Duration of Treatment With Nonsteroidal Anti-Inflammatory Drugs and Impact on Risk of Death and Recurrent Myocardial Infarction in Patients With Prior Myocardial Infarction
A Nationwide Cohort Study

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Background—Despite the fact that nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated among patients with established cardiovascular disease, many receive NSAID treatment for a short period of time. However, little is known about the association between NSAID treatment duration and risk of cardiovascular disease. We therefore studied the duration of NSAID treatment and cardiovascular risk in a nationwide cohort of patients with prior myocardial infarction (MI).

Methods and Results—Patients ≥30 years of age who were admitted with first-time MI during 1997 to 2006 and their subsequent NSAID use were identified by individual-level linkage of nationwide registries of hospitalization and drug dispensing from pharmacies in Denmark. Risk of death and recurrent MI according to duration of NSAID treatment was analyzed by multivariable time-stratified Cox proportional-hazard models and by incidence rates per 1000 person-years. Of the 83,677 patients included, 42.3% received NSAIDs during follow-up. There were 35,257 deaths/recurrent MIs. Overall, NSAID treatment was significantly associated with an increased risk of death/recurrent MI (hazard ratio, 1.45; 95% confidence interval, 1.29 to 1.62) at the beginning of the treatment, and the risk persisted throughout the treatment course (hazard ratio, 1.55; 95% confidence interval, 1.46 to 1.64 after 90 days). Analyses of individual NSAIDs showed that the traditional NSAID diclofenac was associated with the highest risk (hazard ratio, 3.26; 95% confidence interval, 2.57 to 3.86 for death/MI at day 1 to 7 of treatment).

Conclusions—Even short-term treatment with most NSAIDs was associated with increased risk of death and recurrent MI in patients with prior MI. Neither short- nor long-term treatment with NSAIDs is advised in this population, and any NSAID use should be limited from a cardiovascular safety point of view. (Circulation. 2011;123:2226-2235.)

Key Words: antiinflammatory agents, nonsteroidal cyclooxygenase 2 inhibitors mortality myocardial infarction prognosis

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in the general population. However, recent studies have associated NSAID use with increased cardiovascular risk in healthy individuals and in patients with established cardiovascular disease.1–12

Clinical Perspective on p 2235
Most individuals receive NSAID treatment for a short duration, but the timing of risk associated with the use of NSAIDs remains poorly defined. International guidelines discourage NSAID treatment in patients with established cardiovascular disease, eg, myocardial infarction (MI) and heart failure, but if NSAID treatment is unavoidable, guidelines propose that the duration of NSAID treatment should be as short as possible.13 However, little is known about the risk profile of each individual NSAID according to treatment duration or whether there is a safe treatment period for NSAIDs.

Only a few studies have conducted time-to-event analyses for NSAID treatment, and these studies have suggested that an increased risk exists at the initiation of therapy and persists afterward.14–17 Additionally, only 2 randomized studies have been specifically designed to determine the cardiovascular safety
of NSAID treatment, and only 1 study showed that the selective cyclooxygenase-2 (COX-2) inhibitor valdecoxib increased cardiovascular risk in patients undergoing coronary artery bypass surgery already after 1 week of treatment.11,14,18 Both rofecoxib and valdecoxib have been withdrawn from the market, but information on cardiovascular risk according to treatment duration with COX-2 selective and nonselective NSAIDs like diclofenac, ibuprofen, and naproxen in patients with prior MI is absent in the literature. This prompted us to examine whether the duration of NSAID treatment influenced the cardiovascular risk of NSAIDs in a population of patients after MI.

Methods
Population and Data Sources
Each resident in Denmark has a unique and permanent identification number that enables individual-level linkage between nationwide registries. The Danish National Patient Registry keeps records of all hospital admissions in Denmark since 1978.19 Each hospital admission is registered with 1 main discharge coding diagnosis and, if appropriate, 1 or more supplementary diagnoses according to the International Classification of Diseases (ICD) codes (the 8th ICD revision until 1994 and the 10th revision [ICD-10] from 1994). We identified a population of all patients with first-time admission for MI (ICD-10, I21 through I22) from January 1, 1997, to December 31, 2006, in the Danish National Patient Registry. First admission for MI implied that the National Patient Registry had not registered any prior admission for MI in the previous 19 years. We have previously described this method using the time interval from 1995 to 2002.20 In the present study, we used the time interval from 1997 to 2006. We selected 19 years as the limit for previous admissions with MI because that was the maximal time we were able to look back in the register for patients admitted in 1997; this length of history was applied to all patients in our cohort. The database was systematically screened to ensure that any transfer of patients between hospitals was registered as 1 admission because our analysis used the date of discharge to select patients and to calculate the medicine dispensed. We have previously used this method to select a similar population of patients.8 All patients who were alive at discharge after their first-time MI were included in the study. Patients were censored at death or at the end of the study period (December 31, 2006).

The Danish Registry of Medicinal Product Statistics (national prescription registry) keeps records on all drug prescriptions dispensed from Danish pharmacies since 1995. Each drug dispensing is registered according to an international classification of drugs, the Anatomical Therapeutic Chemical (ATC) system, as well as the date of dispensing, quantity dispensed, strength, formulation, and affiliation of the physician issuing the prescription. Because of partial reimbursement of drug expenses by the Danish healthcare system, all pharmacies in Denmark are required to register each drug dispensing in the national prescription registry, ensuring complete registration.21 The Central Person Registry keeps records on vital status and registers all deaths within 14 days of occurrence.

Nonsteroidal Anti-Inflammatory Drugs Use and Concomitant Medication
We identified all claimed prescriptions of NSAIDs (ATC M01A) from the national prescription registry after discharge from index hospitalization (MI). The most commonly used selective COX-2 inhibitors, rofecoxib and celecoxib, and the most commonly used nonselective NSAIDs, ibuprofen, diclofenac, and naproxen, were analyzed separately. All other NSAIDs were analyzed in a common group defined as other NSAIDs.

Concomitant use of β-blockers (ATC C07), angiotensin-converting enzyme inhibitors/angiotensin-2 receptor blockers (ATC C09), statins (ATC C10A), loop diuretics (ATC C03C), spironolactone (ATC C03D), and antidiabetic drugs (ATC A10, a proxy for prevalent diabetes mellitus as done previously22) was identified in the national prescription registry.

Dose and Duration of Treatment
The method used to determine the dose and treatment duration has been described previously.6,6 In brief, for each prescription, treatment periods were calculated for NSAIDs by dividing the number of tablets dispensed by the estimated daily dosage. The estimated daily dose for each individual was calculated by comparing the cumulated dose and the elapsed time between 7 successive prescriptions for the same NSAID, as described in detail previously. High dose was defined as being above the upper limit of the recommended minimal dose for each drug: ibuprofen, >1200 mg; diclofenac, ≥100 mg; naproxen, >500 mg; rofecoxib, >25 mg; and celecoxib, >200 mg.

Comorbidity and Socioeconomic Status
The Ontario acute MI mortality prediction rule, modified for the ICD-10, was used to define comorbidity.23 To further enhance the comorbidity score, we identified discharge coding diagnoses, both primary and supplemental, up to 1 year before the index hospitalization.24

Socioeconomic status was defined as the patient’s individual average annual income during 5 years before the MI index date, which was available from Integrated Database for Labor Market Research. This database is based on information from taxed income gathered by government tax authorities, and is therefore very accurate. The year of the index MI was excluded. The population was divided into quintiles according to the average annual income of patients.

Statistics
Unadjusted incidence rates of events per 1000 person-years for death and death/Re-MI were calculated for all NSAID treatment as a group and for the individual NSAIDs separately. To analyze the time variation in risk, we split the periods of NSAIDs treatment into 1-week intervals up to 14 weeks. We used time-dependent Cox proportional hazard models to analyze risk of death or death/Re-MI associated with NSAID use. Exposure to NSAIDs was included as time-dependent covariates in the models; ie, patients were considered at risk only when they were exposed to the drug. Each individual could have multiple independent treatment courses with the same drug, but also with different drugs. Patients were followed up to the end of the study period or to their first event. Patients who emigrated during the study period were censored on the date of emigration.

All models were adjusted for age, sex, year of index hospitalization, concomitant medication, comorbidity, and socioeconomic status. To analyze the effect of treatment duration, we defined 5 exposure periods from the start of NSAID use: 0 to 7, 8 to 14, 15 to 30, 31 to 90, and >90 days, which were included as time-dependent covariates in the proportional-hazard models. We used 2 different time analyses to obtain a more subtle distribution of time. In the primary time analysis used in the Cox models, we took account of the duration of the exposure periods and the time differences in the treatments. In the secondary time analysis, we calculated crude incidence rates in weekly time intervals up to 14 weeks from start of NSAID use. The validity of the proportional hazard assumption, linearity of continuous variables, and lack of interaction were found to be valid unless otherwise indicated. Cox proportional hazard analyses with time-dependent variables and incidence rates were performed with the Stata statistical package, version 11.0 (Stata Corp LP, College Station, TX). All other statistical analyses and data management were performed with the SAS statistical software package, version 9.1 (SAS Institute Inc, Cary, NC).

Ethics
The Danish Data Protection Agency approved this study (No. 2007–41–1667) and made data at the individual level available to us in an anonymized format when specific individuals could not be identified. In Denmark, retrospective register studies do not require ethics approval from the ethics committees.
A total of 102,138 patients were admitted with first-time MI in the period of 1997 to 2006, of whom 83,675 (81.9%) were discharged alive and included in the study. Mean ± SD age in the population was 68 ± 13.0 years; 63% were men. A detailed description of baseline characteristics of the study sample and distribution between treatment groups is shown in the Table. At least 1 prescription claim for NSAID treatment after discharge was identified for 35,405 patients (42.3%) with prior MI.

Patients taking nonselective NSAIDs were younger and more often men compared with patients taking selective COX-2 inhibitors. This was particularly evident for naproxen; 69% of patients taking naproxen were men.

The most commonly used NSAIDs were ibuprofen (23.2%) and diclofenac (13.4%). Rofecoxib (4.7%) and celecoxib (4.8%) were the most commonly used selective COX-2 inhibitors.

There were 35,257 death/MIs (42.1%) and 29,234 deaths (35.0%) registered during the observation period. Death incidence rates per 1000 person-years were calculated for NSAID treatment in general, and are shown in Figure 1, and for the individual NSAIDs separately, and are shown in Figure 2A through 2F. These analyses supported the results of the time-dependent Cox proportional hazard analyses with an increased...
risk of death (Figure 3). They strengthened the assumption of time independence in NSAID risk. In brief, overall NSAID treatment was associated with statistically significantly increased risk of death at the beginning of the treatment, and the increased risk persisted throughout the course of treatment. Analyses of the individual NSAIDs separately showed that the selective COX-2 inhibitor rofecoxib was associated with increased risk of death after a treatment duration of 7 to 14 days, whereas celecoxib, another selective COX-2 inhibitor, was associated with increased risk of death after a treatment duration of 14 to 30 days. The traditional NSAID diclofenac was associated with increased risk from the beginning of treatment, and the risk persisted throughout the course of treatment. Ibuprofen showed an increased risk when used for >1 week.

Incidence rates per 1000 person-years for death/Re-MI are shown for all NSAIDs grouped together in Figure 4, and for the individual NSAIDs separately in Figure 5A through 5F. These analyses supported the results of the time-dependent Cox proportional hazard analyses, with an increased risk of death/Re-MI associated with short-time NSAID treatment (Figure 6). Overall, NSAID treatment was associated with a significantly increased risk of death/Re-MI from the start of the treatment. Rofecoxib was associated with an increased risk of death/Re-MI already in the first week of the treatment. Celecoxib had an increased risk after 14 to 30 days of treatment. Diclofenac was associated with an increased risk from the beginning of treatment, and the risk persisted throughout the treatment course. Ibuprofen showed an increased risk when used for >1 week. The risk associated with ibuprofen was lower than the risk with the COX-2 selective inhibitors and diclofenac. Finally, naproxen was not associated with an increased risk of death or MI for the entire treatment duration. For the 14-week estimate, which included the period after 14 weeks, the confidence intervals were smaller because the analyses included many more events in this period.

Supplementary Analysis

Using the Wald test, we examined for interactions for each of the NSAIDs with available covariates. Because there was a significant interaction between age and use of diclofenac, we conducted an age-stratified analysis (<60, 60 to 69, 70 to 79, ≥80 years of age) and found that patients ≥80 years of age had a higher risk of death during the first week of treatment when taking diclofenac compared with the other age subgroups (≥80 years of age: hazard ratio, 5.49, P<0.0001; 79 to 70 years of age: hazard ratio, 2.46, P<0.0001; and 69 to 60 years of age: hazard ratio, 2.56, P<0.0001). No other relevant interaction was found.

We performed sensitivity analyses using the Charlson comorbidity index to confirm the robustness of the present conclusions. These analyses gave the same results as using the Ontario acute MI mortality prediction rule (data not shown).

To investigate whether there was time independence in the risk, we calculated cumulative risk for each drug used for <90 days. The results supported our conclusion of increased risk after short-time treatment (not shown). We also made a linear test. These analyses showed significant differences when rofecoxib was taken for 15 to 30 days and for >90 days (P=0.0001). Similarly, there was a significant difference with diclofenac in the periods of 0 to 7 days and 31 to 90 days, (P<0.0001) and between 0 to 7 days and >90 days (P<0.0001). These observations also support our result of increased risk in the beginning of (diclofenac) and early after (rofecoxib) treatment onset.

We estimated that an unmeasured confounder would have to elevate risk by 2.2 to 3.3 to fully explain the increased risk for death/Re-MI observed with overall NSAID treatment.

Discussion

This nationwide study analyzed the risk of death and Re-MI in a large population of patients with prior MI according to duration of NSAID treatment. The main results of the study were that the risks of death and death/Re-MI were independent of the duration of NSAID treatment, and that the risk with some NSAIDs became apparent immediately (diclofenac) or early (rofecoxib and ibuprofen) after treatment onset. These results challenge the view that NSAIDs are not harmful during short-term (1 week) treatment and indicate that a revision of current recommendations regarding NSAID treatment in patients with established cardiovascular disease is required.13

The Vioxx Gastrointestinal Outcomes Research (VIGOR) study was the first to report increased cardiovascular risk in patients taking the selective COX-2 inhibitor rofecoxib compared with patients taking naproxen.1 Several studies have confirmed this risk and extended it to the traditional nonselective NSAIDs.2,8,11,12 Indeed, patients with established cardiovascular disease or patients at increased cardiovascular risk seem to be more vulnerable to the cardiovascular toxicity of NSAIDs.3,6,7,12 Our results support previous studies showing that patients with prior MI are at increased risk when taking NSAIDs, especially diclofenac and the selective COX-2 inhibitors.6 The present study, however, is the first to report time-to-event analyses for selective COX-2 inhibitors.
and nonselective NSAIDs in patients with prior MI in a nationwide cohort.

Time-to-event analyses performed in some of the clinical trials and in register studies of the selective COX-2 inhibitors have shown results similar to ours.\textsuperscript{11,14,17,18,24} For example, Nussmeier et al\textsuperscript{11} found increased cardiovascular risk after only 10 days of treatment with the selective COX-2 inhibitor valdecoxib and its intravenous prodrug parecoxib in patients

Figure 2. A through F, Incidence rates of death per 1000 person-years during treatment with individual nonsteroidal anti-inflammatory drugs (NSAIDs). Treatment periods were split into 1-week intervals. The horizontal line indicates the overall incidence rate for the entire study population. CI indicates confidence interval.
after coronary artery bypass surgery. Levesque et al\textsuperscript{17} found increased risk of MI after only 9 days of treatment with the selective COX-2 inhibitor rofecoxib in a population-based cohort study of elderly subjects starting NSAID therapy. Similar to that study, our study found that the risk with the selective COX-2 inhibitor rofecoxib was increased after only 7 days of treatment. Notably, the risk of death and MI during treatment with diclofenac was increased immediately after the start of treatment, and persisted. It is noteworthy that a commonly used nonselective NSAID like diclofenac is associated with an even higher risk of death at the beginning of the course of treatment than the selective COX-2 inhibitor rofecoxib, which was withdrawn from the market in 2004.

Our data challenge the current recommendations by the American Heart Association regarding NSAID treatment in patients with established cardiovascular disease, because we demonstrate that even short-term NSAID treatment is associated with increased cardiovascular risk in patients with prior MI; ie, there essentially appears to be no safe therapeutic window for NSAID treatment.\textsuperscript{13} Therefore, the current approach of recommending short-duration treatment in patients with established cardiovascular disease who require NSAIDs may need revision. It would seem prudent to limit NSAID use in patients with cardiovascular disease and to get the message out to clinicians taking care of these patients that NSAIDs are potentially harmful, even for short-term treatment.

In accordance with other studies, we found that naproxen was the NSAID with the lowest cardiovascular risk. The results might indicate that naproxen should be the preferred NSAID if NSAID treatment cannot be avoided. However, it is important to note that in the VIGOR study naproxen was associated with higher risk of gastrointestinal bleeding than rofecoxib, and that gastrointestinal bleeding in patients with prior MI is associated with worse prognosis.\textsuperscript{25} Indeed, the adverse prognostic impact of gastrointestinal bleeding further supports a very conservative approach to use of NSAIDs in patients with prior MI.

**Study Strengths and Limitations**

The main strength of this study is the completeness of data from a nationwide cohort and the avoidance of selection bias resulting from race, age, sex, socioeconomic status, affiliation to selected hospitals, or healthcare systems. The positive predictive value of the diagnosis of MI has been found to be very high in the registry.\textsuperscript{26} In the nationwide prescription registry, all Danish pharmacies are required to register all

![Figure 3. Time-dependent Cox proportional hazard analysis of risk of death according to duration of nonsteroidal antiinflammatory drug (NSAID) treatment in patients with prior myocardial infarction. HR indicates hazard ratio; CI, confidence interval.](http://circ.ahajournals.org/Downloaded from)
dispensed prescriptions, ensuring complete registration. The only NSAID available in Denmark over the counter without a prescription is ibuprofen (since 2001) and only in low doses (200 mg) and in limited quantity (100 tablets) at each dispensing. Therefore, it is unlikely that over-the-counter use of NSAIDs had a major effect on the study results.

The main limitation of the study is inherent to the observational design. There is a lack of information about important clinical parameters such as blood pressure, body mass index, smoking habits, lipid levels, and left ventricular ejection fraction. Therefore, the effect of unmeasured confounders cannot be excluded. Our calculations showed that if an unmeasured confounder or a combination of confounders was present in 20% of the cohort treated with NSAIDs, the confounder would have to elevate the risk by a factor 2.2 to 3.3 to explain the increased risk observed in our study. The existence of such a confounder or combination of confounders is highly unlikely, but not entirely impossible, because we had no information on other important risk factors such as smoking, lipid levels, or body mass index.

In the Cox models, we provide control of available confounders, but the control for confounding by indication, ie, that the patients taking NSAIDs were more prone to be sick than those not treated with these agents, may not have been adequate. We did not have any information about the precise indication for initiation of NSAID treatment. Thus, the disease or the pain causing a condition treated with an NSAID could alone indicate a condition with increased risk of cardiovascular disease or death. This condition might raise the cardiovascular risk independently and therefore be associated with increased cardiovascular risk rather than the drugs. Furthermore, the first symptoms of coronary heart disease can be interpreted as muscular pain and thereafter progress to MI. Nonsteroidal anti-inflammatory drugs are not recommended or used to treat cardiovascular disease, and angina is not likely to be treated with NSAIDs. However, we cannot rule out the possibility that this take place. To test for these biases, we performed a series of sensitivity analyses that supported our results. In the analysis, we excluded patients with rheumatic disease, which did not change the results. We observed different risks between the individual NSAIDs, which are used for similar indications, as well as a clear correlation between the degree of COX-2 inhibition and risk, indicating the predominant importance of the drugs (rather than the drug indications) and a clear dose-dependent increase in risk. Thus, although the risk of confounding by indication cannot be eliminated, we have no reason to believe that confounding by indication alone could drive the results.

Another limitation is the effect of information bias. The patients do not necessarily take their medications consecutively, leading to the fact that the prescription may run longer and the patients therefore are exposed later than the database might indicate. There would be no measurable consequences for the rest of the population, because data from individuals taking therapy without being identified as being on a prescription would be diluted in the data from the much larger population not on therapy. However, to control for this phenomenon, we examined whether the increased risk with overall NSAID use and with the individual NSAIDs persisted after treatment was stopped. We divided the periods of not taking NSAID into time intervals of 0, 7, 14, 30, and 90 days, and used the Cox proportional hazard models. For overall NSAID use, the increased risk returned to baseline shortly after treatment was discontinued. For the individual NSAIDs, the same trend was seen with diclofenac and ibuprofen, but for the selective Cox-2 inhibitor rofecoxib, the risk was persistently increased after treatment was stopped. This latter observation appears to strengthen our study conclusions,
because the same result with rofecoxib was found very recently in an analysis of data from a previous clinical trial.27

Information on prior hospital and in-hospital drug use was not included in the analyses because the purpose of the present study was to analyze the effect of NSAID use in the period after discharge from MI. Patients who used any NSAIDs before the index hospitalization and during the hospital stay would be classified as nonusers, because they do not claim a prescription

Figure 5. A through F. Incidence rates of death/recurrent myocardial infarction (Re-MI) per 1000 person-years during treatment with individual nonsteroidal anti-inflammatory drugs (NSAIDs). Treatment periods were split into 1-week intervals. The horizontal line indicates the overall incidence rate for the entire study population. CI indicates confidence interval.
in the study period. However, we believe this potential misclassification had only a small, if any, influence on the findings because it is confined to a small period of time after the admission. Furthermore, if there was a significant effect of prior NSAID use on our results, this would influence the results by moving the risk estimates toward the null and hence dilutes any association between exposure and outcome.

Conclusions and Clinical Implications
This nationwide study of patients with prior MI demonstrated that short-term treatment with most NSAIDs is associated with increased cardiovascular risk. Notably, commonly used NSAIDs, such as diclofenac, which in some countries is available over the counter without any expert advice on potential side effects, were associated with increased risk treatment onset, and the risk continued to persist during the course of treatment. Particularly worrying is the fact that diclofenac was associated with higher cardiovascular risk than the selective COX-2 inhibitor rofecoxib, which was withdrawn from the market in 2004 owing to its unfavorable cardiovascular risk profile.

The present results indicate that there is no apparent safe therapeutic window for NSAIDs in patients with prior MI and challenge the current recommendations of low-dose and short-term use of NSAIDs as being safe. Further studies, preferably randomized clinical studies, are warranted to establish the cardiovascular safety of NSAIDs, but given the additional evidence from randomized trials and other observational studies of selective COX-2 inhibitors and nonselective NSAIDs, the accumulating evidence suggests that we must limit NSAID use to the absolute minimum in patients with established cardiovascular disease.

Disclosures
None.

References
Recently, there has been increased awareness of augmented cardiovascular risk associated with use of nonsteroidal anti-inflammatory drugs (NSAIDs), especially among patients with established cardiovascular disease. Earlier studies have indicated acute or subacute effects of both the selective cyclooxygenase-2 inhibitors and nonselective NSAIDs on the cardiovascular system. These adverse events were closely tied to the timing of taking the drugs, and most patients were receiving treatment for a short period of time. However, at present, there is a lack of data on the impact of NSAID treatment duration on cardiovascular risk. The present study addresses the risk of all NSAIDs in a selected population of post–myocardial infarction patients. We present a comprehensive analysis of the effect of duration of NSAID treatment on cardiovascular risk. The present study addresses the risk of all NSAIDs in a selected population of post–myocardial infarction patients. We present a comprehensive analysis of the effect of duration of NSAID treatment on cardiovascular risk. The present study addresses the risk of all NSAIDs in a selected population of post–myocardial infarction patients. We present a comprehensive analysis of the effect of duration of NSAID treatment on cardiovascular risk. The present study addresses the risk of all NSAIDs in a selected population of post–myocardial infarction patients. We present a comprehensive analysis of the effect of duration of NSAID treatment on cardiovascular risk.
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