The decline of NSAID gastropathy in rheumatoid arthritis

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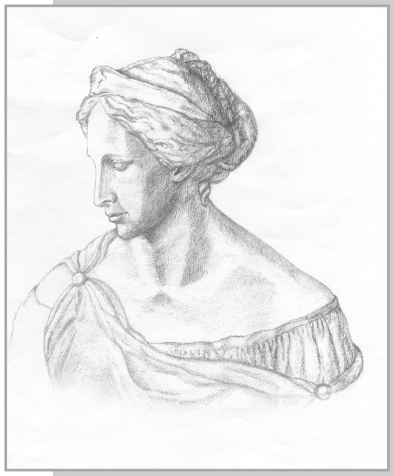
Summary and Discussion



Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed for patients with rheumatic diseases, e.g. rheumatoid arthritis (RA). The use of NSAIDs is associated with dyspepsia, gastrointestinal (GI) ulcers and complications of ulcers (bleedings and perforations), the so-called NSAID gastropathy [1]. In 1990 the frequency of NSAID associated GI ulcers was 20% and one out of five GI ulcers would lead to serious complications. High risk patients for NSAID gastropathy are patients with a higher age and/or a history of a GI ulcer; it is generally accepted that in these patients measures should be taken to prevent NSAID gastropathy [2]. Different preventive strategies for NSAID gastropathy are the combination of a NSAID with a prostaglandin analogue (misoprostol) [3], the development of selective cyclooxygenase-2 inhibitors (COXIBs) [4,5], the concomitant use of a gastroprotective drug (proton pump inhibitor [6,7] or high dose H2 antagonist [8]) or eradication of *Helicobacter pylori (H. pylori)* [9-11]. The different strategies and costs for the prevention of NSAID gastropathy are described in **Chapter 2**.

Since the nineties in the past century, NSAID gastropathy has gained much interest. Patients with arthritis require NSAIDs and their prescribing rheumatologists were asked, about their opinion of NSAID-gastropathy, by means of a questionnaire (**Chapter 3**).

In 1996 COXIBs were not yet available and the effect of eradication of *H. pylori* was not yet elucidated. A that time the best option to prevent NSAID associated GI ulcers was to add a prostaglandin analogue or a proton pump inhibitor. Since January 1997 rheumatologists in greater Amsterdam, the Netherlands, have prescribed a prophylactic agent for patients with RA at high risk for NSAID gastropathy (over 60 years of age and/or previous GI ulcer) according to a new guideline, and we assessed the incidence of clinically manifest GI ulcers and their complications in RA patients (**Chapter 4**). Several years later, after the introduction of COXIBs, the incidence of clinically manifest ulcers and their complications in the same group of patients was determined again (**Chapter 5**).
H. pylori infection is another important cause of GI ulcers. After eradication *H. pylori* the GI ulcer is cured in non-NSAID-treated patients [12], however, in NSAID-treated patients the effect of *H. pylori* is more complex [13]. since 1997 several studies have investigated the effect of eradication of *H. pylori* in NSAID starters or chronic users, preventing the development of gastroduodenal ulcers [9-11]. The results of these studies are inconsistent; the studies comprised NSAID starters, as well as short-term and long-term users, and ongoing NSAID users, and the end points were primary or secondary prevention of GI ulcers.
In 1997 we started a study to investigate *H. pylori* eradication in chronic NSAID users for the prevention of gastroduodenal ulcer development. Firstly, we assessed the prevalence of IgG antibodies of *H. pylori* in patients with rheumatic diseases (**Chapter 6**). Secondly, in a large

randomised multi centre trial, we studied the effect of eradication of *H. pylori* on NSAID gastropathy (**HERA** study) in rheumatic diseases (**Chapter 7**).

Patients with RA have an enhanced cardiovascular (CV) morbidity and mortality [14,15]. Increased CV risk are caused by 1. The chronic inflammatory process in RA [16], 2. An increased prevalence of traditional risk factors [17], 3. In chronic diseases, such as RA, unrelated conditions such as cardiovascular risk factors are frequently undertreated [15], and 4. The use of NSAIDs/COXIBs.
COXIBs are just as effective as NSAIDs with respect to the treatment of patients with arthritis, but are associated with significantly less GI side effects [4,5]. On the other hand, the use of COXIBs is associated with an enhanced rate of serious CV events, in comparison with placebo [18]. It is now clear that most ´traditional´ NSAIDs are also associated with serious CV events [18,19].
The incidence of CV events in RA patients is described in **Chapter 8**. Because of the association of inflammation in RA and atherosclerosis we investigated the effect of eradication of *H. pylori* on inflammation and serum lipid profile (**Chapter 9**).**Chapter 2** is an overview of the different strategies, safety and costs of measures for prevention of NSAID gastropathy in the late nineties of the past century. Protective strategies are advocated in patients with high risk for NSAID gastropathy (age over 60 years and/or previous GI ulcer) [2]. Different strategies for the prevention of NSAID gastropathy are: using a COXIB, adding a gastroprotective drug (i.e. prostaglandin analogue, H2-receptor antagonist or proton pump inhibitor) or eradicating *H. pylori*. Adding a prostaglandin analogue or a proton pump inhibitor turned out to be both safe and cost-effective [3,6,7].

Since rheumatologists prescribe NSAIDs for patients with arthritis and because of the severity of NSAID gastropathy in the late nineties, we assessed the opinion of these doctors about NSAID gastropathy. **Chapter 3** describes the results of this study.
In September 1997, at the annual meeting of the Dutch Society for Rheumatology, questionnaires about NSAID gastropathy were distributed among rheumatologists and rheumatology trainees. Eighty-nine (72%) questionnaires were filled. Age (>60 years) and previous GI ulcers were indicated as being the most important risk factors. Dutch rheumatologists followed different strategies for the prevention of NSAID gastropathy, with a slight preference for proton pump inhibitors and the use of COX-2 selective NSAIDs over acid inhibitors or prostaglandin analogues.

In the early nineties NSAID gastropathy was a major issue, due to its severity and prevalence. There were limited data available about the incidence of NSAID gastropathy in daily practice.
Therefore, in **Chapter 4** we investigated the incidence of clinically manifest GI ulcers and their complications in patients with rheumatoid arthritis, during a period in which prophylaxis was recommended. In January 1997 rheumatologists in greater Amsterdam, of the Jan van Breemen

Institute (JBI) and VU University medical center (VUmc), started to prescribe prophylactic agents in RA patients at high risk for NSAID-gastropathy, defined as aged 60 or older and/or GI ulcers in their medical history, in order to reduce NSAID-gastropathy. Within one year, three questionnaires were sent to all RA patients of our outpatient clinics (n=2680). The patients were asked if they had had a gastroscopy and/or complication of an GI ulcer in the preceding months. In case of a GI event (GI ulcer or complication), it was analyzed whether the event was related to a compliance failure or to a policy failure (=no prophylaxis prescribed when it was recommended). The response rate of the three questionnaires was 88%, 76% and 77%, respectively. All three questionnaires were filled in by 1856 patients; NSAIDs were used in 1246 (67%) patients. 731 (58%) of the NSAID-users were in the high risk group of which 357 (49%) used gastroprotection.

Clinically manifest GI ulcers occurred in 7 high risk NSAID-users (4 gastric ulcers, 2 duodenal ulcers and in 1 patient both gastric and duodenal ulcers). Complications of GI ulcers were diagnosed in 8 (other) patients: 7 (upper) GI bleedings and 1 GI perforation. Hence, the incidence during 1 year of clinically manifest ulcers in the high risk group is 1.0% and of complications of ulcers 1.1%, altogether 2.1%. In the group of 15 patients with GI events, only 1 patient did not take the adequately prescribed gastroprotective drugs (compliance failure). Gastroprotective drugs were not prescribed in 7 patients (policy failure), whereas in the remaining 7 patients gastroprotective drugs were adequately prescribed and used.

The incidence of clinically manifest GI ulcers and its complications in RA patients with high risk for NSAID gastropathy is relatively low. Comparison of the results of our study with the results of other studies is difficult, due to the different study designs, different patients groups and different underlying diseases. In the COXIB trials and the trials with proton pump inhibition for the secondary prevention of NSAID gastropathy, the GI ulcer rate and its complications is between 1 and 4% [4,6].

The low rate of clinically manifest GI ulcers and its complications in our study might be related to our strategy to prescribe prophylactic agents for these patient, which is in line with the protected NSAID users or COXIBs users reported by other investigators.

In **Chapter 5** the follow up of the incidence of symptomatic GI ulcers and ulcer complications in RA patients is presented.

In 2003, during the use of protective strategies for NSAID gastropathy and COXIBs, three questionnaires were sent again to all RA patients in Amsterdam.

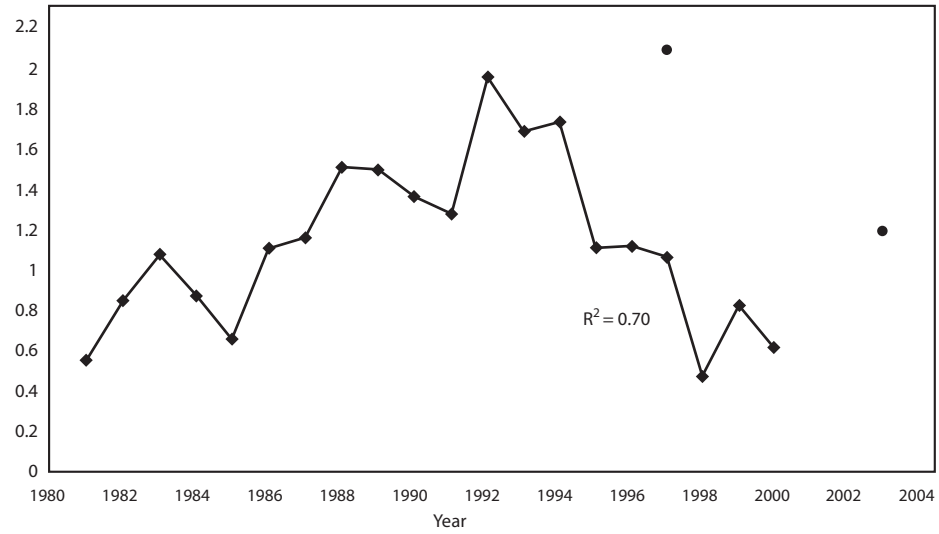
Compared with 1997, the use of classical NSAIDs decreased from 67% to 51% in 2003, and 14% of the patients used COXIBs in 2003 (in contrast with 0% in 1997).

The treatment of RA changed throughout the years: in the first study in 1997 disease modifying antirheumatic drug (DMARD, second line antirheumatic drug) mono-therapy was more

commonly used and in the second study in 2003 combination therapy with two or more DMARDs or biologicals was more frequently used, i.e. ´aggressive´ therapy. This change in treatment is reflected in our study results: the use of biologicals was in 0% in 1997 and 16% in 2003, and the use of DMARDs (including methotrexate): was 76% in 1997 and 70% in 2003. Altogether, a more ´aggressive´ therapy over a period of seven years, 86% in 2003 and 76% in 1997.

The incidence of GI events in high risk patients was 1.2% (95% C.I. 0.2-2.3) which turns out to be substantially lower than the 2.1% observed in 1997, albeit this difference did not reach statistical significance (p=0.3).

In 64% (95% C.I. 61-68) of the high risk patients, acid suppressive drugs, i.e. proton-pump inhibitors, prostaglandin analogues or high doses of H2-antagonists, were used. In 1997 this percentage was significantly lower, i.e. 49% (45-52; p<0.0001). The compliance to the Dutch guideline for the prevention of NSAID related gastropathy was almost 75%, and 64% of the patients used acid suppressive drugs and 11% COXIBs. This study reveals a decline of NSAID induced GI events, which is similar to that observed in the US (figure 1) [20]. In the US the risk of serious NSAID gastropathy (% patients with hospitalization involving gastrointestinal ulcers, severe gastritis, bleeding, obstruction, or perforation of the gastrointestinal tract and related conditions) has declined by 67% in RA since 1992. This period of decline was associated with lower doses of NSAIDs, the use



Percentage of rheumatoid arthritis patients with serious gastrointestinal (GI) events that required hospitalization, over time in the US (◆—◆) and percentage clinical manifest GI ulcers and ulcer complications (●).

Figure 1: The decline of NSAID gastropathy in the United States and the Netherlands

of proton-pump inhibitors and the use of less toxic NSAIDs. The decline in our study is most likely due to a more strict adherence to guidelines for the prevention of NSAID gastropathy, and a better treatment of rheumatoid arthritis.
Another potential preventive strategy for NSAID gastropathy in the late nineties was the eradication of the bacteria *H. pylori*. *H. pylori* and NSAIDs are both independent causes of peptic ulcer diseases [12,21,22]. It is unclear whether interactions will occur if patients have *H. pylori* and NSAIDs concomitantly.
In one study with chronic NSAIDs users, *H. pylori* does not alter the development of peptic ulcer disease [21]. However, in a meta-analysis of 16 endoscopic studies of 1625 NSAID users, a synergistic relation between *H. pylori* and NSAIDs in the development of gastroduodenal ulcers is demonstrated. Uncomplicated peptic ulcer disease was twice as common in *H. pylori* positive NSAID users, compared with *H. pylori* negative NSAID users [22].
Worldwide the prevalence of *H. pylori* is decreasing [23], probably because of a better hygiene. In 1990 the seroprevalence of *H. pylori* in healthy Dutch blood donors was 49% [24]. It is not known whether the prevalence of *H. pylori* is decreasing in RA patients, and due to the possibility to eradicate *H. pylori* in NSAID users in order to prevent NSAID gastropathy, we studied the seroprevalence of *H. pylori* infection in rheumatic patients on chronic NSAIDs (**Chapter 6**) and the effect of eradication of *H. pylori* on the incidence of gastroduodenal ulcers in patients on long-term NSAID treatment (**Chapter 7**).

In **Chapter 6** the seroprevalence of IgG-antibodies of *H. pylori* in 1214 patients with rheumatic diseases and chronic NSAID treatment is reported.
H. pylori IgG-antibodies can be measured by a specific serologic assay [25]. In our group of patients with rheumatic diseases the IgG-antibodies to *H. pylori* were found in 39%, and this increased gradually according to age: from 25% in patients between 40–50 to 48% in patients aged between 70-80 ($p<0.0001$). No difference was observed between men and women. The seroprevalence of *H. pylori* in patients with rheumatic diseases treated with NSAIDs is substantial (39%), which is comparable to the worldwide decrease of prevalence of *H. pylori* infection. This is probably established by a better hygiene and the ongoing use of the eradication of *H. pylori* therapy. In conclusion, the seroprevalence of *H. pylori* is still substantial in patients with rheumatic diseases.

In **Chapter 7** we investigated, whether *H. pylori* eradication reduces the incidence of gastroduodenal ulcers in patients receiving long-term treatment with NSAIDs, in a large, randomized, double blind, placebo-controlled study, the so called **HERA** (**H**. pylori **E**radicatie in **RA**) study.
Between May 2000 and June 2002 patients with rheumatic diseases, from the outpatients

clinics of Utrecht, Enschede, Arnhem, Heerlen and Amsterdam were screened on anti-*H. pylori* antibodies. 347 *H. pylori* positive patients were randomized and received either placebo (175 patients) or *H. pylori* eradication therapy with omeprazole, amoxicillin and clarithromycin for 7 days (172 patients). The primary end point was the presence of an endoscopically proven gastric or duodenal ulcer at 3 months from baseline. Secondary endpoints were the number of patients with a symptomatic ulcer (defined as gastroduodenal ulcer found after work-up for dyspepsia), ulcer complication, such as bleeding and perforation, dyspepsia and adverse events during one year. The baseline characteristics in the eradication group and in the placebo group did not differ: mean age was 60, predominantly female (60%) and RA (61%). The most commonly used NSAIDs were diclofenac (29%), naproxen (18%), and ibuprofen (13%). Forty-eight percent of the patients used a gastroprotective drug in combination with a NSAID; 9% of the patients used a COXIB (including 4% using a combination of a COXIB and gastroprotective drugs). Hence, 53% of the patients used a gastroprotective drug and/or a COXIB. Thirty-seven patients (11%) had a GI ulcer history.

At 3 months, gastroduodenal ulcers were diagnosed in 6 (4%) patients in the eradication group (five gastric and one duodenal ulcer) and 8 (5%) patients in the placebo group (six gastric and two duodenal ulcers) (p =.645). None of the patients developed symptomatic ulcer, GI bleeding or perforation during the total study period of 12 months. Dyspeptic complaints did not differ between the study groups (p =.98), 35 out of 172 (20%) in the eradication group and 4 out of 175 (2%) in the placebo group reported significantly higher adverse reactions, probably related to the study medication (p <.001).

In conclusion, in chronic NSAID users eradication of *H. pylori* has no beneficial effect on the incidence of gastroduodenal ulcers, or the occurrence of dyspepsia, and it is even associated with more frequent side-effects than previously implemented strategies used to prevent gastropathy without additional eradication treatment. Thus, *H. pylori* eradication in patients with long-term NSAID treatment is not warranted.

Since the insights of NSAID gastropathy are largely under control, the comorbidity of RA has shifted from the gastroduodenal tract to the cardiovascular tract in the last decade.

Recent literature reveals a higher risk of CVD in RA [14,26]. Inflammation might play the key role in atherosclerosis and in RA [16,27,28]. Other factors could be a more frequent appearance of traditional risk factors of CVD (e.g. smoking, hypertension) in RA patients [17], the use of NSAIDs/COXIBs [4,5] and the ´under-treatment´ of (cardiovascular) comorbidity in patients with chronic diseases [15].

In **Chapter 8** the incidence of CV events in RA patients is described. Between September 2003 and August 2004, three questionnaires were sent to all RA patients in our database registry. This registry contains all outpatients of the departments of rheumatology of JBI and VUmc, in Amsterdam, the Netherlands. Patients were asked about incident CV events occurring within the previous four months, according to a standard protocol. CV events were defined as coronary events (myocardial infarction, coronary bypass operation, and angioplasty), cerebrovascular events (transient ischemic attack, stroke, carotid endarteriectomy) or peripheral arterial disease. All events, including deaths and their causes, were verified through chart review.
A total of 12,532 questionnaires was sent to 4,125 RA patients. 2,099 patients (51%) filled in at least one questionnaire, comprising 1,557 patient years. The mean age of the patients was 61 and 72% of the patients was female.
The annual incidence of CV events in the total RA group was 2.6 (95% CI 1.8-3.4) per 100 patient years, in comparison with 1.0% in the general Dutch population [29]. CV events occurred in 41 patients: 19 patients experienced coronary events, 14 patients cerebrovascular events and 8 patients peripheral arterial events.
The increased incidence of CVD in RA is associated with 1. Inflammation: patients without CV events used more methotrexate than patients with CV events, which is in line with other studies [30], demonstrating the CV protective effect of methotrexate which is probably mediated by the suppression of inflammation. 2. Traditional risk factors for CVD: patients with CV events were 11 years older ($p<0.0001$) and mostly male ($p=0.02$) compared with the RA patients without CV events. The use of aspirin (or other anti-platelet agents) as a surrogate marker for a history of CVD (at baseline) was observed in 18 (44%) patients with CV events and 236 (11%) patients without CV events ($p<0.0001$). And 3. The use of NSAIDs/COXIBs: patients with CV events used significantly less (particularly non selective) NSAIDs prior to the onset of the event, than the patients without CV events. This would suggest a ´protective effect´ of NSAIDs, but it is more likely the result of restrained prescriptions of COXIBs and NSAIDs for high risk patients for CVD.
In summary, the present study reveals a doubled incidence of cardiovascular events in RA patients in comparison with the general Dutch population, emphasizing the need for cardiovascular risk management in RA by reducing inflammation, controlling the traditional risk factors for CVD and lowering NSAID/COXIB use.

Chapter 9 describes the effect of *H. pylori* eradication on C-reactive protein (CRP) and the lipid profile in patients with rheumatic diseases using chronic NSAIDs.
H. pylori induce (gastric) inflammation with a raised CRP and as CRP is inversely associated with (accelerated) atherosclerosis development [31,32], it is hypothesized that eradication of *H. pylori* might lower CRP and influence cardiovascular risk.

Stored blood samples were examined for CRP and lipid profile. At least one blood sample of 175 patients from the original 347 of the HERA study was available. ApoA-1 increased in the eradication group from baseline to three months ($p<0.05$). There was also a trend for increasing HDL cholesterol level and decreasing apoB/apoA-1 ratio whereas the other lipid values did not change. There was no change of CRP levels in time.
To summarize, the effects of *H. pylori* eradication on the lipid profile and CRP levels were limited and transient in patients with rheumatic diseases. Hence, it is unlikely that eradication of *H. pylori* will significantly alters the cardiovascular risk through these pathways.

Discussion

This thesis demonstrates a decline of NSAID gastropathy in RA, which is in line with the observations in the United States [22]. Possible causes are:

1. The implementation of gastro-preventive strategies for patients at risk for NSAID gastropathy;
2. The more frequent use of proton pump inhibitors;
3. The use of COXIBs;
4. Reduced inflammation by a better and more `aggressive` treatment of RA;
5. Less frequent use of NSAIDs, probably because of the improved treatment of RA.

The issue of NSAID gastropathy, within the field of rheumatologists, seems to be largely under control. However, in daily clinical practices of family physicians or medical specialists other than rheumatologists, significant GI events still occur, particularly in patients with concomitant use of aspirin or anticoagulants, and without gastroprotection [33,34].
At the American Congress of Rheumatology in 2007, American investigators re-evaluated the incidence of NSAID gastropathy, and, in contrast with their expectations, they observed an increase of NSAID gastropathy, probably due to the fear of the cardiovascular side effects of COXIBs. Another Dutch study showed a decline of hospital admissions for gastric ulcers, due to a decrease of *H. pylori* infection and the widespread increasing use of proton pump inhibitors (PPIs) [35]. The admission rates for complicated ulcer diseases increased, due to an increased use of NSAIDs and (still) inadequate implementation of preventive strategies for NSAID gastropathy [35]. In a recent published review the reported incidence and prevalence of peptic ulcer disease (PUD) have declined. However, temporal trends in the rate of hospitalizations for complications of PUD varied, from increasing to declining [36].

In a time trend analysis, the incidence rate of upper GI bleeding decreased, but the incidence of complicated PUD remained stable [37].
The need for ongoing reassessment of NSAID gastropathy is evident, particularly in daily practice of other medical specialists or family physicians [38].

This thesis reveals no favourable effect of eradication of *H. pylori* on the incidence of GI ulcers and their complications in chronic NSAID users. In contrast, other studies have shown the beneficial effects of eradication of *H. pylori* in NSAID-starters [9,10]. However, for the daily practice of a rheumatologist this is not relevant as most of his patients are already on chronic NSAIDs.
The recommendations in the Maastricht III consensus report of *H. pylori* infection and NSAIDs, emphasize that H. pylori eradication is important in chronic NSAID users but insufficient in the prevention of NSAID related ulcer diseases: 1. In naive NSAID users *H. pylori* eradication may prevent peptic ulcer and bleeding; 2. In patients receiving long-term NSAIDs, with peptic ulcer and/or ulcer bleeding, PPI maintenance treatment is better than *H. pylori* eradication in the prevention of ulcer recurrence and/or bleeding; 3. Aspirin-using patients with a GI bleeding should be tested for *H. pylori* and, if positive, they should receive eradication therapy. However, in daily practices of rheumatologists this strategy has not been incorporated. Hence, we advocate this strategy in aspirin-using patients receiving long-term PPI treatment for the prevention of NSAID ulcers, to reduce the PPI-*H. pylori* interaction leading to accelerated loss of specialised glands and atrophic gastritis.
More research needs to be done on the impact of the precancerous risk of H. pylori and concomitantly use of NSAIDs [39].

Cardiovascular disease, in addition to NSAID gastropathy, is another comorbidity in RA that has acquired more and more attention for the past two decades. This is due to 1) the recognition that RA itself is a ´new´ cardiovascular risk factor, which is largely related to the inflammatory process [26], and 2) the use of NSAIDs or COXIBs and their inherent cardiovascular side effect profile [18,40]. Therefore, the lowest possible dose of NSAIDs or COXIBs should be prescribed, and

Table: strategy of the balance of benefits and risks of NSAIDs/COXIBs

	Cardiovascular risk	
	Low	High
Gastrointestinal risk		
Low	NSAIDs	NSAIDs/COXIBs, aspirin and PPI
High	COXIBs, NSAIDs and PPI	Avoid NSAIDs/COXIBs

of the "traditional" NSAIDs, naproxen, might have the lowest CV risk when compared with other "traditional" NSAIDs and COXIBs [34].

Tailor-made therapy with respect to the prevention of NSAID gastropathy has largely been accomplished for patients within the field of the rheumatologists. However, in daily practices of family physicians and other medical specialists (i.e. general surgeons, orthopaedic surgeons) NSAIDs are frequently prescribed.
If NSAID use is inevitable, the lowest-risk NSAID should be prescribed. The choice of the lowest-risk of NSAID should be predicated by an assessment of the patients´ CV and GI risk, the costs and effectiveness: balance of benefits and risk (table): 1. Patients with low GI risk and low CV risk: NSAIDs; 2. Patients with high GI risk and low CV risk: NSAIDs and proton pump inhibitor (PPI) or COXIBs; 3. Patients with low GI risk and high CV risk: COXIBs or NSAIDs, aspirin and PPI; 4. Patients with high GI risk and high CV risk: no NSAIDs and/or COXIBs.

Nevertheless, besides gastrointestinal comorbidity, there is nowadays more and more attention for cardiovascular comorbidity in RA. Obviously this thesis indicates an unmet need for cardiovascular risk management in patients with RA. This can be accomplished by ´aggressive´ treatment of RA, thereby reducing inflammation, screening (and if necessary treating) and carefully balancing the benefits and the adverse events of the prescribed drug, especially NSAIDs and COXIBs.

References

1 Roth SH. NSAID gastropathy. A new understanding. Arch Intern Med. 1996;156(15):1623-8.
2 Fries JF, Miller SR, Spitz PW, Williams CA, Hubert HB, Bloch DA. Identification of patients at risk for gastropathy associated with NSAID use. J Rheumatol Suppl. 1990;20:12-9.3.
3 Raskin JB, White RH, Jackson JE, Weaver AL, Tindall EA, Lies RB, et al. Misoprostol dosage in the prevention of nonsteroidal anti-inflammatory drug-induced gastric and duodenal ulcers: a comparison of three regimens. Ann Intern Med. 1995;123:344-50.
4 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;343:1520-8.
5 Laine L, Curtis SP, Cryer B, Kaur A, Cannon CP: MEDAL Steering Committee. Assessment of upper gastrointestinal safety of 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. 2007;369:465-73.
6 Hawkey CJ, Karrasch JA, Szczepañski L, Walker DG, Barkun A, Swannell AJ, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. Omeprazole versus Misoprostol for NSAID-induced Ulcer Management (OMNIUM) Study Group. N Engl J Med. 1998;338:727-34.

7 Yeomans ND, Tulassay Z, Juhász L, Rácz I, Howard JM, v. 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;338:719-26.
8 Taha AS, Hudson N, Hawkey CJ, Swannell AJ, Trye PN, Cottrell J, et al. Famotidine for the prevention of gastric and duodenal ulcers caused by nonsteroidal antiinflammatory drugs. N Engl J Med. 1996;334(22):1435-9.
9 Chan FK, Sung JJ, Chung SC, To KF, Yung MY, Leung VK, et al. Randomised trial of eradication of Helicobacter pylori before non-steroidal anti-inflammatory drug therapy to prevent peptic ulcers. Lancet. 1997;350:975-9.
10 Chan FK, To KF, Wu JC, Yung MY, Leung VK, Kwok T, et al. Eradication of Helicobacter pylori and risk of peptic ulcers in patients starting long-term treatment with non-steroidal anti-inflammatory drugs: a randomized trial. Lancet. 2002;359-13.
11 Hawkey CJ, Tulassay Z, Szczepanski L, v. Rensburg CJ, Filipowicz-Sosnowska A, Lanas A, et al. Randomised controlled trial of Helicobacter pylori eradication in patients on non-steroidal anti-Inflammatory drugs: HELP NSAIDs study. Lancet. 1998;352:1016-21.
12 Kuipers EJ, Thijs JC, Festen HP. The prevalence of Helicobacter pylori in peptic ulcer disease. Aliment Pharmacol Ther. 1995;9 suppl 2:59-69.
13 Malfertheiner P, Megraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, et al. Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. Gut. 2007 Jun;56(6):772-81.
14 Wolfe F, Mitchell DM, Sibley JT, Fries JF, Bloch DA, Williams CA et al. The mortality of rheumatoid arthritis. Arthritis Rheum. 1994;37:481-94.
15 Boers M, Dijkmans B, Gabriel S, Maradit-Kremers H, O'Dell J, Pincus T. Making an impact on mortality in rheumatoid arthritis: targeting cardiovascular comorbidity. Arthritis Rheum. 2004;50:1734-39.
16 Abou-Raya A, Abou-Raya S. Inflammation: a pivotal link between autoimmune diseases and atherosclerosis. Autoimmun Rev. 2006;5(5):331-7
17 Del Rincon I, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum. 2001;44:2737-45.
18 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 Jun 3;332(7553):1302-8.
19 Cannon CP, Curtis SP, FitzGerald GA, Krum H, Kaur A, Bolognese JA, et al; MEDAL Steering Committee. 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 Nov 18;368(9549):1771-81.
20 Fries JF, Murtagh KN, Bennett M, Zatarain E, Lingala B, Bruce B. The rise and decline of nonsteroidal antiinflammatory drug-associated gastropathy in rheumatoid arthritis. Arthritis Rheum. 2004;50:2433-40.
21 Kim JG, Graham DY. Helicobacter pylori infection and development of gastric or duodenal ulcer in arthritic patients receiving chronic NSAID therapy. The Misoprostol Study Group. Am J Gastroenterol. 1994;89:203-7.
22 Huang JQ, Sridar S, Hunt RH. Role of Helicobacter pylori infection and non-steroidal anti-

inflammatory drugs in peptic-ulcer disease: a meta-analysis. Lancet. 2002;359:14-22.
23 Roosendaal R, Kuipers EJ, Buitenwerf J, van uffelen C, Meuwissen SG, et al. Helicobacter pylori and the birth cohort effect: evidence of a continuous decrease of infection rates in childhood. Am J Gastroenterol. 1997;92:1480-2.
24 Loffeld RJ, Stobberingh E, van Spreeuwel JP, Flendrig JA, Arends JW.. The prevalence of anti-Helicobacter (Campylobacter) pylori antibodies in patients and healthy blood donors. J Med Microbiol. 1990;32:105-9.
25 Meijer BC, Thijs JC, Kleibeuker JH, van Zwet AA, Berrelkamp RJ. Evaluation of eight enzyme immunoassays for detection of immunoglobulin G against Helicobacter pylori. J Clin Microbiol. 1997;35:292-4.
26 Nurmohamed MT, van Halm VP, Dijkmans BA. Cardiovascular risk profile of antirheumatic agents in patients with osteoarthritis and rheumatoid arthritis. Drugs. 2002;62(11):1599-609.
27 Gonzalez-Gay MA, Gonzalez-Juanatey C, Martin J. Rheumatoid arthritis: a disease associated with accelerated atherogenesis. Semin Arthritis Rheum. 2005;35:8-17.
28 Del Rincón I, Escalante A. Atherosclerotic cardiovascular disease in rheumatoid arthritis. Curr Rheumatol Rep. 2003;5:278-86.
29 Koek HL, Van Dis SJ, Peters RJG, Bots ML. Hoofdstuk 1. Hart- en vaatziekten in Nederland in Van Leest LATM, Koek HL, Van Trijp MJCA, et al. Hart- en vaatziekten in Nederland 2005, cijfers over incidentie en prevalentie. Den Haag: Nederlandse Hartstichting, 2005: 23.
30 Van Halm VP, Nurmohamed MT, Twisk JW, Dijkmans BA, Voskuyl AE. Disease-modifying antirheumatic drugs are associated with a reduced risk for cardiovascular disease in patients with rheumatoid arthritis: a case control study. Arthritis Res Ther. 2006;8(5):R151.
31 Li JJ, Fang CH. C-reactive protein is not only an inflammatory marker but also a direct cause of cardiovascular diseases. Med Hypotheses. 2004;62:499-506.
32 Ridker PM. Connecting the role of C-reactive protein and statins in cardiovascular disease. Clin Cardiol. 2003;26:III39-44.
33 Scheiman JM, Prevention of NSAID-Induced Ulcers. Curr Treat Options Gastroenterol. 2008 Mar;11(2):125-34.
34 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;370:2138-51.
35 Post PN, Kuipers EJ, Meijer GA. Declining incidence of peptic ulcer but not of its complications: a nation-wide study in The Netherlands. Aliment Pharmacol Ther. 2006;23:1587-93.
36 Sung JJ, Kuipers EJ, El-Serag HB. Systematic review: the global incidence and prevalence of peptic ulcer disease. Aliment Pharmacol Ther. 2009;29(9):938-46.
37 Van Leerdam ME, Vreeburg EM, Rauws EA, Geraedts AA, Tijssen JG, Reitsma JB, Tytgat GN. Acute upper GI bleeding: did anything change? Time trend analysis of incidence and outcome of acute upper GI bleeding between 1993/1994 and 2000. Am J Gastroenterol. 2003;98(7):1494-9.
38 Sturkenboom MCJM, Burke, TA, Dieleman JP, Tangelder MJD, Lee F, Goldstein JL. Underutilization of preventive strategies in patients receiving NSAIDs. Rheumatology. 2003;42 Suppl 3:iii23-31.
39 Kuipers EJ, Sipponen P. Helicobacter pylori eradication for the prevention of gastric cancer. Helicobacter. 2006;11:52-7.
40 Warner TD, Mitchell JA. COX-2 selectivity alone does not define the cardiovascular risks associated with non-steroidal anti-inflammatory drugs. Lancet. 2008;371:270-3.