acid.]. Pharm Weekbl 2003; 138:104-107.

(150) Van Ryn J, Kink-Eiband M, Kuritsch I, Feifel U, Hanft G, Wallenstein G et al. Meloxicam does not affect the antiplatelet effect of aspirin in healthy male and female volunteers. J Clin Pharmacol 2004; 44(7):777-784.

(151) Fleuren HWHA, Klein Gunnewiek JMT, De Metz M, Vollaard EJ. [Effect of meloxicam on thromboxane production of 80 mg acetylsalicylic acid. Interaction is clinical not relevance.]. Pharm Weekbl 2005; 140:372-374.

(152) ADAPT Research Group. Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT). PLoS Clin Trials 2006; 1(7):e33.

(153) Farkouh ME, Greenberg JD, Jeger RV, Ramanathan K, Verheugt FW, Chesebro JH et al. Cardiovascular outcomes in high risk patients with osteoarthritis treated with ibuprofen, naproxen or lumiracoxib. Ann Rheum Dis 2007; 66(6):764-770.

(154) Galliard-Grigioni KS, Reinhart WH. A randomized, controlled study on the influence of acetaminophen, diclofenac, or naproxen on aspirin-induced inhibition of platelet aggregation. Eur J Pharmacol 2009; 609(1-3):96-99.

(155) Oldenhof J, Hochberg M, Schiff M, Brune K. Effect of maximum OTC doses of naproxen sodium or acetaminophen on low-dose aspirin inhibition of serum thromboxane B(2). Curr Med Res Opin 2010.

(156) Capone ML, Tacconelli S, Sciulli MG, Grana M, Ricciotti E, Minuz P et al. Clinical pharmacology of platelet, monocyte, and vascular cyclooxygenase inhibition by naproxen and low-dose aspirin in healthy subjects. Circulation 2004; 109(12):1468-1471.

(157) Hinz B, Cheremina O, Besz D, Zlotnick S, Brune K. Impact of naproxen sodium at over-the-counter doses on cyclooxygenase isoforms in human volunteers. Int J Clin Pharmacol Ther 2008; 46(4):180-186.

(158) Schiff M, Hochberg MC, Oldenhof J, Brune K. Platelet inhibitory effects of OTC doses of naproxen sodium compared with prescription dose naproxen sodium and low-dose aspirin. Curr Med Res Opin 2009; 25(10):2471-2477.

(159) Laine L, Maller ES, Yu C, Quan H, Simon T. Ulcer formation with low-dose enteric-coated aspirin and the effect of COX-2 selective inhibition: a double-blind trial. Gastroenterology 2004; 127(2):395-402.

(160) Schnitzer TJ, Burmester GR, Mysler E, Hochberg MC, Doherty M, Ehrsam E et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. Lancet 2004; 364(9435):665-674.

(161) Nielsen GL, Sørensen HT, Mellemkjoer L, Blot WJ, McLaughlin JK, Tage-Jensen U et al. Risk of hospitalization resulting from upper gastrointestinal bleeding among patients taking corticosteroids: a register-based cohort study. Am J Med 2001; 111(7):541-545.

(162) Sørensen HT, Mellemkjaer L, Blot WJ, Nielsen GL, Steffensen FH, McLaughlin JK et al. Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. Am J Gastroenterol 2000; 95(9):2218-2224.

(163) Conn HO, Blitzer BL. Nonassociation of adrenocorticosteroid therapy and peptic ulcer. N Engl J Med 1976; 294(9):473-479.

(164) Yuan Y, Tsoi K, Hunt RH. Selective serotonin reuptake inhibitors and risk of upper GI bleeding: confusion or confounding? Am J Med 2006; 119(9):719-727.

(165) de Abajo FJ, Montero D, Rodriguez LA, Madurga M. Antidepressants and risk of upper gastrointestinal bleeding. Basic Clin Pharmacol Toxicol 2006; 98(3):304-310.

(166) de Abajo FJ, Rodriguez LA, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. BMJ 1999; 319(7217):1106-1109.

(167) Dalton SO, Johansen C, Mellemkjaer L, Norgard B, Sorensen HT, Olsen JH. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. Arch Intern Med 2003; 163(1):59-64.

(168) Mackay A, Stevenson RD. Gastric ulceration induced by spironolactone. Lancet 1977; 1(8009):481.

(169) Goodman MJ. Gastric ulceration induced by spironolactone. Lancet 1977; 1(8014):752.

(170) Doll R, Langman MJ, Shawdon HH. Treatment of gastric ulcer with carbenoxolone: antagonistic effect of spironolactone. Gut 1968; 9(1):42-45.

(171) Verhamme K, Mosis G, Dieleman J, Stricker B, Sturkenboom M. Spironolactone and risk of upper gastrointestinal events: population based case-control study. BMJ 2006; 333(7563):330.

(172) Russo A, Autelitano M, Bisanti L. Spironolactone and gastrointestinal bleeding: a population based study. Pharmacoepidemiol Drug Saf 2008; 17(5):495-500.

(173) Gulmez SE, Lassen AT, Aalykke C, Dall M, Andries A, Andersen BS et al. Spironolactone use and the risk of upper gastrointestinal bleeding: a population-based case-control study. Br J Clin Pharmacol 2008; 66(2):294-299.

(174) Ng FH, Wong SY, Chang CM, Chen WH, Kng C, Lanas AI et al. High incidence of clopidogrel-associated gastrointestinal bleeding in patients with previous peptic ulcer disease. Aliment Pharmacol Ther 2003; 18(4):443-449.

(175) Lai KC, Lam SK, Chu KM, Wong BC, Hui WM, Hu WH et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. N Engl J Med 2002; 346(26):2033-2038.

(176) Chan FK, Ching JY, Hung LC, Wong VW, Leung VK, Kung NN et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. N Engl J Med 2005; 352(3):238-244.

(177) Lai KC, Chu KM, Hui WM, Wong BC, Hung WK, Loo CK et al. Esomeprazole with aspirin versus clopidogrel for prevention of recurrent gastrointestinal ulcer complications. Clin Gastroenterol Hepatol 2006; 4(7):860-865.

(178) Yeomans N, Lanas A, Labenz J, van Zanten SV, van RC, Racz I et al. Efficacy of esomeprazole (20 mg once daily) for reducing the risk of gastroduodenal ulcers associated with continuous use of low-dose aspirin. Am J Gastroenterol 2008; 103(10):2465-2473.

(179) Taha AS, McCloskey C, Prasad R, Bezlyak V. Famotidine for the prevention of peptic ulcers and oesophagitis in patients taking low-dose aspirin (FAMOUS): a phase III, randomised, double-blind, placebo-controlled trial. Lancet 2009; 374(9684):119-125.

(180) Ng FH, Wong SY, Lam KF, Chu WM, Chan P, Ling YH et al. Famotidine is inferior to pantoprazole in preventing recurrence of aspirin-related peptic ulcers or erosions. Gastroenterology 2010; 138(1):82-88.

(181) Hawkey CJ, Weinstein WM, Smalley W, Gitton X, Sallstig P, Stricker K et al. Effect of risk factors on complicated and uncomplicated ulcers in the TARGET lumiracoxib outcomes study. Gastroenterology 2007; 133(1):57-64.

(182) Leong RW. Differences in peptic ulcer between the East and the West. Gastroenterol Clin North Am 2009; 38(2):363-379.

(183) Serebruany V, Goto S. Clopidogrel and proton pump inhibitors: Gastric protection at expense of vascular benefit? Thromb Haemost 2009; 101(4):607-609.

(184) Wijns W, Kolh P, Danchin N, Di MC, Falk V, Folliguet T et al. Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2010.

(185) Silber S, Albertsson P, Aviles FF, Camici PG, Colombo A, Hamm C et al. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary

Interventions of the European Society of Cardiology. Eur Heart J 2005; 26(8):804-847.

(186) Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK et al. 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: developed in collaboration With the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians: 2007 Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction, Writing on Behalf of the 2004 Writing Committee. Circulation 2008; 117(2):296-329.

(187) Smith SC, Jr., Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation 2006; 113(19):2363-2372.

(188) Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007; 357(20):2001-2015.

(189) Halkes PH, van GJ, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. Lancet 2006; 367(9523):1665-1673.

(190) Sacco RL, Diener HC, Yusuf S, Cotton D, Ounpuu S, Lawton WA et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. N Engl J Med 2008; 359(12):1238-1251.

(191) Little SH, Massel DR. Antiplatelet and anticoagulation for patients with prosthetic heart valves. Cochrane Database Syst Rev 2003;(4):CD003464.

(192) Lanas A, Fuentes J, Benito R, Serrano P, Bajador E, Sainz R. Helicobacter pylori increases the risk of upper gastrointestinal bleeding in patients taking low-dose aspirin. Aliment Pharmacol Ther 2002; 16(4):779-786.

(193) Chan FK, Chung SC, Suen BY, Lee YT, Leung WK, Leung VK et al. Preventing recurrent upper gastrointestinal bleeding in patients with Helicobacter pylori infection who are taking low-dose aspirin or naproxen. N Engl J Med 2001; 344(13):967-973.

(194) Anonymous. Primary prevention of ulcers in patients taking aspirin or NSAIDs. Med Lett Drugs Ther 2010; 52(1333):17-19.

(195) Lanas A, Garcia-Rodriguez LA, Arroyo MT, Bujanda L, Gomollon F, Forne M et al. Effect of antisecretory drugs and nitrates on the risk of ulcer bleeding associated with nonsteroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants. Am J Gastroenterol 2007; 102(3):507-515.

(196) Lanas A, Garcia-Rodriguez LA, Arroyo MT, Bujanda L, Gomollon F, Forne M et al. Effect of antisecretory drugs and nitrates on the risk of ulcer bleeding associated with

nonsteroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants. Am J Gastroenterol 2007; 102(3):507-515.

(197) Ng FH, Lam KF, Wong SY, Chang CM, Lau YK, Yuen WC et al. Upper gastrointestinal bleeding in patients with aspirin and clopidogrel co-therapy. Digestion 2008; 77(3-4):173-177.

(198) Ng FH, Wong SY, Lam KF, Chu WM, Chan P, Ling YH et al. Famotidine is inferior to pantoprazole in preventing recurrence of aspirin-related peptic ulcers or erosions. Gastroenterology 2010; 138(1):82-88.

(199) Rostom A, Dube C, Wells G, Tugwell P, Welch V, Jolicoeur E et al. Prevention of NSAID-induced gastroduodenal ulcers. Cochrane Database Syst Rev 2002;(4):CD002296.

(200) Hooper L, Brown TJ, Elliott R, Payne K, Roberts C, Symmons D. The effectiveness of five strategies for the prevention of gastrointestinal toxicity induced by non-steroidal anti-inflammatory drugs: systematic review. BMJ 2004; 329(7472):948.

(201) Würtz M, Grove EL, Kristensen SD, Hvas AM. The antiplatelet effect of aspirin is reduced by proton pump inhibitors in patients with coronary artery disease. Heart 2010; 96(5):368-371.

(202) Adamopoulos AB, Sakizlis GN, Nasothimiou EG, Anastasopoulou I, Anastasakou E, Kotsi P et al. Do proton pump inhibitors attenuate the effect of aspirin on platelet aggregation? A randomized crossover study. J Cardiovasc Pharmacol 2009; 54(2):163-168.

(203) Kasprzak M, Kozinski M, Bielis L, Boinska J, Plazuk W, Marciniak A et al. Pantoprazole may enhance antiplatelet effect of enteric-coated aspirin in patients with acute coronary syndrome. Cardiol J 2009; 16(6):535-544.

(204) Iñarrea P, Esteva F, Cornudella R, Lanas A. Omeprazole does not interfere with the antiplatelet effect of low-dose aspirin in man. Scand J Gastroenterol 2000; 35(3):242-246.

(205) Niazi M, Andersson T, Naucler E, Sundin M, Naesdal J. Evaluation of the pharmacokinetic interaction between esomeprazole (40 mg) and acetylsalicylic acid (325 mg) in healthy volunteers. Int J Clin Pharmacol Ther 2009; 47(9):564-569.

(206) Lev EI, Ramabadran RS, Guthikonda S, Patel R, Kleiman A, Granada JF et al. Effect of ranitidine on the antiplatelet effects of aspirin in healthy human subjects. Am J Cardiol 2007; 99(1):124-128.

(207) Ali T, Roberts DN, Tierney WM. Long-term safety concerns with proton pump inhibitors. Am J Med 2009; 122(10):896-903.

(208) Saini SD, Schoenfeld P, Fendrick AM, Scheiman J. Cost-effectiveness of proton pump inhibitor cotherapy in patients taking long-term, low-dose aspirin for secondary cardiovascular prevention. Arch Intern Med 2008; 168(15):1684-1690.

(209) Pignone M. Invited commentary. Arch Intern Med 2008; 168:1691.

(210) Pezalla E, Day D, Pulliadath I. Initial assessment of clinical impact of a drug interaction between clopidogrel and proton pump inhibitors. J Am Coll Cardiol 2008; 52(12):1038-1039.

(211) Dunn SP, Macaulay TE, Brennan DM, et al. Baseline proton pump inhibitor use is associated with increased cardiovascular events with and without the use of clopidogrel in the CREDO trial. Circulation 2008; 118(Issue 18 Suppl):S815.

(212) Dunn SP, Macaulay TE, Brennan DM, et al. Baseline proton pump inhibitor use is associated with increased cardiovascular events with and without the use of clopidogrel in the CREDO trial. Circulation 2008; 118(Issue 18 Suppl):S815.

(213) Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA 2009; 301(9):937-944.

(214) Stanek EJ, Aubert RE, Flockhart DA, Kreutz RP, Yao J, Breall JA et al. A national study of the effect of individual proton pump inhibitors on cardiovascular outcomes in patients treated with clopidogrel following coronary stenting: The Clopidogrel Medco Outcomes Study. Presented at 32nd annual scientific sessions of the Society of Cardiovascular Angiography and Intervention, 6 May 2009. [Available at: www.scai.org/pdf/20090506Medcoabstract.pdf [accessed Jun 16 2009]]. 2009.
Ref Type: Data File

(215) Wang SSW, Tsai S-S, Hsu P-C, Yang C-Y, Wu D-C. Concomitant use of clopidogrel and proton pump inhibitors or cimetidine after acute myocardial infarction would increase the risk of re-infarction. Am J Gastroenterol 2009; 104(12):3116-3117.

(216) Rassen JA, Choudhry NK, Avorn J, Schneeweiss S. Cardiovascular outcomes and mortality in patients using clopidogrel with proton pump inhibitors after percutaneous coronary intervention or acute coronary syndrome. Circulation 2009; 120(23):2322-2329.

(217) O'Donoghue ML, Braunwald E, Antman EM, Murphy SA, Bates ER, Rozenman Y et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. Lancet 2009; 374(9694):989-997.

(218) Ray WA, Murray KT, Griffin MR, Chung CP, Smalley WE, Hall K et al. Outcomes with concurrent use of clopidogrel and proton-pump inhibitors: a cohort study. Ann Intern Med 2010; 152(6):337-345.

(219) Wood S. COGENT: No CV events but significant GI benefits of PPI omeprazole (Transcatheter Cardiovascular Therapeutics Meeting, September 24, 2009, San Francisco). [Available at: http://www.theheart.org/article/1007145.do [accessed Apr 17, 2010]]. 2009.
Ref Type: Data File

(220) Gilard M, Arnaud B, Cornily JC, Le GG, Lacut K, Le CG et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the

randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. J Am Coll Cardiol 2008; 51(3):256-260.

(221) Small DS, Farid NA, Payne CD, Weerakkody GJ, Li YG, Brandt JT et al. Effects of the proton pump inhibitor lansoprazole on the pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel. J Clin Pharmacol 2008; 48(4):475-484.

(222) Cuisset T, Frere C, Quilici J, Poyet R, Gaborit B, Bali L et al. Comparison of omeprazole and pantoprazole influence on a high 150-mg clopidogrel maintenance dose the PACA (Proton Pump Inhibitors And Clopidogrel Association) prospective randomized study. J Am Coll Cardiol 2009; 54(13):1149-1153.

(223) Anonymous. Clopidogrel (marketed as Plavix) and omeprazole (marketed as Prilosec) - drug interaction. [Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm190848.htm [posted Nov 11, 2009, and accessed Jan 17, 2010]]. 2009. Silver Spring, U.S. Food and Drug Administration.
Ref Type: Data File

(224) Anonymous. [Drug database of the Royal Dutch Association for the advancement of Pharmacy]. [Available at: http://kennisbank.knmp.nl/home.asp [accessed different times between october and december 2007]]. 2007. Den Haag, Koninklijke Nederlandse Maatschappij ter Bevordering der Pharmacie.
Ref Type: Data File

(225) van den Bemt BJ, Benraad HB, Rasker JJ. [Cardiovascular and gastrointestinal risks associated with selective and non-selective NSAIDs]. Ned Tijdschr Geneeskd 2007; 151(19):1062-1067.

(226) Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med 2000; 343(21):1520-8, 2.

(227) Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 2000; 284(10):1247-1255.

(228) Cannon CP, Curtis SP, FitzGerald GA, Krum H, Kaur A, Bolognese JA et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. Lancet 2006; 368(9549):1771-1781.

(229) Juni P, Rutjes AW, Dieppe PA. Are selective COX 2 inhibitors superior to traditional non steroidal anti-inflammatory drugs? BMJ 2002; 324(7349):1287-1288.

(230) Ofman JJ, MacLean CH, Straus WL, Morton SC, Berger ML, Roth EA et al. A meta-analysis of severe upper gastrointestinal complications of nonsteroidal antiinflammatory drugs. J Rheumatol 2002; 29(4):804-812.

(231) Herings RM, Goettsch WG. Inadequate prevention of NSAID-induced gastrointestinal events. Ann Pharmacother 2004; 38(5):760-763.

(232) Moride Y, Ducruet T, Boivin JF, Moore N, Perreault S, Zhao S. Prescription channeling of COX-2 inhibitors and traditional nonselective nonsteroidal anti-inflammatory drugs: a population-based case-control study. Arthritis Res Ther 2005; 7(2):R333-R342.

(233) MacDonald TM, Morant SV, Goldstein JL, Burke TA, Pettitt D. Channelling bias and the incidence of gastrointestinal haemorrhage in users of meloxicam, coxibs, and older, non-specific non-steroidal anti-inflammatory drugs. Gut 2003; 52(9):1265-1270.

(234) Chan FK, Hung LC, Suen BY, Wu JC, Lee KC, Leung VK et al. Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. N Engl J Med 2002; 347(26):2104-2110.

(235) Battistella M, Mamdami MM, Juurlink DN, Rabeneck L, Laupacis A. Risk of upper gastrointestinal hemorrhage in warfarin users treated with nonselective NSAIDs or COX-2 inhibitors. Arch Intern Med 2005; 165(2):189-192.

(236) Helin-Salmivaara A, Huttunen T, Gronroos JM, Klaukka T, Huupponen R. Risk of serious upper gastrointestinal events with concurrent use of NSAIDs and SSRIs: a case-control study in the general population. Eur J Clin Pharmacol 2007; 63(4):403-408.

(237) Helin-Salmivaara A, Huttunen T, Gronroos JM, Klaukka T, Huupponen R. Risk of serious upper gastrointestinal events with concurrent use of NSAIDs and SSRIs: a case-control study in the general population. Eur J Clin Pharmacol 2007; 63(4):403-408.

(238) Anonymous. [Drug database of the Royal Dutch Association for the advancement of Pharmacy]. [Available at: http://kennisbank.knmp.nl/home.asp [accessed different times between october and december 2007]]. 2007. Den Haag, Koninklijke Nederlandse Maatschappij ter Bevordering der Pharmacie. Ref Type: Data File

(239) Laporte JR, Ibanez L, Vidal X, Vendrell L, Leone R. Upper gastrointestinal bleeding associated with the use of NSAIDs: newer versus older agents. Drug Saf 2004; 27(6):411-420.

(240) Ashworth NL, Peloso PM, Muhajarine N, Stang M. Risk of hospitalization with peptic ulcer disease or gastrointestinal hemorrhage associated with nabumetone, Arthrotec, diclofenac, and naproxen in a population based cohort study. J Rheumatol 2005; 32(11):2212-2217.

(241) Hippisley-Cox J, Coupland C, Logan R. Risk of adverse gastrointestinal outcomes in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. BMJ 2005; 331(7528):1310-1316.

(242) Cryer B. A COX-2-specific inhibitor plus a proton-pump inhibitor: is this a reasonable approach to reduction in NSAIDs' GI toxicity? Am J Gastroenterol 2006; 101(4):711-713.

(243) Swift GL, Rhodes J. Are non-steroidal anti-inflammatory drugs always necessary? A general practice survey. Br J Clin Pract 1992; 46(2):92-94.

(244) Ray WA, Stein CM, Byrd V, Shorr R, Pichert JW, Gideon P et al. Educational program for physicians to reduce use of non-steroidal anti-inflammatory drugs among community-dwelling elderly persons: a randomized controlled trial. Med Care 2001; 39(5):425-435.

(245) Stein CM, Griffin MR, Taylor JA, Pichert JW, Brandt KD, Ray WA. Educational program for nursing home physicians and staff to reduce use of non-steroidal anti-inflammatory drugs among nursing home residents: a randomized controlled trial. Med Care 2001; 39(5):436-445.

(246) March L, Irwig L, Schwarz J, Simpson J, Chock C, Brooks P. n of 1 trials comparing a non-steroidal anti-inflammatory drug with paracetamol in osteoarthritis. BMJ 1994; 309(6961):1041-1045.

(247) Rostom A, Muir K, Dube C, Jolicoeur E, Boucher M, Joyce J et al. Gastrointestinal safety of cyclooxygenase-2 inhibitors: a Cochrane Collaboration systematic review. Clin Gastroenterol Hepatol 2007; 5(7):818-28, 828.

(248) Leontiadis GI, Sreedharan A, Dorward S, Barton P, Delaney B, Howden CW et al. Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding. Health Technol Assess 2007; 11(51):1-164.

(249) Vergara M, Catalan M, Gisbert JP, Calvet X. Meta-analysis: role of Helicobacter pylori eradication in the prevention of peptic ulcer in NSAID users. Aliment Pharmacol Ther 2005; 21(12):1411-1418.

(250) de Leest HT, Steen KS, Lems WF, Bijlsma JW, van de Laar MA, Huisman AM et al. Eradication of Helicobacter pylori does not reduce the incidence of gastroduodenal ulcers in patients on long-term NSAID treatment: double-blind, randomized, placebo-controlled trial. Helicobacter 2007; 12(5):477-485.

(251) Goldstein JL, Howard KB, Walton SM, McLaughlin TP, Kruzikas DT. Impact of adherence to concomitant gastroprotective therapy on nonsteroidal-related gastroduodenal ulcer complications. Clin Gastroenterol Hepatol 2006; 4(11):1337-1345.

(252) Abraham NS, Hartman C, Castillo D, Richardson P, Smalley W. Effectiveness of national provider prescription of PPI gastroprotection among elderly NSAID users. Am J Gastroenterol 2008; 103(2):323-332.

(253) Lazzaroni M, Porro GB. Management of NSAID-induced gastrointestinal toxicity: focus on proton pump inhibitors. Drugs 2009; 69(1):51-69.

(254) Abraham NS, Hartman C, Hasche J. Reduced hospitalization cost for upper gastrointestinal events that occur among elderly veterans who are gastroprotected. Clin Gastroenterol Hepatol 2010; 8(4):350-356.

(255) VAN Soest EM, Sturkenboom MC, Dieleman JP, Verhamme KM, Siersema PD, Kuipers EJ. Adherence to gastroprotection and the risk of NSAID-related upper gastrointestinal ulcers and haemorrhage. Aliment Pharmacol Ther 2007; 26(2):265-275.

(256) Sturkenboom MC, Burke TA, Tangelder MJ, Dieleman JP, Walton S, Goldstein JL. Adherence to proton pump inhibitors or H2-receptor antagonists during the use of non-steroidal anti-inflammatory drugs. Aliment Pharmacol Ther 2003; 18(11-12):1137-1147.

(257) Chan FK, Wong VW, Suen BY, Wu JC, Ching JY, Hung LC et al. Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. Lancet 2007; 369(9573):1621-1626.

(258) Anonymous. Public CHMP assessment report for medicinal products containing non-selective non steroidal antiinflammatory drugs (NSAIDs). Procedure No. EMEA/H/A-5.3/800 under Article 5(3) of Regulation (EC) No 726/2004. [Available at: http://www.emea.europa.eu/pdfs/human/opiniongen/44213006en.pdf [accessed Dec 16, 2007]]. 2006. London, European Medicines Agency (EMEA). Ref Type: Data File

(259) Anonymous. Questions and Answers on COX-2 Inhibitors. Doc. Ref. EMEA/62978/2005. [available at: http://www.ema.europa.eu/htms/human/press/cox2QA.htm#Q6]. 2007. London, European Medicines Agency (EMEA). Ref Type: Data File

(260) Andersohn F, Schade R, Suissa S, Garbe E. Cyclooxygenase-2 selective nonsteroidal anti-inflammatory drugs and the risk of ischemic stroke: a nested case-control study. Stroke 2006; 37(7):1725-1730.

(261) Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ 2006; 332(7553):1302-1308.

(262) McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. JAMA 2006; 296(13):1633-1644.

(263) Hernandez-Diaz S, Varas-Lorenzo C, Garcia Rodriguez LA. Non-steroidal antiinflammatory drugs and the risk of acute myocardial infarction. Basic Clin Pharmacol Toxicol 2006; 98(3):266-274.

(264) Lai KC, Chu KM, Hui WM, Wong BC, Hu WH, Wong WM et al. Celecoxib compared with lansoprazole and naproxen to prevent gastrointestinal ulcer complications. Am J Med 2005; 118(11):1271-1278.

(265) Goldstein JL, Cryer B, Amer F, Hunt B. Celecoxib plus aspirin versus naproxen and lansoprazole plus aspirin: a randomized, double-blind, endoscopic trial. Clin Gastroenterol Hepatol 2007; 5(10):1167-1174.

(266) Goldstein JL, Johanson JF, Hawkey CJ, Suchower LJ, Brown KA. Clinical trial: healing of NSAID-associated gastric ulcers in patients continuing NSAID therapy - a randomized study comparing ranitidine with esomeprazole. Aliment Pharmacol Ther 2007; 26(8):1101-1111.

(267) Chan FKL. Proton-pump inhibitors in peptic ulcer disease. Lancet 2008; 372:1198-1200.

(268) Chan FK, Hung LC, Suen BY, Wong VW, Hui AJ, Wu JC et al. Celecoxib versus diclofenac plus omeprazole in high-risk arthritis patients: results of a randomized double-blind trial. Gastroenterology 2004; 127(4):1038-1043.

(269) Scheiman JM, Yeomans ND, Talley NJ, Vakil N, Chan FK, Tulassay Z et al. Prevention of ulcers by esomeprazole in at-risk patients using non-selective NSAIDs and COX-2 inhibitors. Am J Gastroenterol 2006; 101(4):701-710.

(270) Fries JF, Bruce B. Rates of serious gastrointestinal events from low dose use of acetylsalicylic acid, acetaminophen, and ibuprofen in patients with osteoarthritis and rheumatoid arthritis. J Rheumatol 2003; 30(10):2226-2233.

(271) Tarone RE, Blot WJ, McLaughlin JK. Nonselective nonaspirin nonsteroidal anti-inflammatory drugs and gastrointestinal bleeding: relative and absolute risk estimates from recent epidemiologic studies. Am J Ther 2004; 11(1):17-25.

(272) Lewis JD, Kimmel SE, Localio AR, Metz DC, Farrar JT, Nessel L et al. Risk of serious upper gastrointestinal toxicity with over-the-counter nonaspirin nonsteroidal anti-inflammatory drugs. Gastroenterology 2005; 129(6):1865-1874.

(273) Biskupiak JE, Brixner DI, Howard K, Oderda GM. Gastrointestinal complications of over-the-counter nonsteroidal antiinflammatory drugs. J Pain Palliat Care Pharmacother 2006; 20(3):7-14.

(274) Pigeon P, Robillard E, Clarke GD, Burnett I. A prospective survey to compare the suitability profiles of over-the-counter ibuprofen and paracetamol use in a French general practitioner-controlled population. Clin Drug Investig 2006; 26(10):575-581.

(275) Tent M. [Even I was suprised by the 'General Status' of ibuprofen 200mg]. Pharm Weekbl 2010; 36:16-19.

(276) Anonymous. Appendix to motivation for classification system of legal status of supply for antiinflammatories (NSAIDs) and acetylsalicylic acid, defined by the MEB on 2 July 2009. 2010. The Hague, The Netherlands, Medicines Evaluation Board. Ref Type: Data File

(277) Kalksma R, Leemhuis MP. Hyponatriëmie bij gebruik van thiazidediuretica: let op combinaties van geneesmiddelen die dit effect versterken. Ned Tijdschr Geneeskd 2002; 146(33):1521-1525.

(278) Sharabi Y, Illan R, Kamari Y, Cohen H, Nadler M, Messerli FH et al. Diuretic induced hyponatraemia in elderly hypertensive women. J Hum Hypertens 2002; 16(9):631-635.

(279) Chow KM, Szeto CC, Wong TY, Leung CB, Li PK. Risk factors for thiazide-induced hyponatraemia. QJM 2003; 96(12):911-917.

(280) Clayton JA, Rodgers S, Blakey J, Avery A, Hall IP. Thiazide diuretic prescription and electrolyte abnormalities in primary care. Br J Clin Pharmacol 2006; 61(1):87-95.

(281) Friedman E, Shadel M, Halkin H, Farfel Z. Thiazide-induced hyponatremia. Reproducibility by single dose rechallenge and an analysis of pathogenesis. Ann Intern Med 1989; 110(1):24-30.

(282) Adrogué HJ, Madias NE. Hyponatremia. N Engl J Med 2000; 342(21):1581-1589 (see also correspondence in N Engl J Med 2000;343:886-8).

(283) Fourlanos S, Greenberg P. Managing drug-induced hyponatraemia in adults. Aust Prescriber 2003; 26:114-117.

(284) Kirby D, Harrigan S, Ames D. Hyponatraemia in elderly psychiatric patients treated with Selective Serotonin Reuptake Inhibitors and venlafaxine: a retrospective controlled study in an inpatient unit. Int J Geriatr Psychiatry 2002; 17(3):231-237.

(285) Rosner MH. Severe hyponatremia associated with the combined use of thiazide diuretics and selective serotonin reuptake inhibitors. Am J Med Sci 2004; 327(2):109-111.

(286) Jacob S, Spinler SA. Hyponatremia associated with selective serotonin-reuptake inhibitors in older adults. Ann Pharmacother 2006; 40(9):1618-1622.

(287) Roxanas M, Hibbert E, Field M. Venlafaxine hyponatraemia: incidence, mechanism and management. Aust N Z J Psychiatry 2007; 41(5):411-418.

(288) De Gier JJ. [Comment on drug monitoring 2007/2008]. Houten: Health Base; 2007.

(289) Rutten FH, Walma EP, Kruizinga GI, Bakx HCA, Van Lieshout J. [The practice guideline 'heart failure'from the Dutch College of General Practitioners]. Huisarts Wet 2005; 48(2):64-76.

(290) Schnieders M, Kolb G. Exsikkose im Alter. Med Klin (Munich) 2004; 99(8):453-460.

(291) Siegel D, Hulley SB, Black DM, Cheitlin MD, Sebastian A, Seeley DG et al. Diuretics, serum and intracellular electrolyte levels, and ventricular arrhythmias in hypertensive men. JAMA 1992; 267(8):1083-1089.

(292) Siscovick DS, Raghunathan TE, Psaty BM, Koepsell TD, Wicklund KG, Lin X et al. Diuretic therapy for hypertension and the risk of primary cardiac arrest. N Engl J Med 1994; 330(26):1852-1857.

(293) Hoes AW, Grobbee DE, Lubsen J, Man in 't Veld AJ, van der DE, Hofman A. Diuretics, beta-blockers, and the risk for sudden cardiac death in hypertensive patients. Ann Intern Med 1995; 123(7):481-487.

(294) Franse LV, Pahor M, Di BM, Somes GW, Cushman WC, Applegate WB. Hypokalemia associated with diuretic use and cardiovascular events in the Systolic Hypertension in the Elderly Program. Hypertension 2000; 35(5):1025-1030.

(295) Greenberg A. Diuretic complications. Am J Med Sci 2000; 319(1):10-24.

(296) Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr. et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003; 42(6):1206-1252.

(297) Papademetriou V. Diuretics, hypokalemia, and cardiac arrhythmia: a 20-year controversy. J Clin Hypertens (Greenwich) 2006; 8(2):86-92.

(298) Anonymous. [The Dutch College of General Practitioners practice guideline 'cardiovascular risk management']. [Available at: http://nhg.artsennet.nl/uri/?uri=AMGATE_6059_104_TICH_R1785801378709573 [accessed Nov 4, 2007]]. 2006. Utrecht, The Dutch College of General Practitioners.
Ref Type: Data File

(299) Anonymous. [The Dutch Institute for Health Care improvement (CBO) guideline 'cardiovascular risk management']. [Available at http://www.cbo.nl/product/richtlijnen/folder20021023121843/rl_cvrm_2006.pdf [accessed Nov 4, 2007]]. 2006. Utrecht, The Dutch Institute for Health Care improvement (CBO) and the Dutch Society of General Practitioners.
Ref Type: Data File

(300) Knight EL, Avorn J. Quality indicators for appropriate medication use in vulnerable elders. Ann Intern Med 2001; 135(8 Pt 2):703-710.

(301) Van Loenen AC. [Pharmacotherapeutic compass]. [Available at: http://www.fk.cvz.nl/ [Accessed various times in Oct - Dec 2007]]. 2007. Amstelveen, College voor zorgverzekeringen.
Ref Type: Data File

(302) Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. N Engl J Med 2004; 351(6):585-592.

(303) Reardon LC, Macpherson DS. Hyperkalemia in outpatients using angiotensin-converting enzyme inhibitors. How much should we worry? Arch Intern Med 1998; 158(1):26-32.

(304) Raebel MA, McClure DL, Simon SR, Chan KA, Feldstein A, Andrade SE et al. Laboratory monitoring of potassium and creatinine in ambulatory patients receiving angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Pharmacoepidemiol Drug Saf 2007; 16(1):55-64.

(305) Verhave JC, Kramers C, Wetzels JFM. [More accurate impression of renal function. New formula leads to better estimates.]. Pharm Weekbl 2007; 142(No.40):18-21+56.

(306) Apperloo JJ, Gerlag PG, Beerenhout CH, Vader HL. [Estimating renal function based on creatinine clearance: application of different formulas and correction for obese patients]. Ned Tijdschr Geneeskd 2007; 151(18):1016-1023.

(307) Rosa RM, Silva P, Young JB, Landsberg L, Brown RS, Rowe JW et al. Adrenergic modulation of extrarenal potassium disposal. N Engl J Med 1980; 302(8):431-434.

(308) Reid JL, Whyte KF, Struthers AD. Epinephrine-induced hypokalemia: the role of beta adrenoceptors. Am J Cardiol 1986; 57(12):23F-27F.

(309) Anonymous. Rasilez: summary of product characteristics. [Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000780/WC500047010.pdf [accessed May 08, 2010]]. 2007. London, European Medicines Agency.
Ref Type: Data File

(310) Chrysant SG, Murray AV, Hoppe UC, Dattani D, Patel S, Hsu H et al. Long-term safety, tolerability and efficacy of aliskiren in combination with valsartan in patients with hypertension: a 6-month interim analysis. Curr Med Res Opin 2008; 24(4):1039-1047.

(311) Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK. Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med 2008; 358(23):2433-2446.

(312) Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 2004; 351(6):543-551.

(313) Raebel MA, McClure DL, Chan KA, Simon SR, Feldstein AC, Lafata JE et al. Laboratory evaluation of potassium and creatinine among ambulatory patients prescribed spironolactone: are we monitoring for hyperkalemia? Ann Pharmacother 2007; 41(2):193-200.

(314) Bruggink-André de la Porte PW, Lok DJ, van Veldhuisen DJ, van Wijngaarden J, Cornel JH, Zuithoff NP et al. Added value of a physician-and-nurse-directed heart failure clinic: results from the Deventer-Alkmaar heart failure study. Heart 2007; 93(7):819-825.

(315) Bruggink-André de la Porte PW, Lok DJ, van WJ, Cornel JH, Pruijsers-Lamers D, van Veldhuisen DJ et al. Heart failure programmes in countries with a primary care-based health care system. Are additional trials necessary? Design of the DEAL-HF study. Eur J Heart Fail 2005; 7(5):910-920.

(316) Blue L, Lang E, McMurray JJ, Davie AP, McDonagh TA, Murdoch DR et al. Randomised controlled trial of specialist nurse intervention in heart failure. BMJ 2001; 323(7315):715-718.

(317) Murchie P, Campbell NC, Ritchie LD, Simpson JA, Thain J. Secondary prevention clinics for coronary heart disease: four year follow up of a randomised controlled trial in primary care. BMJ 2003; 326(7380):84.

(318) Ducharme A, Doyon O, White M, Rouleau JL, Brophy JM. Impact of care at a multidisciplinary congestive heart failure clinic: a randomized trial. CMAJ 2005; 173(1):40-45.

(319) Anonymous. [The Dutch Institute for Health Care improvement (CBO) guideline 'heart failure']. 2002. Utrecht, The Netherlands Society of Cardiology. Ref Type: Data File

(320) Palmer BF. Renal dysfunction complicating the treatment of hypertension. N Engl J Med 2002; 347(16):1256-1261.

(321) Bleumink GS, Feenstra J, Sturkenboom MC, Stricker BH. Nonsteroidal anti-inflammatory drugs and heart failure. Drugs 2003; 63(6):525-534.

(322) Kalra PA, Kumwenda M, MacDowall P, Roland MO. Questionnaire study and audit of use of angiotensin converting enzyme inhibitor and monitoring in general practice: the need for guidelines to prevent renal failure. BMJ 1999; 318(7178):234-237.

(323) Huerta C, Castellsague J, Varas-Lorenzo C, Garcia Rodriguez LA. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. Am J Kidney Dis 2005; 45(3):531-539.

(324) Schneider V, Levesque LE, Zhang B, Hutchinson T, Brophy JM. Association of selective and conventional nonsteroidal antiinflammatory drugs with acute renal failure: A population-based, nested case-control analysis. Am J Epidemiol 2006; 164(9):881-889.

(325) Gooch K, Culleton BF, Manns BJ, Zhang J, Alfonso H, Tonelli M et al. NSAID use and progression of chronic kidney disease. Am J Med 2007; 120(3):280-287.

(326) Henry D, Page J, Whyte I, Nanra R, Hall C. Consumption of non-steroidal anti-inflammatory drugs and the development of functional renal impairment in elderly subjects. Results of a case-control study. Br J Clin Pharmacol 1997; 44(1):85-90.

(327) Anonymous. [The Dutch College of General Practitioners practice guideline 'arthritis']. 2009. Utrecht, the Netherlands, Nederlandse huisartsengenootschap. Ref Type: Data File

(328) Bouvy ML, Heerdink ER, Hoes AW, Leufkens HG. Effects of NSAIDs on the incidence of hospitalisations for renal dysfunction in users of ACE inhibitors. Drug Saf 2003; 26(13):983-989.

(329) Thomas MC. Diuretics, ACE inhibitors and NSAIDs - the triple whammy. Med J Aust 2000; 172(4):184-185.

(330) Loboz KK, Shenfield GM. Drug combinations and impaired renal function -- the 'triple whammy'. Br J Clin Pharmacol 2005; 59(2):239-243.

(331) Boyd IW, Mathew TH, Thomas MC. COX-2 inhibitors and renal failure: the triple whammy revisited. Med J Aust 2000; 173(5):274.

(332) Perazella MA. Drug-induced renal failure: update on new medications and unique mechanisms of nephrotoxicity. Am J Med Sci 2003; 325(6):349-362.

(333) Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med 2000; 160(5):685-693.

(334) Perez-Ruiz F, Calabozo M, Herrero-Beites AM, Garcia-Erauskin G, Pijoan JI. Improvement of renal function in patients with chronic gout after proper control of hyperuricemia and gouty bouts. Nephron 2000; 86(3):287-291.

(335) Edwards NL. Case 9: initiation of urate-lowering therapy for advanced gout complicated by chronic renal insufficiency. Am J Med 2006; 119(11 Suppl 1):S29-S31.

(336) Winzenberg T, Zochling J. Colchicine--what is its place in the management of acute gout? Aust Fam Physician 2007; 36(7):529-530.

(337) Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognized public health problem. Arch Intern Med 2000; 160(6):777-784.

(338) Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. J Am Geriatr Soc 1999; 47(1):30-39.

(339) Ensrud KE, Blackwell T, Mangione CM, Bowman PJ, Bauer DC, Schwartz A et al. Central nervous system active medications and risk for fractures in older women. Arch Intern Med 2003; 163(8):949-957.

(340) Daal JO, Van Lieshout JJ. [Elderly and drugs:dizziness and falls]. Geneesmiddelenbulletin 2003; 37(nr.7).

(341) Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. J Am Geriatr Soc 1999; 47(1):40-50.

(342) Ziere G, Dieleman JP, Hofman A, Pols HA, van der Cammen TJ, Stricker BH. Polypharmacy and falls in the middle age and elderly population. Br J Clin Pharmacol 2006; 61(2):218-223.

(343) Anonymous. [The Dutch Institute for Health Care improvement (CBO) guideline 'to prevent accidental falls in elderly']. Utrecht: The Dutch Institute for Health Care improvement CBO; 2004.

(344) Ziere G. Risk factors for falls and fall-related fractures in the elderly. Ph.D. thesis. Rotterdam: Erasmus University; 2007.

(345) Mannesse CK, Derkx FH, de Ridder MA, Man in 't Veld AJ, van der Cammen TJ. Contribution of adverse drug reactions to hospital admission of older patients. Age Ageing 2000; 29(1):35-39.

(346) Weiner DK, Hanlon JT, Studenski SA. Effects of central nervous system polypharmacy on falls liability in community-dwelling elderly. Gerontology 1998; 44(4):217-221.

(347) Cumming RG, Le Couteur DG. Benzodiazepines and risk of hip fractures in older people: a review of the evidence. CNS Drugs 2003; 17(11):825-837.

(348) Herings RM, Stricker BH, de Boer A, Bakker A, Sturmans F. Benzodiazepines and the risk of falling leading to femur fractures. Dosage more important than elimination half-life. Arch Intern Med 1995; 155(16):1801-1807.

(349) Wang PS, Bohn RL, Glynn RJ, Mogun H, Avorn J. Hazardous benzodiazepine regimens in the elderly: effects of half-life, dosage, and duration on risk of hip fracture. Am J Psychiatry 2001; 158(6):892-898.

(350) Abrahamowicz M, Bartlett G, Tamblyn R, du BR. Modeling cumulative dose and exposure duration provided insights regarding the associations between benzodiazepines and injuries. J Clin Epidemiol 2006; 59(4):393-403.

(351) Wagner AK, Zhang F, Soumerai SB, Walker AM, Gurwitz JH, Glynn RJ et al. Benzodiazepine use and hip fractures in the elderly: who is at greatest risk? Arch Intern Med 2004; 164(14):1567-1572.

(352) Landi F, Onder G, Cesari M, Barillaro C, Russo A, Bernabei R. Psychotropic medications and risk for falls among community-dwelling frail older people: an observational study. J Gerontol A Biol Sci Med Sci 2005; 60(5):622-626.

(353) Gillespie LD, Gillespie WJ, Robertson MC, Lamb SE, Cumming RG, Rowe BH. Interventions for preventing falls in elderly people. Cochrane Database Syst Rev 2003;(4):CD000340.

(354) Campbell AJ, Robertson MC, Gardner MM, Norton RN, Buchner DM. Psychotropic medication withdrawal and a home-based exercise program to prevent falls: a randomized, controlled trial. J Am Geriatr Soc 1999; 47(7):850-853.

(355) Van der Velde N, Stricker BH, Pols HA, van der Cammen TJ. Risk of falls after withdrawal of fall-risk-increasing drugs: a prospective cohort study. Br J Clin Pharmacol 2006.

(356) Knuistingh Neven A, Lucassen PLBJ, Bonsema K, Teunissen H, Verduijn MM, Bouma M. [The practice guideline 'sleep disorders and tranquillizers (first revision)] of the Dutch College of General Practitioners. Huisarts Wet 2005; 48:402-415.

(357) Gorgels WJ, Oude Voshaar RC, Mol AJ, van de Lisdonk EH, van Balkom AJ, van den Hoogen HJ et al. Discontinuation of long-term benzodiazepine use by sending a letter to users in family practice: a prospective controlled intervention study. Drug Alcohol Depend 2005; 78(1):49-56.

(358) Oude Voshaar RC, Gorgels WJ, Mol AJ, Couvee JE, van Balkom AJ, Zitman FG. Behandelmethoden om langdurig benzodiazepinegebruik te staken. Ned Tijdschr Geneeskd 2001; 145(28):1347-1350.

(359) Ten Wolde GB. Computer-gegenereerde patiëntenvoorlichting gericht op discontinuering van chronisch benzodiazepinegebruik. Leiden: Universiteit Leiden; 2005.

(360) Haumschild MJ, Karfonta TL, Haumschild MS, Phillips SE. Clinical and economic outcomes of a fall-focused pharmaceutical intervention program. Am J Health Syst Pharm 2003; 60(10):1029-1032.

(361) van Staa TP. The pathogenesis, epidemiology and management of glucocorticoid-induced osteoporosis. Calcif Tissue Int 2006; 79(3):129-137.

(362) van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. J Bone Miner Res 2000; 15(6):993-1000.

(363) van Staa TP, Geusens P, Pols HA, de Laet C, Leufkens HG, Cooper C. A simple score for estimating the long-term risk of fracture in patients using oral glucocorticoids. QJM 2005; 98(3):191-198.

(364) van Staa TP, Leufkens HG, Cooper C. Utility of medical and drug history in fracture risk prediction among men and women. Bone 2002; 31(4):508-514.

(365) De Vries F, Bracke M, Leufkens HG, Lammers JW, Cooper C, van Staa TP. Fracture risk with intermittent high-dose oral glucocorticoid therapy. Arthritis Rheum 2007; 56(1):208-214.

(366) Anonymous. [The Dutch Institute for Health Care improvement (CBO) guideline 'Osteoporosis' (second revision)]. Utrecht: The Dutch Institute for Health Care improvement CBO; 2002.

(367) Anonymous. [The Dutch Institute for Health Care improvement (CBO) guideline 'Osteoporosis' (second revision)]. Utrecht: The Dutch Institute for Health Care improvement CBO; 2002.

(368) Elders PJM, Leusink GL, Graafmans WC, Bolhuis AP, Van der Spoel OP, Van Keimpema JC et al. [The practice guideline 'Osteoporosis' of the Dutch College of General Practitioners.(First revision)]. Huisarts Wet 2005; 48:559-570.

(369) Veitch PC, Clifton-Bligh RJ. Long-acting sulfonylureas -- long-acting hypoglycaemia. Med J Aust 2004; 180(2):84-85.

(370) Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. Arch Intern Med 1997; 157(15):1681-1686.

(371) van Staa T, Abenhaim L, Monette J. Rates of hypoglycemia in users of sulfonylureas. J Clin Epidemiol 1997; 50(6):735-741.

(372) Stahl M, Berger W. Higher incidence of severe hypoglycaemia leading to hospital admission in Type 2 diabetic patients treated with long-acting versus short-acting sulphonylureas. Diabet Med 1999; 16(7):586-590.

(373) Holstein A, Plaschke A, Ptak M, Egberts EH, El-Din J, Brockmoller J et al. Association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycaemic agents. Br J Clin Pharmacol 2005; 60(1):103-106.

(374) Denneboom W, De Smet PAGM, Stricker BHC. Drug-induced hypoglycaemia in elderly users of antidiabetic agents. Incidence and risk factors. In: Denneboom W, editor. Improving medication safety in the elderly. Ph.D. Thesis. Nijmegen: Radboud University; 2007.

(375) Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. JAMA 2003; 289(13):1652-1658.

(376) Rutten GEHM, De Grauw WJC, Nijpels G, Goudswaard AN, Uitewaal PJM, Van der Does EE et al. [The practice guideline 'Diabetes mellitus type 2' of the Dutch College of General Practitioners (Second revision)]. Huisarts Wet 2006; 49:137-152.

(377) Vingerhoets RW, van Marum RJ, Jansen PA. [The Beers List as an aid to prevent adverse drug reactions in elderly patients]. Ned Tijdschr Geneeskd 2005; 149(38):2099-2103.

(378) Niewoehner DE, Erbland ML, Deupree RH, Collins D, Gross NJ, Light RW et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. N Engl J Med 1999; 340(25):1941-1947.

(379) Gurwitz JH, Bohn RL, Glynn RJ, Monane M, Mogun H, Avorn J. Glucocorticoids and the risk for initiation of hypoglycemic therapy. Arch Intern Med 1994; 154(1):97-101.

(380) Braithwaite SS, Barr WG, Rahman A, Quddusi S. Managing diabetes during glucocorticoid therapy. How to avoid metabolic emergencies. Postgrad Med 1998; 104(5):163-166, 171, 175-6.

(381) Uzu T, Harada T, Sakaguchi M, Kanasaki M, Isshiki K, Araki S et al. Glucocorticoid-induced diabetes mellitus: prevalence and risk factors in primary renal diseases. Nephron Clin Pract 2007; 105(2):c54-c57.

(382) Hoogwerf B, Danese RD. Drug selection and the management of corticosteroid-related diabetes mellitus. Rheum Dis Clin North Am 1999; 25(3):489-505.

(383) Palatnik A, Kates R. Bradycardia and medications: identify the dangerous pace. Nurs Manage 2003; 34(6):56A-56F.

(384) Crouch MA, Limon L, Cassano AT. Clinical relevance and management of drug-related QT interval prolongation. Pharmacotherapy 2003; 23(7):881-908.

(385) Aarnoudse AL, Dieleman JP, Stricker BH. Age- and gender-specific incidence of hospitalisation for digoxin intoxication. Drug Saf 2007; 30(5):431-436.

(386) Shapiro VW, Podrazik P. Undiagnosed hypothyroidism: a risk factor for digoxin toxicity. Am J Emerg Med 1993; 11(6):670-671.

(387) Pahor M, Guralnik JM, Gambassi G, Bernabei R, Carosella L, Carbonin P. The impact of age on risk of adverse drug reactions to digoxin. For The Gruppo Italiano di Farmacovigilanza nell' Anziano. J Clin Epidemiol 1993; 46(11):1305-1314.

(388) Abad-Santos F, Carcas AJ, Ibanez C, Frias J. Digoxin level and clinical manifestations as determinants in the diagnosis of digoxin toxicity. Ther Drug Monit 2000; 22(2):163-168.

(389) Steiness E, Olesen KH. Cardiac arrhythmias induced by hypokalaemia and potassium loss during maintenance digoxin therapy. Br Heart J 1976; 38(2):167-172.

(390) Steiness E. Suppression of renal excretion of digoxin in hypokalemic patients. Clin Pharmacol Ther 1978; 23(5):511-514.

(391) Magnani B, Malini PL. Cardiac glycosides. Drug interactions of clinical significance. Drug Saf 1995; 12(2):97-109.

(392) Campbell TJ, MacDonald PS. Digoxin in heart failure and cardiac arrhythmias. Med J Aust 2003; 179(2):98-102.

(393) Yang T, Roden DM. Extracellular potassium modulation of drug block of IKr. Implications for torsade de pointes and reverse use-dependence. Circulation 1996; 93(3):407-411.

(394) Anonymous. [State of the health care 2004. Patient safety: The application of medicines and medical appliances in care institutions and at home]. Den Haag: Inspectie voor de Gezondheidszorg, Staatstoezicht op de Volksgezondheid; 2004.

(395) Panchal SJ, Muller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. Int J Clin Pract 2007; 61(7):1181-1187.

(396) Schoorl J, Zylicz Z. [Laxative policy for terminal patients ineffective]. Ned Tijdschr Geneeskd 1997; 141(17):823-826.

(397) Max EK, Hernandez JJ, Sturpe DA, Zuckerman IH. Prophylaxis for opioid-induced constipation in elderly long-term care residents: a cross-sectional study of Medicare beneficiaries. Am J Geriatr Pharmacother 2007; 5(2):129-136.

(398) Swegle JM, Logemann C. Management of common opioid-induced adverse effects. Am Fam Physician 2006; 74(8):1347-1354.

(399) Bouvy ML, Buurma H, Egberts TC. Laxative prescribing in relation to opioid use and the influence of pharmacy-based intervention. J Clin Pharm Ther 2002; 27(2):107-110.

(400) Anonymous. [Care for opiate users may be better]. Pharm Weekbl 2004; 139:225.

(401) Dik E, Diepenmaat B. [Suggestion for therapy improvement. Addition of laxatives to morphine related drugs]. Pharm Weekbl 1999; 134:1348-1352.

(402) Cole MG, McCusker J, Bellavance F, Primeau FJ, Bailey RF, Bonnycastle MJ et al. Systematic detection and multidisciplinary care of delirium in older medical inpatients: a randomized trial. CMAJ 2002; 167(7):753-759.

(403) Larkin PJ, Sykes NP, Centeno C, Ellershaw JE, Elsner F, Eugene B et al. The management of constipation in palliative care: clinical practice recommendations. Palliat Med 2008; 22(7):796-807.

(404) Brouwers JRBJ, Delhaas EM. [Medical treatment in patients with chronic pain]. Geneesmiddelenbulletin 1998; 32:111-118.

(405) De Smet PA. Hospital admissions related to medications and implementing guidelines. Arch Intern Med 2009; 169(8):810-811.

(406) Fugh-Berman A, Ahari S. Following the script: how drug reps make friends and influence doctors. PLoS Med 2007; 4(4):e150.

(407) van der Hooft CS, Sturkenboom MC, van GK, Kingma HJ, Stricker BH. Adverse drug reaction-related hospitalisations: a nationwide study in The Netherlands. Drug Saf 2006; 29(2):161-168.

(408) Van Sorge-Greve A. [Personal opinion]. Feb 2008. 2008. Nijmegen, INR Trombosedienst.
Ref Type: Data File

(409) Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA 2004; 292(16):1955-1960.

(410) Gulmez SE, Holm A, Frederiksen H, Jensen TG, Pedersen C, Hallas J. Use of proton pump inhibitors and the risk of community-acquired pneumonia: a population-based case-control study. Arch Intern Med 2007; 167(9):950-955.

(411) Rodriguez LA, Ruigomez A, Wallander MA, Johansson S. Acid-suppressive drugs and community-acquired pneumonia. Epidemiology 2009; 20(6):800-806.

(412) Myles PR, Hubbard RB, McKeever TM, Pogson Z, Smith CJ, Gibson JE. Risk of community-acquired pneumonia and the use of statins, ace inhibitors and gastric acid suppressants: a population-based case-control study. Pharmacoepidemiol Drug Saf 2009; 18(4):269-275.

(413) Sarkar M, Hennessy S, Yang YX. Proton-pump inhibitor use and the risk for community-acquired pneumonia. Ann Intern Med 2008; 149(6):391-398.

(414) Myles PR, Hubbard RB, Gibson JE, Pogson Z, Smith CJ, McKeever TM. The impact of statins, ACE inhibitors and gastric acid suppressants on pneumonia mortality in a UK general practice population cohort. Pharmacoepidemiol Drug Saf 2009; 18(8):697-703.

(415) Roughead EE, Ramsay EN, Pratt NL, Ryan P, Gilbert AL. Proton-pump inhibitors and the risk of antibiotic use and hospitalisation for pneumonia. Med J Aust 2009; 190(3):114-116.

(416) Talley NJ. Risks of proton-pump inhibitors: what every doctor should know. Med J Aust 2009; 190(3):109-110.

(417) Levine M, Walter S, Lee H, Haines T, Holbrook A, Moyer V. Users' guides to the medical literature. IV. How to use an article about harm. Evidence-Based Medicine Working Group. JAMA 1994; 271(20):1615-1619.

(418) Hennekens CH, Buring JE. Epidemiology in medicine. Boston: Little, Brown & company; 1987.

(419) Shapiro S. Bias in the evaluation of low-magnitude associations: an empirical perspective. Am J Epidemiol 2000; 151(10):939-945.

(420) Shakir SA, Layton D. Causal association in pharmacovigilance and pharmacoepidemiology: thoughts on the application of the Austin Bradford-Hill criteria. Drug Saf 2002; 25(6):467-471.

(421) Kaye JA, Jick H. Proton pump inhibitor use and risk of hip fractures in patients without major risk factors. Pharmacotherapy 2008; 28(8):951-959.

(422) Corley DA, Kubo A, Zhao W, Quesenberry C. Proton Pump Inhibitors and Histamine-2 Receptor Antagonists are Associated with Hip Fractures among At-Risk Patients. Gastroenterology 2010.

(423) Laine L. Proton pump inhibitors and bone fractures? Am J Gastroenterol 2009; 104(2 Suppl):S21-S26.

(424) Fournier MR, Targownik LE, Leslie WD. Proton pump inhibitors, osteoporosis, and osteoporosis-related fractures. Maturitas 2009; 64(1):9-13.

(425) Yu EW, Blackwell T, Ensrud KE, Hillier TA, Lane NE, Orwoll E et al. Acid-suppressive medications and risk of bone loss and fracture in older adults. Calcif Tissue Int 2008; 83(4):251-259.

(426) O'Connell MB, Madden DM, Murray AM, Heaney RP, Kerzner LJ. Effects of proton pump inhibitors on calcium carbonate absorption in women: a randomized crossover trial. Am J Med 2005; 118(7):778-781.

(427) Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA 2006; 296(24):2947-2953.

(428) Voelker R. Common drugs can harm elderly patients. JAMA 2009; 302(6):614-615.

(429) Vestergaard P, Rejnmark L, Mosekilde L. Proton pump inhibitors, histamine H2 receptor antagonists, and other antacid medications and the risk of fracture. Calcif Tissue Int 2006; 79(2):76-83.

(430) Targownik LE, Lix LM, Metge CJ, Prior HJ, Leung S, Leslie WD. Use of proton pump inhibitors and risk of osteoporosis-related fractures. CMAJ 2008; 179(4):319-326.

(431) Roux C, Briot K, Gossec L, Kolta S, Blenk T, Felsenberg D et al. Increase in vertebral fracture risk in postmenopausal women using omeprazole. Calcif Tissue Int 2009; 84(1):13-19.

(432) Yeomans ND, Tulassay Z, Juhasz L, Racz I, Howard JM, van Rensburg CJ et al. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs. Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-associated Ulcer Treatment (ASTRONAUT) Study Group. N Engl J Med 1998; 338(11):719-726.

(433) Tørring ML, Riis A, Christensen S, Thomsen RW, Jepsen P, Sondergaard J et al. Perforated peptic ulcer and short-term mortality among tramadol users. Br J Clin Pharmacol 2008; 65(4):565-572.

(434) Lanas A, Serrano P, Bajador E, Fuentes J, Sainz R. Risk of upper gastrointestinal bleeding associated with non-aspirin cardiovascular drugs, analgesics and nonsteroidal anti-inflammatory drugs. Eur J Gastroenterol Hepatol 2003; 15(2):173-178.